ChemPubSoc Europe

DOI: 10.1002/chem.201304086

CHEMISTRY
A European Journal
Full Paper

Natural Products

A General Strategy for the Catalytic, Highly Enantio- and Diastereoselective Synthesis of Indolizidine-Based Alkaloids

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Dedicated to the memory of John W. Daly

Abstract: Sixteen indolizidine-based alkaloids (IBAs) that were isolated as poison constituents of the skin of frogs were synthesized in a highly flexible and stereoselective manner. As a key step, a three-component, organocatalytic, highly enantio- and diastereoselective vinylogous Mukaiyama–Mannich reaction was employed furnishing optically highly enriched butyrolactams as central intermediates on a multigram scale. The attached six-membered ring was constructed through cyclization of the pendant enoate moiety onto the pyrrolidine ring. The absolute configuration of the bridgehead chiral center and the adjacent 8-position was established in the initial vinylogous Mannich reaction, whereas the 3- and 5-substituents were introduced through organometallic addition at a late stage of the synthesis with full stereochemical control from the substrate. With this strategy, simple as well as even more complex alkaloids were accessible in good overall yields as single stereoisomers. These syntheses also served to establish the absolute and relative configuration of those IBAs that had never been synthesized before.

Introduction

Naturally occurring alkaloids have always attracted the attention of chemists on the basis of their documented biological activity and their fascinating chemical structure. It was already known to Native American huntsmen that certain ingredients in the skin of peculiar colored frogs from Central and South American regions (*Phyllobates species*) can be used as poisons. During the last five decades, over 80 genera and 11 families of poison-dart frogs (e.g., *Dendrobatidae*, *Mantelline* frogs or *Bufonid* toads) were systematically investigated[1] and found to accommodate a huge variety of natural products, albeit in only very little amounts. It is especially due to the enormous efforts of John W. Daly[2] that we nowadays know about the existence of no less than 240 indolizidine-based alkaloids (IBAs).[3,4] IBAs are commonly found in skin glands of poison frogs but empirical data provided evidence for a dietary source—ants, mites, and other arthropods.[5] Poison frogs, therefore, must be able to sequester different IBAs without being intoxicated and use them on their own to defend themselves against predators. Some IBAs have been shown to be effective, noncompetitive blockers for nicotinic receptor channels,[6] which render them promising candidates against diseases such as Alzheimer's disease, schizophrenia, epilepsy, and Parkinson's disease.[7] Given a general synthetic access towards a broad variety of IBAs, additional biological testing might uncover further beneficial features of this class of natural products.

IBAs differ in their substituents and their substitution pattern (Figure 1). In particular, 5-mono (**1**), as well as 3,5- and 5,8-disubstituted[8] IBAs (**2** and **3**) are prominent representatives and in almost all cases IBAs are substituted with simple alkyl chains. Additionally, 6,7-dihydro-5,8-disubstituted IBAs, such as the indolizidine 179 (**4**) are known and although those natural products are solely found as trace alkaloids in dendrobatid, mantellid, and bufonid anurans, they are part of an interesting class of indolizidines with about 30 members.[3] Even more interestingly, the 5,6,8-trisubstituted indolizidine 195G (**5**) was isolated from the mite *scheloribates laevigatus* and represents

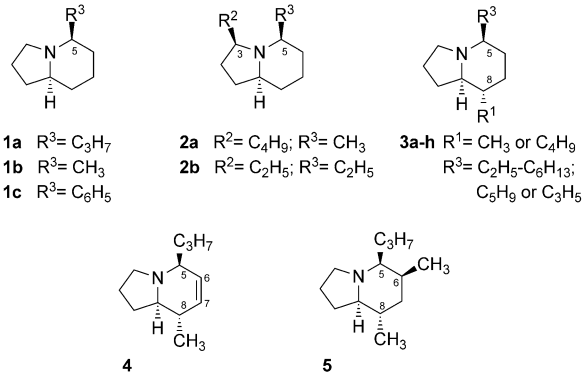

Figure 1. Commonly found substitution patterns in IBAs.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304086.

a class of roughly 70 alkaloids found in *dendrobatidae*.[9] Structure–activity relationship studies regarding the substitution pattern and the nature of substituents of the indolizidine core (e.g., unsaturation in the side chain; length of the side chain) are ongoing and represent a current research field.[10]

Due to their scarcity, most IBAs have solely been characterized by means of FTIR- and GCMS-analysis making a stereochemical assignment very difficult. Thus, whereas in some cases, the relative configuration has been established, the absolute configuration of most IBAs remains unknown to date. Consequently, efforts directed at the total synthesis of these natural products not only demonstrates the power and efficiency of new stereoselective synthesis methodology and additionally provides material for biological testing, but are also important for their correct stereochemical assignment. It therefore comes as no surprise that IBAs have become interesting and challenging synthetic targets over the last decades and synthetic endeavors have been reviewed extensively on a regular basis since 1984.[11]

First synthetic approaches toward IBAs date back to the 1970s.[12] With the ongoing discovery of further alkaloids from anurans, synthetic attempts have become more and more target-oriented and monomorine (**2a**), as well as some other 3,5-disubstituted indolizidines, were synthetized in a diastereoselective fashion.[13] Subsequently, ex-chiral-pool strategies were developed to access a select natural product as a single enantiomer by a specifically tailored total synthesis.[14] Some 5-mono-[15] and 5,8-disubstituted IBAs[16] were synthesized from amino acids[17] and their derivatives,[18] as well as from pyroglutamic acid.[19] Alternatively, chiral auxiliary-based strategies (e.g., with (*S*)-(−)- or (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine [SAMP/RAMP]),[20] carbohydrates,[21] amino alcohols,[22] or *N*-sulfinylimines)[23] have been developed and used extensively to furnish optically active IBAs with partially excellent diastereoselectivities. Most recently, highly elegant and creative diastereoselective approaches[24] featuring a hydroamination strategy and a reductive cross-coupling and [3+2] cycloaddition reaction were reported by Shenvi et al.[25] and the Micalizio group,[26] respectively. Catalytic, enantioselective approaches however, to access these important natural products have been reported much less frequently and are often limited to a specific substitution pattern within the indolizidine core.[27] Transition-metal-catalyzed allylic amination,[28] Heck,[29] and dihydroxylation[30] reactions have been developed with good success for this purpose and gave rise to select natural products.[31] Recently, a novel approach that employs the partial hydrogenation of a substituted indolizine core with a N-heterocyclic carbene (NHC)-based catalyst was published by the Glorius group.[32] In addition, a few organocatalytic enantioselective approaches,[33] such as the proline-catalyzed asymmetric α-amination/Horner–Wadsworth–Emmons olefination sequence[34] or an α-aminoxylation of aldehydes were developed.[35]

In 2012 we established a new strategy towards the total synthesis of variously substituted IBAs.[36] As a central key step we employed a Brønsted acid catalyzed, highly enantioselective vinylogous Mukaiyama–Mannich reaction (VMMR)[37,38] of an acyclic silyl dienolate, a γ-oxo ester and *para*-anisidine to furnish γ-lactams as key intermediates.[39] (+)-Coniceine and (+)-indolizidine 167B (**1a**) as well as (+)-monomorine (**2a**) and disubstituted indolizidine (+)-167A (**3a**) were synthesized from a versatile central building block that was available on a multigram scale (Figure 2).

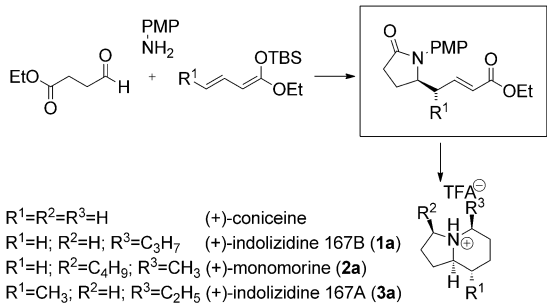


Figure 2. New strategy to access indolizidine-based alkaloids.

Herein, we wish to report a full account of our work that further details our studies and significantly extends beyond our previous results. We have now developed a general and flexible strategy for the catalytic, enantioselective synthesis of highly substituted indolizidines that we have applied towards the synthesis of more than a dozen diversely substituted natural products. We are now in a position to address five stereogenic centers within the indolizidine core individually and have completed the synthesis of 5-mono (**1a**–**c**), 3,5-disubstituted (**2a**,**b**) as well as many 5,8-disubstituted indolizidines (**3a**–**h**), 6,7-dihydro indolizidine 179 (**4**) as well as the 5,6,8-trisubstituted indolizidine 195G (**5**). The flexibility of our strategy allows us to vary the 3-, 5-, 6-, and 8-substituents in a broad range rendering our approach a very general one. Our retrosynthetic approach (Figure 3) called for the late-stage introduction of the 5- and 6-substituents into the indolizidinone core that itself was derived from the Boc-protected pyrrolidine. That in turn was derived from a substrate-controlled, diastereo- and chemoselective alkylation of the pyrrolidinone. This key intermediate should eventually be accessible following our protocol for the Brønsted acid catalyzed highly enantioselective VMMR with the ester-functionalized aldehyde. As chiral Brønsted acid catalyst 1,1′-bis-2-naphthol (BINOL)-based phosphoric acids (**7**) were to be employed to provide the asymmetric induction.[40]

Whereas the three substituents R^2–R^4 would accordingly be incorporated at a late stage of the synthesis with a beneficial effect on the flexibility, both the bridgehead chiral carbon center and the adjacent C8-center were to be established in the central VMMR.

Results and Discussion

Optimization of the VMMR

In our initial studies we had found an optimal protocol for the execution of the VMMR that was based on the in situ formation of the imine at low temperature and subsequent addition

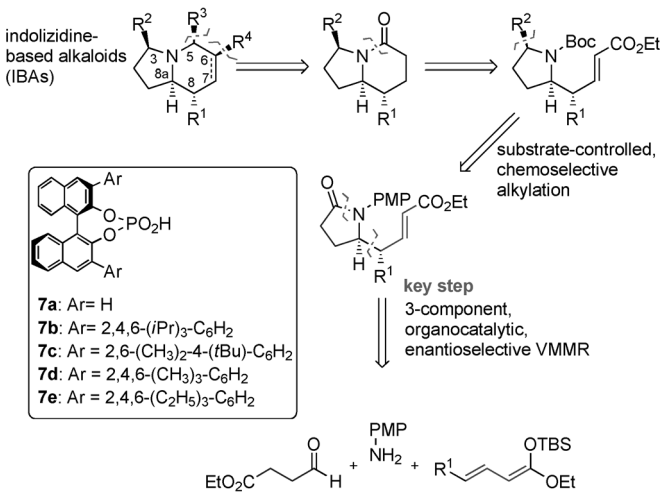
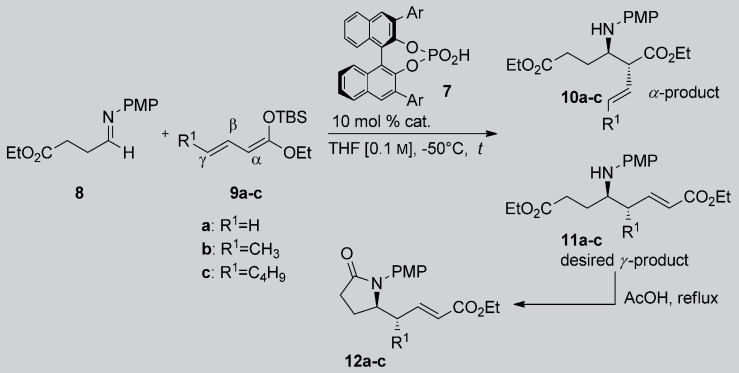


Figure 3. Retrosynthetic approach.

of the catalyst and freshly distilled nucleophile. Thus, the aldimine **8** was formed at −50 °C within typically 30 min from the corresponding aldehyde and *para*-anisidine (HPLC-control). Subsequently, 3,3′-triisopropylphenyl-substituted BINOL-based phosphoric acid, the TRIP-phosphoric acid[41] (**7b**, 10 mol%) and vinylketene silyl acetal **9a** (R^1 = H) were added one after another and the open-chain vinylogous Mannich product **11a** was obtained in 70% yield with 99% *ee* within 15 min on a laboratory scale (0.1 mmol) (Table 1, entry 1). No regioisomeric α-product (**10a**) was formed under these conditions. A previous catalyst screening had revealed that the TRIP catalyst (**7b**) was the chiral Brønsted acid of choice for this particular transformation, both in terms of yield and enantioselectivity.[39] Interestingly, we observed that upon prolonged reaction times, the open-chain product slowly cyclized to furnish lactam **12a** that could be easily purified by chromatography. We eventually found that this cyclization was accelerated when the crude mixture—after completion of the carbon–carbon bond-forming event—was treated directly with acetic acid for one hour at reflux. A simple filtration through a silica gel pad delivered the desired lactam **12a** in an enhanced yield of 80% over the two steps and with identical *ee* (entry 2).

We then focused our attention on γ-alkyl substituted vinylketene silyl acetals as nucleophiles in the light of the role of this substituent for the 8-position within the indolizidine core. When the γ-methyl-substituted dienolate **9b** ($R^1 = CH_3$) was submitted to the reaction with imine **8** under the optimized conditions a mixture of regioisomers **10b** and **11b** was obtained in a combined yield of only 34% after 54 h (entry 3). The diastereoselectivity and enantioselectivity, however, were encouraging with 25:1 (*anti*/*syn*) for the γ-product and 95% *ee* for the major diastereomer, respectively. We reasoned that the transition state might be sterically overloaded due to the additional substituent within the dienolate. Hence, we screened further BINOL-based phosphoric acids with smaller substituents in the 3,3′-position. With the 3,3′-unsubstituted phosphoric acid **7a**, the VMMR was already completed after 30 h and the yield was increased to 65%. However, the regio- and diastereoselectivity was very low and the products were obtained as racemic mixtures (entry 4). Compared to the TRIP-catalyst (**7b**), phosphoric acid **7c** with an increased steric demand in the *para*-position of the aryl substituent and a decreased steric demand in both *ortho*-positions, gave superior results. The product was obtained with an excellent enantioselectivity of 97% and a diastereoselectivity of 39:1. Merely the reaction time and the yield needed to be further optimized (entry 5). As slim substituents on the aryl substituents seemed to have a beneficial effect, we tested the 3,3′-mesityl-substituted phosphoric acid **7d**. The enantioselectivity was still excellent and a complete γ-selectivity was observed. The reaction was also comparably fast and afforded the *anti*-product **11b** in 74% yield with a very good diastereoselectivity of 22:1 after 30 h. By further slightly increasing the steric bulk of the aryl substituent, the best result was eventually obtained with the 2,4,6-triethylphenyl-substituted phospho-

Table 1. Optimization of the VMMR.



Entry	**9** (R^1)	Cat.	*t* [h]	Yield [%]	γ/α[a]	d.r.[b]	*ee*[b] [%]
1	**9a** (H)	**7b**	0.25	70 (**11a**)	1:0	–	99
2	**9a** (H)	**7b**	0.25	80 (**12a**)	1:0	–	99
3	**9b** (Me)	**7b**	54	34 (**11b**)	3.9:1	25:1	95
4	**9b** (Me)	**7a**	30	65 (**11b**)	1:1.7	1:1.6	*rac*
5	**9b** (Me)	**7c**	72	47 (**11b**)	n.d.	39:1	97
6	**9b** (Me)	**7d**	30	74 (**12b**)	1:0	22:1	93
7	**9b** (Me)	**7e**	120	63 (**11b**)	1:0	>99:1	98
8	**9c** (*n*Bu)	**7b**	18	59 (**12c**)	1:0	18:1	99
9	**9c** (*n*Bu)	**7d**	72	80 (**12c**)	1:0	20:1	97
10	**9c** (*n*Bu)	**7e**	18	84 (**12c**)	1:0	22:1	>99

[a] Determined from crude ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis.

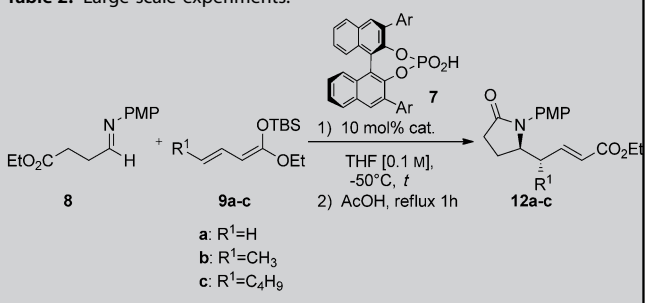
ric acid **7e**. Thus, the product was obtained as one single regio- and diastereomer with an excellent enantioselectivity of 98% in 63% yield.

The reaction optimization and catalyst screening with the dienolate **9c** ($R^1 = C_4H_9$) went comparably well. A first reaction with the catalyst **7b** gave the γ-lactam **12c** as a single regioisomer in excellent enantioselectivity (99%) and high diastereoselectivity (18:1) after 18 h. However, the yield was only moderate at 59% (Table 11, entry 8). With catalyst **7d** the yield improved to 80% while maintaining excellent levels of regio-, diastereo-, and enantioselectivity (entry 9). The best result was eventually obtained with catalyst **7e** that gave rise to VMMR-product **12c** with a very good yield over two steps and outstanding levels of regio-, diastereo-, and enantioselectivity (entry 10).

Scaling up

After we had carefully investigated optimal conditions, we envisaged a scaling-up of this key transformation (Table 2). In some cases merely a prolongation of the reaction time was necessary. More importantly, it became apparent that isolation of the respective lactam **12** instead of the open-chain VMMR-product **11** was advantageous (vide supra). Therefore, the open-chain products **11a–c** were directly transformed into the corresponding lactams **12a–c** through addition of acetic acid and the heating of this mixture for 1 h at reflux.

Table 2. Large-scale experiments.



Entry	Product (R^1)	Cat.	Scale [mmol]	*t* [h]	Yield [%]	d.r.[a]	*ee*[a] [%]
1	**12a** (H)	**7b**	0.1	0.25	80	–	99
2	**12a** (H)	**7b**	32	16	86 (67)[b]	–	96 (>99)[b]
3	**12b** (Me)	**7d**	35	28	77 (61)[b]	28:1	96 (>99)[b]
4	**12c** (*n*Bu)	**7e**	33	41	93	22:1	>99

[a] Determined by chiral HPLC analysis. [b] After recrystallization.

In the case of unsubstituted dienolate **9a**, the yield was increased but the enantioselectivity slightly eroded. Noteworthy, is that the concentration of the reaction mixture had to be maintained at 0.1 M to avoid further loss in selectivity. In the case of dienolate **9b** the enantioselectivity and yield increased slightly relative to the reaction on a laboratory scale (compare Table 1, entry 6 and Table 2, entry 3). A prolongation of the reaction time was not necessary and the product was obtained with very good diastereoselectivity. However, we were pleased to find that both **12a** and **12b** solidified upon standing at room temperature and could be recrystallized from methyl-*tert*-butyl ether, which gave us the lactams in multigram amounts as single diastereomers and enantiomers, respectively (Figure 4). The relative and absolute configuration was unambiguously assigned based on X-ray-crystallography of single crystals of **12a** and **12b**, respectively (for further information, please see the Supporting Information).

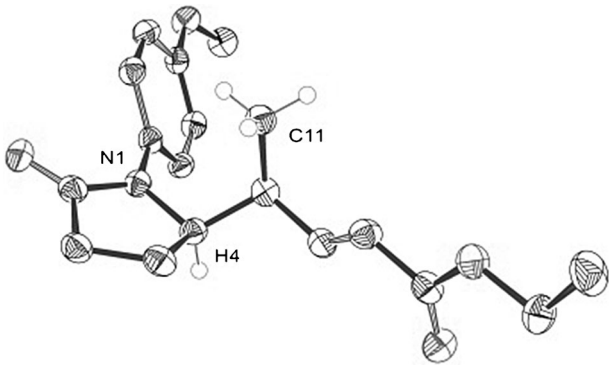


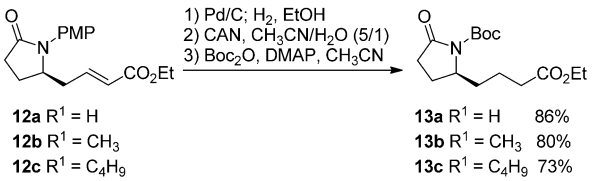
Figure 4. X-ray-crystal structure of **12b**.[52]

Fortunately, in the case of the dienolate **9c** the enantioselectivity of the reaction was not affected by the scaling-up process and 11.0 g of lactam **12c** were obtained over two steps (93% yield) in a single run as a homogenous regioisomer and enantiomer with excellent diastereoselectivity (entry 4).

5-Monosubstituted IBAs

With enantiomerically and diastereomerically pure **12a–c** in hand we first attempted the synthesis of 5-monosubstituted IBAs. For this purpose it was necessary that lactam **12a** was first hydrogenated, subsequently PMP-deprotected, and finally Boc-protected to furnish the corresponding imide **13a** in excellent overall yield (Scheme 1).

Unfortunately, this deprotecting/reprotecting sequence was inevitable since all attempts to employ a Boc-protected imine in the key step failed. Fortunately and in contrast to the polymethylpentene (PMP)-protected tertiary lactam, the imide **13a** now offered the possibility to undergo chemoselective transformations at the imide carbonyl group, such as reduction

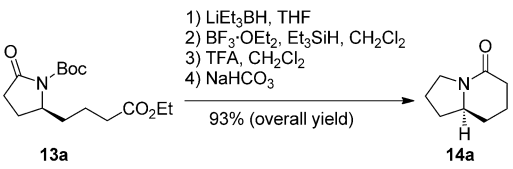


12a R^1 = H
12b R^1 = CH_3
12c R^1 = C_4H_9

13a R^1 = H 86%
13b R^1 = CH_3 80%
13c R^1 = C_4H_9 73%

Scheme 1. Formation of imides **13a–c**. Boc = *tert*-butoxycarbonyl; DMAP = 4-dimethylaminopyridine.

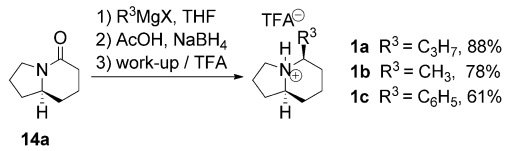
and/or alkylation reactions in the presence of the ester moiety. Thus, **13a** was converted into the pyrrolidine by sequential reduction with superhydride and a combination of triethyl silane and boron trifluoride etherate (Scheme 2).[42] Subsequent Boc-



Scheme 2. Conversion into the indolizidinone core. TFA = trifluoroacetic acid.

deprotection and cyclization gave rise to indolizidinone **14a** in almost quantitative yield over four steps.[43]

With **14a** in hand, its conversion into the indolizidines **1a**–**c** was undertaken (Scheme 3).[44] A sequence comprising Grignard addition, acid-catalyzed dehydration and subsequent reduction of the formed iminium ion under substrate-control furnished **1a**–**c** after trifluoroacetic acid (TFA) treatment as TFA

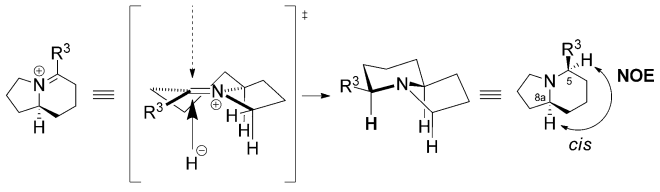


Scheme 3. Synthesis of 5-monoubsituted IBAs.

salts in typically excellent yields and as single enantio- and diastereomers. To avoid dimerization processes triggered by the equilibrium of the formed iminium ion with its enamine it was important to add the reducing agent at low temperatures prior to the treatment with acetic acid.

For stereoelectronic reasons,[45] the hydride preferentially attacks the iminium ion in such a way (Scheme 4, solid arrow), that the reaction proceeds through the energetically favored chair-like transition state to furnish preferentially the kinetic 5,8a-*cis* products. The rather unfavored pathway would lead through a twist-boat transition state (Scheme 4, dotted arrow).

To support this stereochemical assignment, we synthesized the non-naturally occurring 5-phenyl-substituted indolizidine **1c**. Usually—as in the case of 5-alkyl-subsituted IBAs—the signal for the 5-CH-proton is not isolated in the proton NMR and hence a nuclear Overhauser effect (NOE) between 5-CH



Scheme 4. Substrate-controlled reduction of the bicyclic iminium ion and NOE studies.

and 8a-CH cannot be measured in a reliable and reproducible manner. However, in the case of the **1c**, all crucial proton signals were separated and a strong NOE was observed between the 5-CH- and the 8a-CH-proton.

It is important to note that all IBAs were isolated as TFA-salts because the free indolizidines were very volatile, extremely prone to oxidation and thus difficult to analyze. In combination with their high lipophilicity (and ability to penetrate the skin) and potential biological activities, a non-volatile, air-stable, less lipophilic form was more convenient to handle. Furthermore, opposed to the commonly used routine found in the literature (i.e., proton NMR spectroscopic studies of the free amine in for example, deuterated chloroform), all TFA salts were measured in deuterated methanol or dimethyl sulfoxide and sharp spectra were obtained that clearly showed the absence of further diastereomeric signals or byproducts. ^{19}F-spectra supplemented our findings. As a beneficial side effect, this way, for example, the TFA salt **2a** could be stored at room temperature for over one year without any signs of decomposition and the yields exceeded those reported in the literature quite significantly in all cases. Conclusively, through the above mentioned route, indolizidine 167B (**1a**), indolizidine 139 (**1b**), and the phenyl-substituted indolizidine 201 (**1c**) were obtained in excellent overall yields of 56, 54, and 42% over ten steps, respectively, by a unified, catalytic strategy and as single diastereomers and enantiomers.

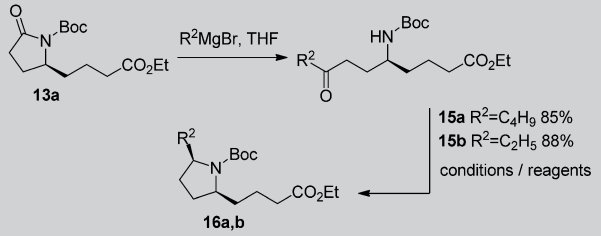
3,5-Disubstituted IBAs

To access IBAs, such as monomorine (**2a**) or other 3,5-disubstituted IBAs, we anticipated that our central building block, imide **13a**, could be ring-opened by addition of a Grignard reagent and again ring-closed reductively in a highly diastereoselective manner by using substrate control.[46] Indeed, various Grignard reagents were chemoselectively added to imide **13a** and furnished amino ketones **15a** and **15b** in good yields. Unfortunately, initial attempts to use boron trifluoride etherate as Lewis acids and sodium borohydride as the reducing agent failed (Table 3). On the one hand, when kept at low temperatures (−78 °C) (Table 3, entry 1), the conversion did not exceed 50% and the product was isolated in 40% yield albeit with excellent diastereoselectivity (>25:1). On the other hand, when allowed to warm to room temperature (entry 2), side reactions occurred and a complex and inseparable mixture of products was obtained.

Most likely, at elevated temperatures, partial Boc-deprotection was an issue that presumably led to several side reactions, for example, intermolecular attack of the amine onto the ester and/or ketone carbonyl center. However, Lewis acid supported cyclization and reduction with a combination of triphenyl silane and *tris*-pentafluorophenyl borane[47] proved extremely successful and gave rise exclusively to the corresponding 2,5-disubstituted pyrrolidines **16a** and **16b** that were obtained in very good to excellent yields as single diastereomers on a multigram scale (Table 3, entry 6).

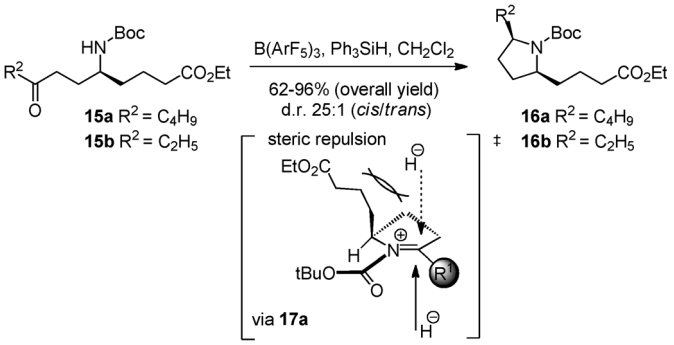
The outcome of this substrate-controlled, highly diastereoselective transformation is easily explained by the steric influence

Table 3. Substrate-controlled reductive cyclization.



Entry	R^2	Conditions	Reagents	Conversion [%][c]	Yield [%]	d.r.[b]
1	C_2H_5	THF −78 °C	$BF_3{\cdot}OEt_2$ (1.1 equiv)/Et_3SiH (1.1 equiv)	50	40[a]	>25:1
2	C_2H_5	THF −78 °C→−r.t.	$BF_3{\cdot}OEt_2$ (1.1 equiv)/Et_3SiH (1.1 equiv)	>60	n.d.[d]	n.d.
3	C_2H_5	THF 3 h, −78 °C	$BF_3{\cdot}OEt_2$ (5.0 equiv)/Et_3SiH (1.1 equiv)	>99	n.d.	1:1
4	C_2H_5	CH_2Cl_2 −78 °C→r.t.	$B(ArF_5)_3$ (0.2 equiv)/Ph_3SiH (3.0 equiv)	>99	62	>25:1
5	C_2H_5	CH_2Cl_2 −78 °C→r.t.	$B(ArF_5)_3$ (0.3 equiv)/Ph_3SiH (0.3 equiv)	>99	79	>25:1
6	C_4H_9	CH_2Cl_2 −78 °C→r.t.	$B(ArF_5)_3$ (0.3 equiv)/Ph_3SiH (0.3 equiv)	>99	96[a]	>25:1

[a] Based on recovered starting material. [b] Determined from crude ^1H NMR spectroscopy. [c] Determined from TLC analysis. [d] n.d. = not determined.



Scheme 5. Reduction of the cyclic iminium ion.

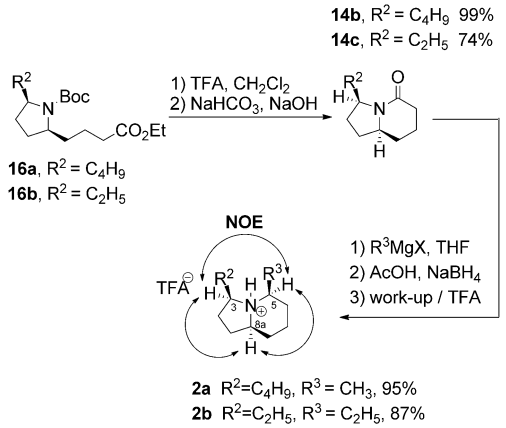
of the 2-substituent (Scheme 5). In the likely transition-state **17a** the upper side of the cyclic iminium ion is effectively shielded by the axially oriented alkyl substituent leading the hydride attack to the opposite side. After the attack from the bottom side, 2,5-*cis*-configured pyrrolidines **16a** and **16b** were obtained. Following our previously established protocol, lactams **14b** and **14c** were obtained through deprotection and cyclization and further converted into indolizidines **2a** and **2b** through Grignard addition with the requisite organometallic reagent, dehydration, and iminium ion reduction, all of which proceeded in excellent yields (Scheme 6).

At the stage of the final monomorine TFA salt, NOE experiments provided evidence for the relative configuration. A strong NOE between all three *cis*-configured protons (Scheme 6) was measured in both directions, respectively, proving the highly *cis*-stereoselective formation of the pyrrolidines **16a** and **16b**. Whereas monomorine (**2a**) has been synthesized before,[48] this study represents the first total synthesis of indolizidine 181A (**2b**).

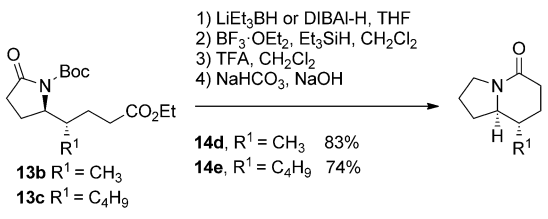
5,8-Disubstituted IBAs

To access IBAs with a 5,8-substitution pattern, such as (+)-indolizidine 167A (**3a**), we started from vinylogous Mannich products **12b** and **12c** carrying two stereogenic centers and converted them into the enantiomerically and diastereomerically pure saturated imides **13b** and **13c** as described above (Scheme 1). Applying the same sequence of events described for the synthesis of 5-mono-substituted IBAs, the conversion into the 8-substituted indolizidinones proceeded without problems and furnished **14d** and **14e** in excellent overall yields on a multigram scale (Scheme 7).

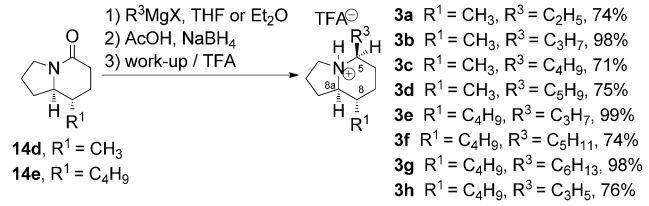
As anticipated, Grignard addition onto the lactam carbonyl moiety went smoothly and subsequent reduction of the bicyclic iminium ion gave exclusively the 5,8-*trans* and 5,8a-*cis*-configured IBAs **3a**–**h** as TFA salts in excellent overall yields (Scheme 8).[49] According to the Schlenk equilibrium, it was of crucial importance for the success of this transformation to employ the more reactive Grignard reagent in diethyl ether rather than in tetrahydrofuran.



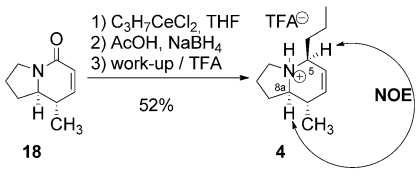
Scheme 6. Formation of 3,5-disubstituted IBAs and NOE studies.



Scheme 7. Formation of 8-substituted indolizidinones **14d** and **14e**. DIBAL-H = diisobutylaluminum hydride.



Scheme 8. Formation of 5,8-disubstituted IBAs.

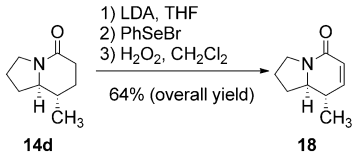


Scheme 10. Conversion into indolizidine **179** and NOE experiments.

Conclusively, eight 5,8-disubstituted IBAs were obtained from indolizidinone **14d** and **14e**, respectively, some of which were synthesized for the first time (indolizidine 167A (**3a**), 181B (**3b**), 195I (**3c**), and 265P (**3g**)).

6,7-Dihydro IBA

Indolizidine **179** (**4**), a trace alkaloid isolated from anurans, contains an unsaturation in the six-membered ring that we expected to be synthetically accessible from lactam **14d**. In the event, the enolate was formed with LDA and trapped with phenyl selenic bromide, which furnished the corresponding α-seleno lactam. Upon oxidation with hydrogen peroxide an elimination process was triggered and gave rise to α,β-unsaturated lactam **18** in 64% overall yield (Scheme 9).[50]



Scheme 9. Formation of the α,β-unsaturated bicyclic lactam. LDA = lithium diisopropylamide.

Addition of a propyl cerium chloride reagent[51] in THF at −78 °C gave rise to the hemiaminal that under acidic conditions led to the bicyclic iminium ion. Reduction of the latter with sodium borohydride proceeded again with complete diastereoselectivity and indolizidine 179 (**4**) was obtained as the TFA salt in moderate yield. A strong NOE between 5-CH and 8a-CH was observed in both directions that confirmed the 5,8a-*cis*-relationship (Scheme 10).

The comparably low yield of this last transformation was most likely due to the formation of the dialkylated indolizidine that we could isolate in 10% yield additionally.

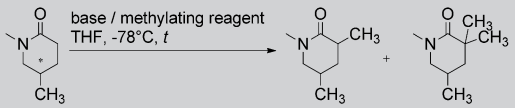
5,6,8-Trisubstituted IBAs

Based on our retrosynthetic approach, we envisaged that the indolizidinone can also be used as a latent nucleophile and alkyl substituents can be introduced to the 6-position by enolate alkylation. The stereogenic centers at C8 and the bridgehead carbon center were expected to have an impact on the diastereoselectivity of this transformation. To test this hypothesis and establish conditions for the alkylation, 1,5-dimethylpiperidinone **19** was employed as model compound and treated with methylating agents under various conditions (Table 4).

It turned out that more than stoichiometric amounts of base and methylating agent were essential to convert all starting materials into product and 1.5 equivalents of both LDA and methyl iodide were optimal to produce the desired lactam **20a** in quantitative yield (Table 4, entry 3). With only stoichiometric amounts, roughly 50% of the starting material was recovered, whereas with 3 equivalents of both LDA and methyl iodide, 53% of the dialkylated product **20b** was obtained along with only 34% of the desired monoalkylated lactam **20a** (compare entries 1 and 3). Reactions with alkali-metal hexamethyldisilazides (LiHMDS, NaHMDS, and KHMDS) when employed as bases failed to furnish any product. The presence of DMPU had no effect on either the yield or selectivity. The diastereoselectivity of the reaction, however, was only very moderate in all cases studied.

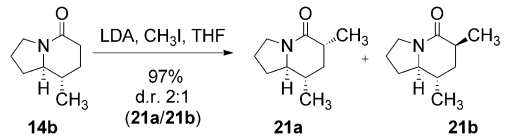
When the above-established conditions were applied to indolizidinone **14d** as the substrate, the α-methylated lactam **21** was obtained in almost quantitative yield as a 2:1-mixture of diastereomers that were separable by column chromatography (Scheme 11). Finally, individual C5-alkylation of **21a** and **21b** with propylmagnesium chloride followed by acid-catalyzed dehydration and iminium-ion reduction with sodium borohydride delivered indolizidine 195G (**5**) and *epi*-195G (*epi*-**5**) in quantitative yield and as single diastereomers, respectively

Table 4. Model studies for amide enolate alkylation.

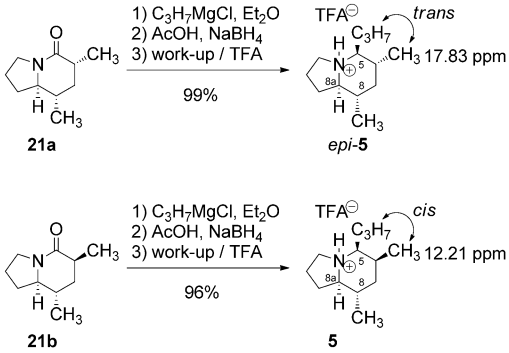


Entry	Base	Methylating reagent	*t* [h]	Yield [%][a]	d.r.[b]
1	LDA (1.1 equiv)	CH_3I (1.5 equiv)	3	42	2:1
2	LDA (3.0 equiv)	CH_3I (3.0 equiv)	2	34 (**20a**)/53 (**20b**)	1:1
3	LDA (1.5 equiv)	CH_3I (1.5 equiv)	2	>99	2:1
4	LHMDS[c] (1.2 equiv)	CH_3I (2.0 equiv)	4	n.c.[c]	n.d.
5	LDA (1.5 equiv)	CH_3I (1.5 equiv)/DMPU[c] (1.5 equiv)	2	>99	2:1

[a] Isolated yield. [b] Determined from crude ^{1}H NMR spectroscopy. [c] DMPU = 1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one; LHMDS = lithium hexamethyl disilazide; n.c. = no conversion.



Scheme 11. Methylation of indolizidinone **14d**.



Scheme 12. Synthesis of indolizidine **195G** and *epi*-**195G**.

(Scheme 12). Comparison of the chemical shifts for the methyl group at C6 in **5** and *epi*-**5**, respectively provided evidence for the relative configuration as depicted (γ-effect). Most notably, the diastereoselectivity of the iminium-ion reduction was solely governed by the configuration of the bridgehead chiral center and was not affected by the additional chiral center at C6 at all.

Accordingly, this general strategy is applicable to 6-alkylated indolizidines as well although the modest selectivity of the enolate alkylation appears as a current limitation.

Conclusions

In conclusion, we have established a general, catalytic, and highly stereoselective synthetic access toward a broad range of diversely substituted indolizidine-based alkaloids. 5-Monosubstituted, 3,5- and 5,8-disubsituted, 5,6,8-trisubstituted indolizidines, and one 6,7-dihydroindolizidine were easily accessible by a unified synthetic strategy. As a key step, we employed the Brønsted acid catalyzed vinylogous Mukaiyama–Mannich reaction that we had developed earlier in our laboratories and which was easily run on a multigram scale and set the first two stereogenic enters with typically excellent stereocontrol. The remaining chiral centers and substituents were incorporated at a late stage of the synthesis under substrate control rendering our approach highly flexible and general. Overall, we have disclosed the total synthesis of three 5-monosubstituted IBAs (indolizidine 139, 167B, and 209), two 3,5-disubstituted IBAs (monomorine and indolizidine 181A), and eight 5,8-disubstituted IBAs (indolizidine 167A, 181B, 195I, 207A, 221K, 223V, 251N, and 265P) some of which were synthesized for the first time. Furthermore, even more complex IBAs, such as the 5,6,8-trisubsituted indolizidine 195G (**5**) and its epimer or the 6,7-dihydro indolizidine 179 were accessible with slight adjustments according to our protocol. The isolation of IBAs as TFA salts has been found optimal in terms of yield, analysis, and long-term storage of these highly valuable alkaloids and is therefore strongly recommended for future endeavors. Finally, we expect this strategy to be applicable towards the synthesis of even more complex indolizidines.

Experimental Section

General

All reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen or argon. Tetrahydrofuran and diethylether were dried over Na and benzophenone, CH_2Cl_2 was dried over CaH. Abs. ethanol (< 99.8%) was purchased from VWR and used directly. All reactions were monitored by TLC analysis on precoated silica gel SIL G/UV254 plates (Machery, Nagel) or HPLC analysis. Flash column chromatography was performed by using Merck silica gel 60 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded by using VARIAN Gemini 300 (300 MHz) spectrometer or a Bruker Avance DRX 400 (400 MHz) spectrometer at 25 °C if not stated otherwise. IR spectra were obtained by using a FTIR spectrometer (Genesis ATI, Mattson/Unicam). Melting points are uncorrected. Optical rotations were measured by using a Polarotronic polarometer (Schmidt & Haensch). HPLC analyses were performed by using a JASCO MD-2010 plus instrument with a chiral stationary phase column (Chiralcel ODH, purchased from Daicel). Mass spectra were measured at 70 eV (EI) by using a Finnigan MAT 95A spectrometer. HRMS (ESI/Na+) were measured by using a Bruker Daltonics APEX II. GCMS measurements were performed on an AGILENT 5975B VL.MSD (mass) combined with an AGILENT 6890N (GC) equipped with an injector (7683B) and autosampler (7683) from AGILENT. Samples were run starting with an initial temperature of 100 (DB100S) or 50 °C (DB50S) (initial time 1.0 min). Temperature was raised by 50 °C min^{-1} up to a final temperature of 300 °C. Analytic data is presented as follows: retention time (*m/z* values with descending order in rel. intensity). Compound **9a**, **9b**, and **9c**,[38] $B(ArF_5)_3$,[47] and catalysts (**7a**–**e**)[38] were synthesized by following literature procedures or along the lines.

General X-ray crystallography

The data were collected on a Gemini diffractometer (Agilent Technologies) by using $Cu_{K\alpha}$ radiation ($\lambda = 1.5418$ Å), ω-scan rotation. Data reduction was performed with the CrysAlisPro (CrysAlisPro: Data collection and data reduction software package, Agilent Technologies) including the program SCALE3 ABSPACK (SCALE3 ABSPACK: empirical absorption correction by using spherical harmonics) for empirical absorption correction. The structures were solved by direct methods with SIR2004. The refinement of all non-hydrogen atoms was performed anisotropically, the hydrogen atoms isotropically with SHELXL-97. The structure figure was generated with ORTEP.

General methods

Compound 12a: 4-Methoxyaniline (3.97 g, 32.3 mmol, 1.05 equiv) was dissolved in THF (300 mL) in a 500 mL round-bottomed flask to give a pale yellow solution and cooled to −55 °C. After 30 min, ethyl-4-oxobutanoate (4.00 g, 30.7 mmol, 1.00 equiv) was added by a syringe and the corresponding solution was allowed to stir for a further 30 min. Then TRIP-catalyst (**7b**) (1.74 g, 2.31 mmol, 7.5 mol%) was added and the resulting suspension was stirred for 30 min until a pale reddish solution was formed. Subsequently ice-

cold **9a** (21 g, 92 mmol, 3.0 equiv) was added slowly over a period of 20 min. The reaction mixture was allowed to stir over night and was subsequently concentrated to give a dark-yellow/brown oil. The crude product was further dissolved in glacial acetic acid (80 mL), heated to reflux conditions, and stirred for 1 h. The resulting dark-red solution was concentrated, and the crude product further subjected to a silica gel column and eluted with methyl *tert*-butyl ether (MTBE) to give a pale-grey solid: 8.1 g (87%, 96% *ee*). The solid was then either recrystallized from MTBE or from layering a toluene solution with hexane to give colorless needles: 6.24 g (67%, >99% *ee*). R_f = 0.2 (MTBE); m.p. = 72–73 °C; $[\alpha]_D^{24} = +76.2$ (> 99% *ee*, *c* = 0.99 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.10 (m, 2H), 7.00–6.82 (m, 2H), 6.77 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.80 (d, *J* = 15.0 Hz, 1H), 4.24 (tdd, *J* = 8.5, 5.0, 3.5 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 2.65–2.43 (m, 3H), 2.39–2.23 (m, 2H), 1.85 (dddd, *J* = 13.0, 9.5, 7.0, 5.0 Hz, 1H), 1.26 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 174.4, 166.0, 158.2, 142.8, 130.1, 126.7, 126.4, 125.1, 114.8, 60.65, 59.18, 55.68, 36.45, 31.01, 23.76, 14.43 ppm; IR (KBr): $\tilde{\nu}$ = 3306, 2978, 2955, 2837, 1707, 1678, 1608, 1584, 1512, 1466, 1444, 1428, 1415, 1396, 1367, 1314, 1294, 1264, 1246, 1220, 1174, 1141, 1120, 1107, 1092, 1061, 1023, 830, 814, 791, 773, 713, 663, 641, 617, 578 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{21}NO_4$: 326.1368 $[M+Na]^+$; found: 326.1363; HPLC Chiralcel-OD-H isocratic (hexane/*i*PrOH 70/30, flow: 1.0 mL min^{-1}: λ = 204 t_R(minor enantiomer) = 13.29. t_R(major enantiomer) = 19.87 min; GCMS (DB100S): 6.64 min (190.1, 134.1, 303.2).

Compound 12b: 4-Methoxyaniline (2.08 g, 16.9 mmol, 1.00 equiv) was dissolved in THF (0.1 M) in a 250 mL round-bottomed flask to give a pale-yellow solution and cooled to −50 °C. After 10 min, ethyl-4-oxobutanoate (2.20 g, 16.9 mmol, 1.00 equiv) was added by a syringe and the corresponding solution was allowed to stir for a further 10 min. Then 3,3′-mesityl substituted BINOL-bases phosphoric acid **7e**, the Mes-catalyst (**7e**) (988 mg, 1.69 mmol, 10 mol%) was added and the resulting suspension was stirred for 15 min until a pale-reddish solution was formed. Subsequently ice-cold **9b** (8.2 g, 33.8 mmol, 2.0 equiv) was added slowly over a period of 10 min. The reaction mixture was allowed to stir for 26 h and subsequently allowed to warm to room temperature. Glacial acetic acid (20 mL) was added to the crude product and the mixture heated to reflux conditions and stirred for 1 h. The resulting dark-red solution was concentrated and the crude product further subjected to a silica gel column and eluted with MTBE → EtOAc to give a white solid: 3.66 g (68%, d.r. = 37:1, 93% *ee*). The solid was then recrystallized from MTBE to give a colorless solid: 2.63 g (49%, d.r. = > 99:1, >99% *ee*). R_f = 0.52 (MTBE); m.p. = 63–65 °C; $[\alpha]_D^{24} = -5.4$ (d.r. = > 99:1, >99% *ee*, *c* = 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 9.0 Hz, 2H); 6.91 (d, *J* = 9.0 Hz, 2H); 6.82 (dd, *J* = 16.0, 6.5 Hz, 1H); 5.80 (dd, *J* = 16.0, 1.5 Hz, 1H); 4.32 (dt, *J* = 8.5, 4.0 Hz, 1H); 4.16 (q, *J* = 7.0 Hz, 2H); 3.78 (s, 3H); 2.68 (mc, 1H); 2.61–2.46 (m, 2H); 2.14 (mc, 1H); 1.85 (mc, 1H); 1.26 (t, *J* = 7.0 Hz, 3H); 0.94 ppm (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 174.5; 166.3; 157.9; 149.1; 130.0; 126.1; 122.2; 114.6; 62.70; 60.53; 55.54; 37.51; 31.31; 18.75; 14.32; 11.12 ppm; IR (KBr): $\tilde{\nu}$ = 3445, 2979, 2961, 2920, 2863, 2844, 1713, 1682, 1656, 1612, 1583, 1517, 1464, 1448, 1426, 1404, 1368, 1316, 1293, 1256, 1232, 1195, 1162, 1138, 1116, 1038, 1029, 983, 909, 866, 831, 749, 648, 564, 540, 512 ppm; HRMS (ESI): *m/z*: calcd for $C_{18}H_{23}NO_4$: 340.15193 $[M+Na]^+$; found: 340.15209; HPLC Chiralcel-OD-H isocratic (hexane/*i*PrOH 70:30, flow: 1.0 mL min^{-1}): λ = 220 t_{R1} = 41.91, t_{R2} = 64.54 min; GCMS: (DB50S): 8.99 min (190).

Compound 12c: 4-Methoxyaniline (4.05 g, 32.9 mmol, 1.00 equiv) was dissolved in THF (0.1 M) in a 1 L round-bottomed flask to give a pale-yellow solution and cooled to −50 °C. After 10 min, ethyl-4-oxobutanoate (4.28 g, 32.9 mmol, 1.00 equiv) was added by a syringe and the corresponding solution was allowed to stir for a further 15 min. Then, **7e** (2.20 g, 3.29 mmol, 10 mol%) was added and the resulting suspension was stirred for 15 min until a pale-reddish solution was formed. Subsequently ice-cold **9c** (18.7 g, 65.8 mmol, 2.00 equiv) was added slowly over a period of 10 min. The reaction mixture was allowed to stir for 41 h and subsequently allowed to warm to room temperature. Glacial acetic acid (40 mL) was added to the crude product and the mixture was heated to reflux conditions and stirred for 4 h. The resulting dark-red solution was concentrated and the crude product further subjected to a silica gel column and eluted with MTBE → EtOAc to give a yellow oil: 11.0 g (93%, d.r. = 22:1, >99% *ee*). R_f = 0.34 (MTBE); $[\alpha]_D^{22} = +1.4$ (d.r. = 22:1, >99% *ee*, *c* = 1.02 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.72 (dd, *J* = 16.0, 9.0 Hz, 1H), 5.79 (d, *J* = 16.0 Hz, 1H), 4.28–4.20 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.67–2.47 (m, 2H), 2.47–2.36 (m, 1H), 2.28–2.13 (m, 1H), 2.04–1.88 (m, 1H), 1.48–1.35 (m, 1H), 1.29 (t, *J* = 7.0, 3H), 1.31–1.23 (m, 1H), 1.21–1.07 (m, 3H), 0.91 (m, 1H), 0.80 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 174.7, 166.1, 157.9, 148.1, 130.0, 126.3, 123.5, 114.5, 63.25, 60.48, 55.47, 44.43, 31.15, 29.47, 26.14, 22.56, 19.75, 14.26, 13.91 pm; IR (film): $\tilde{\nu}$ = 2956, 2932, 2871, 2859, 2838, 1716, 1697, 1652, 1610, 1513, 1465, 1443, 1425, 1398, 1368, 1293, 1250, 1179, 1138, 1121, 1105, 1036, 984, 913, 832, 731 ppm; HRMS (ESI): *m/z*: calcd for $C_{21}H_{30}NO_4$: 360.21693 $[M+H]^+$; found: 360.21670; calcd for $C_{21}H_{30}NO_4$ $[M+Na]^+$: 382.19888; found: 382.19871; HPLC Chiralcel-AS-H isocratic (hexane/*i*PrOH 70:30, flow: 1.0 mL min^{-1}): λ = 220 t_{R1} = 24.43, t_{R2} = 55.53 min; GCMS (DB50S): 9.31 min *m/z*: 359.3 $[M]^{\cdot+}$, 190.1 $[M-C_{10}H_{17}O_2]^{\cdot+}$.

Towards compound 13a (three-step synthesis): Compound **12a** (6.24 g, 20.6 mmol, 1 equiv) was dissolved in ethanol (40 mL) in a 100 mL round-bottomed flask to give a colorless solution. Pd/C (1.10 g, 1.00 mmol) was added and the dark suspension treated with hydrogen by a balloon. The crude mixture was stirred for 10 min and subsequently filtered over Celite to give a colorless solid (**12a-1**): 6.30 g (>99%); R_f = 0.50 (EtOAc/MeOH, 25:1); m.p. = 34 °C; $[\alpha]_D^{24} = +45.8$ (*c* = 1.01 in EtOH); ^{1}H NMR (300 MHz, DMSO): δ = 7.35–7.20 (m, 2H), 7.02–6.88 (m, 2H), 4.26–4.11 (m_c, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 2.49–2.29 (m, 2H), 2.26–2.18 (m, 3H), 1.83–1.66 (m_c, 1H), 1.57–1.35 (m, 3H), 1.33–1.22 (m, 1H), 1.11 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO): δ = 173.2, 172.5, 156.7, 130.7, 125.4, 113.9, 59.7, 58.57, 55.18, 33.22, 32.23, 30.58, 23.21, 19.71, 14.04 ppm; IR (film): $\tilde{\nu}$ = 3437, 2938, 2838, 2359, 1731, 1662, 1609, 1586, 1513, 1444, 1321, 1250, 1181, 1120, 1033, 834, 780, 734, 660, 614, 556, 520 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{23}NO_4$: 328.1519 $[M+Na]^+$; found: 340.1520; GCMS: (DB100S): 6.51 min (190, 305, 260).

Compound 12a-2: Compound **12a-1** (6.28 g, 20.6 mmol, 1.00 equiv) was dissolved in a 1 L round-bottomed flask in a mixture of acetonitrile/water (5:1 [0.04 M]) to give a colorless solution and cooled to 0 °C. After 10 min, ceric ammonium nitrate (CAN) (24.8 g, 45.3 mmol, 2.20 equiv) was added in small portions whereupon the colorless solution turned yellow, purple, then dark red. After complete addition, the reaction mixture was allowed to stir for 10 min and was subsequently quenched at 0 °C by addition of sat. sodium bicarbonate solution (75 mL). Additional solid potassium carbonate (2 g) was added to basify the crude reddish, grey suspension. The suspension was filtered and the residual solid washed extensively with EtOAc. The phases were separated and the aqueous layer extracted with EtOAc (5 × 50 mL) until TLC analysis suggested completion. The combined organic layers were concentrated and subsequently dried over Na_2SO_4, filtered, concentrat-

ed in vacuum, and subsequently subjected to a silica gel column. Chromatography of the crude product by using an eluent system with a gradient from EtOAc→EtOAc/MeOH (30:1)→EtOAc/MeOH (9:1) yielded the deprotected lactam **12a-2** as a white solid: 3.6 g (87%). $R_f = 0.3$ (EtOAc/MeOH, 9:1); m.p. = 53 °C; $[\alpha]_D^{24} = -14.9$ ($c =$ 0.40 in EtOH); ^{1}H NMR (300 MHz, DMSO): $\delta = 7.72$ (br s, 1H), 4.05 (q, $J = 7.0$ Hz, 2H), 3.55–3.39 (m_c, 1H), 2.29 (t, $J = 7.0$ Hz, 2H), 2.15–2.05 (m, 3H), 1.70–1.24 (m, 5H), 1.18 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO): $\delta = 176.5$, 172.7, 59.70, 53.24, 35.73, 33.35, 29.95, 26.60, 20.77, 14.33 ppm; IR (film): $\tilde{\nu} = 3341$, 2933, 1732, 1683, 1377, 1315, 1251, 1180, 1096, 1034, 825, 651, 505 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{17}NO_3$: 222.1101 $[M+Na]^+$; found: 222.1102; calcd for $C_{20}H_{34}N_2O_6$: 421.2309 $[2M+Na]^+$; found: 421.2309; GCMS (DB100S): 4.83 min (84, 154, 199).

Compound 13a: Compound **12a-2** (3.30 g, 16.6 mmol, 1.00 equiv) was dissolved in acetonitrile (20 mL) in a 50 mL round-bottomed flask to give a yellow solution and cooled to 0 °C. Boc_2O (3.98 g, 4.23 mL, 18.2 mmol, 1.1 equiv) and DMAP (202 mg, 1.66 mmol, 0.10 eq) were added and the crude mixture subsequently allowed to warm to room temperature and stirred overnight. After 18 h TLC analysis suggested complete conversion and hence the crude mixture was concentrated in vacuum and subjected to a silica gel column. Chromatography with MTBE/Hex (1:1) yielded the imide as a colorless oil in quantitative yield: 4.96 g (>99%); $R_f = 0.15$ (MTBE/Hex 1:1); $[\alpha]_D^{24} = +59.7$ ($c = 1.00$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.13$–4.02 (m, 3H), 2.54 (ddd, $J = 18.0$, 11.0, 9.0 Hz, 1H), 2.38 (ddd, $J = 18.0$, 9.0, 3.5 Hz, 1H), 2.30 (td, $J = 7.0$, 3.5 Hz, 2H), 2.15–1.99 (m, 1H), 1.82–1.71 (m, 2H), 1.71–1.51 (m, 4H), 1.48 (s, 9H), 1.21 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C{^{1}H} NMR(100 MHz, $CDCl_3$): $\delta =$ 174.3, 173.2, 150.1, 82.99, 60.58, 57.86, 34.06, 33.42, 31.52, 28.22, 22.65, 21.24, 14.43 ppm; IR (KBr): $\tilde{\nu} = 3383$, 2978, 2934, 1782, 1732, 1698, 1597, 1586, 1547, 1474, 1456, 1437, 1410, 1383, 1371, 1352, 1312, 1299, 1252, 1183, 1083, 1069, 1042, 1020, 902, 848, 833, 792, 756, 690, 650, 614, 581 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{25}NO_5$: 322.1625 $[M+Na]^+$; found: 322.1624.

Toward compound 13b (three-step synthesis): Compound **12b** (77.0 mg, 234 μmol, 1.00 equiv) was dissolved in a mixture of acetonitrile/water (5:1, 0.04 M) in a 25 mL round-bottomed flask to give a colorless solution and the mixture was cooled to 0 °C. After 5 min, CAN (293 mg, 534 μmol, 2.20 equiv) was added in small portions whereupon the colorless solution turned yellow, then purple, then dark red. After complete addition, the reaction mixture was allowed to stir for 10 min and was subsequently quenched at 0 °C by addition of sat. sodium bicarbonate solution (10 mL). Additional solid potassium carbonate (~0.5 g) was added to basify the crude reddish, grey suspension. The crude mixture was diluted with EtOAc (20 mL) and stirred for 5 min at 0 °C and then a further 5 min at room temperature. The suspension was filtered and the residual solid washed extensively with EtOAc. The phases were separated and the aqueous layer extracted with EtOAc (4×20 mL) until TLC analysis suggested completion. The combined organic layers were concentrated and subsequently dried over Na_2SO_4, filtered, concentrated in vacuum, and subsequently subjected to a silica gel column. Chromatography of the crude product using EtOAc as the eluent yielded the deprotected lactam (**12b-1**) as a white solid: 41 mg (80%); $R_f = 0.21$ (EtOAc); m.p. = 89–91 °C; $[\alpha]_D^{28} = +57.7°$ ($c = 1.01$ in d.r. > 99/1, >99% *ee*, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.77$ (dd, $J = 15.5$, 8.5 Hz, 1H); 6.50 (br s, 1H); 5.86 (d, $J = 15.5$ Hz, 1H); 4.17 (q, $J = 7.0$ Hz, 2H); 3.56 (q, $J = 7.0$ Hz, 1H); 2.42–2.12 (m, 4H); 1.76 (m_c, 1H); 1.27 (t, $J = 7.0$ Hz, 3H); 1.06 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta =$ 178.2, 166.2, 148.9, 123.0, 60.57, 58.04, 42.61, 30.31, 24.77, 15.26, 14.32 ppm; IR (KBr): $\tilde{\nu} = 3447$, 3206, 2985, 2942, 2905, 2878, 1717, 1697, 1654, 1476, 1455, 1444, 1424, 1395, 1369, 1354, 1337, 1293, 1259, 1200, 1174, 1115, 1076, 1036, 1002, 984, 910, 871, 764, 729, 671, 501 cm^{-1}; GCMS (DB50S): 7.28 min: *m/z*: 84.0 $[M-C_7H_{11}O_2]^+$; HRMS (ESI): *m/z*: calcd for $C_{11}H_{17}NO_3$: 234.11006 $[M+Na]^+$; found: 234.11021.

Compound 12b-2: Compound **12b-1** (895 mg, 4.24 mmol, 1.00 equiv) was dissolved in acetonitrile (10 mL) in a 50 mL round-bottomed flask and the mixture was cooled to 0 °C. Boc_2O (2.77 g, 12.7 mmol, 3.0 equiv) and DMAP (52 mg, 424 μmol, 0.10 equiv) were added and the crude mixture subsequently allowed to warm to room temperature and stirred overnight. After 1 d TLC analysis suggested complete conversion and hence the crude mixture was concentrated in vacuum and subjected to a silica gel column. Chromatography with MTBE/Hex (1:1) yielded the imide (**12b-2**) as a pale-yellow oil in quantitative yield: 1.31 g (>99%); $R_f = 0.24$ (Hex/MTBE = 1:1); $[\alpha]_D^{26} = +31.4°$ ($c = 1.02$ in $CHCl_3$, d.r. > 99/1, >99% *ee*,); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.88$ (dd, $J = 15.5$, 7.0 Hz, 1H); 5.86 (dd, $J = 15.5$, 1.5 Hz, 1H); 4.27 (ddd, $J = 9.0$, 5.0, 2.0 Hz, 1H); 4.19 (q, $J = 7.0$ Hz, 2H); 2.96 (m_c, 1H); 2.62–2.36 (m, 2H); 2.05 (m_c, 1H); 1.79 (m_c, 1H); 1.56 (s, 9H); 1.29 (t, $J = 7.0$ Hz, 3H); 1.05 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta =$ 174.4; 166.4; 150.1; 149.2; 122.4; 83.43; 60.62; 60.48; 39.49; 32.13; 28.15; 19.27; 14.39; 12.90 ppm; IR (film): $\tilde{\nu} = 3420$, 2979, 2936, 1787, 1751, 1716, 1653, 1458, 1368, 1307, 1256, 1188, 1155, 1034, 984, 955, 919, 849, 777, 599 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{25}NO_5$: 334.16249 $[M+Na]^+$; found: 334.16263.

Compound 13b: Compound **12b-2** (1.03 g, 3.31 mmol, 1.00 equiv) was dissolved in ethanol (50 mL) in a 100 mL round-bottomed flask to give a colorless solution. Pd/C (176 mg, 10 wt.%, 0.05 equiv) was added and the dark suspension treated with hydrogen by a balloon. The crude mixture was stirred for 40 min and subsequently filtered over Celite to give a colorless solid that was subjected to a silica gel column chromatograph with MTBE as the eluent. The purified product was obtained as a yellow oil: 1.03 g (>99%); $R_f = 0.39$ (Hex/MTBE = 1:1); $[\alpha]_D^{25} = +50.0°$ ($c = 1.04$ in $CHCl_3$, d.r. > 99:1, >99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.15$ (m_c, 1H); 4.10 (q, $J = 7.0$ Hz, 2H); 2.57–2.21 (m, 4H); 2.11 (m_c, 1H); 1.98 (m_c, 1H); 1.78 (m_c, 1H); 1.64 (m_c, 1H); 1.50 (m_c, 1H); 1.49 (s, 9H); 1.23 (t, $J = 7.0$ Hz, 3H); 0.82 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 174.9$; 173.3; 150.0; 82.96; 61.01; 60.52; 35.24; 32.39; 32.34; 28.51; 28.10; 17.74; 14.29; 12.97 ppm; IR (film): $\tilde{\nu} = 2978$, 2935, 1784, 1736, 1716, 1707, 1472, 1422, 1391, 1369, 1305, 1258, 1157, 1093, 1042, 1022, 917, 850, 780, 599, 460 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{27}NO_5$: 336.17814 $[M+Na]^+$; found: 336.17832; calcd for $C_{32}H_{54}N_2O_{10}$: 649.36707 $[2M+Na]^+$; found: 649.36716.

Toward 13c (three-step synthesis): Compound **12c** (10.3 g, 28.5 mmol, 1.00 equiv) was dissolved in a mixture of acetonitrile/water (5:1, 0.04 M) in a 2 L round-bottomed flask to give a colorless solution and the mixture was cooled to 0 °C. After 5 min, CAN (34.4 g, 62.7 mmol, 2.20 equiv) was added in small portions whereupon the colorless solution turned yellow, then purple, then dark red. After complete addition, the reaction mixture was allowed to stir for 10 min and was subsequently quenched at 0 °C by addition of sat. sodium bicarbonate solution (500 mL). The crude mixture was diluted with EtOAc (200 mL) and stirred for 5 min at 0 °C and for a further 5 min at room temperature. The suspension was filtered over Celite and the residual solid washed extensively with EtOAc. The phases were separated and the aqueous layer extracted with EtOAc (5×150 mL) until TLC analysis suggested completion. The combined organic layers were concentrated and subsequently dried over Na_2SO_4, filtered, concentrated in vacuum and subsequently subjected to a silica gel column. Chromatography of the

crude product by using EtOAc as the eluent yielded the deprotected lactam (**12c-1**) as a white solid: 6.12 g (85%). R_f=0.34 (EtOAc); $[\alpha]_D^{25}=-15.2^\circ$ (c=1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.67 (dd, J=15.5, 10.0 Hz, 1H); 6.35 (br s, 1H); 5.87 (d, J=15.5 Hz, 1H); 4.18 (q, J=7.0 Hz, 2H); 3.60 (q, J=7.0 Hz, 1H); 2.35–2.29 (m, 2H); 2.23 (m_c, 1H); 2.14 (m_c, 1H); 1.77 (m_c, 1H); 1.49 (m_c, 1H); 1.36–1.07 (m, 5H); 1.28 (t, J=7.0 Hz, 3H); 0.86 ppm (t, J=7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ=178.7, 166.2, 148.2, 124.6, 60.75, 57.57, 48.98, 30.26, 29.91, 29.40, 25.35, 22.66, 14.32, 14.00 ppm; IR (film): $\tilde{\nu}$=3646, 3333, 2956, 2929, 2871, 2860, 2359, 2341, 1715, 1697, 1682, 1652, 1469, 1384, 1369, 1267, 1209, 1179, 1160, 1138, 1095, 1038, 988, 911, 865, 824, 785, 730 cm^{-1}; GCMS (DB50S): 7.51 min m/z: 84.0 $[M-C_{10}H_{17}O_2]^{+}$; HRMS (ESI): m/z: calcd for $C_{14}H_{23}NO_3$: 276.15701 $[M+Na]^+$; found: 276.15706.

Compound 12c-2: Compound **12c-1** (5.65 g, 22.3 mmol, 1.00 equiv) was dissolved in acetonitrile (50 mL) in a 250 mL round-bottomed flask and the mixture was cooled to 0 °C. Boc_2O (14.6 g, 66.9 mmol, 3.00 equiv) and DMAP (272 mg, 2.23 mmol, 0.10 equiv) were added and the crude mixture subsequently allowed to warm to room temperature. After 4 d TLC analysis suggested complete conversion and hence the crude mixture was concentrated in vacuum and subjected to a silica gel column. Chromatography with MTBE/Hex (1:1) yielded the imide as pale-yellow oil: 6.75 g (86%); R_f=0.26 (Hex/MTBE=1:1); $[\alpha]_D^{25}=+42.0^\circ$ (c=1.05 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.76 (dd, J=15.5, 9.5 Hz, 1H); 5.84 (dd, J=15.5, 0.5 Hz, 1H); 4.20 (m_c, 1H); 4.17 (q, J=7.0 Hz, 2H); 2.64 (m_c, 1H); 2.59–2.36 (m, 2H); 2.08 (m_c, 1H); 1.88 (m_c, 1H); 1.51 (s, 9H); 1.47–1.04 (m, 6H); 1.28 (t, J=7.0 Hz, 3H); 0.86 ppm (t, J=7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ= 174.4; 166.1; 150.1; 148.4; 123.9; 83.33; 60.58; 60.56; 46.23; 31.95; 29.73; 28.20; 28.10; 22.68; 20.36; 14.37; 14.02 ppm; IR (film): $\tilde{\nu}$= 2978, 2959, 2933, 2872, 2861, 1787, 1752, 1718, 1653, 1460, 1368, 1308, 1257, 1155, 1041, 985, 930, 910, 849, 778, 598 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{31}NO_5$: 376.20944 $[M+Na]^+$; found: 376.20971; calcd for $C_{38}H_{62}N_2O_{10}$: 729.42967 $[2M+Na]^+$; found: 729.42954.

Compound 13c: Compound **12c-2** (6.40 g, 18.1 mmol, 1.00 equiv) was dissolved in ethanol (90 mL) in a 250 mL round-bottomed flask to give a colorless solution. Pd/C (867 mg, 10 wt%, 0.05 equiv) was added and the dark suspension treated with hydrogen by a balloon. The crude mixture was stirred for 2.5 h and subsequently filtered over Celite to give a yellow oil that was subjected to a silica gel column chromatograph with MTBE as the eluent. The purified product was obtained as pale-yellow oil: 6.40 g (>99%); R_f=0.26 (Hex/MTBE=1:1); $[\alpha]_D^{25}=+63.6^\circ$ (c=1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.20 (dt, J=9.5, 3.0 Hz, 1H); 4.13 (q, J=7.0 Hz, 2H); 2.59–2.42 (m, 2H); 2.42–2.26 (m, 2H); 2.08–1.88 (m, 2H); 1.87–1.72 (m, 2H); 1.52 (s, 9H); 1.49–1.04 (m, 7H); 1.25 (t, J=7.0 Hz, 3H); 0.86 ppm (d, J=7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=175.0, 173.4, 149.96, 82.96, 60.56, 59.66, 40.20, 32.52, 32.31, 29.93, 28.13, 27.93, 25.98, 22.94, 17.97, 14.32, 14.06 ppm; IR (film): $\tilde{\nu}$=2977, 2958, 2932, 2872. 2862, 1785, 1737, 1715, 1458, 1422, 1369, 1305, 1256, 1159, 1098, 1041, 1021, 917, 850, 781, 599, 459 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{19}H_{33}NO_5$: 378.22509 $[M+Na]^+$; found: 378.22500.

Toward 14a (two-step synthesis): Compound **13a** (4.60 g, 15.4 mmol, 1.00 equiv) was dissolved in THF (300 mL) in a 500 mL round-bottomed flask to give a colorless solution and cooled to −78 °C. Lithium triethylborohydride (18.44 mL, 1 M in THF, 1.2 equiv) was added slowly over a period of 30 min. The reaction mixture was then allowed to stir for 30 min at −78 °C and subsequently quenched by addition of sat. sodium bicarbonate solution (25 mL). The crude suspension was warmed to 0 °C and further treated with hydrogen peroxide (1.57 mL, 35 wt.% in water, 1.00 equiv) and stirred for 30 min. The organic layer was removed in vacuum and the aqueous layer extracted with CH_2Cl_2 (5×50 mL). The recombined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude hemiaminal product was further used without any purification. The crude product was dissolved in CH_2Cl_2 (300 mL), treated with triethylsilane (2.70 mL, 16.9 mmol, 1.10 equiv), and cooled to −78 °C. After 10 min boron trifluoride etherate (2.14 mL, 16.9 mmol, 1.10 equiv) was added and the reaction mixture stirred for 30 min. Then again triethylsilane (2.70 mL, 16.9 mmol, 1.10 equiv) and boron trifluoride etherate (2.14 mL, 16.9 mmol, 1.10 equiv) were added to force the reaction to completion. The resulting mixture was stirred for 2 h and was then quenched by addition of sat. sodium bicarbonate solution (50 mL). Layers were separated and the aqueous layer extracted with CH_2Cl_2 (5×50 mL). The recombined organic layers were dried over Na_2SO_4, filtered, subjected to a silica gel column and eluted with MTBE/Hex (1:3) to give a pale-yellow oil (**13a-1**): 3.67 g (84%). R_f=0.36 (MTBE/Hex 2:1); $[\alpha]_D^{24}=+41.9$ (c=1.00 in EtOH); ^{1}H NMR (300 MHz, [D$_6$]DMSO [90 °C]): δ=4.05 (q, J=7.0 Hz, 2H), 3.73–3.58 (m, 1H), 3.29 (dt, J=10.5, 7.5 Hz, 1H), 3.16 (ddd, J=10.5, 7.5, 5.0 Hz, 1H), 2.27 (t, J=7.0 Hz, 2H), 1.99–1.45 (m, 7H), 1.39 (s, 9H), 1.38–1.27 (m, 1H), 1.18 ppm (t, J=7.0 Hz, 3H); ^{13}C{^{1}H} NMR- (75 MHz, [D$_6$]DMSO [90 °C]): δ=172.1, 153.2, 77.63, 59.06, 56.06, 45.50, 33.23, 33.17, 29.60, 27.78, 22.47, 20.84, 13.57 ppm; IR (film): $\tilde{\nu}$=2973, 2933, 2874, 2360, 1735, 1694, 1653, 1636, 1558, 1540, 1508, 1478, 1455, 1395, 1365, 1341, 1311, 1287, 1251, 1173, 1118, 1103, 1033, 916, 879, 861, 772 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{27}NO_4$: 308.1832 $[M+Na]^+$; found: 308.1832.

Compound 14a: Compound **13a–1** (3.00 g, 10.5 mmol) was dissolved in CH_2Cl_2 (105 mL) in a 250 mL round-bottomed flask to give a pale-yellow solution and cooled to 0 °C. TFA (10.0 mL, 130 mmol) was added slowly by a syringe and the resulting mixture was allowed to warm to room temperature and was stirred for 30 min. The mixture was concentrated in vacuum to give yellow oil that was directly suspended in aqueous sodium bicarbonate solution (100 mL) and stirred for 2 h at room temperature. The aqueous layer was further basified (pH ~ 14) by addition of 2 M NaOH and extracted with CH_2Cl_2 (3×30 mL). The recombined organic layers were dried over Na_2SO_4, filtered, and subjected to a silica gel column. Elution with CH_2Cl_2 and 5% MeOH yielded the product as colorless liquid that solidifies upon cooling to temperatures below 0 °C: 1.45 g (99%); R_f=0.5 (CH_2Cl_2/5% MeOH); $[\alpha]_D^{24}=+18.8$ (c=1.28 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.67–3.52 (m, 1H), 3.51–3.31 (m, 2H), 2.51–2.36 (m, 1H), 2.34–2.18 (m, 1H), 2.16–2.03 (m, 2H), 1.99–1.88 (m, 2H), 1.82–1.62 (m_c, 2H), 1.51–1.35 (m_c, 1H), 1.33–1.17 ppm (m_c, 1H); ^{13}C{^{1}H} NMR(100 MHz, $CDCl_3$): δ=169.2, 59.4, 44.93, 33.67, 31.13, 29.26, 22.25, 21.28 ppm; IR (film): $\tilde{\nu}$=3452, 2944, 2880, 1731, 1626, 1455, 1414, 1383, 1372, 1328, 1308, 1252, 1213, 1168, 1143, 1119, 1099, 1071, 1053, 1016, 992, 917, 841, 636, 566, 452, 425 cm^{-1}; HRMS (EI): m/z: calcd for $C_8H_{13}NO$: 139.0997 $[M]^+$; found: 139.0999; GCMS (DB100S): 5.68 min (83, 139, 70).

Compound 14b: This compound was synthesized along the lines of the synthesis toward **14a** by starting from **16a** (for further information please see the Supporting Information). Yield: 89%; R_f= 0.21 (MTBE); $[\alpha]_D^{24}=-44.1$ (c=0.86 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.07–3.75 (m, 1H), 3.35 (tdd, J=11.0, 5.0, 3.0 Hz, 1H), 2.54–2.20 (m, 2H), 2.09–1.83 (m, 4H), 1.85–1.45 (m, 4H), 1.45–1.04 (m, 6H), 0.88 ppm (t, J=7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ=169.6, 60.15, 57.50, 32.69, 31.67, 31.25, 29.55, 29.04, 27.80, 22.93, 21.40, 14.32 ppm; IR (film): $\tilde{\nu}$=3475, 3147, 2953, 2869, 2859, 1727, 1643, 1463, 1440, 1409, 1373, 1333, 1317, 1306, 1223, 1213,

1201, 1186, 1163, 1127, 1103, 1065, 964, 901, 641, 567, 453 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{12}H_{22}NO$: 196.16959 $[M+H]^+$; found: 196.16971.

Compound 14c: This compound was synthesized along the lines of the synthesis toward **14a** by starting from **16b** (for further information please see the Supporting Information). Yield: 74%; R_f = 0.22 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{24} = -56.3$ (c = 0.96 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98–3.76 (m, 1H), 3.34 (tdd, J = 11.0, 5.0, 3.0 Hz, 1H), 2.37–2.15 (m, 2H), 2.12–1.06 (m, 10H), 0.82 ppm (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR(75 MHz, $CDCl_3$): δ = 169.56, 60.07, 58.55, 31.49, 31.13, 29.33, 27.12, 25.40, 21.24, 10.72 ppm; IR (film): $\tilde{\nu}$ = 3420, 2965, 2939, 2876, 1725, 1672, 1615, 1463, 1411, 1382, 1352, 1335, 1246, 1201, 1174, 719, 699, 668, 642, 617, 602 cm^{-1}, HRMS (ESI): *m/z*: calcd for $C_{10}H_{17}NONa$: 190.12024 $[M+Na]^+$; found: 190.12031; calcd for $C_{20}H_{34}N_2O_2Na$: 357.25125 $[2M+Na]^+$; found: 357.25121; GCMS (DB100S): 4.647 min (138, 83.9, 55.0).

Compound 14d: This compound was synthesized along the lines of the synthesis of **14a** by starting from **13b-1** (for further information please see the Supporting Information); Yield: 83%; R_f = 0.30 (CH_2Cl_2/MeOH = 95:5); M.p. = 53–55 °C; $[\alpha]_D^{22} = +24.2^\circ$ (c = 1.04 in EtOH, d.r. > 99:1, > 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (m_c, 1H); 3.45 (m_c, 1H); 2.98 (m_c, 1H); 2.44 (m_c, 1H); 2.32 (m_c, 1H); 2.13 (m_c, 1H); 1.94 (m_c, 1H); 1.87–1.62 (m, 2H); 1.51–1.28 (m, 3H); 1.01 ppm (dd, J = 5.5 Hz, J = 2.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1; 65.26; 45.36; 35.55; 32.44; 31.64; 30.22; 22.26; 18.34 ppm; IR (KBr): $\tilde{\nu}$ = 3346, 3246, 2943, 2885, 2872, 1707, 1748, 1627, 1469, 1454, 1412, 1381, 1331, 1309, 1291, 1282, 1235, 1226, 1211, 1199, 1161, 1144, 1174, 987, 915, 831, 745, 703, 664, 579, 492, 413 cm^{-1}; GCMS (DB50S): *m/z*: 153.1 $[M]^{\cdot+}$, 111.0 $[M-C_3H_6]^{\cdot+}$; HRMS (ESI): *m/z*: calcd for $C_9H_{15}NO$: 176.10459 $[M+Na]^+$; found: 176.10478; calcd for $C_{18}H_{30}N_2O_2$: 329.21995 $[2M+Na]^+$; found.: 329.22005.

Compound 14e: This compound was synthesized along the lines of the synthesis toward **14a** by starting from **13c-1** (for further information please see the Supporting Information). Yield: 74%; R_f = 0.24 (CH_2Cl_2/MeOH = 95:5); $[\alpha]_D^{22} = +55.6^\circ$ (c = 1.47 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.57 (m_c, 1H); 3.45 (m_c, 1H); 3.06 (m_c, 1H); 2.47 (m_c, 1H); 2.29 (m_c, 1H); 2.16 (m_c, 1H); 2.01–1.88 (m, 2H); 1.71 (ttd, J = 12.5, 10.0, 6.5 Hz, 1H); 1.56–1.09 (m, 9H); 0.89 ppm (t, = 7.0, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 169.2, 64.22, 45.25, 40.42, 32.49, 32.28, 31.56, 28.80, 27.03, 22.99, 22.25, 14.07 ppm; IR (film): $\tilde{\nu}$ = 3464, 2954, 2927, 2870, 2861, 1647, 1638, 1459, 1415, 1383, 1324, 1287, 1278, 1233, 1204, 1190, 1147, 960, 837, 728, 667, 598, 581, 566 cm^{-1}; GCMS (DB50S): 6.78 min *m/z*: 195.1 $[M]^{\cdot+}$; HRMS (ESI): *m/z*: calcd for $C_{12}H_{21}NO$: 218.15154 $[M+Na]^+$; found.: 218.15173; calcd for $C_{24}H_{42}N_2O_2$: 413.31384 $[2M+Na]^+$; found: 413.31364.

Compound 15b: Compound **13a** (1.75 g, 5.85 mmol, 1.00 equiv) was dissolved in THF (117 mL) in a 250 mL round-bottomed flask to give a colorless solution and cooled to −78 °C. Ethyl magnesium chloride (4.33 mL, 11.7 mmol (2.7 M in THF), 2.0 equiv) was added and the crude yellow mixture stirred for 3.5 h. The reaction was quenched by addition of sat. NH_4Cl (50 mL) and the layers separated. The aqueous layer was extracted with MTBE (3×100 mL). The recombined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was subjected to a silica gel column and eluted with MTBE/Hex 1:3 to give a colorless oil: 1.69 g (88%); R_f = 0.2 (MTBE/Hex 1:1); $[\alpha]_D^{24} = +10.9$ (c = 0.36 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26 (d, J = 9.5 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.62–3.41 (m, 1H), 2.46 (t, J = 7.0 Hz, 2H), 2.41 (q, J = 7.5 Hz, 2H), 2.30 (td, J = 7.5, 2.5 Hz, 2H), 1.90–1.45 (m, 6H), 1.42 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H), 1.04 ppm (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$): δ = 211.5, 173.5, 155.9, 79.25, 60.40, 50.36, 39.04, 36.25, 35.48, 34.10, 29.49, 28.51, 21.46, 14.37, 7.97 ppm; IR (film): $\tilde{\nu}$ = 3365, 2977, 2938, 2360, 1731, 1714, 1519, 1455, 1416, 1390, 1366, 1300, 1247, 1172, 1115, 1097, 1079, 1027, 866, 780, 751, 667, 641, 626 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{31}NO_5$: 352.20944 $[M+Na]^+$; found: 352.20920; GCMS (DB50S): 7.17 min (184, 240, 126, 260).

Compound 15a: This compound was synthesized along the lines of the synthesis of **15b** (for further information please see the Supporting Information). Yield: 85%; R_f = 0.14 (MTBE/Hex 1:2); $[\alpha]_D^{24} = -34.1$ (c = 1.11 in EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26 (d, J = 9.5 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.58–3.45 (m_c, 1H), 2.47 (td, J = 7.0, 2.0 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.31 (td, J = 7.5, 2.5 Hz, 2H), 1.84–1.52 (m, 8H), 1.43 (s, 9H), 1.37–1.28 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H), 0.90 ppm (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$): δ = 211.2, 173.6, 156.0, 79.24, 60.43, 50.39, 42.92, 39.48, 35.53, 34.15, 29.38, 28.57, 26.14, 22.53, 21.51, 14.42, 14.04 ppm; IR (film): $\tilde{\nu}$ = 3367, 2957, 2934, 2873, 1731, 1715, 1519, 1447, 1391, 1366, 1299, 1245, 1173, 1130, 1085, 1028, 975, 862, 835, 780, 751, 637, 598, 462, 452, 411 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{35}NO_5$: 380.24074 $[M+Na]^+$; found: 380.24085; calcd for $C_{38}H_{70}N_2O_{10}$: 737.49227 $[2M+Na]^+$; found: 737.49164.

Compound 16b: $B(ArF_5)_3$ (787 mg, 1.54 mmol, 0.30 equiv) dissolved in CH_2Cl_2 (10 mL) in a 100 mL round-bottomed flask and Ph_3SiH (4.01 g, 15.4 mmol, 3.00 equiv) was added as a solution in CH_2Cl_2 (10 mL) at room temperature. Compound **15a** (1.69 g, 5.13 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (30 mL), cooled to −78 °C, and treated with the aforementioned freshly prepared mixture of $Ph_3SiH/B(ArF_5)_3$. The resulting mixture was allowed to slowly warm to room temperature and stirred for 72 h. The reaction was quenched by addition of sat. sodium bicarbonate solution (30 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was subjected to a silica gel column and eluted with MTBE/Hex 1:4→1:2 to give a colorless oil: 1.26 g (79%); R_f = 0.45 (MTBE/Hex 1:2); $[\alpha]_D^{24} = +40.4$ (c = 0.2 in EtOH); ^{1}H NMR (300 MHz, [D$_6$]DMSO [90 °C]): δ = 4.05 (q, J = 7.0 Hz, 2H), 3.78–3.43 (m, 2H), 2.27 (t, J = 7.0 Hz, 2H), 1.96–1.82 (m, 2H), 1.77–1.45 (m, 6H), 1.40 (s, 9H), 1.36–1.23 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H), 0.82 ppm (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR(75 MHz, [D$_6$]DMSO, 90 °C): δ = 172.1, 153.7, 77.55, 58.99, 58.88, 57.22, 34.47, 33.21, 28.63, 28.11, 27.71, 27.56, 20.97, 13.54, 9.59 ppm; IR (film): $\tilde{\nu}$ = 2966, 2934, 2875, 1736, 1692, 1478, 1461, 1455, 1391, 1366, 1324, 1301, 1252, 1174, 1104, 1049, 1030, 914, 873, 858, 772, 710, 701, 512, 459 cm^{-1}, HRMS (ESI): *m/z*: calcd for $C_{17}H_{32}NO_4$: 314.23258 $[M+H]^+$; found: 314.23260; calcd for $C_{17}H_{31}NO_4Na$: 336.21453 $[M+Na]^+$; found: 336.21447.

Compound 16a: This compound was synthesized along the lines of the synthesis of **16b** (for further information please see the Supporting Information). Yield: 96%; R_f = 0.33 (MTBE/Hex 1:5); $[\alpha]_D^{24} = +8.27$ (c = 1.09 in EtOH); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 90 °C): δ = 4.05 (q, J = 7.0 Hz, 2H), 3.75–3.58 (m, 2H), 2.27 (t, J = 7.0 Hz, 2H), 1.99–1.79 (m, 2H), 1.73–1.47 (m, 6H), 1.39 (s, 9H), 1.35–1.22 (m, 6H), 1.18 (t, J = 7.0 Hz, 3H), 0.87 ppm (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR(75 MHz, [D$_6$]DMSO, 90 °C) δ = 173.3, 154.8, 78.73, 60.16, 58.67, 58.32, 35.79, 35.66, 34.38, 29.84, 29.82, 28.90, 28.63, 22.67, 22.13, 14.71, 14.38 ppm; IR (film): $\tilde{\nu}$ = 3450, 3369, 2960, 2932, 2872, 1736, 1691, 1548, 1478, 1455, 1389, 1365, 1321, 1250, 1174, 1104, 1030, 939, 907, 858, 773, 745, 709, 700, 513, 460 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{35}NO_4$: 364.24583 $[M+Na]^+$; found: 364.24559; calcd for $C_{38}H_{70}N_2O_8$: 705.50244 $[2M+Na]^+$; found: 705.50190.

Compound 18: Diisopropylamine (350 μL, 2.48 mmol, 1.50 equiv) was dissolved in dry THF (8 mL) in a 25 mL round-bottomed flask

was and cooled to 0 °C. *n*BuLi (1.03 mL, 2.5 M in THF, 1.55 equiv) was added. The reaction mixture was then allowed to stir for 1 h at 0 °C, cooled to −78 °C, and treated with **14d** (253 mg, 1.65 mmol, 1.00 equiv). After 1.5 h, the reaction mixture was treated with PhSeBr (546 mg, 2.32 mmol, 1.40 equiv), stirred for 3 h, and subsequently quenched by addition of sat. sodium bicarbonate solution (6 mL). The crude suspension was warmed to room temperature and extracted with EtOAc (3×40 mL). The recombined organic layers were washed with brine (2×40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and treated with an excess of hydrogen peroxide (2.50 mL, 28.3 mmol, 17.1 equiv). After 1 h the reaction mixture was subsequently quenched by addition of distilled water (10 mL). Layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×20 mL). The recombined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuum, and subjected to a silica gel column. Elution with CH_2Cl_2 and MeOH (99:1→98:2) yielded the product as colorless oil: 160 mg (64%); R_f = 0.14 (CH_2Cl_2/MeOH = 98:2); $[\alpha]_D^{25}$ = −29.7° (*c* = 1.01 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.22 (dd, *J* = 10.0, 1.5, 1H), 5.88 (dd, *J* = 10.0, 3.0, 1H), 3.64 (m_c, 1H), 3.44 (m_c, 1H), 3.29 (m_c, 1H), 2.34 (m_c, 1H), 2.22 (m_c, 1H), 2.00 (m_c, 1H), 1.75 (m_c, 1H), 1.57 (m_c, 1H), 1.11 ppm (d, *J* = 7.0, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.5, 145.2, 125.3, 63.20, 44.39, 36.60, 32.62, 22.79, 17.06 ppm; IR (film): $\tilde{\nu}$ = 3464, 2966, 2933, 2877, 2359, 2341, 1724, 1660, 1597, 1459, 1386, 1371, 1351, 1324, 1286, 1267, 1206, 1160, 1135, 819, 756, 744, 680, 604, 505, 436 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_9H_{13}NO$: 175.08894 $[M+Na]^+$; found: 175.08909; calcd for $C_{18}H_{26}N_2O_2$: 325.18865 $[2M+Na]^+$; found.: 325.18839; GCMS (DB50S): 5.83 min *m/z*: 151.1 $[M]^{\cdot+}$.

General procedure (A) for the functionalization of indolizidinones: R^3MgX (3–5 equiv) was added to an ice-cold stirred solution of indolizidinone (1 equiv) in THF (0.06 M) and the resulting mixture was subsequently allowed to warm to room temperature. Sodium borohydride (2–3 equiv) and acetic acid (excess) were added at −10 or 0 °C and the resulting suspension stirred for 1 h at ambient temperatures. The resulting mixture was basified by addition of 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (5×10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum (400 mbar, 25 °C) to get a crude oil. Workup procedures and further details are given for each individual IBA in the Supporting Information.

Compound 1a: According to general procedure A 72.6 mg (80%) were obtained. R_f = 0.15 (Et_2O/Hex 1/10 on AlOx-TLC, free amine); $[\alpha]_D^{22}$ = +59.6 (*c* = 0.24 in EtOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 3.84–3.60 (m, 1H), 3.21–3.08 (m, 2H), 3.09–2.87 (m, 1H), 2.41–2.23 (m, 1H), 2.25–1.80 (m, 6H), 1.80–1.31 (m, 8H), 0.99 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR(100 MHz, [D$_6$]DMSO) δ = 66.59, 63.02, 49.76, 33.34, 28.16, 27.99, 27.27, 22.20, 18.84, 17.88, 13.71 ppm; ^{19}F NMR(280 MHz, $CDCl_3$): δ = −76.16 ppm; IR (film): $\tilde{\nu}$ = 3668, 3448, 3004, 2955, 2939, 2871, 2675, 2652, 2620, 2584, 2541, 2502, 2407, 1680, 1472, 1455, 1433, 1423, 1385, 1204, 1181, 1132, 1085, 1075, 1061, 1028, 1010, 987, 836, 802, 722, 708, 596, 517 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{11}H_{22}N$: 168.1747 $[M+H]^+$; found: 168.1748; calcd for $C_{24}H_{44}N_2O_2F_3$: 449.3349 $[2M+TFA]^+$; found: 449.3351; calcd for $C_{22}H_{44}N_2Cl$: 371.3188 $[2M+Cl]^+$; found: 371.3188; GCMS (DB50S-Slowramp/of the free amine): 6.61 min (124, 96, 70).

Compound 1b: According to general procedure A 64 mg (80%) were obtained. R_f = 0.20 (Et_2O/pentan 1:6 on AlO*x*-TLC (free amine)); ^{1}H NMR (300 MHz, CD_3OD): δ = 3.80–3.60 (m, 1H), 3.20–3.09 (m, 2H), 3.10–2.93 (m, 1H), 2.29 (dddd, *J* = 12.5, 9.5, 6.5, 3.0 Hz, 1H), 2.21–1.85 (m, 5H), 1.73–1.43 (m, 4H), 1.37 ppm (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ = 67.31, 60.47, 50.53, 31.62, 28.48, 27.83, 22.53, 18.78, 17.41 ppm; ^{19}F NMR (280 MHz, CD_3OD): δ = −77.36 ppm; IR (film): $\tilde{\nu}$ = 3445, 2954, 2932, 2852, 2728, 1771, 1732, 1683, 1458, 1420, 1383, 1260, 1201, 1181, 1131, 1081, 1035, 833, 800, 720, 706, 638, 596, 487, 447 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{36}N_2O_2F_3$: 393.27234 $[2M+TFA]^+$; found: 393.27243; GCMS (DB50S of the free amine): 4.30 min (124, 96, 139).

Compound 1c: According to general procedure A 139 mg (65%) were obtained. R_f = 0.30 (Et_2O/Hex 1:20 on AlOx-TLC, free amine); R_f = 0.30 (Et_2O/Hex 1:20 on AlOx-TLC, free amine), $[\alpha]_D^{22}$ = +18.5 (*c* = 0.54 in EtOH), ^{1}H NMR (300 MHz, CD_3OD): δ = 7.62–7.36 (m, 5H), 4.22–4.06 (m, 1H), 3.41–3.29 (m, 1H), 3.08–2.88 (m, 2H), 2.35–2.19 (m, 2H), 2.16–1.68 ppm (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ = 135.8, 129.7, 129.3, 127.6, 68.97, 68.44, 51.40, 31.38, 28.38, 27.64, 23.11, 18.68 ppm; ^{19}F NMR (280 MHz, CD_3OD): δ = −77.69 ppm; IR (film): $\tilde{\nu}$ = 3430, 3009, 2951, 2871, 2726, 2666, 2612, 2565, 2526, 1778, 1734, 1671, 1499, 1487, 1457, 1434, 1384, 1200, 1132, 1081, 1064, 1026, 1015, 831, 799, 758, 719, 702, 616, 594, 541 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{19}N$: 202.15903 $[M]^+$; found: 202.15906.

Compound 2a: According to general procedure A 150 mg (95%) were obtained. R_f = 0.24 (MTBE/Hex 1:10 on AlOx-DC, free amine); $[\alpha]_D^{20}$ = −71.7 (*c* = 1.08 in EtOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.59–3.47 (m, 1H), 3.31–3.25 (m, 1H), 3.21–3.08 (m, 1H), 2.32–2.18 (m, 1H), 2.16–2.03 (m, 2H), 1.99–1.87 (m, 3H), 1.84–1.73 (m, 2H), 1.71–1.56 (m, 4H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.41–1.29 (m, 4H), 1.03–0.83 ppm (m, 3H); ^{13}C{^{1}H} NMR(100 MHz, CD_3OD): δ = 71.19, 67.01, 63.73, 35.60, 33.50, 30.00, 29.62, 29.14, 28.32, 23.80, 23.34, 19.90, 14.19 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −77.70 ppm; IR (film): $\tilde{\nu}$ = 3438, 2961, 2938, 2875, 2696, 1780, 1739, 1670, 1457, 1428, 1384, 1312, 1202, 1173, 1079, 1036, 1015, 966, 829, 811, 798, 719, 705, 605, 595, 518, 487, 472 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{26}N$: 196.20598 $[M+H]^+$; found: 196.20607.

Compound 2b: According to general procedure A 568 mg (87%) were obtained. R_f = 0.60 (Et_2O/Pentan 1:5 on AlO*x*-DC (free amine)); $[\alpha]_D^{22}$ = −32.5 (*c* = 0.06 in EtOH), ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.69 (m, 1H), 2.43–2.23 (m, 2H), 1.59–0.58 (m, 14H), 0.22 (t, *J* = 7.5 Hz, 3H), 0.20 ppm (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 67.67, 66.91, 63.88, 32.79, 31.34, 31.14, 30.63, 29.44, 28.48, 25.03, 11.33, 10.89 ppm; ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = −78.51 ppm; IR (film): $\tilde{\nu}$ = 3408, 2955, 2921, 2872, 2850, 2660, 1714, 1659, 1651, 1461, 1434, 1383, 1261, 1203, 1178, 1106, 1049, 1012, 988, 969, 803, 727, 719, 637, 613, 552, 536, 520, 507, 496, 483, 470, 458, 451, 420, 406 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{12}H_{24}N$: 182.19033 $[M+H]^+$; found: 182.19038.

Compound 3a: According to general procedure A 74 mg (81%) were obtained. R_f = 0.10 (Hex/Et_2O = 10:1, ALO*x*, free amine); $[\alpha]_D^{24}$ = +39.5° (*c* = 0.81 in MeOH, d.r. > 99:1, > 99% *ee*); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.74 (ddd, *J* = 12.0, 9.0, 3.5 Hz, 1H); 3.05 (m_c, 1H); 2.96 (m_c, 1H); 2.83 (td, *J* = 11.5 Hz, *J* = 6.5 Hz, 1H); 2.36 (m_c, 1H); 2.19–1.87 (m, 5H); 1.77–1.61 (m, 2H); 1.61–1.38 (m, 2H); 1.37–1.22 (m, 2H); 1.03 (d, *J* = 6.5 Hz, 3H); 1.01 ppm (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ = 73.69, 66.60, 52.04, 35.93, 32.55, 29.50, 28.29, 26.02, 20.07, 18.34, 9.715 ppm; ^{19}F NMR (282 MHz, CD_3OD): δ = −77.45 ppm; IR (film): $\tilde{\nu}$ = 3437, 2971, 2940, 2887, 2771, 2721, 2676, 2623, 2572, 1778, 1732, 1672, 1462, 1436, 1385, 1202, 1143, 1086, 1073, 1053, 1006, 834, 799, 721, 707, 596 cm^{-1}; GCMS (DB50S): *m/z*: 167.1 $[M]^{\cdot+}$, 138.1 $[M-C_2H_5]^{\cdot+}$, 96.0 $[M-C_5H_{11}]^{\cdot+}$; HRMS (ESI): calcd for $C_{13}H_{22}F_3NO_2$: 168.17468 $[M-TFA]^+$; found: 168.17488; calcd for $C_{24}H_{44}F_3N_2O_2$: 449.33494 $[2M-TFA]^+$; found: 449.33454.

Compound 3b: According to general procedure A 98 mg (98%) were obtained. R_f = 0.16 (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{24}$ = +42.0° (*c* = 1.00 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 3.75

(ddd, $J=12.0$, 8.5, 3.5 Hz, 1H), 3.04 (m, 2H), 2.83 (td, $J=11.5$, 6.0 Hz, 1H), 2.36 (m_c, 1H), 2.18–1.80 (m, 5H), 1.77–1.62 (m, 2H), 1.59–1.21 (m, 5H), 1.03 (d, $J=6.5$ Hz, 3H), 0.98 ppm (t, $J=7.0$, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, CD_3OD): $\delta=73.60$, 65.28, 52.09, 35.90, 35.12, 32.55, 30.08, 28.32, 20.05, 19.45, 18.35, 14.08 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.24$ ppm; IR (KBr): $\tilde{\nu}=3435$, 2962, 2934, 2878, 2644, 2601, 2548, 1671, 1459, 1418, 1387, 1200, 1175, 1128, 1085, 1051, 997, 830, 798, 720 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{24}F_3NO_2$: 182.19033 $[M-TFA]^+$; found: 182.19035; GCMS (DB50S/of the free amine): 5.11 min *m/z*: 181.1 $[M]^{\cdot+}$, 138.1 $[M-C_3H_7]^{\cdot+}$, 96.0 $[M-C_6H_{13}]^{\cdot+}$.

Compound 3c: According to general procedure A 57 mg (71%) were obtained. $R_f=0.18$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{25}=+37.9^\circ$ ($c=1.00$ in MeOH); ^1H NMR (300 MHz, CD_3OD): $\delta=3.75$ (ddd, $J=12.0$, 9.0, 3.5 Hz, 1H), 3.12–2.96 (m, 2H), 2.83 (td, $J=11.5$, 6.5 Hz, 1H), 2.37 (m_c, 1H), 2.21–1.83 (m, 5H), 1.77–1.61 (m, 2H), 1.61–1.19 (m, 7H), 1.03 (d, $J=6.5$ Hz, 3H), 0.96 ppm (t, $J=7.0$ Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): $\delta=73.62$, 65.46, 52.08, 35.93, 32.79, 32.56, 30.14, 28.32, 28.28, 23.50, 20.05, 18.35, 14.13 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.37$ ppm; IR (film): $\tilde{\nu}=3423$, 2961, 2936, 2875, 2587, 2543, 1771, 1732, 1682, 1671, 1460, 1440, 1417, 1385, 1200, 1179, 1133, 1051, 829, 798, 719, 708, 597 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{26}F_3NO_2$: 196.20598 $[M-TFA]^+$; found: 196.20595; GCMS (DB50S/of the free amine): 5.43 min *m/z*: 195.1 $[M]^{\cdot+}$, 138.1 $[M-C_4H_9]^{\cdot+}$, 96.0 $[M-C_7H_{15}]^{\cdot+}$.

Compound 3d: According to general procedure A 72 mg (75%) were obtained. $R_f=0.10$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{25}=+47.1^\circ$ ($c=0.68$ in MeOH); ^1H NMR (300 MHz, CD_3OD): $\delta=5.82$ (ddt, $J=17.0$, 10.0, 6.5 Hz, 1H), 5.13–4.95 (m, 2H), 3.74 (ddd, $J=12.0$, 8.5, 3.5, 1H), 3.13–2.97 (m, 2H), 2.84 (td, $J=11.5$, 6.5 Hz, 1H), 2.35 (m_c, 1H), 2.21 −1.85 (m, 7H), 1.77–1.21 (m, 7H), 1.03 ppm (d, $J=6.5$, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): $\delta=138.95$, 115.84, 73.64, 65.32, 52.11, 35.89, 34.31, 32.54, 32.42, 30.13, 28.31, 25.40, 20.05, 18.35 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.69$ ppm; IR (film): $\tilde{\nu}=3077$, 2963, 2932, 1773, 1737, 1685, 1669, 1460, 1445, 1414, 1386, 1261, 1198, 1119, 1054, 914, 705, 662, 406 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{26}F_3NO_2$: 208.20598 $[M-TFA]^+$; found: 208.20596; GCMS (DB50S/of the free amine): 5.67 min *m/z*: 207.1 $[M]^{\cdot+}$, 138.1 $[M-C_5H_9]^{\cdot+}$, 96.0 $[M-C_8H_{15}]^{\cdot+}$.

Compound 3e: According to general procedure A 99 mg (99%) were obtained. $R_f=0.33$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{24}=+48.6^\circ$ ($c=0.99$ in MeOH); ^1H NMR (300 MHz, CD_3OD): $\delta=3.75$ (ddd, $J=11.5$, 9.0, 4.0 Hz, 1H), 3.11–2.98 (m, 2H), 2.91 (td, $J=11.5$, 6.5 Hz, 1H), 2.38 (dddd, $J=13.0$, 9.5, 6.5, 3.0 Hz, 1H), 2.22–1.95 (m, 4H), 1.87 (m_c, 1H), 1.77–1.15 (m, 14H), 0.99 (t, $J=7.0$ Hz, 3H), 0.93 ppm (t, $J=7.0$, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): $\delta=161.5$ (d, $J=37.0$ Hz), 117.5 (d, $J=290.0$ Hz), 72.79, 65.28, 52.07, 40.69, 35.14, 33.14, 30.05, 29.51, 29.21, 28.45, 23.78, 20.11, 19.45, 14.24, 14.09 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.74$ ppm; IR (film): $\tilde{\nu}=3439$, 2963, 2937, 2876, 2749, 2698, 2566, 1779, 1739, 1692, 1668, 1456, 1384, 1202, 1051, 993, 923, 832, 798, 720, 707, 594, 457 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{30}F_3NO_2$: 224.23728 $[M-TFA]^+$; found: 224.23719; GCMS (DB50S/of the free amine): 5.97 min *m/z*: 223.2 $[M]^{\cdot+}$, 180.1 $[M-C_3H_7]^{\cdot+}$.

Compound 3f: According to general procedure A 78 mg (75%) were obtained. $R_f=0.48$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{25}=+52.7^\circ$ ($c=1.02$ in MeOH); ^1H NMR (300 MHz, CD_3OD): $\delta=3.75$ (ddd, $J=11.5$, 9.0, 4.0 Hz, 1H), 3.14–2.97 (m, 2H), 2.91 (td, $J=11.5$, 6.5 Hz, 1H), 2.38 (dddd, $J=13.0$, 9.5, 6.5, 3.0 Hz, 1H), 2.23–1.82 (m, 5H), 1.78–1.14 (m, 18H), 1.04–0.82 ppm (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): $\delta=161.7$ (d, $J=36.5$ Hz), 117.6 (d, $J=290.0$ Hz), 72.79, 65.46, 52.05, 40.64, 33.14, 33.02, 32.64, 30.04, 29.52, 29.20, 28.43, 25.82, 23.77, 23.46, 20.11, 14.25, 14.25 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.63$ ppm; IR (film): $\tilde{\nu}=3431$, 2958, 2934, 2864, 2696, 2591, 1779, 1740, 1671, 1460, 1384, 1200, 1181, 1140, 1050, 832, 798, 720, 707, 595 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{34}F_3NO_2$: 252.26858 $[M-TFA]^+$; found: 252.26832; GCMS (DB50S/of the free amine): 6.54 min *m/z*: 251.2 $[M]^{\cdot+}$, 180.1 $[M-C_5H_{11}]^{\cdot+}$.

Compound 3g: According to general procedure A 103 mg (98%) were obtained. $R_f=0.39$ (Hex/Et_2O = 6:1, ALOx, free amine), $[\alpha]_D^{25}=+47.9^\circ$ ($c=1.00$ in MeOH), ^1H NMR (300 MHz, CD_3OD): $\delta=3.75$ (ddd, $J=12.0$, 9.0, 4.0 Hz, 1H), 3.11–2.97 (m, 2H), 2.91 (td, $J=11.5$, 6.5 Hz, 1H), 2.38 (dddd, $J=13.0$, 9.5, 6.5, 3.0 Hz, 1H), 2.23–1.84 (m, 5H), 1.77–1.14 (m, 20H), 0.99–0.87 ppm (m, 6H), $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): $\delta=72.79$, 65.47, 52.06, 40.66, 33.14, 33.08, 32.73, 30.15, 30.06, 29.52, 29.20, 28.44, 26.12, 23.78, 23.58, 20.11, 14.35, 14.24 ppm, ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.64$ ppm; IR (film): $\tilde{\nu}=3444$, 2958, 2934, 2863, 1779, 1741, 1671, 1457, 1436, 1384, 1201, 1176, 798, 720, 706, 638, 591, 447 cm^{-1}, HRMS (ESI): *m/z*: calcd for $C_{20}H_{36}F_3NO_2$ $[M-TFA]^+$: 266.28423; found: 266.28398; GCMS (DB50S/of the free amine): 6.78 min *m/z*: 265.3 $[M]^{\cdot+}$, 180.1 $[M-C_6H_{13}]^{\cdot+}$.

Compound 3h: According to general procedure A 76 mg (76%) were obtained. $R_f=0.45$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{25}=+41.7^\circ$ ($c=1.01$ in MeOH); ^1H NMR (300 MHz, CD_3OD): $\delta=5.81$ (dddd, $J=16.5$, 10.0, 8.0, 6.5 Hz, 1H), 5.32–5.18 (m, 2H), 3.77 (ddd, $J=11.5$, 9.0, 4.0 Hz, 1H), 3.19–2.99 (m, 2H), 2.93 (td, $J=11.5$, 6.5 Hz, 1H), 2.79–2.60 (m_c, 1H), 2.46–2.25 (m, 2H), 2.18–1.93 (m, 4H), 1.82–1.14 (m, 11H), 0.93 ppm (t, $J=7.0$ Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): $\delta=162.0$ (d, $J=35.5$ Hz), 133.0, 120.2, 117.8 (d, $J=291.0$ Hz), 73.08, 64.77, 52.26, 40.55, 37.66, 33.12, 30.17, 29.47, 29.20, 28.28, 23.77, 20.17, 14.24 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta=-77.67$ ppm, IR (film): $\tilde{\nu}=3445$, 2959, 2935, 2864, 2753, 2699, 2591, 1780, 1747, 1671, 1457, 1444, 1436, 1384, 1202, 1177, 995, 925, 834, 798, 720, 706, 641, 597, 454 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{28}F_3NO_2$: 222.22163 $[M-TFA]^+$; found: 222.22155; GCMS (DB50S/of the free amine): 5.96 min *m/z*: 221.2 $[M]^{\cdot+}$, 180.1 $[M-C_3H_5]^{\cdot+}$.

Compound 4: Predried $CeCl_3$ (380 mg, 1.55 mmol, 5.00 equiv) was heated in vacuum to 160 °C for 2 h. Dry THF (4.9 mL) was added at room temperature and the resulting yellow suspension subjected to an ultrasonic bath for 2 h. The reaction mixture was cooled to −78 °C, treated with propyl magnesium chloride (775 μL, 2.0 M in Et_2O, 5.00 equiv) and stirred for 2.5 h. Compound **18** (47 mg, 0.31 mmol, 1.00 equiv) in THF (0.8 mL) was added by syringe and the resulting mixture warmed to room temperature. After 17 h, the crude mixture was cooled to −10 °C and treated with sodium borohydride (35 mg, 923 μmol, 3.00 equiv) and glacial acetic acid (2 mL). The resulting suspension was stirred for 1 h at ambient temperatures. The mixture was basified by addition of 2 M NaOH (10 mL) and extracted with CH_2Cl_2 (4×50 mL), dried over Na_2SO_4, filtered, and concentrated in a vacuum (400 mbar, 25 °C) to give a crude oil. The crude product was subjected to an AlOx-column and eluted with Hex/Et_2O (15:1). Collected fractions were directly treated with an excess of TFA prior to concentrating the purified product in vacuum. The product was obtained as colorless oil: 47 mg (52%); $R_f=0.63$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{25}=+68.6^\circ$ ($c=1.31$ in MeOH), ^1H NMR (400 MHz, CD_3OD) $\delta=5.84$ (m_c, 1H), 5.77 (m_c, 1H), 5.77 (dt, $J=10.3$, 1.8, 1H), 3.93–3.79 (m, 2H), 3.24–3.06 (m, 2H), 2.59–2.43 (m, 2H), 2.22–2.01 (m, 2H), 1.90 (m_c, 1H), 1.76 (m_c, 1H), 1.68–1.51 (m, 2H), 1.45 (m_c, 1H), 1.14 (d, $J=7.0$, 3H), 1.02 ppm (t, $J=7.0$, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): $\delta=133.7$, 124.9, 70.51, 64.08, 52.93, 36.07, 34.39, 28.72, 20.98, 19.21, 17.82, 14.07 ppm, ^{19}F NMR (282 MHz, CD_3OD) $\delta=-77.60$ ppm; IR (film): $\tilde{\nu}=3437$, 2969, 2939, 2880, 2667, 2537, 1777, 1677, 1460,

1429, 1385, 1203, 1137, 1052, 836, 800, 769, 721, 708, 597, 518 cm^{-1}, HRMS (ESI): *m/z*: calcd for $C_{17}H_{28}F_3NO_2$: 180.17468 $[M-TFA]^+$; found: 180.17474; GCMS (DB50S/of the free amine): 5.05 min *m/z*: 179.2 $[M]^{\cdot+}$, 136.1 $[M-C_3H_7]^{\cdot+}$.

Compound 20a: Diisopropylamine (165 μL, 1.16 mmol, 1.50 equiv) was dissolved in dry THF (5 mL) and cooled to 0 °C. *n*BuLi (480 μL, 2.5 M in THF, 1.55 equiv) was added. The reaction mixture was then allowed to stir for 1 h at 0 °C, cooled to −78 °C, and treated with **X** (98 mg, 0.77 mmol, 1.00 equiv). After 1.5 h, the reaction mixture was treated with methyl iodide (72 μL, 1.16 mmol, 1.50 equiv), stirred for 2.5 h at −78 °C, and subsequently warmed to room temperature. The reaction mixture was quenched by addition of dist. water (5 mL) and extracted with EtOAc (3×20 mL). The recombined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product (d.r. = 2:1) was subjected to a silica gel column and eluted with CH_2Cl_2/MeOH (98:2) to give 12% (13 mg) of the major diastereomer and 88% (96 mg) of the diastereomeric mixture; $R_f = 0.50$ (CH_2Cl_2/MeOH = 98:2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (m_c, 1H); 2.93 (m_c, 1H); 2.89 (s, 3H); 2.34 (m_c, 1H); 2.00 (m_c, 1H); 1.88 (m_c, 1H); 1.25 (m_c, 1H); 1.20 (d, J = 7.0 Hz, 3H); 0.97 ppm (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 173.1$, 57.67, 39.08, 36.70, 29.04, 19.05, 17.78 ppm.

Compound 21a: This compound was synthesized along the lines of the synthesis of **20a**. Yield 97 mg (97%). The crude product (d.r. = 2:1) was subjected to a silica gel column and eluted with CH_2Cl_2/MeOH (98:2). A second silica gel column using MTBE/Hex (2:1)→CH_2Cl_2/MeOH (98:2) as the eluent yielded both diastereomers as colorless oils. $R_f = 0.21$ (MTBE); $[\alpha]_D^{24} = +45.4^\circ$ (c = 1.01 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.55$ (m_c, 1H); 3.42 (m_c, 1H); 3.00 (td, J = 10.5, 5.0 Hz, 1H); 2.35 (m_c, 1H); 2.11 (m_c, 1H); 2.01–1.85 (m, 2H); 1.71 (m_c, 1H); 1.48 (m_c, 1H); 1.36 (m_c, 1H); 1.22 (d, J = 7.0 Hz, 3H); 1.20 (m_c, 1H); 0.99 ppm (d, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 172.1$, 65.56, 45.35, 39.46, 36.77, 35.22, 32.35, 22.38, 18.11, 18.04 ppm; IR (film): $\tilde{\nu}$ = 3475, 2959, 2928, 2874, 1634, 1664, 1437, 1383, 1329, 1285, 1278, 1209, 1162, 892, 729, 637, 599, 588 cm^{-1}; GCMS (DB50S): 5.83 min *m/z* 167.1 $[M]^{\cdot+}$, 125.0 $[M-C_3H_6]^{\cdot+}$, 97.1 $[M-C_5H_{10}]^{\cdot+}$; HRMS (ESI): *m/z*: calcd for $C_{10}H_{17}NO$: 168.13829 $[M+H]^+$; found: 168.13840; calcd for $C_{20}H_{34}N_2O_2$: 335.26930 $[2M+H]^+$; found.: 335.26916; calcd for $C_{20}H_{34}N_2O_2$: 335.25125 $[2M+Na]^+$; found: 357.25142.

Compound 21b: This compound was synthesized along the lines of the synthesis of **20a**. Yield 97 mg (97%). The crude product (d.r. = 2:1) was subjected to a silica gel column and eluted with CH_2Cl_2/MeOH (98:2). A second silica gel column using MTBE/Hex (2:1)→CH_2Cl_2/MeOH (98:2) as the eluent yielded both diastereomers as colorless oils. $R_f = 0.17$ (MTBE); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.60–3.38 (m, 2H); 2.97 (m_c, 1H); 2.50 (m_c, 1H); 2.12 (m_c, 1H); 1.92 (m, 1H); 1.80–1.50 (m, 4H); 1.38 (m_c, 1H); 1.22 (d, J = 7.5 Hz, 3H); 0.99 ppm (d, J = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): $\delta = 172.8$, 65.32, 45.34, 37.73, 35.28, 32.48, 31.89, 22.45, 19.63, 18.39 ppm; GCMS (DB50S): 5.83 min *m/z*: 167.1 $[M]^{\cdot+}$, 125.0 $[M-C_3H_6]^{\cdot+}$, 97.1 $[M-C_5H_{10}]^{\cdot+}$; HRMS (ESI): *m/z* calcd for $C_{10}H_{17}NO$: 168.13829 $[M+H]^+$; found: 168.13840; calcd for $C_{20}H_{34}N_2O_2$: 335.26930 $[2M+H]^+$; found: 335.26916; calcd for $C_{20}H_{34}N_2O_2$: 335.25125 $[2M+Na]^+$; found: 357.25142.

Compound *epi*-5: According to general procedure A 107 mg (99%) were obtained. $R_f = 0.33$ (Hex/Et_2O = 6:1, ALOx, free amine); $[\alpha]_D^{24} = +25.6^\circ$ (c = 0.63 in MeOH); ^1H NMR (300 MHz, CD_3OD): δ = 3.71 (ddd, J = 11.5, 8.5, 3.5 Hz, 1H), 3.09 (m_c, 1H), 2.88 (td, J = 11.5, 6.5 Hz, 1H), 2.78 (dt, J = 10.5, 3.5 Hz, 1H), 2.35 (m_c, 1H), 2.21 −1.97 (m, 2H), 1.96–1.63 (m, 6H), 1.56–1.43 (m, 2H), 1.10 (m_c, 1H), 1.06–0.97 ppm (m, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): $\delta = 74.10$, 70.49, 52.37, 42.21, 35.29, 34.60, 31.80, 28.02, 20.43, 18.29, 18.00, 17.83, 14.40 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta = -77.73$ ppm; IR (film): $\tilde{\nu}$ = 2969, 2938, 2881, 2788, 2701, 2549, 1780, 1742, 1671, 1461, 1431, 1385, 1202, 1173, 833, 812, 798, 720, 706, 596 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{26}F_3NO_2$: 196.20598 $[M-TFA]^+$; found: 196.20597; calcd for $C_{30}H_{52}F_6N_2O_4$: 505.39754 $[2M-TFA]^+$; found: 505.39770; GCMS (DB50S/of the free amine): 5.34 min *m/z*: 152.1 $[M-C_3H_7]^{\cdot+}$, 110.0 $[M-C_6H_{13}]^{\cdot+}$.

Compound 5: According to general procedure A 32 mg (96%) were obtained. $R_f = 0.42$ (Hex/Et_2O = 6:1, ALOx, free amine); ^1H NMR (300 MHz, CD_3OD): $\delta = 3.70$ (m_c, 1H), 3.18 (dt, J = 11.5, 4.0 Hz, 1H), 3.05 (m_c, 1H), 2.81 (m_c, 1H), 2.32 (m_c, 1H), 2.14–1.97 (m, 2H), 1.90–1.26 (m, 9H), 1.05 (d, J = 7.5 Hz, 3H), 1.03–0.98 ppm (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): $\delta = 74.52$, 67.48, 52.90, 40.14, 32.02, 31.07, 30.45, 28.08, 19.89, 19.25, 18.33, 14.06, 12.21 ppm; ^{19}F NMR (282 MHz, CD_3OD): $\delta = -77.60$ ppm; HRMS (ESI): *m/z*: calcd for $C_{16}H_{26}F_3NO_2$ $[M-TFA]^+$: 196.20598; found.: 196.20597; calcd for $C_{30}H_{52}F_6N_2O_4$ $[2M-TFA]^+$: 505.39754; found: 505.39770; GCMS (DB50S/of the free amine): 5.37 min *m/z*: 152.1 $[M-C_3H_7]^{\cdot+}$, 110.0 $[M-C_6H_{13}]^{\cdot+}$.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft and the Evonik-Stiftung (graduate fellowship to F.A.) for the generous financial support of this work. Donation of chemicals from Evonik, Chemetall, and BASF is gratefully acknowledged. We would like to thank E. Koch for initial work, and J. Sieler for providing X-ray crystallographic data on compounds **12a** and **12b**.

Keywords: large-scale synthesis · Mannich reaction · natural products · organocatalysis · total synthesis

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[52] CCDC-905604 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Structure parameters for **12b**: $C_{18}H_{23}NO_4$, $M = 317.37$, $T = 130.1(10)$ K, orthorhombic space group: $P2_12_12_1$. Protons are omitted for clarity, excluding H4.

Received: October 18, 2013
Published online on January 16, 2014

