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Domino Reactions

From Enantiopure Hydroxyaldehydes to Complex Heterocyclic Scaffolds: Development of Domino Petasis/Diels–Alder and Cross-Metathesis/Michael Addition Reactions

Alexandre Cannillo,[a] Stéphanie Norsikian,*[a] Marie-Elise Tran Huu Dau,[a] Pascal Retailleau,[a] Bogdan I. Iorga,[a] and Jean-Marie Beau*[a, b]

Abstract: One-step assembly of hexahydroisoindole scaffolds by a sequence that combines the Petasis (borono-Mannich) and Diels–Alder reactions is described. The unique selectivity observed experimentally was confirmed by quantum calculations. The current method is applicable to a broad range of substrates, including free sugars, and holds significant potential to efficiently and stereoselectively build new heterocyclic structures. This easy and fast entry to functionalized polycyclic compounds can be pursued by further transformations, for example, additional ring closure by a cross-metathesis/Michael addition domino sequence.

Introduction

Domino processes consist of several bond-forming reactions in a single chemical step and allow the highly efficient synthesis of complex molecules from simple substrates.[1] In recent years, domino reactions have been the subject of intense research due to their undeniable benefits, which include some of the main issues in modern synthetic organic chemistry: atom-, time-, labor-, and waste-economy. Moreover, these reactions often proceed with excellent stereoselectivity and, therefore, the design of new domino reactions is a continuing challenge. Herein, we report the details of an efficient synthesis of perhydroisoindole derivatives by a Petasis (borono-Mannich)/intramolecular Diels–Alder (IMDA) reaction sequence. This provides an easy entry to functionalized polycycles that may undergo further transformations, such as a consecutive domino process that involves cross-metathesis and Michael addition. The result is the construction of enantiopure molecules with a common structural scaffold in which up to six covalent bonds and five asymmetric centers are formed and up to four points of diversity are present. Effective synthetic pathways that lead to new small molecular arrangements able to modulate biological systems are currently in great demand.[2]

The Petasis reaction is a well-known and powerful method that involves the condensation of aryl- or vinyl-boronic acids with amines and carbonyl compounds such as salicylaldehydes, α-keto acids, and α-hydroxy aldehydes.[3] In a single process, aminophenols, aminoacids, or β-amino alcohols derivatives are formed under mild reaction conditions with minimum protecting-group manipulations. With enantiopure α-hydroxy aldehyde derivatives as the carbonyl partner the corresponding enantiopure β-amino alcohols are obtained with exclusively *anti* diastereoselectivity (**B**; Figure 1).[4,5] The reaction may involve a transient iminium species followed by an intramolecular organyl ligand transfer from the activated tetra-coordinated boronate intermediate (**A**; Figure 1).[6] This approach to 1,2-amino alcohols has been commonly utilized as a key step in the synthesis of bioactive molecules and complex natural products, for example, polyfunctionalized pyrrolidines[7] such as **I**–**III**, iminosugars **IV**,[8] conduramines **V**,[5b,9] *N*-acylneuraminic acids **VI**,[10] or anti-influenza agents **VII**.[11] We reasoned that the combination of the Petasis reaction with an intramolecular Diels–Alder reaction would produce new molecular constructs with high efficiency and selectivity.[12] We also believed in the potential to relay the stereochemical information of the Petasis reaction for the installation of additional stereocenters during ring construction in the Diels–Alder step.

Results and Discussion

At the outset of our investigations, the three-component coupling between (*E*)-(3-methylbuta-1,3-dien-1-yl)boronic acid (**1**),

[a] Dr. A. Cannillo, Dr. S. Norsikian, Dr. M.-E. Tran Huu Dau, Dr. P. Retailleau, Dr. B. I. Iorga, Prof. J.-M. Beau
Centre de Recherche de Gif
Institut de Chimie des Substances Naturelles du CNRS
CNRS UPR 2301 Avenue de la Terrasse
91198 Gif-sur-Yvette (France)
Fax: (+33) 169077247
E-mail: stephanie.norsikian@cnrs.fr
jean-marie.beau@u-psud.fr

[b] Prof. J.-M. Beau
Université Paris-Sud and CNRS
Laboratoire de Synthèse de Biomolécules
Institut de Chimie Moléculaire et des Matériaux d'Orsay
91405 Orsay (France)

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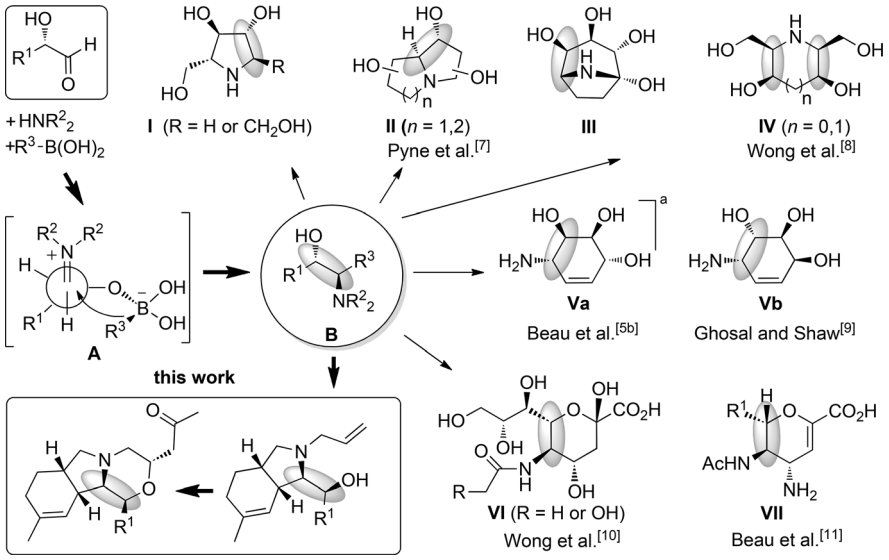
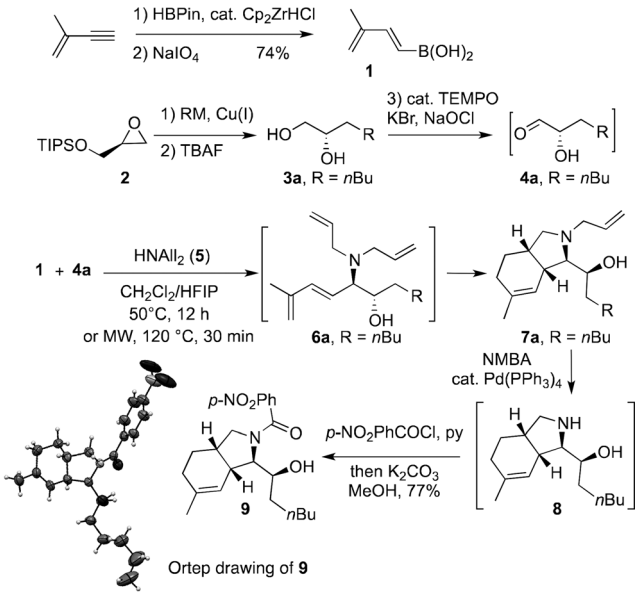


Figure 1. Applications of the Petasis 1,2-aminoalcohol synthesis from boronic acids and α-hydroxy aldehydes. [a] An intramolecular version of this reaction with an exclusive 1,2-*anti* stereoselective outcome, opposite to the one found in the intermolecular process.[5b]

(*S*)-2-hydroxyheptanal (**4a**), and diallylamine (**5**) was examined as a model reaction (Scheme 1).[13] Hydroboration of the corresponding alkyne with pinacolborane (HBPin) catalyzed by $HZrCp_2Cl$[14] followed by oxidation furnished the required boronic acid **1** in 74% yield. α-Hydroxyaldehyde **4a** was prepared from the protected (*R*)-glycidol **2**. Epoxide ring opening with *n*BuLi in the presence of copper iodide and deprotection of the resulting adduct with tetrabutylammonium fluoride (TBAF) gave diol **3a**, which was then oxidized selectively at the primary position with a solution of NaOCl in the presence of KBr and a catalytic amount of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO).[15]



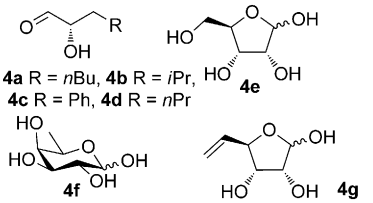
Scheme 1. Preparation of boronic acid **1** and α-hydroxyaldehyde **4a**. Domino Petasis/Diels–Alder reaction from **1**, **4a**, and diallylamine **5** and derivatization of hexahydroisoindole **7a**. Cp = cyclopentadienyl, All = allyl, NMBA = *N*,*N*′-dimethylbarbituric acid. X-ray structure of **9**.

After work up of the oxidation reaction, **4a** was used directly in the Petasis condensation. For this reason and according to our previous work,[11] the reactions were carried out with an excess of **4a** and **5** (2 equiv each) with CH_2Cl_2 or 9:1 CH_2Cl_2/hexafluoroisopropanol (HFIP) as the solvent. The optimal conditions were found to be CH_2Cl_2/HFIP[16] either at 50 °C for 12 h or under microwave irradiation (MW) at 120 °C for 30 min. In each case, the reaction led to the unique formation of the cyclized compound **7a**[13] (R = *n*Bu) in 84 and 91% yield, respectively. In CH_2Cl_2 alone the reaction was less effective and provided the Petasis/Diels–Alder adduct **7a** in lower yields (42% at 50 °C for 12 h). Interestingly, the intramolecular cycloaddition reaction occurred even at room temperature without a trace of uncyclized **6a** (R = *n*Bu). Only cyclized adduct **7a** was obtained (61% in CH_2Cl_2/HFIP for 12 h, 24% in CH_2Cl_2 for 96 h), along with unreacted starting materials. A very favorable preorganization of the two partners for the Diels–Alder reaction is suggested; this was recently quantified in a proximity-induced example.[17] Moreover, of the four possible diastereomers that could be obtained from the cyclization, the formation of a unique isomer was observed with complete stereocontrol at all the newly formed stereogenic centers.[18] The absolute configuration was unambiguously determined by X-ray crystal diffraction analysis of **9**, obtained after deallylation of **7a** and *p*-nitrobenzoylation of the resulting free amine **8** (Scheme 1).[13] The *anti* relationship of the amino alcohol produced during the Petasis reaction was first confirmed by the crystal structure of **9**. It also revealed a *cis* ring-junction geometry, which suggested that the IMDA reaction proceeded through an *endo* transition state (TS). Moreover, an excellent π-facial selectivity of this IMDA was obtained showing the addition of the diene to the *Re* face of the dienophile in the *endo* TS.

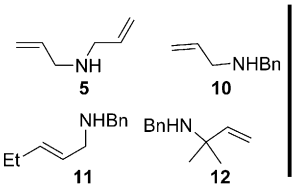
By using the optimized conditions (MW, 120 °C, 30 min), we studied the reaction scope with a series of substrates and the results are shown in Table 1. The reaction of boronic acid **1**, diallylamine **5**, and optically pure α-hydroxy aldehydes **4b–c** or unprotected carbohydrates D-ribose **4e** and D-fucose **4f** gave compounds **7b–c**[13] and **7e–f**[13] (Table 1, entries 1–4), respectively. As above, only one isomer was observed for each compound and their absolute configurations were given by analogy to that of **7a**. Enantiomeric purity of the hexahydroisoindole product **7c** could be confirmed by chiral HPLC analysis.[13]

Table 1. Reaction scope for the domino Petasis/Diels–Alder reaction.

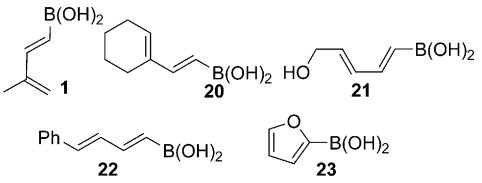
α-Hydroxy aldehydes



Amines



Boronic acids



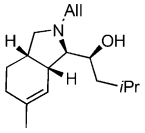
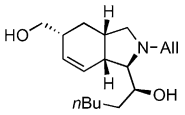
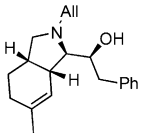
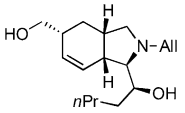
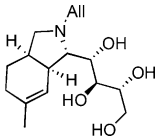
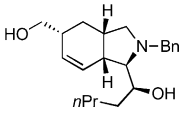
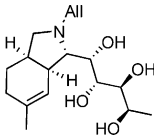
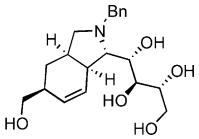
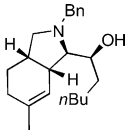
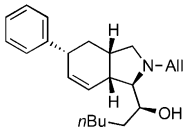
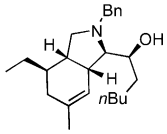
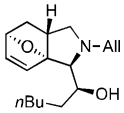
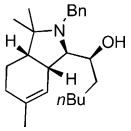
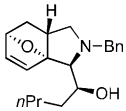
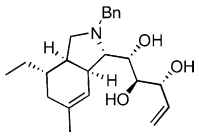
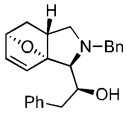
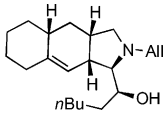
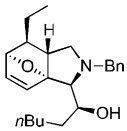
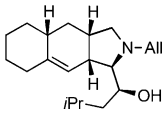
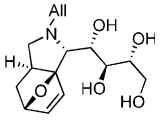
Entry	Substrate	Product (yield [%])[a,b]	Entry	Substrate	Product (yield [%])[a,b]
1	**1+4b+5**	 **7b** (71)	12	**21+4a+5**[c]	 **25a** (94)
2	**1+4c+5**	 **7c** (75)	13	**21+4d+5**[c]	 **25b** (78)
3	**1+4e+5**[c]	 **7e** (73)	14	**21+4d+10**[c]	 **25c** (81)
4	**1+4f+5**[c]	 **7f** (64)	15	**21+4e+10**[c]	 **25d** (79)
5	**1+4a+10**	 **13** (78)	16	**22+4a+5**	 **26** (68)
6	**1+4a+11**[d]	 **14** (78)	17	**23+4a+5**	 **31a** (88)
7	**1+4a+12**[d]	 **15** (54)	18	**23+4d+10**	 **31b** (66)
8	**1+4g+11**[d]	 **18** (75)	19	**23+4c+10**	 **31c** (83)
9	**20+4a+5**	 **24a** (83)	20	**23+4a+11**[d]	 **31d** (59)
10	**20+4b+5**	 **24b** (66)	21	**23+4e+5**[c]	 **31e1**

Table 1. (Continued)

α-Hydroxy aldehydes: **4a** R = *n*Bu, **4b** R = *i*Pr, **4c** R = Ph, **4d** R = *n*Pr; **4e**; **4f**; **4g**

Amines: **5**; **10**; **11**; **12**

Boronic acids: **1**; **20**; **21**; **22**; **23**

Entry	Substrate	Product (yield [%])[a,b]	Entry	Substrate	Product (yield [%])[a,b]
11	**20**+**4c**+**5**	**24c** (86)			**31e2** (89, d.r.[e] = 7:3)

[a] Reaction conditions: boronic acid (1 equiv), α-hydroxyaldehyde (2 equiv), amine (2 equiv), 9:1 CH_2Cl_2/HFIP, MW (120 °C, 30 min), unless otherwise stated. [b] Isolated yield after chromatography, based on boronic acid. [c] 1:1 CH_2Cl_2/HFIP was used. [d] Reaction time = 1.5 h. [e] d.r. = diastereomeric ratio. Bn = benzyl.

In the case of more polar aldoses **4e** and **4f**, the proportion of HFIP was increased (1:1 CH_2Cl_2/HFIP) for solubility. We next studied the reaction of boronic acid **1**, aldehyde **4a**, and readily available substituted allylamines **10**–**12** (Table 1, entries 5–7). For **11** and **12**, the reaction was carried out for 1.5 h (instead of 30 min) to complete the cyclization. In all cases, the reaction yielded the desired compounds in 54–78% as single diastereomers. By using *E*-allylamine **11**, a supplementary asymmetric center was generated in products **14**, **18**, and **31d** (Table 1, entries 6, 8, and 20). The stereochemistry of **14** was assigned on the basis of strong NOEs observed between H-9α and both H-7 and H-10 and also between H-13a and the hydrogen atoms H-20 of the ethyl chain (Figure 2).

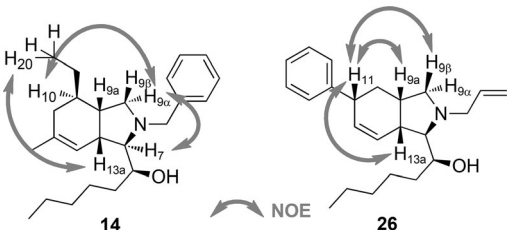
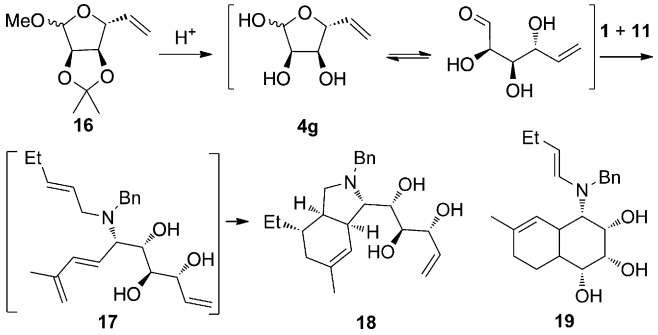


Figure 2. Selected NOEs for hexahydroisoindoles **14** and **26**.

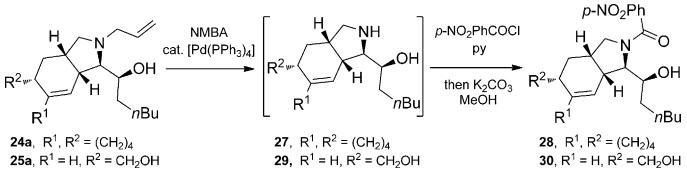
These observations indicate that the IMDA reaction proceeded as reported above, with the addition of the diene to the *Re* face of the dienophile in the *endo* TS. The reaction with *E*-allylamine **11** and boronic acid **1** was also carried out with aldehyde **4g**, which was obtained after deprotection of the known alkene derivative **16**[19] (Scheme 2). Because the IMDA reaction with a substituted allylamine is more difficult, we could expect the reaction with the terminal olefin to furnish fused 6,6-bicyclic compound **19**. However, we isolated only hexahydroisoindole derivative **18** (75%) after the reaction. This confirmed the favorable preorganization of the diene and the allylamine partners in the Diels–Alder reaction (Scheme 2). The same reaction



Scheme 2. One-pot synthesis of hexahydroisoindole **18** from acetal **16** by a Petasis/Diels–Alder domino reaction with amine **11** and boronic acid **1**.

was also carried out with *N*,*N*-dibenzylamine and led only to the Petasis adduct in very low yield without any traces of the cyclized 6,6-bicyclic product.

Other dienic boronic acids, such as **20**–**23**, in combination with different aldehydes and amines (Table 1, entries 9–21) produced the corresponding cyclized adducts as single enantiomers. For **24a**–**c**, **25a**–**d**, and **26**,[20] the *endo* and facial selectivities were the same as previously observed (Table 1, entries 9–16). The structures of **24a** and **25a** were confirmed by X-ray analysis of compounds **28** and **30**, respectively, obtained after deallylation and *p*-nitrobenzoylation (Scheme 3).[13] The stereochemistry of **26** was assigned on the basis of strong NOEs observed between H-11 and H-9a and between H-11 and both H-9β and H-13a (Figure 2). A gram-scale synthesis was carried



Scheme 3. Derivatization of hexahydroisoindoles **24a** and **25a**.

out with **21** (0.64 g, 5 mmol), **4a**, and **5** in 1:1 CH_2Cl_2/HFIP at 50 °C for 16 h to afford **25a** in 90% yield (1.32 g).

With 2-furanylboronic acid **23**, the reaction that involved the Petasis condensation followed by an intramolecular Diels–Alder reaction of the furan diene (IMDAF) led to the synthesis of oxanorbornenes fused to a five-membered heterocycle (Table 1, entries 17–21). The reactions carried out with amines **5**, **10**, or **11** and aldehydes **4a**, **4c**, or **4d** produced the corresponding cyclized adducts as single stereoisomers, whereas with **4e**, we observed the formation of two separable isomers **31e1** and **31e2** in a 7:3 ratio.[21] The structural assignment of adducts **31a–d**, **31e1**, and **31e2** was based on NMR spectroscopic analysis by using ^1H–^1H couplings and NOE experiments (Figure 3, Table 2).[22] These studies showed that the IMDAF reaction proceeded through an *exo* TS and for **31a–d** and **31e1**, the addition of the diene occurred on the *Re* face of the dienophile in the *exo* TS. For instance with **31d**, the relative orientation of the ethyl chain at C10, *trans* to the oxygen bridge, could be deduced from the value of the vicinal coupling constant between the protons H-10 and H-11 ($J = 3$ Hz; Figure 3). Moreover, strong NOEs were observed between H-9α and both H-7 and H-10 and also between H-9a and the hydrogen atoms H-19 of the ethyl chain. For **31e1**, we observed that of the two geminal protons H-8α and H-8β, H-8β coupled with H-9 ($J = 4$ Hz), which is consistent with a dihedral angle of about −40°. No coupling constant was observed between H-8α and H-9 due to a dihedral angle of about 80°. The analysis of the 2D-NOESY data showed NOEs between H-5 and H-7β, between H-7β and H-8β, and between H-7a and both H-7α and H-8α. For **31e2**, the IMDAF reaction also proceeded through an *exo* TS but the addition of the diene occurred on the other side of the dienophile (i.e. the *Si* face). As reported above, the structural assignment was based on NMR spectroscopic analysis by using coupling constants and NOE experiments. For this compound, no coupling constant was observed between H-8β and H-9, whereas H-8α coupled with H-9 ($J = 4$ Hz). Moreover, we observed NOEs between H-7a and both H-7β and H5 and between H-7α and H-8α.

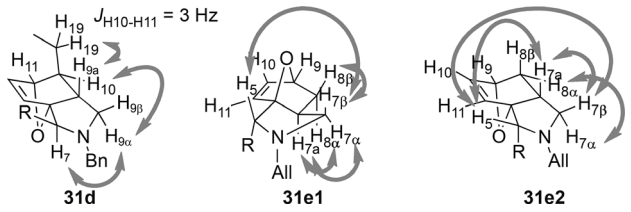


Figure 3. Selected ^1H NMR spectroscopic data and NOEs for oxanorbornenes **31d**, **31e1**, and **31e2**.

Table 2. Comparison of ^1H NMR and ^1H–^1H 2D-NOESY spectral characteristics of isomers **31e1** and **31e2**.

Entry	$^1H/^1H$	31e1		31e2	
		J [Hz]	NOE[a]	J [Hz]	NOE[a]
1	9-8α	0	w	4	m
2	9-8β	4	m	0	w
3	8α-8β	11.5	s	11.5	s
4	8α-7a	7.5	m	4	–
5	8β-7a	3	w	7.5	m
6	7α-7a	nd	w	11.5	–
7	7β-7a	9	–	7	m
8	7α-7β	10.5	s	11.5	s
9	8β-7β	–	m	–	–
10	8α-7α	–	–	–	m
10	7a-11	–	w	–	w
11	8β-10	–	–	–	w
12	8α-10	–	w	–	–
13	7β-5	–	m	–	m
14	7a-5	–	–	–	w

[a] s = strong; m = medium; w = weak.

Computational results

To evaluate the structural and energetic determinants that explain the selectivities observed for the IMDA and IMDAF cycloadditions, a computational study was carried out, which took into account all possible intermediates involved in the formation of the cycloadducts. We started with the generation and geometry optimization of the lowest-energy conformers for compounds **S**[13] and **Sf**, which would result from the Petasis reaction (Figures 4 and 5). For practical reasons, all the calculations were realized by using simplified structures, which contain only the atoms that are pertinent to the reactions considered. In all structures, the hydroxyl group was free form (results presented here) or a borate ester (results presented in the Supporting Information). Small differences were observed between these two series, but the overall results were qualitatively similar and both can explain the experimentally observed selectivities. In the next step we built the near-attack conformations **C1**–**C4** and **Cf1**–**Cf4** that would lead to the final diastereomers **P1**–**P4** and **Pf1**–**Pf4** via the corresponding transition states **TS1**–**TS4** and **TSf1**–**TSf4**.

There were four *endo* (**TS1**, **TS2**, **TSf1**, **TSf2**) and four *exo* (**TS3**, **TS4**, **TSf3**, **TSf4**) possible transition states, which led to products with *cis*- and *trans*-junctions, respectively (Figures 4 and 5). The geometries of all these structures were optimized by using DFT calculations at the B3LYP/6-31G(d,p) level, and the vibrational-frequency calculations confirmed that these conformations were local minima or maxima, as expected. The energy diagrams for these reactions are presented in Figures 4 and 5. It is noteworthy that all structures show an intramolecular hydrogen bond between the amino group and the hydroxyl or borate moiety that is most likely essential for preorganization of the reacting functional groups into favorable positions. This fact is in agreement with the relatively low energy barriers calculated for these reactions (about 23 kcal mol^{-1} relative to the reference structures **S** and **Sf**) and the mild experimental conditions under which these reactions were carried out. The very high (about 60 kcal mol^{-1}) energy barrier calculated for the retro-IMDA reaction suggests that, in this case, the cycloaddition was irreversible, being under kinetic control. On the other hand, Figure 5 shows that the IMDAF was reversible, with similar values for the energy barriers in both directions, and this reaction seemed to be under thermodynamic control.

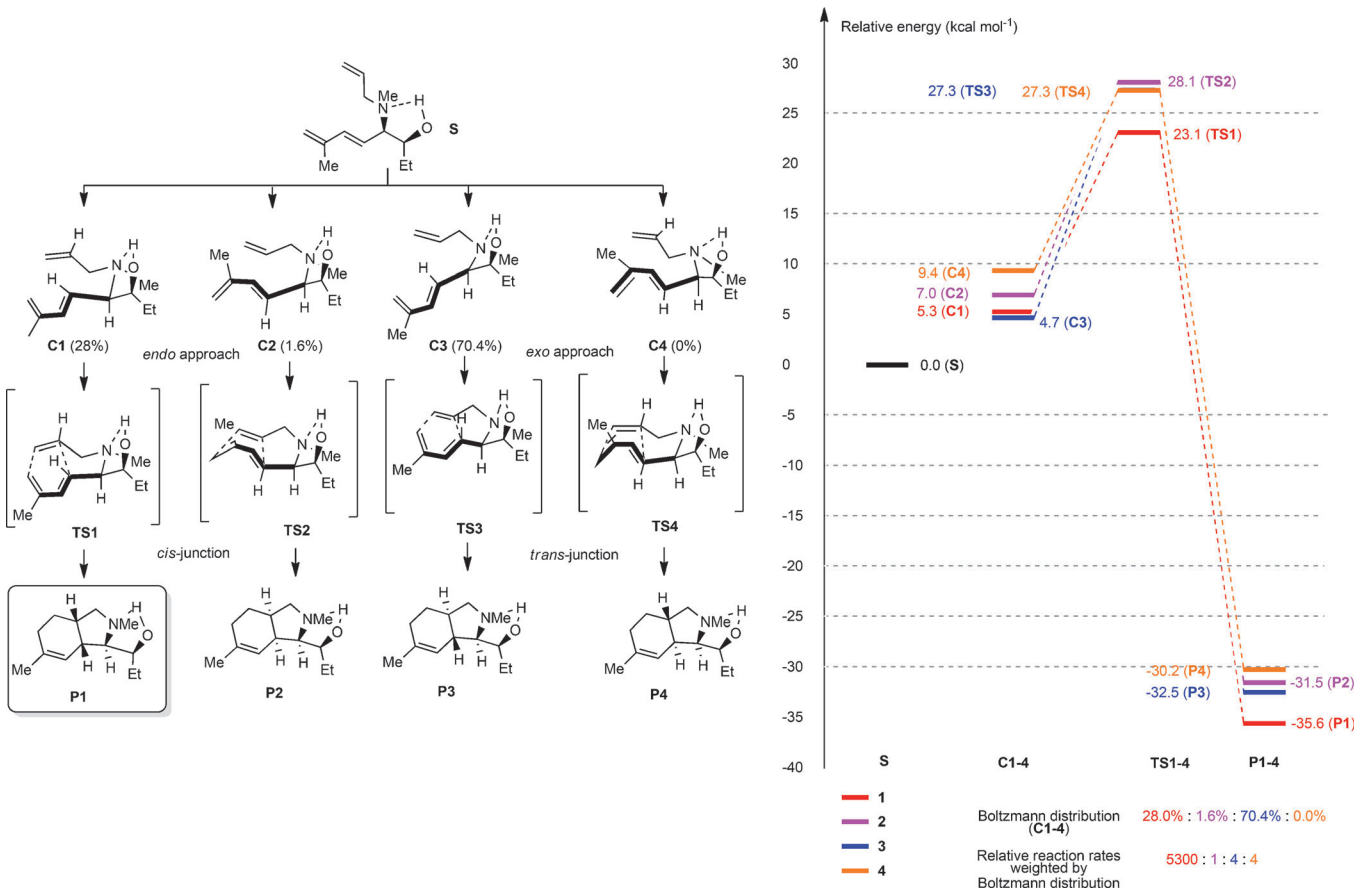


Figure 4. Transition structures and energy diagrams for the intramolecular Diels–Alder reaction of model **S** resulting from the three-component Petasis reaction.

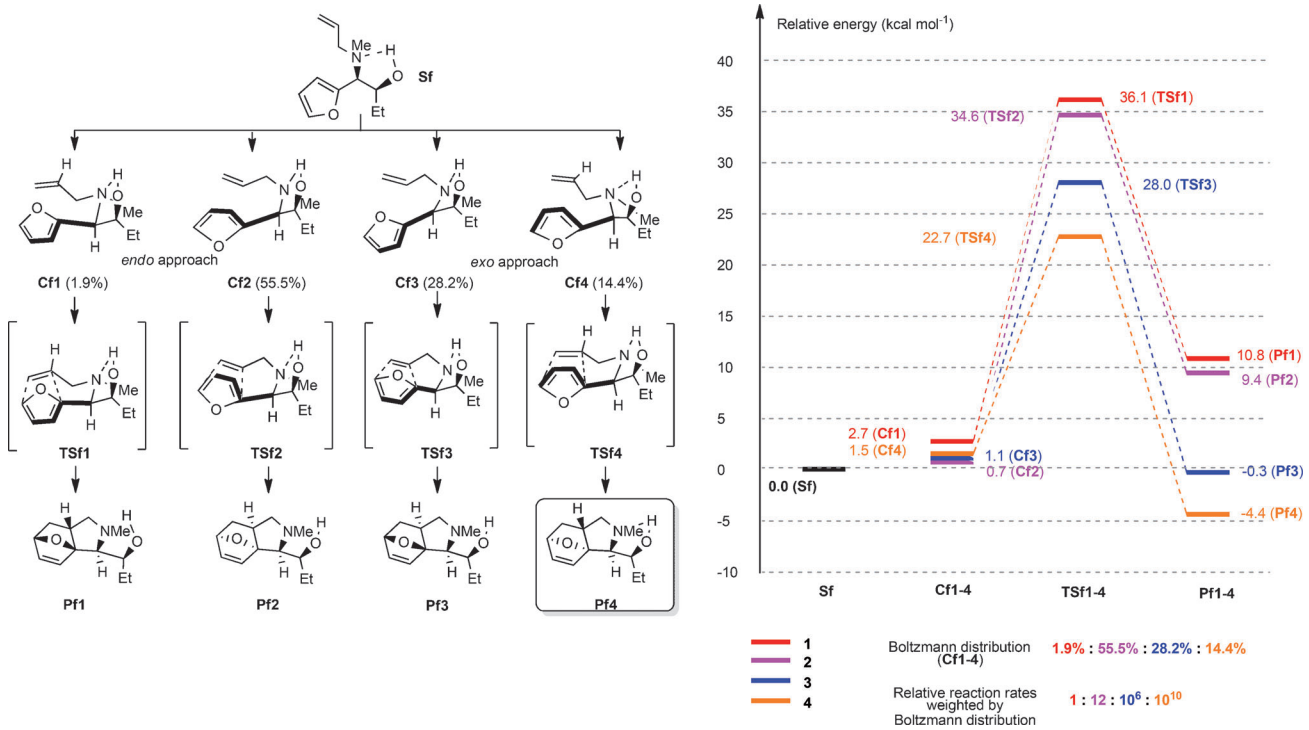


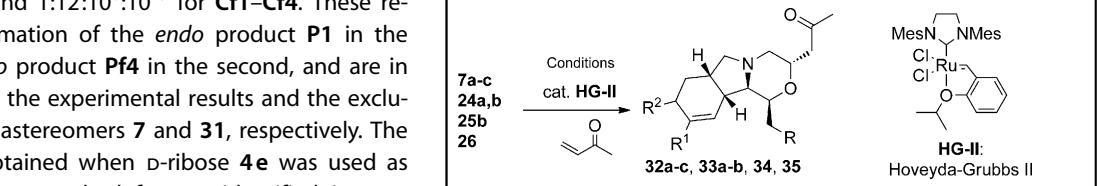
Figure 5. Transition structures and energy diagrams for the intramolecular Diels–Alder reaction of model **Sf** resulting from the three-component Petasis reaction with 2-furanylboronic acid **23**.

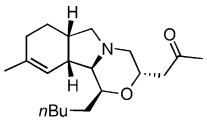
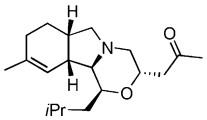
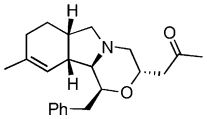
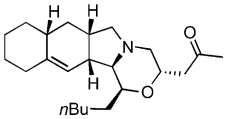
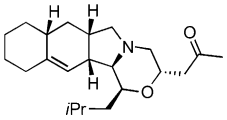
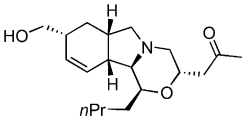
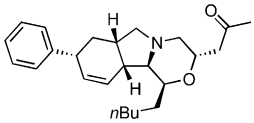
All the near-attack conformers were in rapid-exchange equilibrium (the **C1**–**C4** and **Cf1**–**Cf4** relative energies were 4.7–9.4 and 0.7–2.7 kcal mol^{-1} higher than the most stable conformers **S** and **Sf**, respectively), with Boltzmann distributions of 28.0:1.6:70.4:0.0 (**C1**–**C4**) and 1.9:55.5:28.2:14.4 (**Cf1**–**Cf4**). However, the most abundant conformer was not necessarily the most reactive; the relative reaction rates, weighted by Boltzmann distribution of the initial conformers were 5300:1:4:4 for **C1**–**C4** and 1:12:10^6:10^{10} for **Cf1**–**Cf4**. These results predicted the formation of the *endo* product **P1** in the first case and of the *exo* product **Pf4** in the second, and are in perfect agreement with the experimental results and the exclusive formation of the diastereomers **7** and **31**, respectively. The unexpected mixture obtained when D-ribose **4e** was used as the aldehyde could have resulted from unidentified interactions of the reacting partners with the polyhydroxy side-chain of the sugar.

Post functionalizations

The possibility of further transformations was investigated with selected derivatives. As seen above, de-allylation of **25a** provided free amine **29**[13] (Scheme 3) in 89% yield. The *N*-allyl substituent in **7** was also a useful starting point to increase skeletal complexity and could subsequently act as the nucleophile in a second cross-metathesis/conjugate addition domino sequence, illustrated in Table 3. For this transformation, we first followed the conditions described by Fuwa et al. for the stereoselective synthesis of substituted tetrahydropyrans by domino olefin cross-metathesis/intramolecular oxa-conjugate cyclization.[23] However, upon treatment of a mixture of **7a**, methyl vinyl ketone (10 equiv), and Hoveyda–Grubbs II catalyst **HG-II** (10 mol%) in 1,2-dichloroethane at 80 °C for 15 h, or by using microwave irradiation at 100 °C in CH_2Cl_2 for 30 min, no trace of the desired compound was detected (Table 3, entries 1 and 2). These results may be explained by the presence of the secondary amine, which inhibits the catalytic cycle by competitively binding to the ruthenium metal center. This can be avoided by in situ deactivation of the amino group by addition of Broønsted or Lewis acid. Towards this end, additives such as Ti(O*i*Pr)$_4$[24] or camphorsulfonic acid (CSA) were used. In the latter case, encouraging results were obtained with the formation of the desired morpholine **32a**[13] in 38% yield (1 h, 100 °C, MW; Table 3, entry 4). Because the yield could not be improved with a longer reaction time, we chose to preform the tosylate ammonium salt[25] before the ruthenium-alkylidene catalyzed cross-metathesis with methyl vinyl ketone. After 1 h, the reaction directly provided tricyclic 2,6-*trans*-substituted morpholine **32a** in 55% yield with high diastereoselectivity by one-pot domino metathesis with 1,4-addition of the properly positioned hydroxyl group (Table 3, entry 5). The yield was greatly improved to 86% with an increased reaction time (4 h; Table 3, entry 6). The stereochemistry of the newly created stereocenter was determined by analysis of the 2D-NOESY data, which showed a strong NOE between the hydrogen atom H-6 alpha to the morpholine oxygen and the H-14 protons on the pentyl chain (Figure 6). We also observed NOEs between H-7β and both H-9β and H-6 and between H-9α and H-13b. These results indicate that the morpholine adopts a chair conformation with the pentyl group in an axial orientation and the methyl ketone side-chain in an equatorial orientation.

Table 3. Cross-metathesis/Michael addition domino transformation of hexahydroisoindoles **7a–c**, **24a–b**, **25b**, and **26**.



Entry	Substrate	Conditions[a]	Product (yield [%])[c]		Combined yield [%][d]
1	**7a**	**A**	–	–	–
2	**7a**	**B**	–	–	–
3	**7a**	**C**	–	–	–
4	**7a**	**D**		**32a** (38)	–
5	**7a**	**E**[b]		**32a** (55)	–
6	**7a**	**E**		**32a** (86)	78 (53)[e]
7	**7b**	**E**		**32b** (82)	58
8	**7c**	**E**		**32c** (84)	63
9	**24a**	**E**		**33a** (56)	47 (33)[e]
10	**24b**	**E**		**33b** (65)	43
11	**25b**	**E**		**34** (64)	50 (24)[e]
12	**26**	**E**		**35** (71)	48

[a] Reaction conditions: methyl vinyl ketone (10 equiv), HG-II (Mes = mesityl) cat. (0.1 equiv), **A**: 1,2-dichloroethane, 80 °C, 15 h; **B**: MW, CH_2Cl_2, 100 °C, 30 min; **C**: a) Ti(O*i*Pr)$_4$ (0.3 equiv), b) MW, CH_2Cl_2, 100 °C, 1 h; **D**: a) CSA (1 equiv), b) MW, CH_2Cl_2, 100 °C, 1 h; **E**: a) *p*-Toluenesulfonic acid (TsOH; 1 equiv), b) MW, CH_2Cl_2, 100 °C, 4 h. [b] Conditions **E** for 1 h. [c] Isolated yield after chromatography. [d] Combined yield of the two separated domino transformations based on the starting boronic acid. [e] Entire sequence in a one-pot procedure. Reaction conditions: boronic acid (1 equiv), α-hydroxyaldehyde (2 equiv), amine (2 equiv), 9:1 CH_2Cl_2/HFIP, MW (120 °C, 30 min), then conditions **E** with TsOH (2 equiv).

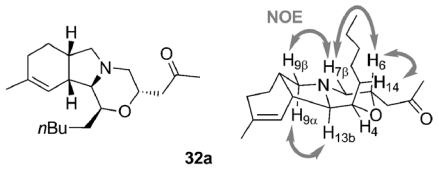
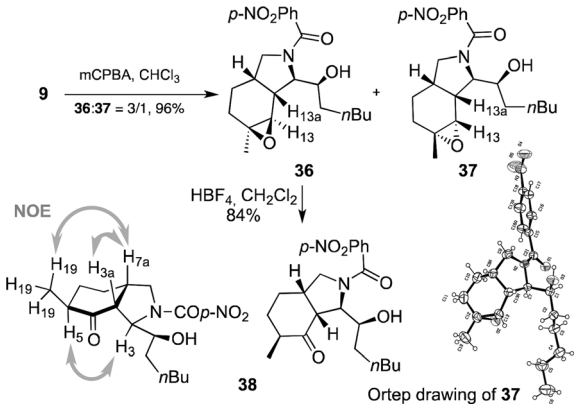


Figure 6. Selected NOEs for morpholine derivative **32a**.

The reaction was also carried out with **7b–c**, **24a–b**, **25b**, and **26** and provided similar results. Enantiopure tri- or tetracyclic scaffolds **32b–c**,[13] **33a–b**,[13] **34**,[13] and **35** were obtained in 56–82% yield (Table 3, entries 7–12). For three examples, the entire sequence of transformations could be performed in the same reaction vessel, starting from the boronic acid, amine, and α-hydroxy aldehyde (Table 3, entries 6, 9, and 11). By avoiding the need for workup and product isolation of the intermediate products, the synthesis was more concise, however with a notable reduction of the overall efficiency relative to the two-pot procedure.

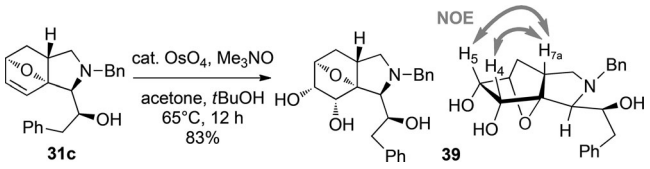
Other transformations were also performed on hexahydroisoindoles. For example, treatment of **9** with *meta*-chloroperbenzoic acid (*m*-CPBA) resulted in the formation of a separable 3:1 mixture of diastereomers **36** and **37** in 96% yield (Scheme 4). In the ^{1}H NMR spectrum of the major diastereomer



Scheme 4. Derivatization of **9** and **36**. X-ray structure of **37**.

36, the H-13 resonance appears as a singlet, indicative of a dihedral angle between the two protons of about 90°, and confirms the attack of the peracid mainly from the convex face of the olefin. On the contrary, for the minor isomer **37** H-13 was coupled to H-13a and appeared as a doublet ($J=4$ Hz), diagnostic of the α-oriented epoxide. In the latter case, the configuration of **37** was unambiguously determined by X-ray crystal diffraction analysis.[26] Exposure of **36** to HBF_4 resulted in stereospecific rearrangement to the ketone **38** in 84% yield (Scheme 4). As expected, the oxirane bond reorganization occurred with an in-plane 1,2-hydrogen shift to give **38** with the secondary methyl group in the pseudo-equatorial position.[27] The β orientation of the Me group in **38** was confirmed by the observation of NOEs between H-5 and H-3 and also between H-19 and H-7a.

The cycloadduct **31c** was transformed to diol **39** by reaction with catalytic OsO_4 in the presence of trimethylamine *N*-oxide. The dihydroxylation reaction occurred exclusively from the *exo* face and produced **39** in 83% yield (Scheme 5), which was confirmed by the NOEs observed between H-7a and both H-4 and H-5.



Scheme 5. Dihydroxylation of **31c**. Selected NOEs for **39**.

Conclusion

A novel sequence of transformations, initiated by the Petasis reaction in a domino sequence with an intramolecular Diels–Alder reaction followed by cross-metathesis and Michael reaction, was successfully developed. The result was the construction of enantiopure polyheterocyclic scaffolds, in which up to six covalent bonds and five asymmetric centers were stereoselectively formed, that contained up to four points of diversity. Notably, the starting enantiopure α-hydroxy aldehydes also included unprotected aldoses. The highly favored and selective intramolecular Diels–Alder reaction was rationalized by DFT calculations, which showed the involvement of an intramolecular hydrogen bond with an important role in preorganization of the reacting functional groups into very favorable positions.

Experimental Section

General

Unless otherwise stated, all reactions were carried out under an argon atmosphere. THF was distilled under argon over sodium benzophenone. Dichloromethane was distilled under argon over CaH_2. Reactions were monitored by analytical TLC on silica gel 60 F_{254} plates and visualized under UV light ($\lambda=254$ nm) and/or by staining with $KMnO_4$, vanillin, or ninhydrin solution. Silica gel (SDS 60 ACC 35–70 mm) was used for column chromatography. Preparative TLC was performed with Merck 60 F_{254} 0.5 mm plates. NMR spectra were recorded with AM 300, AVANCE 300, or AVANCE 500 Bruker spectrometers. Chemical shifts are reported in parts per million (ppm), referenced to the solvent peak of $CDCl_3$ (^{13}C NMR: $\delta=$ 77.23 ppm; ^{1}H NMR: $\delta=7.26$ ppm). Microwave reactions were carried out with a CEM Discover S-Class or Anton Paar Monowave 300 instrument. Melting points (uncorrected) were determined with the aid of a Büchi B-540 apparatus. IR spectra were recorded on a PerkinElmer Spectrum BX instrument with an FTIR system. Optical rotations were measured with an Anton Paar MCP300 polarimeter by using a cell of 1 dm path length.

General procedure a: Domino Petasis/Diels–Alder Reaction

Allylamine (2.0 equiv) and boronic acid (1.0 equiv) were added to a stirred solution of the aldehyde (2.0 equiv) in CH_2Cl_2/HFIP. The re-

sulting mixture was heated to 120 °C by microwave irradiation. Solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

Gram-scale preparation of perhydroisoindole 25 a

Diallylamine **5** (1.23 mL, 10.0 mmol, 2.0 equiv) and boronic acid **21** (640 mg, 5.00 mmol, 1.0 equiv) were added to a stirred solution of aldehyde **4 a** (1.30 g, 10.0 mmol, 2.0 equiv) in 1:1 CH_2Cl_2/HFIP (25 mL). The resulting mixture was heated at 50 °C for 16 h. Solvent evaporation and purification afforded perhydroisoindole **25 a** (1.32 g, 4.50 mmol, 90 %) as a yellow oil.[13]

Hexahydroisoindole 13

General procedure a was followed by using **4 a** (32 mg, 0.25 mmol), **10** (25 μL, 0.20 mmol), and **1** (14 mg, 0.13 mmol) in 9:1 CH_2Cl_2/HFIP (0.6 mL), 30 min. After purification (AcOEt/heptane 5:95–15:85), **13** (32 mg, 0.10 mmol, 78 %) was obtained as a yellow oil. $[\alpha]_D^{25} = +86.0$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.31$–7.18 (m, 5H; H_{Ar}), 5.16 (s, 1H; C*H*=C), 3.95 (d, ^3J(H,H) = 13.0 Hz, 1H; NCH_2Ph), 3.73–3.68 (m, 1H; C*H*OH), 3.25 (d, ^3J(H,H) = 13.0 Hz, 1H; NCH_2Ph), 2.77 (s, 1H; CH_2N), 2.67 (s, 1H; C*H*), 2.24 (s, 1H; C*H*N), 2.20–2.13 (m, 2H; C*H*, CH_2N), 1.86–1.75 (m, 2H; CH_2), 1.63 (s, 3H; CH_3), 1.58–1.49 (m, 4H; CH_2), 1.42–1.36 (m, 2H; CH_2), 1.32–1.30 (m, 4H; CH_2), 0.88 ppm (t, ^3J(H,H) = 6.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 139.74$ (Cq; Ar), 132.32 (*C*=CH), 128.90 (Ar), 128.55 (Ar), 127.25 (Ar), 124.41 (C=*C*H), 75.82 (*C*HN), 69.62 (*C*HOH), 59.02 (*C*H_2Ph), 56.17 (*C*H_2N), 37.17 (*C*H), 35.05 (CH), 33.03 (*C*H_2), 32.29 (*C*H_2), 26.48 (*C*H_2), 25.95 (*C*H_2), 24.35 (*C*H_3), 22.85 (*C*H_2), 22.67 (*C*H_2), 14.29 ppm (*C*H_3); IR: $\tilde{\nu} = 3478$, 2922, 1452, 1071 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{34}NO$: 328.2640; found: 328.2635.

Hexahydroisoindole 14

General procedure a was followed by using **4 a** (49 mg, 0.38 mmol), **11** (66 mg, 0.38 mmol), and **1** (21 mg, 0.19 mmol) in 9:1 CH_2Cl_2/HFIP (0.9 mL) for 1.5 h. After purification (AcOEt/heptane 5:95–2:8), **14** (52 mg, 0.15 mmol, 78 %) was obtained as a yellow oil. $[\alpha]_D^{20} = +56.4$ ($c = 0.70$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.33$–7.24 (m, 5H; H_{Ar}), 5.18 (s, 1H; C*H*=C), 3.99 (d, ^3J(H,H) = 13 Hz, 1H; NCH_2Ph), 3.77–3.75 (m, 1H; C*H*OH), 3.26 (d, ^3J(H,H) = 13 Hz, 1H; NCH_2Ph), 2.86 (dd, ^3J(H,H) = 8.5, 6.5 Hz, 1H; CH_2N), 2.67 (s, 1H; C*H*), 2.29 (s, 1H; C*H*N), 2.20 (dd, ^3J(H,H) = 8.5, 10.5 Hz, 1H; CH_2N), 2.04–1.95 (m, 2H; C*H*, CH_2), 1.66 (s, 4H; CH_2, CH_3), 1.61–1.56 (m, 1H; CH_2), 1.45–1.39 (m, 3H; CH_2, CH_3), 1.35–1.21 (m, 8H; CH_2), 0.92 (t, ^3J(H,H) = 6.5 Hz, 3H; CH_3), 0.85 ppm (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 139.76$ (CqAr), 130.35 (*C*=CH), 128.88 (Ar), 128.54 (Ar), 127.22 (Ar), 123.56 (C=*C*H), 75.33 (*C*HN), 69.60 (*C*HOH), 58.96 (CH_2Ph), 57.47 (*C*H_2N), 40.05 (*C*H), 35.27 (*C*H), 35.17 (*C*H_3), 33.06 (*C*H_2), 32.32 (*C*H_2), 31.24 (*C*H_2), 27.07 (*C*H_2), 26.54 (*C*H_2), 24.57 (*C*H_3), 22.88 (*C*H_2), 14.30 (*C*H_3), 12.46 ppm (*C*H_3); IR: $\tilde{\nu} = 3473$, 2926, 1454, 1028, 736, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{38}NO$: 356.2953; found: 356.2955.

Hexahydroisoindole 25 c

General procedure a was followed by using **4 d** (78 mg, 0.67 mmol), **10** (105 μL, 0.67 mmol), and **21** (43 mg, 0.34 mmol) in 1:1 CH_2Cl_2/HFIP (1.6 mL) for 30 min. After purification (CH_2Cl_2/MeOH/NH_4OH 98.8:1:0.2–94.8:5:0.2), **25 c** (90 mg, 0.27 mmol, 81 %) was obtained as a colorless oil. $[\alpha]_D^{20} = +27.2$ ($c = 0.83$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.34$–7.23 (m, 5H; H_{Ar}), 5.81 (d, ^3J(H,H) = 10.0 Hz, 1H; HC=C*H*), 5.71 (d, ^3J(H,H) = 10.0 Hz, 1H; *H*C=CH), 4.06 (d, ^3J(H,H) = 13.0 Hz, 1H; NCH_2Ph), 3.82 (s, 1H; C*H*OH), 3.59–3.53 (m, 2H; CH_2OH), 3.37 (d, ^3J(H,H) = 13.0 Hz, 1H; NCH_2Ph), 3.24 (t, ^3J(H,H) = 9.0 Hz, 1H; CH_2N), 2.73 (s, 1H; C*H*), 2.56 (d, ^3J(H,H) = 9.0 Hz, 1H; C*H*N), 2.26–2.20 (m, 3H; CH_2N, C*H*), 1.80–1.77 (m, 1H; CH_2), 1.66–1.55 (m, 2H; CH_2), 1.50–1.45 (m, 1H; CH_2), 1.38 (s, 3H; CH_2), 1.14 (q, ^3J(H,H) = 12.0 Hz, 1H; CH_2), 0.93 ppm (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 139.45$ (CqAr), 130.47 (HC=*C*H), 129.35 (HC=CH), 128.71 (Ar), 128.57 (Ar), 127.24 (Ar), 73.14 (*C*HN), 69.08 (*C*HOH), 67.14 (*C*H_2OH), 60.17 (*C*H_2N), 59.23 (NCH_2Ph), 38.11 (*C*H), 37.54 (*C*H), 35.72 (*C*H), 33.04 (*C*H_2), 30.35 (*C*H_2), 29.32 (*C*H_2), 23.06 (*C*H_2), 14.27 ppm (*C*H_3); IR: $\tilde{\nu} = 3395$, 2927, 1453, 1071, 1029 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}NO_2$: 330.2433; found: 330.2433.

Hexahydroisoindole 31 a

General procedure a was followed by using **4 a** (40 mg, 0.31 mmol), **5** (38 μL, 0.31 mmol), and **23** (17 mg, 0.15 mmol) in 9:1 CH_2Cl_2/HFIP (0.8 mL) for 30 min. After purification (AcOEt/heptane/Et_3N 1:9:0–50:49.5:0.5), **31 a** (37 mg, 0.13 mmol, 88 %) was obtained as a yellow oil. $[\alpha]_D^{25} = +37$ ($c = 0.78$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 6.72$ (d, ^3J(H,H) = 6.0 Hz, 1H; HC=C*H*), 6.19 (d, ^3J(H,H) = 6.0 Hz, 1H; *H*C=CH), 5.91–5.83 (m, 1H; *H*C=CH_2), 5.19 (d, ^3J(H,H) = 17.0 Hz, 1H; HC=C*H*$_2$), 5.11 (d, ^3J(H,H) = 10.0 Hz, 1H; *H*C=CH_2), 4.94 (d, ^3J(H,H) = 4.0 Hz, 1H; C*H*O), 3.81 (m, 1H; C*H*OH), 3.45 (dd, ^3J(H,H) = 13.5, 4.5 Hz, 1H; NCH_2Ph), 3.30 (t, ^3J(H,H) = 7.5 Hz, 1H; CH_2N), 3.04 (dd, ^3J(H,H) = 13.5, 7.5 Hz, 1H; NCH_2Ph), 2.70 (s, 1H; C*H*N), 2.12 (t, ^3J(H,H) = 9.5 Hz, 1H; CH_2N), 1.87–1.77 (m, 2H; C*H*, CH_2), 1.62 (dt, ^3J(H,H) = 11.0, 4.0 Hz, 1H; CH_2),1.59–1.51 (m, 2H; CH_2), 1.31 (m, 6H; H-3, CH_2), 0.88 ppm (t, ^3J(H,H) = 6.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 136.54$ (HC=*C*H), 134.74 (*H*C=CH_2), 133.87 (HC=CH), 117.34 (HC=CH_2), 97.79 (*C*HO), 79.03 (*C*HOH), 70.32 (*C*HN), 69.33 (*C*H_2N), 58.12 (*C*H_2C=), 56.82 (CH), 43.29 (*C*H_2), 32.09 (*C*H_2), 29.86 (*C*H_2), 26.69 (*C*H_2), 22.82 (*C*H_2), 14.25 ppm (*C*H_3); IR: $\tilde{\nu} = 3458$, 2934, 2858, 1319, 1050, 967, 917 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}NO_2$: 278.2120; found: 278.2121.

Hexahydroisoindole 31 e1 and 31 e2

General procedure a was followed by using **4 e** (54 mg, 0.36 mmol), **5** (44 μL, 0.36 mmol), and **23** (20 mg, 0.18 mmol) in 1:1 CH_2Cl_2/HFIP (0.9 mL) for 30 min. After purification (CH_2Cl_2/*i*PrOH/NH_4OH 1:0:0–78:20:2), **31 e1** and **31 e2** (87 mg, 0.25 mmol, 83 %) were obtained as a mixture of two diastereomers (7:3, 47 mg, 0.16 mmol, 89 %), which were separated by flash chromatography on silica gel (AcOEt/*i*PrOH/H_2O/NH_4OH 91:4:2:5–78:12:5:5) to afford major product **31 e1** as a brown oil and minor product **31 e2** as a brown oil.

*Compound **31 e1** (major product)*: $[\alpha]_D^{20} = -22.2$ ($c = 0.83$ in $CHCl_3$); ^{1}H NMR (500 MHz, MeOD, 25 °C): $\delta = 6.67$ (d, ^3J(H,H) = 6.0 Hz, 1H; HC=C*H*), 6.26 (dd, ^3J(H,H) = 6.0, 1.5 Hz, 1H; *H*C=CH), 5.93–5.85 (m, 1H; *H*C=CH_2), 5.18 (d, ^3J(H,H) = 17.0 Hz, 1H; HC=C*H*$_2$), 5.08 (d, ^3J(H,H) = 10.0 Hz, 1H; HC=C*H*$_2$), 4.89 (dd, ^3J(H,H) = 1.5, 4.5 Hz, 1H; C*H*OH), 3.85–3.78 (m, 3H; CHOH), 3.77–3.73 (m, 1H; C*H*$_2$OH), 3.65 (dd, ^3J(H,H) = 11.5, 6.0 Hz, 1H; C*H*$_2$OH), 3.55 (dd, ^3J(H,H) = 13.5, 5.5 Hz, 1H; NCH_2Ph), 3.27–3.24 (m, 1H; C*H*N), 3.10 (d, ^3J(H,H) = 2.5 Hz, 1H; C*H*N), 3.03 (dd, ^3J(H,H) = 13.5, 8.0 Hz, 1H; NCH_2Ph), 2.07 (dd, ^3J(H,H) = 10.5, 9.0 Hz, 1H; C*H*N), 1.97–1.91 (m, 1H; CH), 1.61 (dt, ^3J(H,H) = 11.5, 4.0 Hz, 1H; C*H*$_2$), 1.31 ppm (dd, ^3J(H,H) = 11.5, 7.5 Hz, 1H; C*H*$_2$); ^{13}C NMR (125 MHz, MeOD, 25 °C): $\delta = 136.72$ (HC=*C*H), 136.44 (HC=CH_2), 136.34 (HC=CH), 118.32 (HC=*C*H_2), 99.45 (CO), 80.34 (CHO), 75.08 (CHOH), 74.93 (*C*HOH), 73.10 (CHOH), 68.42 (CHN), 64.31 (*C*H_2OH), 59.52, 59.44 (*C*H_2N, NCH_2Ph), 43.68 (CH), 31.39 ppm (*C*H_2); IR: $\tilde{\nu} = 3357$, 2908, 1066, 1029, 920,

705 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{24}NO_5$: 298.1654; found: 298.1655.

*Compound **31e2** (minor product)*: $[\alpha]_D^{20} = -24.0$ ($c = 0.65$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.49$ (d, ^3J(H,H) = 6.0 Hz, 1H; HC=C*H*), 6.34 (dd, ^3J(H,H) = 6.0, 2.0 Hz, 1H; *H*C=CH), 5.94–5.81 (m, 1H; *H*C=CH_2), 5.24–5.18 (m, 2H; HC=CH_2), 5.12 (dd, ^3J(H,H) = 4.0, 2.0 Hz, 1H; C*H*OH), 3.89–3.78 (m, 5H; C*H*OH, CH_2OH), 3.47 (d, ^3J(H,H) = 8.5 Hz, 1H; C*H*N), 3.43–3.28 (m, 2H; NCH_2Ph), 3.09 (dd, ^3J(H,H) = 11.5, 7.0 Hz, 1H; C*H*N), 2.66 (t, ^3J(H,H) = 11.5 Hz, 1H; C*H*N), 2.22–2.13 (m, 1H; *C*H), 1.66 (dt, ^3J(H,H) = 11.5, 4.0 Hz, 1H; CH_2), 1.38 ppm (dd, ^3J(H,H) = 11.5, 7.5 Hz, 1H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 136.95$ (HC=*C*H), 136.17 (HC=CH), 135.00 (HC=CH_2), 119.04 (HC=CH_2), 99.77 (*C*O), 80.72 (*C*HO), 74.97 (*C*HOH), 73.76 (*C*HOH), 71.30 (*C*HOH), 68.00 (*C*HN), 64.18 (*C*H_2OH), 60.35 (NCH_2Ph), 56.13 (*C*H_2N), 42.80 (*C*H), 29.20 ppm (*C*H_2); IR: $\tilde{\nu} = 3351$, 2938, 1419, 1036, 926 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{24}NO_5$: 298.1654; found: 298.1651.

Morpholine 35

Anhydrous TsOH (15 mg, 85.5 μmol, 1.0 equiv) was added to a solution of **25** (29 mg, 85.5 μmol, 1.0 equiv) in dry CH_2Cl_2 (1.8 mL) under an argon atmosphere. The resulting mixture was stirred at rt for 15 min. The solvent was removed under reduced pressure. Dry and degassed CH_2Cl_2 (0.9 mL), methyl vinyl ketone (85 μL, 0.85 mmol, 10 equiv), and Hoveyda–Grubbs II catalyst (5.4 mg, 8.5 μmol, 0.1 equiv) were added to the residue under argon atmosphere. The resulting mixture was heated to 100 °C for 4 h by microwave irradiation. The solvent and excess ketone were removed under reduced pressure (2 h at 1 mbar) and the residue was purified by flash chromatography on silica gel (toluene/acetone/Et_3N 94.9:5:0.1) to afford **35** (23 mg, 60.3 μmol, 71%) as a yellow oil. $[\alpha]_D^{20} = -69.4$ ($c = 0.69$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.32$–7.16 (m, 5H; HAr), 5.91 (d, ^3J(H,H) = 10.0 Hz, 1H; HC=C*H*), 5.72 (dt, ^3J(H,H) = 10.0, 3.0 Hz, 1H; *H*C=CH), 4.13–4.08 (m, 1H; C*H*O), 3.97–3.94 (m, 1H; C*H*O), 3.46 (t, ^3J(H,H) = 8.5 Hz, 1H; CH_2N), 3.29 (d, ^3J(H,H) = 10.0 Hz, 1H; C*H*Ph), 2.93 (d, ^3J(H,H) = 10.5 Hz, 1H; NCH_2), 2.63 (dd, ^3J(H,H) = 15.5, 8.0 Hz, 1H; CH_2C=O), 2.53–2.47 (m, 1H; C*H*), 2.37 (dd, ^3J(H,H) = 15.5, 5.0 Hz, 1H; CH_2C=O), 2.34–2.30 (m, 1H; C*H*), 2.25–2.23 (m, 1H; C*H*N), 2.19 (s, 3H; CH_3), 2.08–2.02 (m, 1H; CH_2), 1.96–1.92 (m, 1H; CH_2), 1.87 (t, ^3J(H,H) = 10.5 Hz, 1H; CH_2), 1.81 (dd, ^3J(H,H) = 9.0, 5.0 Hz, 1H; CH_2N), 1.55–1.50 (m, 1H; CH_2), 1.44–1.32 (m, 6H; CH_2), 1.29–1.25 (m, 1H; CH_2), 0.91 ppm (t, ^3J(H,H) = 6.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta =$ 206.84 (*C*=O), 146.38 (CqAr), 134.23 (HC=CH), 128.74 (Ar), 127.50 (Ar), 126.48 (Ar), 125.80 (HC=*C*H), 74.54 (*C*HO), 67.61 (*C*HN), 64.64 (*C*HO), 61.34 (*C*H_2N), 59.01 (NCH_2), 47.81 (*C*H_2C=O), 42.20 (*C*HPh), 39.78 (*C*H), 38.79 (*C*H_2), 33.64 (*C*H), 32.04 (*C*H_2), 31.25 (*C*H_3), 25.60 (*C*H_2), 25.34 (*C*H_2), 22.88 (*C*H_2), 14.31 ppm (*C*H_3); IR: $\tilde{\nu} = 2922$, 1714, 1355, 1060, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{36}NO_2$: 382.2746; found: 382.2743.

Epoxides 36 and 37

m-CPBA (77 mg, 0.31 mmol, 3.0 equiv) was added to a solution of **9** (40 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at rt for 12 h, diluted with CH_2Cl_2 (10 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (2 mL), then washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (AcOEt/heptane 1:1) to afford major product **36** (30 mg, 74.5 μmol, 72%) as a colorless oil and minor product **37** (10 mg, 24.8 μmol, 24%) as a colorless oil.

*Compound **36** (major product)*: $[\alpha]_D^{20} = +94.2$ ($c = 0.38$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.29$ (d, ^3J(H,H) = 9.0 Hz, 2H; HAr), 7.65 (d, ^3J(H,H) = 9.0 Hz, 2H; HAr), 4.31 (d, ^3J(H,H) = 8.0 Hz, 1H; C*H*N), 3.97 (s, 1H; C*H*OH), 3.76 (br s, 1H; O*H*), 3.60 (dd, ^3J(H,H) = 11.0, 6.0 Hz, 1H; CH_2N), 3.12 (dd, ^3J(H,H) = 11.0, 2.0 Hz, 1H; CH_2N), 3.01 (s, 1H; C*H*O), 2.70 (t, ^3J(H,H) = 8.0 Hz, 1H; C*H*), 2.22–2.12 (m, 1H; C*H*), 1.83–1.79 (m, 2H; CH_2), 1.70–1.38 (m, 5H; CH_2), 1.36 (s, 3H; CH_3), 1.34–1.06 (m, 5H; CH_2), 0.91 ppm (t, ^3J(H,H) = 6.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 169.56$ (*C*=O), 148.94 (CqAr), 142.48 (Ar), 128.30 (Ar), 124.10 (Ar), 73.15 (*C*HOH), 65.78 (*C*HN), 60.63 (*C*HO), 58.33 (*C*O), 56.11 (*C*H_2N), 39.99 (*C*H), 34.04 (*C*H), 32.64 (*C*H_2), 32.08 (*C*H_2), 27.31 (*C*H_2), 26.09 (*C*H_2), 24.33 (*C*H_2), 22.87 (*C*H_3), 21.98 (*C*H_2), 14.26 ppm (*C*H_3); IR: $\tilde{\nu} = 3412$, 2929, 1618, 1596, 1522, 1425, 1347 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_5$: 403.2233; found: 403.2234.

*Compound **37** (minor product)*: $[\alpha]_D^{20} = +83.40$ ($c = 0.50$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.26$ (d, ^3J(H,H) = 9.0 Hz, 2H; HAr), 7.64 (d, ^3J(H,H) = 9.0 Hz, 2H; HAr), 4.57 (d, ^3J(H,H) = 8.5 Hz, 1H; C*H*N), 4.17 (d, ^3J(H,H) = 7.0 Hz, 1H; C*H*OH), 3.61 (dd, ^3J(H,H) = 11.0, 6.0 Hz, 1H; CH_2N), 3.08 (d, ^3J(H,H) = 11.0 Hz, 1H; CH_2N), 3.01 (d, ^3J(H,H) = 4.0 Hz, 1H; C*H*O), 2.77–2.73 (m, 1H; C*H*), 1.95 (d, ^3J(H,H) = 13.0 Hz, 1H; CH_2), 1.92–1.86 (m, 1H; C*H*), 1.70–1.56 (m, 4H; CH_2), 1.49–1.42 (m, 2H; CH_2), 1.37 (s, 3H; CH_3), 1.35–1.24 (m, 4H; CH_2), 1.15–1.09 (m, 1H; CH_2), 0.91 ppm (t, ^3J(H,H) = 6.5 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 168.50$ (*C*=O), 148.78 (CqAr), 143.00 (Ar), 128.41 (Ar), 123.97 (Ar), 72.04 (*C*HOH), 64.41 (*C*HN), 59.44 (*C*O), 59.12 (*C*HO), 56.67 (*C*H_2N), 37.13 (*C*H), 36.29 (*C*H), 33.16 (*C*H_2), 32.10 (*C*H_2), 29.00 (*C*H_2), 26.10 (*C*H_2), 23.01 (*C*H_3), 22.85 (*C*H_2), 22.18 (*C*H_2), 14.27 ppm (*C*H_3); IR: $\tilde{\nu} = 3375$, 2931, 1615, 1594, 1524, 1447, 1349 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_5$: 403.2233; found: 403.2235.

Ketone 38

$HBF_4{\cdot}OEt_2$ (4 μL, 29.4 μmol, 2.2 equiv) was added to a stirred solution of **36** (5.5 mg, 13.7 μmol, 1.0 equiv) in CH_2Cl_2 (0.1 mL). The resulting mixture was stirred at rt for 15 min, diluted with CH_2Cl_2 (5 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (AcOEt/heptane 4:6) to afford **38** (4.6 mg, 11.4 μmol, 84%) as a colorless oil. $[\alpha]_D^{20} = +149.7$ ($c = 0.34$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 8.31$ (d, ^3J(H,H) = 9.0 Hz, 1H; HAr), 7.70 (d, ^3J(H,H) = 9.0 Hz, 1H; HAr), 4.55 (d, ^3J(H,H) = 9.5 Hz 1H; C*H*N), 3.99–3.95 (m, 1H; C*H*OH), 3.62 (dd, ^3J(H,H) = 11.0, 5.0 Hz, 1H; CH_2N), 3.28 (d, ^3J(H,H) = 11.0 Hz, 1H; CH_2N), 3.03 (dd, ^3J(H,H) = 9.5, 7.0 Hz, 1H; C*H*), 2.66–2.61 (m, 1H; CH_3C*H*), 2.59–2.53 (m, 1H; C*H*), 2.06–2.03 (m, 1H; CH_2), 1.69 (d, ^3J(H,H) = 12.0 Hz, 1H; CH_2), 1.51–1.41 (m, 5H; CH_2), 1.32 (s, 5H; CH_2), 1.08 (d, ^3J(H,H) = 6.5 Hz, 3H; CH_3), 0.90 ppm (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta =$ 211.48 (*C*=O), 169.50 (PhC=O), 149.12 (CqAr), 142.33 (Ar), 128.55 (Ar), 124.11 (Ar), 72.45 (CHOH), 65.07 (*C*HN), 57.02 (*C*H_2N), 53.32 (CH), 43.15 (CH), 41.70 (CH_3CH), 33.83 (*C*H_2), 32.26 (*C*H_2), 31.96 (*C*H_2), 26.55 (*C*H_2), 25.92 (*C*H_2), 22.86 (*C*H_2), 14.58 (CH_3), 14.25 ppm (CH_3); IR: $\tilde{\nu} = 3412$, 2931, 1706, 1597, 1523, 1428, 1347 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_5$: 403.2233; found: 403.2231.

Diol 39

Trimethylamine *N*-oxide dihydrate (7 mg, 63.3 μmol, 2.0 equiv) and osmium tetroxide (4 μL, 2.5% *w/w* in *tert*-butanol, 0.41 μmol,

0.013 equiv) were added sequentially to a solution of **36** (11 mg, 31.7 μmol, 1.0 equiv) in acetone (0.65 mL), water (0.21 mL), and pyridine (3 μL, 31.7 μmol, 1.0 equiv). The resulting mixture was stirred at 65 °C for 12 h, diluted with AcOEt (10 mL), and washed with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt/heptane/Et_3N 7:3:0–99.5:0:0.5) to afford **39** (10 mg, 26.2 mmol, 83%) as a yellow oil. $[\alpha]_D^{20} = +7.6$ ($c = 0.45$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.38$–7.22 (m, 10H; HAr), 4.42 (s, 1H; C*H*O), 4.20 (d, ^3J(H,H) = 13.5 Hz, 1H; NCH_2Ph), 4.07 (d, ^3J(H,H) = 6.0 Hz, 1H; C*H*OH), 3.97–3.92 (m, 2H; 2×C*H*OH), 3.78 (d, ^3J(H,H) = 13.5 Hz, 1H; NCH_2Ph), 3.66 (d, ^3J(H,H) = 13.5 Hz, 1H; CH_2Ph), 3.35 (t, ^3J(H,H) = 9.5 Hz, 1H; CH_2N), 2.60 (t, ^3J(H,H) = 13.5 Hz, 1H; CH_2Ph), 2.28–2.22 (m, 1H; C*H*), 2.17 (t, ^3J(H,H) = 9.5 Hz, 1H; CH_2N), 1.58 ppm (s, 2H; CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 139.88$ (CqAr), 138.42 (CqAr), 129.73 (CAr), 129.24 (CAr), 128.57 (CAr), 127.20 (CAr), 99.36 (Cq), 83.77 (*C*HO), 75.68 (*C*HOH), 75.50 (*C*HOH), 71.53 (*C*HOH), 70.41 (*C*HN), 63.04 (NCH_2Ph), 60.66 (CH_2N), 42.47 (*C*H), 41.21 (CH_2Ph), 32.88 ppm (CH_2); IR: $\tilde{\nu} = 3348$, 2924, 1453, 1067, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}NO_4$: 382.2018; found: 382.2020.

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