Synthesis of New Constrained Tricyclic Amines and Tricyclic Aminophosphonates Containing the 2-Azatricyclo[3.3.0.0^{3,6}]octane Skeleton

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A short and easy method for the preparation of the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton is described. The key step consists of an intramolecular ring closure of an *endo*-oriented amino group and an *exo*-oriented bromine atom. The amines were prepared through reduction of a suitable bicyclic imine. Nucleophilic addition of phosphite to the imines gave the corresponding aminophosphonates, which could be ring-closed to the tricyclic aminophosphonates through an analogous pathway.

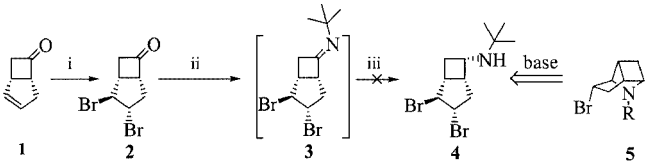
Introduction

The development of conformationally constrained molecules is of major importance in pharmaceutical and medicinal chemistry, as well as in the field of catalysis. In the medicinal field, constrained molecules are important in the study of the active centres of enzymes, the study of receptors, the folding of proteins etc.[1−4] In catalysis, conformationally locked molecules are used as ligands for metal-catalysed reactions.[5] Our group became interested in 2-azabicyclo[2.1.1]hexanes because their basic skeleton is that of 2,4-methanoproline.[6−8]

2,4-Methanoproline, a non-proteinogenic amino acid and the only natural compound so far known to contain the 2-azabicyclo[2.1.1]hexane skeleton, was isolated from the seeds of *Ateleia herbert smithii Pittier*.[9,10] The seeds of this tree are reported to be rejected by over 100 seed predators including numerous insects and rodents. After the isolation of 2,4-methanoproline in 1980, it was thought that this compound was responsible for the refusal of the seeds by predators. Because of this possible biological activity and the rare bicyclic skeleton, several routes to this class of compounds were developed in our laboratory.[6−8] Since antifeedant activity was detected in some methanoproline-related derivatives and because of our general interest in heterocyclic aminophosphonates, the approach to the constrained 2-azabicyclo[2.1.1]hexane skeleton has been applied to the even more constrained tricyclic 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton, which was prepared for the first time in our group.[11] The constrained 2-azatricyclo[3.3.0.0^{3,6}]octane chemistry will also be further evaluated for the synthesis of new ligands.

Results and Discussion

The initial plan for the preparation of the constrained 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton **5** started from the bicyclic ketone **1** (Scheme 1).[12] The bromination of this compound proceeds regioselectively, and the stereochemistry has been described in the literature.[13] The observed stereochemistry results from the *exo* attack of bromide on the bromonium complex formed in situ. After the preparation of ketone **2**, attempts to prepare the corresponding imine **3** were undertaken. The synthesis of imine **3** by the use of titanium(IV) chloride under standard conditions was evaluated, but always produced a complex reaction mixture. Under standard conditions, the ketone was mixed with the amine, and the titanium(IV) chloride (dissolved in a small amount of pentane) was added dropwise at 0 °C. The inverse addition was also evaluated. In this case the ketone was mixed with the titanium(IV) chloride, and the amine was added dropwise. This procedure sometimes gives better results, especially when the amine is causing side reactions, but in this specific case several side products were also formed together with imine **3**.



Scheme 1. Reagents and conditions: i) CCl_4, Br_2;[13] ii) $TiCl_4$, $NH_2C(CH_3)_3$; iii) 1.5 equiv. $LiAlH_4$, THF, room temp., overnight

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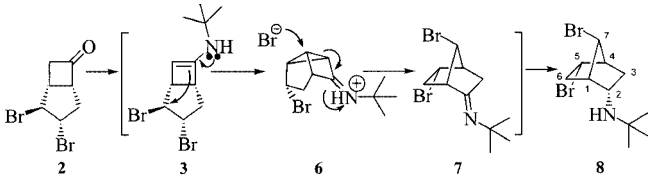
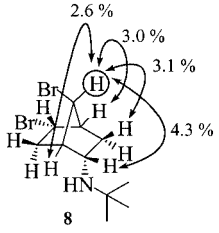
By performing the reaction at low temperature (−78 °C) for a short time (1 h), though, the imine **3** could be prepared. However, the compound proved to be very unstable. In addition, the spectral characterisation was very complex since the imine was formed as a mixture of (*E*) and (*Z*) isomers and some traces of side products were present. The imine was therefore directly reduced with lithium aluminium hydride after its preparation, to evaluate the ring closure to the tricyclic compound **5**. It was anticipated that hydride should preferentially attack from the *exo*-face, affording a mixture consisting mainly of the *endo*-oriented amine **4** and some *exo* derivative. Only the *exo*-oriented bromide atom should be intramolecularly substitutable by the *endo*-oriented amino group to provide the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton. Unfortunately, a very complex reaction mixture was obtained, and so the reaction was repeated at room temperature rather than at reflux in THF. This, though, also resulted in a mixture of compounds. In order to obtain information on the competing reactions, the mixture was purified by column chromatography, and only traces of what was believed to be amine **4** were obtained. Since only a small amount (26%) of this material was isolated, its structure and especially its stereochemistry were uncertain. However, the isolated compound proved to be fairly stable, since heating with 1 equivalent of sodium hydride overnight showed no reaction. The spectroscopic data still indicated that two bromine atoms and an N−H group were present. After thorough spectral analysis, the structure appeared to be the norbornene **8** (Scheme 2) instead of the desired amine **4**.

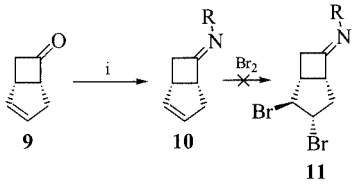


Scheme 2. Reagents and conditions: i) 0.6 equiv. $TiCl_4$, 3 equiv. $NH_2C(CH_3)_3$, THF, room temp., overnight; yield 26%



This structure was confirmed by DEPT, COSY, DFQCOSY, H-H COSY, H-C COSY, HMBC and NOE experiments. In the NOE experiment, the C*H*Br (C7) was irradiated and energy transfer to the two bridgehead protons, $CH_{3a}H_{3b}$ and the C*H*NH-*t*Bu protons was observed. Together with the other spectral evidence, this observation confirms the formation of **8**. Mechanistically, a rearrangement of the imine **3** took place during the formation of the imine. Reaction of the corresponding enamine could give rise to the tricyclic structure **6**, which undergoes a ring-expansion to **7**, which could subsequently be reduced by $LiAlH_4$ to afford the norbornene structure **8**. The imine **3** was probably also reduced but gave a complex reaction mixture. After purification by column chromatography, only the stable compound **8** was isolated. Several analogous ring-expansions of ketone **1** have been described, which supports the proposed reaction mechanism and the formation of the tricyclic intermediate **6**.[14−17]

To overcome these problems, an alternative pathway was evaluated. The imines **10** were prepared directly from the ketone **9** in good yields through the use of $TiCl_4$ as activating and drying agent (Scheme 3). However, direct bromination of imines **10** was also unsuccessful, so the reduction of the imines **10** was performed prior to the bromination.



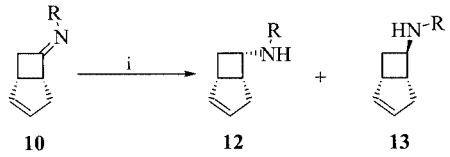
Scheme 3. Reagents and conditions: i) $TiCl_4$, NH_2R; a) R = isopropyl 95%; b) R = *n*-propyl 95%; c) R = *tert*-butyl 84%; d) R = isobutyl 89%

Lithium aluminium hydride was used to reduce the imines, and the corresponding amines were obtained as a mixture of diastereoisomers (Scheme 4). The yields of the reactions were good, but depending on the alkyl group, some separations of the diastereoisomers were problematic due to the high polarity and the high affinity of the amines for silica. This explains the moderate yields obtained for the pure diastereoisomers.

Table 1. Yields of the isolated amines **12** and **13** obtained after reduction of the corresponding imine **10**

R	Yield *cis* isomer **12**[a]	Yield of *trans* isomer **13**[a]
a: isopropyl	53%	not isolated
b: *n*-propyl	44%	not isolated
c: *tert*-butyl	84%	3%
d: isobutyl	66%	6%

[a] Yield after purification by flash chromatography.



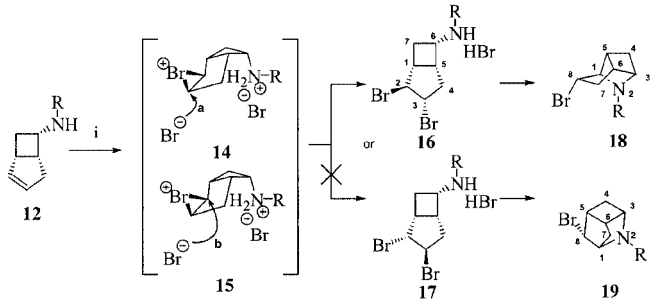
Scheme 4. Reagents and conditions: i) 1.5 equiv. $LiAlH_4$, 0 °C, overnight, room temp.

Because of the preferential *exo* attack of hydride, the *cis* isomer is always the major diastereoisomer formed, which is of interest since this is the only isomer that can give rise to a tricyclic skeleton. During the bromination, the amino group was first protected as a hydrobromide salt. In a

classical bromination reaction the amine is protected, bromine is added by use of HBr, and afterwards the acid is neutralised by washing of the reaction mixture with a saturated $NaHCO_3$ solution. In this particular case, the bromination was performed in dichloromethane and during the reaction a white powder precipitated from the reaction mixture. After the mixture had been stirred overnight at room temperature, some dry diethyl ether was added to improve the salt formation and the suspension was filtered and washed thoroughly with dry diethyl ether. This procedure applied for all the compounds described and the hydrobromides were isolated in good yields.

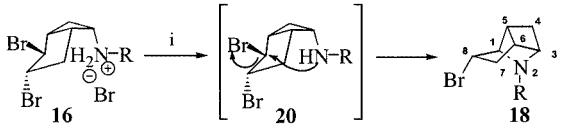
When the remaining filtrate was evaporated, only small amounts of starting material **12** could be detected but no end product **16** was present, which confirmed the complete precipitation of the product. The white isolated powder was the pure hydrobromide salt **16**, and no hydrobromide salt of the starting material was present. Although many hydrobromide and hydrochloride salts are hygroscopic and therefore difficult to handle, these compounds were very stable after drying under high vacuum. When kept in a closed vessel, they remain stable for months at room temperature without any degradation. This makes these compounds easy to handle, so they can be prepared on relatively large scales.

An important issue in this reaction is the regioselectivity of the bromination. After the initial formation of the bromonium ion, bromide can open the bromonium salt either by route **a** or by route **b**. Route **a** (Scheme 5) would normally be favoured since the bromide attacks from the less hindered side of the molecule, but an attack from the other side cannot be ruled out, so it was uncertain whether the isolated compound formed was **16** (route **a**) or **17** (route **b**).



Scheme 5. Reagents and conditions: i) 1.05 equiv. HBr (48% HBr in H_2O), 5 min 0 °C, 1.05 equiv. Br_2, about 12 h, room temp.; yield of **16**, a) R = isopropyl, yield 95%; b) R = *n*-propyl, yield 76%; c) R = *tert*-butyl, 80%; d) R = isobutyl, 81%.

In order to determine the stereochemical outcome of the bromination, the free amine **20** was prepared (Scheme 6) and all its protons were assigned by 2D-spectroscopy (H-H; H-C; HMBC) (see Exp. Sect.).



Scheme 6. Reagents and conditions: i) 1 equiv. NEt_3, ΔT (reflux overnight) (CH_3CN); yield **18**: a) R = isopropyl, yield 81%; b) R = *n*-propyl, yield 61%; c) R = *tert*-butyl, yield 72%; d) R = isobutyl, yield 84%

Unfortunately, no absolute conclusions concerning the stereochemistry could be drawn on the basis of the couplings constants.

The ring-closing step was therefore performed first, because two structurally different amines (**18** or **19**) would be obtained, verifying the stereochemistry of the bromination.

The amines **20** are not very stable and have to be used on the day of preparation, because degradation proceeds spontaneously at room temperature. The ring-closure was evaluated with several bases, including NaH, KO*t*Bu, LDA and triethylamine. In most cases a mixture of compounds was obtained, except in that of the weaker base triethylamine. Heating of the free amine **20** at reflux with 1 equivalent of triethylamine in acetonitrile for 14 h gave a pure ring-closed product (Scheme 6).

The tricyclic amines **18** could also be prepared by addition of 2 equivalents of triethylamine to the hydrobromide salts **16** and heating of the reaction mixture in acetonitrile at reflux overnight. The advantage of the latter method was that deprotection and ring-closure proceeded in one step, but the disadvantage was that small traces of side product were present together with the tricyclic compound. When the procedure was performed in two steps, no side products were formed. Only the *exo*-oriented bromide atom can be substituted intramolecularly to afford one of the tricyclic compounds **18** or **19**. The spectra were thoroughly analysed to determine the structure. Only the *tert*-butyl derivative is discussed, since the spectra of the other alkyl derivatives were analogous.

From some characteristic coupling constants in the H-H COSY spectrum, it was concluded that the product formed has the structure **18c**. The CHBr proton at C8 can be assigned without any doubt, and the other protons were assigned by starting from this proton. This CHBr proton clearly couples with the two protons of a CH_2 system (C7). In structure **19**, there is no reason to believe that this CHBr proton should couple with both protons of a CH_2 group. On the other hand, only one proton, probably H^{7b} (*exo*-oriented proton), should couple with H^6. This can be fully understood if a three-dimensional model is analysed. The tricyclic structure is highly constrained, and so a three-dimensional model gives a good prediction of the torsion angles. The torsion angle between H^{7a} (*endo*-oriented proton) and H^6 is almost 90°, which according to the Karplus equation should result in a coupling constant close to zero. Assuming structure **19**, no reason why H^{7a} and H^{7b} should not both couple with H^6 can be found.

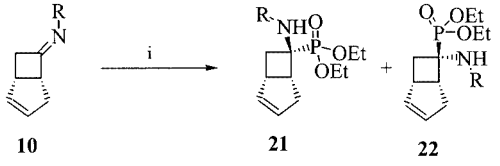
Another characteristic coupling is present due to the constrained structure. Proton H^3 couples with proton H^5 because of the perfect W-conformation, which is consistent with coupling data for the 2,4-methanoproline skeleton. All this information, together with the mass spectrum, which clearly shows the presence of only one bromine atom, suggested the conclusion that the compound formed is **18c**. To the best of our knowledge, the constrained 2-azatricyclo[3.3.0.$0^{3,6}$]octane skeleton has been obtained in our lab for the first time as an amino acid mimic.[11] The ring-closure was evaluated with different alkyl substituents on the N-atom and the tricyclic compounds were isolated in good yields.

Because of our interest in heterocyclic aminophosphonates as amino acid mimics, this pathway was further extended with phosphite as a nucleophile. After addition of the silylated phosphite to imine **10**, the amino phosphonates **21/22** could be prepared in moderate yield (Scheme 7). These compounds were obtained as a mixture of diastereoisomers (8:92) which were separated by column chromatography. The *endo*-oriented amino derivative **22** was the major diastereoisomer, due to the preferential *exo* attack of the nucleophile onto the imine **10**. The two diastereoisomers were separated because only the major diastereoisomer is of further interest for the preparation of tricyclic amines.

Table 2. Yields and reaction times for the preparation of the aminophosphonates **21** and **22**

R	*exo*-**22**/*endo*-**21**	Yield **21** + **22**	Reaction time (days)
a: isopropyl	93:7	58% (32%)[a]	13
b: *n*-propyl	85:15	70% (41%)[a]	7
c: *tert*-butyl	95:5	74% (30%)[a]	20
d: isobutyl	92:8	68% (45%)[a]	16

[a] Isolated yield of **22** after purification by flash chromatography.

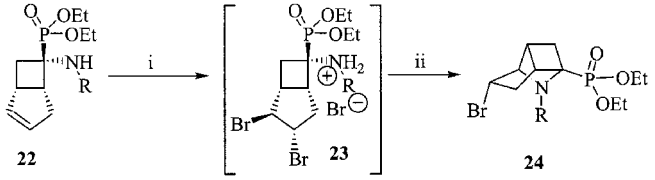


Scheme 7. Reagents and conditions; i) $Me_3SiOP(OEt)_2$, room temp.

The formation of the aminophosphonates was very slow (about 2 weeks at room temperature). The reaction could be accelerated by heating of the mixture in dichloromethane at reflux but this gave rise to the formation of side products. When the reaction was performed at room temperature, no side products were formed and an acid/base extraction was performed to remove the excess of phosphite. During the bromination step the free amine was protected as a hydrobromide salt by a procedure analogous to that described above (Scheme 8). Unfortunately, the hydrobromide salt **23** did not crystallise and could not be isolated, since it was very hygroscopic and therefore difficult to handle. However, the brominated compound **23** could be isolated after basic workup, but had to be used immediately in the next step as it was very unstable and degraded rapidly at room temperature.

Table 3. Yields of the tricyclic aminophosphonates **24**

R	Yield **24**
a: isopropyl	99%
b: *n*-propyl	88%
c: *tert*-butyl	82%
d: isobutyl	96%



Scheme 8. Reagents and conditions: i) 1.05 equiv. HBr (48% HBr in H_2O), 1.05 equiv. Br_2, extraction with satd. $NaHCO_3$; ii) 1.1 equiv. NEt_3, ΔT (reflux overnight, CH_3CN)

The final ring closure was performed by addition of 1.1 equivalent of triethylamine and heating of the mixture in acetonitrile for 14 h. The tricyclic compounds **24** were obtained as pure products in very good yield, and this procedure represents a straightforward synthesis of a series of highly constrained aminophosphonates.

Conclusion

The preparation of tricyclic amines and tricyclic aminophosphonates containing the 2-azatricyclo[3.3.0.$0^{3,6}$]octane skeleton through an intramolecular nucleophilic substitution reaction is described. In a short and convenient pathway (four steps from the bicyclic ketone **1**; six steps in total) the highly constrained skeleton could be obtained in moderate to good yield.

Experimental Section

General Remarks: ^1H NMR were recorded at 270 MHz (Jeol JNM EX270) with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were recorded at 67.8 MHz. Mass spectra were obtained with a mass spectrometer (70 eV) by use of direct inlet or GC-MS coupling (RSL, 200, 20m, capillary column, i.d. 0.53 mm, He carrier gas). Diethyl ether and THF were dried and distilled from sodium (benzophenone ketyl control). Dichloromethane was dried and distilled over calcium hydride.

Amine 8: $LiAlH_4$ (0.06 g, 1.1 equiv.) in dry THF (1 mL) solution was stirred at 0 °C under nitrogen, and a solution of imine **7** (0.45 g) in dry THF (8 mL) was slowly added. After the addition was complete, the reaction mixture was heated under reflux overnight. Water was added until gas evolution ceased. The mixture was filtered through celite and after evaporation of the solvent,

an oil was obtained and purified by column chromatography. Pure compound **8** (0.12 g, 26%) was obtained. R_f = 0.24 (hexane/EtOAc, 85:15). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 1.69 (dd, *J* = 13.7, *J* = 4.8 Hz, 1 H), 2.08 (ddd, *J* = 13.4, *J* = 4.6, *J* = 2.1 Hz, 1 H), 2.17 (ddd, *J* = 17.4, *J* = 4.4, *J* = 2.1 Hz, 1 H), 2.27 (br. s, 1 H), 2.45−2.46 (m, 1 H), 2.49−2.56 (m, 1 H), 3.17−3.24 (m, 1 H), 4.08 (s, 1 H), 4.75−4.82 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 30.15 (q), 30.58 (t), 35.00 (t), 50.08 (d), 50.48 (d), 50.80 (s), 50.85 (d), 52.42 (d), 55.08 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2966, 2867 cm^{-1}. ES MS: *m*/*z* = 328/326/324 [M^+ + H].

General Procedure for the Synthesis of the Imines 10: Primary amine (74.4 mmol, 4 equiv.) was added to a solution of the ketone **9** (18.6 mmol) in dry diethyl ether (25 mL), followed by dropwise addition at 0 °C of titanium(IV) chloride (0.6 equiv.) in pentane (5 mL). The reaction mixture was stirred overnight at room temperature, filtered, poured into 20 mL of sodium hydroxide (1 N), and extracted with diethyl ether. After drying ($MgSO_4$), filtration and evaporation of the solvent, imines **10** were obtained as oils of sufficient purity for further use (> 95% purity).

Imine 10a: Yield 95% (63:37). ^{1}H NMR (270 MHz, $CDCl_3$); major, *minor*, not assigned: δ = 1.06 (d, *J* = 6.3 Hz, 3 H), 1.10 (d, *J* = 6.3 Hz, 3 H), *1.11* (d, *J* = 6.3 Hz, 3 H), *1.15* (d, *J* = 6.3 Hz, 3 H), 2.50−2.64 (m, 3 H), 3.01 (dd, *J* = 16.2, *J* = 8.3 Hz, 1 H), *3.09* (ddd, *J* = 16.8, *J* = 8.6, *J* = 1.3 Hz, 1 H), 3.27−3.38 (m, 1 H), 3.36 (sept, *J* = 6.3 Hz, 1 H), *3.62* (qq, *J* = 6.3, *J* = 6.3 Hz, 1 H), 3.66−3.74 (m, 1 H), *5.78* (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): Major: δ = 23.58 (q), 23.90 (q), 37.20 (t), 39.71 (d), 41.06 (d), 51.54 (d), 51.93 (d), 132.00 (d), 132.08 (d), 173.12 (s) ppm. Minor: 22.67 (q), 22.73 (q), 37.09 (t), 39.17 (d), 44.76 (d), 49.22 (d), 50.24 (d), 130.65 (d), 133.28 (d), 171.48 (s) ppm. IR (NaCl): $\tilde{\nu}$ = 1706 cm^{-1}. EI MS (70 eV): *m*/*z* = 149 (3) [M^+], 107 (11), 83 (46), 80 (20), 79 (34), 67 (20), 66 (100).

Imine 10b: Yield 95% (76:24). ^{1}H NMR (270 MHz, $CDCl_3$); major, *minor*, not assigned: δ = 0.88 (t, *J* = 7.4 Hz, 3 H), *0.94* (t, *J* = 7.4 Hz, 3 H), 1.60 (sext, *J* = 7.5 Hz, 2 H), 2.50−2.59 (m, 1 H), 2.50−2.60 (m, 1 H), 2.65−2.71 (m, 1 H), 2.99 (dd, *J* = 16.3, *J* = 8.4 Hz, 1 H), 3.13 (t, *J* = 6.6 Hz, 2 H), 3.30−3.40 (m, 1 H), 3.66−3.76 (m, 1 H), 5.80 (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): Major: δ = 11.91 (q), 23.76 (t), 37.18 (t), 39.68 (d), 41.44 (d), 52.08 (d), 53.58 (t), 131.95 (d), 133.12 (d), 175.25 (s) ppm; Minor: 12.06 (q), 24.12 (t), 36.33 (t), 39.08 (d), 44.82 (t), 49.38 (d), 54.27 (t), 130.67 (d), 133.01 (d), 173.72 (s) ppm. IR (NaCl): $\tilde{\nu}$ = 1709 cm^{-1}. EI MS (70 eV): *m*/*z* = 149 (4) [M^+], 107 (4), 83 (29), 80 (13), 79 (38), 77 (13), 66 (100), 65 (9), 40 (51).

Imine 10c: Only the spectra of the major isomer are given. Yield 84% (94:6). ^{1}H NMR (270 MHz, $CDCl_3$): Major: δ = 1.18 (s, 9 H), 2.53−2.63 (m, 2 H), 2.73 (dt, *J* = 15.9, *J* = 2.9 Hz, 1 H), 3.16−3.28 (m, 1 H), 3.25−3.35 (m, 1 H), 3.65−3.75 (m, 1 H), 5.78 (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): Major: δ = 30.04 (q), 37.70 (t), 40.25 (d), 45.48 (t), 53.78 (d), 56.14 (s), 132.20 (d), 133.26 (d), 172.11 (s) ppm. IR (NaCl): $\tilde{\nu}$ = 1704 cm^{-1}. EI MS (70 eV): *m*/*z* = 163 (2) [M^+], 107 (10), 66 (25), 57 (100).

Imine 10d: Yield 89% (79:21). ^{1}H NMR (270 MHz, $CDCl_3$); major, *minor*, not assigned: δ = 0.88 (d, *J* = 6.6 Hz, 6 H), *0.92* (d, *J* = 7.3 Hz, 3 H), *0.95* (d, *J* = 6.9 Hz, 3 H), 1.89 (sept, *J* = 6.6 Hz, 1 H), 2.49−2.75 (m, 1 H), 2.56−2.60 (m, 1 H), *2.55−2.60* (m, 1 H), 2.61−2.75 (m, 1 H), 2.97 (dd, *J* = 15.5, *J* = 8.6 Hz, 1 H), 2.98 (d, *J* = 6.6 Hz, 2 H), 3.30−3.38 (m, 1 H), 3.70−3.77 (m, 1 H), 5.78 (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): Major: δ = 20.65 (q), 20.68 (q), 29.47 (d), 37.25 (t), 39.60 (d), 41.62 (t), 52.08 (d), 59.86 (t), 132.02 (d), 133.13 (d), 175.29 (s) ppm. Minor: 20.79 (q), 20.88 (q), 29.69 (d), 36.24 (t), 38.99 (d), 44.91 (t), 49.42 (d), 60.22 (t), 130.67 (d), 133.20 (d), 175.18 (s) ppm. IR (NaCl): $\tilde{\nu}$ = 1709 cm^{-1}. EI MS (70 eV): *m*/*z* = 163 (5) [M^+], 107 (10), 91 (12), 86 (64), 84 (100), 66 (88), 57 (97).

General Procedure for the Preparation of Amines 12 and 13

Reduction of Imines 10: $LiAlH_4$ (0.46 g, 1.5 equiv.) was stirred in dry diethyl ether (10 mL) at 0 °C and under a N_2 atmosphere in an oven-dried 100-mL flask. A solution of imine **10c** (1.25 g, 1 equiv.) in dry diethyl ether (20 mL) was added dropwise at this temperature. The suspension was stirred overnight at room temperature and a few drops of water were added until the gas evolution ceased. The mixture was filtered through a mixture of $MgSO_4$ and celite (1:1) and washed thoroughly with dry dichloromethane. The filtrate was evaporated, and amine **12c** (1.19 g) was obtained as an oil (yield 94%). The two diastereoisomers were separated by column chromatography and the major isomer was obtained in 84% yield. The minor isomer was isolated in 3% yield.

Amine 12a: R_f = 0.27 (EtOAc/MeOH/NEt_3, 98:1:1) Yield 53%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 5.9 Hz, 3 H), 1.02 (d, *J* = 6.27 Hz, 3 H), 1.34 (dddd, *J* = 12.5, *J* = 6.5, *J* = 5.4, *J* = 0.7 Hz, 1 H), 2.44−2.50 (m, 2 H), 2.57−2.66 (m, 1 H), 2.68 (sept, *J* = 6.3 Hz, 1 H), 2.97−3.05 (m, 1 H), 3.05−3.16 (m, 1 H), 3.59 (td, *J* = 8.0, *J* = 8.1 Hz, 1 H), 5.78 (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 22.70 (q), 23.36 (q), 32.04 (t), 38.22 (t), 40.47 (d), 40.92 (d), 46.34 (d), 49.72 (d), 131.84 (d), 135.70 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2963 cm^{-1}. EI MS (70 eV): *m*/*z* = no [M^+], 136 (25), 85 (100), 70 (90).

Amine 12b: R_f = 0.09 (EtOAc/MeOH, 96:4). Yield 44%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.33−1.41 (m, 1 H), 1.48 (hex, *J* = 7.4 Hz, 2 H), 2.41 (t, *J* = 7.4 Hz, 2 H), 2.42−2.49 (m, 2 H), 2.61 (dddd, *J* = 12.3, *J* = 9.0 Hz, 7.9, *J* = 1.7 Hz, 1 H), 3.01−3.09 (m, 1 H), 3.10−3.16 (m, 1 H), 3.41−3.51 (m, 1 H), 5.79 (s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 11.99 (q), 23.47 (t), 31.90 (t), 37.54 (t), 40.36 (d), 40.75 (d), 49.83 (t), 52.54 (d), 131.84 (d), 135.69 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3303, 2957 cm^{-1}. EI MS (70 eV): *m*/*z* = 151 (2) [M^+], 150 (5), 136 (8), 122 (13), 108 (7), 91 (26), 85 (84), 70 (77), 57 (16), 56 (100).

Amine 13c: R_f = 0.13 (EtOAc/MeOH/NEt_3, 96:3:1). Yield 3%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 1.89 (ddd, *J* = 11.5, *J* = 8.6, *J* = 8.6 Hz, 1 H), 2.15−2.23 (m, 1 H), 2.25−2.36 (m, 1 H), 2.50−2.56 (m, 1 H), 2.57−2.63 (m, 1 H), 3.05−3.13 (m, 2 H), 5.71−5.73 (m, 1 H), 5.77−5.81 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 30.01 (q), 39.03 (t), 39.19 (t), 40.16 (d), 47.74 (d), 50.76 (s), 54.54 (d), 130.53 (d), 134.61 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3048 cm^{-1}. EI MS (70 eV): *m*/*z* = 165 (3) [M^+], 150 (15), 108 (17), 99 (71), 94 (31), 84 (100), 57 (21), 43 (39).

Amine 12c: R_f = 0.34 (EtOAc/MeOH/NEt_3, 96:3:1). Yield 84%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.05 (s, 9 H), 1.23−1.41 (m, 1 H), 2.39 (dd, *J* = 17.5, *J* = 10.2 Hz, 1 H), 2.59−2.71 (m, 2 H), 2.89−2.97 (m, 1 H), 3.06−3.16 (m, 1 H), 3.68 (ddd, *J* = 8.6, *J* = 8.4, *J* = 8.4 Hz, 1 H), 5.78 (s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 29.96 (q), 32.13 (t), 40.16 (d), 41.11 (t), 43.81 (d), 46.56 (d), 50.51 (s), 132.00 (d), 135.45 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3048, 1606 cm^{-1}. EI MS (70 eV): *m*/*z* = 165 (4) [M^+], 150 (12), 108 (15), 99 (73), 94 (25), 84 (100), 57 (27), 43 (36).

Amine 12d: R_f = 0.3 (EtOAc/hexanes, 90:10). Yield 66%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.33−1.41 (m, 1 H), 1.70 (sept, *J* = 6.6 Hz, 1 H), 2.26 (d, *J* = 6.6 Hz, 2 H), 2.36−2.50 (m, 2 H), 2.54−2.67 (m, 1

H), 3.03−3.18 (m, 2 H), 3.39−3.49 (m, 1 H), 5.79 (br. s, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.83 (q), 20.90 (q), 28.72 (d), 31.82 (t), 37.43 (t), 40.31 (d), 40.66 (d), 52.61 (d), 55.90 (t), 131.86 (d), 135.65 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2954 cm^{-1}. EI MS (70 eV): *m*/*z* = 165 (3) [M$^+$], 164 (2), 150 (3), 122 (23), 99 (65), 91 (26), 84 (37), 56 (100), 44 (32).

Amine 13d: R_f = 0.1 (EtOAc/hexanes, 90:10). Yield 6%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.6 Hz, 6 H), 1.71 (sept, *J* = 6.6 Hz, 1 H), 1.89 (ddd, *J* = 11.6 Hz, 8.4, *J* = 8.4 Hz, 1 H), 2.13 (ddd, *J* = 11.5, *J* = 7.8, *J* = 2.7 Hz, 1 H), 2.23−2.40 (m, 3 H), 2.55−2.61 (m, 2 H), 2.90−2.98 (m, 1 H), 3.10−3.16 (m, 1 H), 5.69−5.72 (m, 1 H), 5.78−5.82 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.81 (q), 28.54 (d), 35.56 (t), 39.42 (t), 40.09 (d), 45.48 (d), 55.35 (t), 60.25 (d), 130.55 (d), 134.59 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3295, 2954 cm^{-1}. EI MS (70 eV): *m*/*z* = 165 (3) [M$^+$], 164 (3), 150 (6), 122 (25), 99 (63), 93 (26), 91 (30), 84 (35), 56 (100), 44 (37).

Bromination of Amines 12 to Obtain Ammonium Salts 16: A solution of amine **12** (3.3 mmol) was dissolved in dry dichloromethane (5 mL) and cooled to 0 °C in an ice bath. A concentrated hydrobromic acid solution (1.02 equiv.; 3.96 mmol; 48% HBr in H_2O) was added and the mixture was stirred vigorously for 15 minutes. After this time, bromine (3.96 mmol, 1.02 equiv.) dissolved in a small amount of dichloromethane was added, and the reaction was warmed to room temperature overnight. During this period a white powder was formed, and dry diethyl ether (10 mL) was added to improve the yield of the formed salt. The suspension was filtered and the hydrobromide **16** was washed thoroughly with dry diethyl ether and dried under high vacuum. These salts are only slightly hygroscopic and are very stable in a closed vessel when stored at room temperature. The free amine can be generated from these salts by dissolving in a saturated $NaHCO_3$ solution and performing an extraction with dichloromethane. The organic layer was dried with $MgSO_4$ overnight. The $MgSO_4$ was filtered off and after evaporation of the solvent the pure amine **20** was obtained as an oil. These compounds are less stable and should preferably be used on the day of their preparation.

Ammonium Salt 16a: White powder, m.p. 182.3−182.9 °C (degradation). Yield 95%. ^{1}H NMR (270 MHz, CD_3OD): δ = 1.32 (d, *J* = 6.6 Hz, 3 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 2.35−2.53 (m, 2 H), 2.56−2.67 (m, 1 H), 2.83−2.99 (m, 2 H), 3.23−3.32 (m, 1 H), 3.37 (sept, *J* = 6.6 Hz, 1 H), 3.94−4.03 (m, 1 H), 4.24−4.37 (m, 2 H) ppm. ^{13}C NMR (68 MHz, CD_3OD): δ = 19.23 (q), 19.86 (q), 35.00 (t), 36.32 (t), 43.04 (d), 43.90 (d), 47.96 (d), 51.72 (d), 56.53 (d), 60.56 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3436, 2924 cm^{-1}. ES MS: *m*/*z* = 314/312/310 (100) [M$^+$].

Ammonium Salt 16b: White powder, m.p. 156.1−158.5 °C (degradation temperature). Yield 76%. ^{1}H NMR (270 MHz, CD_3OD): δ = 1.02 (t, *J* = 7.4 Hz, 3 H), 1.72 (hex, *J* = 7.4 Hz, 2 H), 2.33−2.52 (m, 2 H), 2.64 (ddd, *J* = 13.7, *J* = 8.4, *J* = 6.4 Hz, 1 H), 2.81 (m, 4 H), 3.19−3.28 (m, 1 H), 3.30−3.22 (m, 1 H), 3.85−3.94 (m, 1 H), 4.25−4.38 (m, 2 H) ppm. ^{13}C NMR (68 MHz, CD_3OD): δ = 11.32 (q), 20.52 (t), 33.84 (t), 36.05 (t), 42.41 (d), 43.47 (d), 56.51 (d), 60.56 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3430, 2903 cm^{-1}. ES MS: *m*/*z* = 314/312/310 (100) [M$^+$].

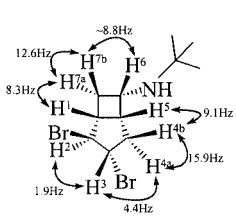
Ammonium Salt 16c: White powder, m.p. 197.1−200 °C (degradation). Yield 80%. ^{1}H NMR (270 MHz, DMSO): δ = 1.26 (s, 9 H), 2.34−2.47 (m, 2 H), 2.55−2.69 (m, 1 H), 2.73−2.81 (m, 2 H), 3.09−3.16 (m, 1 H), 3.92−3.97 (m, 1 H), 4.29−4.36 (m, 2 H), 8.56−8.64 (m, 2 H) ppm. ^{13}C NMR (68 MHz, DMSO): δ = 25.43 (q), 34.86 (t), 34.95 (t), 41.81 (d), 41.90 (d), 43.20 (d), 56.37 (d), 57.29 (s), 60.52 (d) ppm. IR (KBr): $\tilde{\nu}$ = 2765, 3430 cm^{-1}. ES MS: *m*/*z* = 328/326/324 (100) [M$^+$].

Ammonium Salt 16d: White powder, m.p. 167−168 °C (degradation). Yield 81%. ^{1}H NMR (270 MHz, DMSO): δ = 0.94 (d, *J* = 6.3 Hz, 3 H), 0.96 (d, *J* = 6.3 Hz, 3 H), 1.97 (non, *J* = 6.6 Hz, 1 H), 2.37−2.79 (m, 7 H), 3.05−3.10 (m, 1 H), 3.75−3.81 (m, 1 H), 4.31−4.34 (m, 2 H) ppm. ^{13}C NMR (68 MHz, DMSO): δ = 19.91 (q), 20.05 (q), 25.18 (d), 32.22 (t), 33.94 (t), 40.16 (d), 40.65 (d), 48.27 (d), 51.91 (t), 56.24 (d), 60.54 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3427 cm^{-1}. ES MS: *m*/*z* = 328/326/324 (100) [M$^+$].

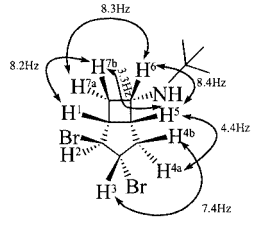
Amine 20a: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H), 1.94 (br. s, 1 H), 2.21 (ddd, *J* = 12.8, *J* = 8.0, *J* = 8.0 Hz, 1 H), 2.33 (ddd, *J* = 16.0, *J* = 3.5, *J* = 3.5 Hz, 1 H), 2.56−2.85 (m, 3 H), 2.98 (ddd, *J* = 8.3, *J* = 8.3, *J* = 7.6 Hz, 1 H), 3.25−3.36 (m, 1 H), 3.47 (ddd, *J* = 8.6, *J* = 8.4, *J* = 8.4 Hz, 1 H), 4.49 (s, 1 H), 4.66−4.71 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 22.77 (q), 23.40 (q), 34.41 (t), 35.94 (t), 44.06 (d), 45.25 (d), 46.00 (d), 46.59 (d), 57.34 (d), 60.77 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2818 cm^{-1}. ES MS: *m*/*z* = 314/312/310 (100) [M$^+$ + 1].

Amine 20b: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.50 (hex, *J* = 7.4 Hz, 2 H), 2.21 (ddd, *J* = 13.0, *J* = 7.4, *J* = 7.3 Hz, 1 H), 2.33 (ddd, *J* = 16.2, *J* = 3.1, *J* = 3.1 Hz, 1 H), 2.45 (t, *J* = 7.3 Hz, 2 H), 2.55−2.68 (m, 1 H), 2.78 (ddd, *J* = 16.4, *J* = 8.5, *J* = 7.9 Hz, 1 H), 2.94−3.03 (m, 1 H), 3.28−3.41 (m, 2 H), 4.50 (s, 1 H), 4.67−4.71 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 11.93 (q), 23.20 (t), 34.20 (t), 35.33 (t), 43.97 (d), 44.64 (d), 48.88 (t), 49.09 (d), 57.30 (d), 66.81 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2957 cm^{-1}. ES MS: *m*/*z* = 314/312/310 (100) [M$^+$ + 1].

Amine 20c: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 1.69 (br. s, 1 H), 2.20 (ddd, *J* = 12.6 Hz, 8.2 Hz, 8.2 Hz, 1 H), 2.44 (ddd, *J* = 15.9, *J* = 4.2, *J* = 4.2 Hz, 1 H), 2.58−2.78 (m, 2 H), 2.92 (ddd, *J* = 8.2, *J* = 8.2, *J* = 7.8 Hz, 1 H), 3.23−3.55 (m, 1 H), 3.51 (ddd, *J* = 8.4, *J* = 8.3, *J* = 8.3 Hz, 1 H), 4.44 (d, *J* = 0.7 Hz, 1 H), 4.61, 4.66 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 29.88 (q), 34.70 (t), 38.56 (t), 43.95 (d), 44.13 (d), 47.26 (d), 50.91 (s), 57.11 (d), 61.01 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2964 cm^{-1}. ES MS: *m*/*z* = 328/326/324 (100) [M$^+$ + 1], 272/270/268 (20) [M$^+$ − *t*Bu]. The coupling constants of **20c** were determined by HOMO experiments.



20c



20c

Amine 20d: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 1.74 (non, *J* = 6.6 Hz, 1 H), 2.17−2.40 (m, 4 H), 2.56−2.68 (m, 1 H), 2.80 (ddd, *J* = 16.2, *J* = 8.9, *J* = 7.4 Hz, 1 H), 2.95−3.03 (m, 1 H), 3.25−3.41 (m, 2 H), 4.50 (s, 1 H), 4.67−4.71 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.79 (q), 20.90 (q), 28.54 (d), 34.16 (t), 35.15 (t), 44.02 (d), 44.55 (d), 49.29 (d), 55.02 (t), 57.38 (d), 60.70 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2955 cm^{-1}. ES MS: *m*/*z* = 328/326/324 (100) [M$^+$ + 1].

Synthesis of Tricyclic Amines 18: The free amines **20** (0.64 mmol) were dissolved in acetonitrile (25 mL), and triethylamine (0.64 mmol, 1 equiv.) was added. After addition of these reagents, the reaction mixture was heated under reflux overnight. The mixture was washed with a saturated $NaHCO_3$ solution and extracted with dichloromethane. After drying of the organic phase with $MgSO_4$, the solution was filtered and the solvent was removed under reduced pressure. The *endo*-*N*-alkyl-8-bromo-2-azatricyclo[3.3.0.0^{3,6}]octanes were obtained as almost pure compounds. All products were isolated as liquids.

***endo*-8-Bromo-*N*-isopropyl-2-azatricyclo[3.3.0.0^{3,6}]octane (18a):** Yield 81%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.3 Hz, 3 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.67 (ddd, *J* = 8.3, *J* = 2, *J* = 2 Hz, 1 H), 1.80 (dd, *J* = 13.2, *J* = 7.6 Hz, 1 H), 1.87 (d, *J* = 8.3 Hz, 1 H), 1.95 (ddd, *J* = 13.2, *J* = 9.6, *J* = 4.9 Hz, 1 H), 2.31−2.33 (m, 1 H), 2.54−2.64 (m, 1 H), 2.60 (sept, *J* = 6.3 Hz, 1 H), 3.07 (br. s, 1 H), 3.63 (br. d, *J* = 6.6 Hz, 1 H), 4.10 (ddd, *J* = 9.3, *J* = 7.5, *J* = 1.7 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.41 (q), 23.38 (q), 29.99 (t), 32.87 (t), 45.10 (d), 49.22 (d), 51.36 (d), 54.02 (d), 63.79 (d), 67.89 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2971 cm^{-1}. EI MS (70 eV): *m*/*z* = 229/231 (26) [M$^+$], 216/214 (20), 150 (100), 108 (48), 91 (38), 80 (22), $C_{10}H_{16}BrN$ (230.1): calcd. C 52.19, H 7.01; found C 52.51, H 7.09.

***endo*-8-Bromo-*N*-propyl-2-azatricyclo[3.3.0.0^{3,6}]octane (18b):** Yield 61%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H), 1.59−1.7 (m, 2 H), 1.65−1.75 (m, 1 H), 1.84 (dd, *J* = 13.4, *J* = 7.4 Hz, 1 H), 1.96 (dd, *J* = 14.2, *J* = 8.6 Hz, 1 H), 1.98 (dd, *J* = 13.4, *J* = 9.4 Hz, 1 H), 2.37−2.39 (m, 1 H), 2.41−2.50 (m, 2 H), 2.60−2.63 (m, 1 H), 2.94 (br. s, 1 H), 3.48 (br. d, *J* = 6.6 Hz, 1 H), 4.10 (ddd, *J* = 9.3, *J* = 7.5, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.09 (q), 22.35 (t), 30.78 (t), 33.24 (t), 45.55 (d), 52.24 (d), 54.02 (d), 54.68 (t), 66.79 (d), 69.20 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2934 cm^{-1}. ES MS (70 eV): *m*/*z* = 231/229 (20) [M$^+$], 202/200 (16), 150 (100), 122 (17), 91 (21). $C_{10}H_{16}BrN$ (230.1): calcd. C 52.19, H 7.01; found C 52.07, H 7.13.

***endo*-8-Bromo-*N*-*tert*-butyl-2-azatricyclo[3.3.0.0^{3,6}]octane (18c):** Yield 72%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 1.69 (br. d, *J* = 8.3 Hz, 1 H), 1.74 (dd, *J* = 12.6, *J* = 7.9 Hz, 1 H), 1.81 (d, *J* = 7.9 Hz, 1 H), 1.87 (ddd, *J* = 12.6, *J* = 8.9, *J* = 4.6 Hz, 1 H), 2.25−2.26 (m, 1 H), 2.52−2.55 (m, 1 H), 3.43 (br. s, 1 H), 3.64 (br. d, *J* = 6.6 Hz, 1 H), 4.06 (dt, *J* = 8.5, *J* = 1 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 30.37 (q), 32.90 (t), 34.54 (t), 44.92 (d), 52.27 (s), 52.58 (d), 54.91 (d), 63.61 (d), 64.08 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2968 cm^{-1}. EI MS (70 eV): *m*/*z* = 245/243 (13) [M$^+$], 230/228 (20), 164 (21), 108 (100), 91 (32), 80 (17). $C_{11}H_{18}BrN$ (244.2): calcd. C 54.11, H 7.43; found C 54.09, H 7.44.

***endo*-8-Bromo-*N*-isobutyl-2-azatricyclo[3.3.0.0^{3,6}]octane (18d):** Yield 84%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.67−1.98 (m, 5 H), 2.16 (dd, *J* = 12.2, *J* = 7.9 Hz, 1 H), 2.36 (dd, *J* = 12.3, *J* = 6.1 Hz, 1 H), 2.33−2.35 (m, 1 H), 2.56−2.60 (m, 1 H), 2.85 (br. s, 1 H), 3.37 (d, *J* = 6.6 Hz, 1 H), 4.07 (ddd, *J* = 9.2, *J* = 7.6, *J* = 1.3 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 21.11 (t), 21.33 (t), 27.76 (d), 31.11 (t), 33.39 (t), 45.52 (d), 52.24 (d), 54.81 (d), 61.51 (t), 70.60 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 2974 (br.) cm^{-1}. EI MS (70 eV): *m*/*z* = 245/243 (16) [M$^+$], 202/200 (60), 164 (100), 120 (16), 108 (35). $C_{11}H_{18}BrN$ (244.2): calcd. C 54.11, H 7.43; found C 54.25, H 7.32.

Route to Tricyclic Aminophosphonates 24

Aminophosphonate 22a: Triethylamine (1.61 g, 1.2 equiv., 16 mmol) and diethyl phosphite (2.04 g, 1.1 equiv., 1.4 mmol) were stirred in dry dichloromethane (40 mL) at 0 °C for 30 minutes in a 100 mL flask (under N_2). Trimethylsilyl chloride (1.75 g) was added dropwise by syringe. After the mixture had been stirred for another 30 minutes, imine **10a** (1.96 g, 1.0 equiv., 13 mmol) was added dropwise. The reaction was completed after 13 days. The reaction mixture was extracted twice with aqueous HCl solution (2 N, 100 mL). The water layer was basified with NaOH solution (4 N) and extracted with dichloromethane (3 × 70 mL). The combined organic phases were dried with $MgSO_4$ overnight. After filtration and evaporation of the solvent, the product (2.20 g) was obtained (32 mmol, 58% yield) as a mixture of diastereoisomers (92:8 from ^{31}P NMR). Separation of the isomers was performed by flash chromatography. The major compound (R_f = 0.39) was obtained as an oil in a yield of 55%. The other isomer was isolated as an oil in a yield of 6% (R_f = 0.19). R_f = 0.39 (EtOAc/MeOH/hexanes, 96:2:2). Major: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.3 Hz, 3 H), 1.04 (d, *J* = 6.3 Hz, 3 H), 1.35 (dt, *J* = 7.0, *J* = 1.7 Hz, 6 H), 1.79 (ddd, *J* = 17.9, *J* = 12.6, *J* = 5.2 Hz, 1 H), 2.40 (ddd, *J* = 17.5, *J* = 9.4, *J* = 1.5 Hz, 1 H), 2.63−2.79 (m, 1 H), 2.88 (dddd, *J* = 17.5, *J* = 5.4, *J* = 2.7, *J* = 2.6 Hz, 1 H), 3.10−3.30 (m, 3 H), 4.18 (dq, *J* = 7.3, *J* = 1.0 Hz, 2 H), 4.21 (dq, *J* = 7.3, *J* = 1.0 Hz, 2 H), 5.72−5.76 (m, 1 H), 5.80−5.82 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.63 (q × d, $J_{C,P}$ = 6.1 Hz), 24.78 (q), 25.35 (q), 32.51 (t × d, $J_{C,P}$ = 4.9 Hz), 36.08 (t), 40.49 (d × d, $J_{C,P}$ = 6.1 Hz), 41.85 (d × d, $J_{C,P}$ = 2.4 Hz), 45.29 (d × d, $J_{C,P}$ = 3.6 Hz), 56.14 (s × d, $J_{C,P}$ = 148.3 Hz), 62.02 (t × d, $J_{C,P}$ = 8.0 Hz), 62.07 (t × d, $J_{C,P}$ = 8.0 Hz), 132.54 (d), 133.91 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3470, 1244 cm^{-1}. EI MS (70 eV): *m*/*z* = 287 (11) [M$^+$], 244 (15), 221 (68), 206 (31), 178 (17), 177 (26), 150 (37), 138 (18), 111 (53), 108 (23), 107 (23), 106 (24), 84 (49), 83 (100), 65 (35). ^{31}P NMR (109 MHz, $CDCl_3$): δ = 29.86 ppm.

Aminophosphonate 21a: R_f, = 0.19 (EtOAc/MeOH/hexanes, 96:2:2). **Minor:** ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.3 Hz, 6 H), 1.30 (dt, *J* = 7.1, *J* = 1.7 Hz, 6 H), 2.03−2.14 (m, 1 H), 2.33 (dt, *J* = 13.2, *J* = 5.0 Hz, 1 H), 2.55 (dd, *J* = 17.7, *J* = 10.4 Hz, 1 H), 2.87−3.01 (m, 1 H), 2.91−3.01 (m, 1 H), 3.29 (dsept, *J* = 6.4, *J* = 1.2 Hz, 1 H), 3.35−3.48 (m, 1 H), 4.04−4.16 (m, 4 H), 5.68−5.71 (m, 1 H), 5.76−5.79 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.58 (q × d, $J_{C,P}$ = 6.2 Hz), 25.03 (q), 25.39 (q), 35.81 (t × d, $J_{C,P}$ = 2.5 Hz), 38.27 (t), 40.75 (d × d, $J_{C,P}$ = 10.9 Hz), 45.05 (d × d, $J_{C,P}$ = 4.8 Hz), 45.97 (d × d, $J_{C,P}$ = 3.7 Hz), 60.42 (s × d, $J_{C,P}$ = 138.0 Hz), 61.08 (t × d, $J_{C,P}$ = 7.3 Hz), 61.75 (t × d, $J_{C,P}$ = 8.5 Hz), 132.16 (d) ppm. IR (NaCl): $\tilde{\nu}$ = 3437, 1234 cm^{-1}. ES MS: *m*/*z* = 150 (100) [M$^+$ + 1]. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 26.19 ppm.

Diethyl (6-Propylamino)bicyclo[3.2.0]hept-2-en-6-yl)phosphonate (22b): R_f = 0.38 (EtOAc/MeOH/PET, 90:2:8). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.35 (t, *J* = 7.1 Hz, 6 H), 1.63 (ddd, *J* = 16.8, *J* = 12.4, *J* = 4.8 Hz, 1 H), 2.45 (ddd, *J* = 17.4, *J* = 9.3, *J* = 1.7 Hz, 1 H), 2.50−2.70 (m, 2 H), 2.65−2.75 (m, 1 H), 2.77 (dddd, *J* = 17.2, *J* = 5.2, *J* = 2.6, *J* = 2.4 Hz, 1 H), 3.10−3.25 (m, 1 H), 3.20−3.30 (m, 1 H), 4.18 (dq, *J* = 6.9, *J* = 6.9 Hz, 4 H), 5.76 (br. d, *J* = 5.2 Hz, 1 H), 5.81 (br. d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 11.73 (q), 16.67 (q × d, $J_{C,P}$ = 6.1 Hz), 24.28 (t), 32.26 (t × d, $J_{C,P}$ = 4.9 Hz), 36.05 (t), 40.20 (d), 40.29 (d), 46.34 (t), 56.23 (s × d, $J_{C,P}$ = 148.3 Hz), 61.96 (t × d, $J_{C,P}$ = 7.3 Hz), 134.14 (d), 132.59 (d) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 29.86 ppm. IR (NaCl): $\tilde{\nu}$ = 3470, 1241 cm^{-1}. EI MS (70 eV): *m*/*z* = 287 (2) [M$^+$], 221 (50), 192 (24), 175 (52), 150 (39), 138 (41), 111 (39), 96 (30), 91 (100), 84 (50), 83 (76), 65 (32), 43 (31).

Diethyl (6-*tert*-Butylamino)bicyclo[3.2.0]hept-2-en-6-yl)phosphonate (22c): R_f = 0.35 (EtOAc 100%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 1.35 (t, *J* = 6.6 Hz, 6 H), 1.97 (ddd, *J* = 20.7, *J* = 13.0, *J* = 5.7 Hz, 1 H), 2.39 (dd, *J* = 17.0, *J* = 9.7 Hz, 1 H), 2.66−2.81 (m, 1 H), 3.00 (br. d, *J* = 18.6 Hz, 1 H), 3.10−3.22 (m, 2 H), 4.10−4.23 (m, 4 H), 5.71−5.73 (m, 1 H), 5.81−5.83 (m, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.54 (d, *J* = 6.1 Hz), 37.66 (s), 40.65 (d, *J* = 3.7 Hz), 43.40 (d, *J* = 3.6 Hz), 51.34 (s), 55.39 (d, *J* = 147.7 Hz), 61.89 (d, 8.6 Hz), 62.20 (d, *J* = 7.9 Hz), 132.74 (s), 133.74 (s) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 30.96 ppm. IR (NaCl): ṽ = 3436, 1225 cm^{-1}. ES MS: *m*/*z* = 302 (15) [M$^+$ + 1], 164 (100).

Diethyl (6-Isobutylamino)bicyclo[3.2.0]hept-2-en-6-yl)phosphonate (22d): R_f = 0.33 (EtOAc 100%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 6 H), 1.35 (t, *J* = 6.6 Hz, 6 H), 1.55−1.70 (m, 2 H), 2.37−2.54 (m, 3 H), 2.58−2.72 (m, 1 H), 2.79−2.86 (m, 1 H), 3.17−3.28 (m, 2 H), 4.17 (dq, *J* = 7.8, *J* = 1.7 Hz, 2 H), 4.19 (dq, *J* = 7.1, *J* = 1.7 Hz, 2 H), 5.76−5.82 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.66 (q), 20.52 (q), 20.65 (q), 29.76 (d), 32.13 (t), 35.45 (t), 40.32 (d), 51.90 (t), 56.04 (s × d, $J_{C,P}$ = 146.5 Hz), 61.82 (t × d, *J* = 6.1 Hz), 132.59 (d), 134.01 (d) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 29.97 ppm. IR (NaCl): ṽ = 3468, 1241 cm^{-1}. ES MS: *m*/*z* = 302 (17) [M$^+$ + 1], 164 (100).

Aminophosphonate 23a: This compound was prepared in the same way as used to prepare the brominated amines **20**. The product was isolated as an oil. This product proved to be very unstable and had to be used in the next step after its preparation. $R_{f'}$ = 0.30 (100% EtOAc). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.3 Hz, 3 H), 1.08 (d, *J* = 6.0 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 6 H), 2.33 (ddd, *J* = 20.2, *J* = 12.9, *J* = 7.5 Hz, 1 H), 2.50−2.62 (ddd, *J* = 15.3, *J* = 9.1, *J* = 7.3 Hz, 1 H), 2.70−2.87 (m, 2 H), 3.02−3.12 (m, 1 H), 3.19−3.34 (m, 2 H), 4.19 (dq, *J* = 7.5, *J* = 1.7 Hz, 2 H), 4.21 (dq, *J* = 7.0, *J* = 1.7 Hz, 2 H), 4.34 (dd, *J* = 4.9, *J* = 2.5 Hz, 1 H), 4.47 (ddd, *J* = 4.9, *J* = 6.6, *J* = 6.7 Hz, 1 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.59 (q × d, $J_{C,P}$ = 6.1 Hz), 24.13 (q), 24.65 (q), 34.58 (t × d, $J_{C,P}$ = 6.1 Hz), 36.33 (t), 43.93 (d × d, $J_{C,P}$ = 2.4 Hz), 45.38 (d × d, $J_{C,P}$ = 3.6 Hz), 46.07 (d), 53.93 (s × d, $J_{C,P}$ = 150.1 Hz), 56.46 (d), 60.50 (d), 62.25 (t × d, $J_{C,P}$ = 8.5 Hz), 62.38 (t × d, *J* = 8.5 Hz) ppm. IR (NaCl): ṽ = 3311, 1247 cm^{-1}. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 28.98 ppm.

Diethyl *endo*-(8-Bromo-2-isopropyl-2-azatricyclo[3.3.0.0^{3,6}]octan-3-yl)phosphonate (24a): This compound was prepared in the same way as used for the *endo*-*N*-alkyl-8-bromo-2-azatricyclo[3.3.0.0^{3,6}]octanes **18**. The product was isolated as a liquid oil. Yield 92%. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.6 Hz, 3 H), 1.30 (d, *J* = 6.6 Hz, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 1.88 (dd, *J* = 13.5, *J* = 8.1 Hz, 1 H), 1.91−2.01 (m, 1 H), 2.06 (d, *J* = 8.2 Hz, 1 H), 2.14 (dd, *J* = 8.2, *J* = 1.0 Hz, 1 H), 2.61 (d, *J* = 4.0 Hz, 1 H), 2.66 (d, *J* = 22.1 Hz, 1 H), 3.50 (sept, *J* = 6.6 Hz, 1 H), 3.55 (br. s, 1 H), 4.04−4.18 (m, 1 H, HBr), 4.06−4.30 (m, 4 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.52 (q × d, $J_{C,P}$ = 7.3 Hz), 21.92 (q), 26.34 (q), 32.60 (t), 35.69 (t × d, $J_{C,P}$ = 7.3 Hz), 44.68 (d × d, *J* = 25.6 Hz), 49.45 (d), 53.85 (d), 55.94 (d), 61.37 (t × d, $J_{C,P}$ = 6.1 Hz), 62.33 (t × d, $J_{C,P}$ = 6.1 Hz), 65.32 (d × d, $J_{C,P}$ = 14.7 Hz), 71.36 (s × d, $J_{C,P}$ = 175.8 Hz) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 20.77 ppm. IR (NaCl): ṽ = 1243 cm^{-1}. EI MS (70 eV): *m*/*z* = 365/367 (1) [M$^+$], 286 (43), 216 (27), 188 (34), 148 (24), 106 (100), 79 (21). $C_{14}H_{25}BrNO_3P$: calcd. C 45.91, H 6.88; found C 45.75, H 6.79.

Diethyl *endo*-(8-Bromo-2-propyl-2-azatricyclo[3.3.0.0^{3,6}]oct-3-yl)phosphonate (24b): ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.3 Hz, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.56−1.76 (m, 2 H), 1.85 (dd, *J* = 13.7, *J* = 7.9 Hz, 1 H), 2.03 (ddd, *J* = 13.7, *J* = 9.5, *J* = 4.5 Hz, 1 H), 2.09 (dd, *J* = 8.3, *J* = 2.1 Hz, 1 H), 2.22 (dd, *J* = 8.3, *J* = 1.3 Hz, 1 H), 2.37 (ddd, *J* = 12.5, *J* = 8.3, *J* = 4.6 Hz, 1 H), 2.64 (dd, *J* = 7.9, *J* = 3.3 Hz, 1 H), 2.68 (d, *J* = 28.4 Hz, 1 H), 3.05 (br. s, 1 H), 3.07 (ddd, *J* = 12.0, *J* = 8.6, *J* = 8.6 Hz, 1 H), 4.05−4.12 (m, 1 H), 4.07−4.21 (m, 2 H), 4.14−4.33 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.09 (q), 16.51 (q × d, $J_{C,P}$ = 3.6 Hz), 16.58 (q × d, $J_{C,P}$ = 6.2 Hz), 22.59 (t), 32.60 (t), 32.96 (t × d, $J_{C,P}$ = 6.1 Hz), 44.75 (d × d, $J_{C,P}$ = 25.7 Hz), 53.24 (d), 53.31 (t), 55.58 (d), 61.41 (t × d, $J_{C,P}$ = 6.1 Hz), 62.87 (t × d, $J_{C,P}$ = 6.1 Hz), 70.60 (s × d, $J_{C,P}$ = 175.7 Hz), 71.30 (d × d, $J_{C,P}$ = 14.7 Hz) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 20.88 ppm. IR (NaCl): ṽ = 1248 cm^{-1}. ES MS: *m*/*z* = 380/382 (100) [M$^+$ + 1]. $C_{14}H_{25}BrNO_3P$: calcd. C 45.91, H 6.88; found C 45.80, H 6.84.

Diethyl *endo*-(8-Bromo-2-*tert*-butyl-2-azatricyclo[3.3.0.0^{3,6}]oct-3-yl)phosphonate (24c): ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 1.34 (t, *J* = 7.0 Hz, 3 H), 1.34 (s, 9 H), 1.86−2.02 (m, 2 H), 2.07 (dd, *J* = 8.3, *J* = 1.3 Hz, 1 H), 2.15 (d, *J* = 8.3 Hz, 1 H), 2.59 (d, *J* = 18.6 Hz, 1 H), 2.67−2.71 (m, 1 H), 3.75−3.76 (m, 1 H), 4.03−4.09 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.40 (q × d, $J_{C,P}$ = 6.1 Hz), 16.58 (q × d, $J_{C,P}$ = 6.2 Hz), 30.87 (q), 32.72 (t), 36.37 (t × d, $J_{C,P}$ = 7.4 Hz), 43.84 (d × d, $J_{C,P}$ = 25.6 Hz), 54.05 (s), 54.70 (d), 57.27 (d × d, $J_{C,P}$ = 2.4 Hz), 61.71 (d × d, $J_{C,P}$ = 7.4 Hz), 61.80 (t × d, $J_{C,P}$ = 4.8 Hz), 66.23 (d × d, $J_{C,P}$ = 15.8 Hz), 70.59 (s × d, $J_{C,P}$ = 174.5 Hz) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 22.65 ppm. IR (NaCl): ṽ = 1247 cm^{-1}. ES MS: *m*/*z* = 380/382 (25) [M$^+$ + 1], 323/325 (100). $C_{15}H_{27}BrNO_3P$: calcd. C 47.38, H 7.16; found C 47.40, H 7.15.

Diethyl *endo*-(8-Bromo-2-isobutyl-2-azatricyclo[3.3.0.0^{3,6}]oct-3-yl)phosphonate (24d): ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H), 1.79−1.94 (m, 1 H), 1.86−1.96 (m, 1 H), 1.94−2.02 (m, 1 H), 2.09 (dd, *J* = 8.3, *J* = 2.0 Hz, 1 H), 2.23 (dd, *J* = 12.3, *J* = 2.8 Hz, 1 H), 2.62−2.65 (m, 1 H), 2.69−2.78 (m, 1 H), 2.71 (d, *J* = 8.3 Hz, 1 H), 3.01 (s, 1 H), 4.05−4.12 (m, 1 H), 4.06−4.29 (m, 2 H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 16.54 (q × d, $J_{C,P}$ = 3.7 Hz), 16.59 (q × d, $J_{C,P}$ = 2.4 Hz), 21.13 (q), 21.24 (q), 27.31 (d), 32.43 (t), 32.89 (t × d, $J_{C,P}$ = 6.1 Hz), 44.77 (d × d, $J_{C,P}$ = 25.6 Hz), 53.00 (d), 55.47 (d), 59.87 (t), 61.23 (t × d, $J_{C,P}$ = 6.1 Hz), 62.44 (t × d, $J_{C,P}$ = 4.9 Hz), 70.52 (s × d, $J_{C,P}$ = 177.1 Hz), 72.33 (d × d, $J_{C,P}$ = 14.7 Hz) ppm. ^{31}P NMR (109 MHz, $CDCl_3$): δ = 20.88 ppm. IR (NaCl): ṽ = 1250 cm^{-1}. ES MS: *m*/*z* = 380/382 (100) [M$^+$ + 1]. $C_{15}H_{27}BrNO_3P$: calcd. C 47.38, H 7.16; found C 47.29, H 7.07.

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