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Utilizing terpene derivatives in the synthesis of annulated terpene-imidazoles with application in the nitroaldol reaction

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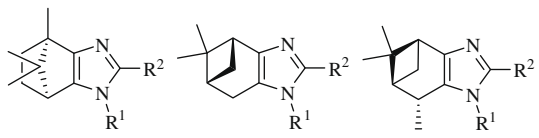
ABSTRACT

Two classes of terpene derivatives (diketones and monoximes) were condensed into annulated terpene-imidazoles using two general methods. Method A, involving the condensation of terpene diketones and aldehydes, gave lower yields than Method B, which employed terpene monoximes and amines. The mechanism of Method B is discussed. Using both methods, overall 11 new imidazole ligands were synthesized and fully characterized. The molecular structures of the side product **16** and intermediate **4b** were also characterized by X-ray analysis. Regarding **1a**, *N*-methylation and subsequent *ortho*-lithiation and quenching with diphenylphosphinechloride were proven. The synthesized ligands were tested in the Henry reaction providing reaction times 24–72 h and enantioselectivities up to 32% especially for the pyridine 2-substituted ligands **1c**, **2c**, **3b** and *N*,*P*-ligand **17**.

1. Introduction

Naturally occurring monoterpenes and their incorporation into more complex heterocyclic molecules such as pyridines, bipyridines, terpyridines, phenanthrolines or imines have attracted the efforts of organic chemists over the past two decades.[1–7] Annulation of the monoterpene moiety renders a unique class of chiral N,N-coordinating ligands that are, upon complexation of a suitable transition metal, widely applied as catalysts in various asymmetric reactions (e.g. cyclopropanation, allylic substitution/oxidation, hydrosilylation or Henry reaction).[1–4,7] The most common terpene motives come from monocyclic menthane or bicyclic terpenes such as carane, pinane or bornane as well as from their derivatives. Whereas the synthesis of six-membered heterocycles annulated with terpene moieties seems to have been proven, five-membered analogues remain a challenge. Very few examples of terpene-annulated five-membered (di)azoles are currently reported in the literature. A multistep reaction of glyoxalmonohydrazone and camphor enolate affords camphor-annulated pyrrole derivatives.[8] Camphor-pyrazole derivatives were synthesized by the reaction of 3-hydroxymethyl or 3-formylcamphor with semicarbazides or hydrazines.[9,10] Camphor-annulated pyrazoles were also applied in the synthesis of chiral 2,6-di-*N*-pyrazolylpyridines.[11] However, no attempts to prepare terpene-imidazoles have so far been reported in the literature and, therefore, we focused, herein, on the derivatives bearing a terpene unit fused directly with an imidazole ring (Fig. 1). Terpenes such as (1*R*)-(+)-camphor, (1*S*)-(−)-β-pinene and (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol were used as readily available and inexpensive starting materials. Hydroxyketones,[12–14] bromoketones,[15,16] diketones[17–19] or α-nitrosoketones (monoximes)[20] as suitable 1,2-bifunctional electrophiles (in our case generated from terpenes) and aldehydes or amines as counterparts are the most often employed starting compounds in such condensations leading to an imidazole ring. To the best of our knowledge, no attention has been paid to the compounds proposed in Figure 1 and, therefore, we herein report the synthesis, properties and full spectroscopic characterization of imidazoles **1–3** featuring three different annulated terpene moieties and five (hetero)aromatic substituents at the 2-position as well as their preliminary application as optically active N-ligands in the Henry reaction.



1 **2** **3**

R^1 = H, CH_3
R^2 = Ph, 2-(PPh_2)Ph, 1-naphthalene, 2-pyridine, 2-furane, 2-thiophene

Figure 1. Annulated terpene-imidazoles.

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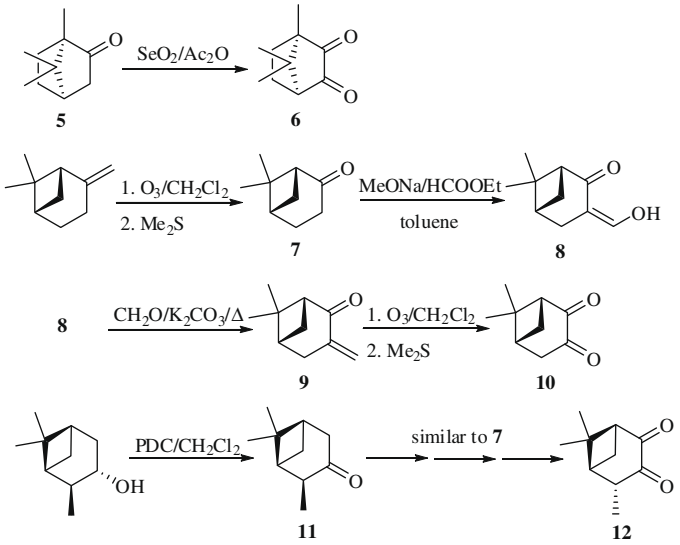
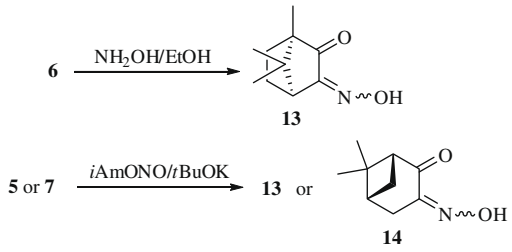
2. Result and discussion

In order to prepare precursors suited for condensation into an imidazole, the appropriate terpene diketones were synthesized. The (1*R*)-(+)-camphor was directly oxidized by SeO_2 to furnish camphorquinone **6** in a nearly quantitative yield.[21] Starting from the available (1*S*)-(−)-β-pinene involving ozonolysis followed by reduction with dimethylsulfide, (+)-nopinone **7** could be isolated in 80% yield.[22] A subsequent formylation using ethylformate[23] and treatment with formaldehyde[24] afforded α,β-unsaturated ketone **9** in 62% overall yield. The repeated ozonolysis and dimethylsulfide reduction of **9** afforded the desired PinDione[25] **10** in 70% yield. A similar three-step reaction sequence applied to (+)-isopinocampheon **11**, prepared by the oxidation[26] of the commercially available (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol, gave the third desired diketone **12** (Scheme 1) in 61% overall yield with a reversed absolute configuration of the methyl group at C-4.[4]



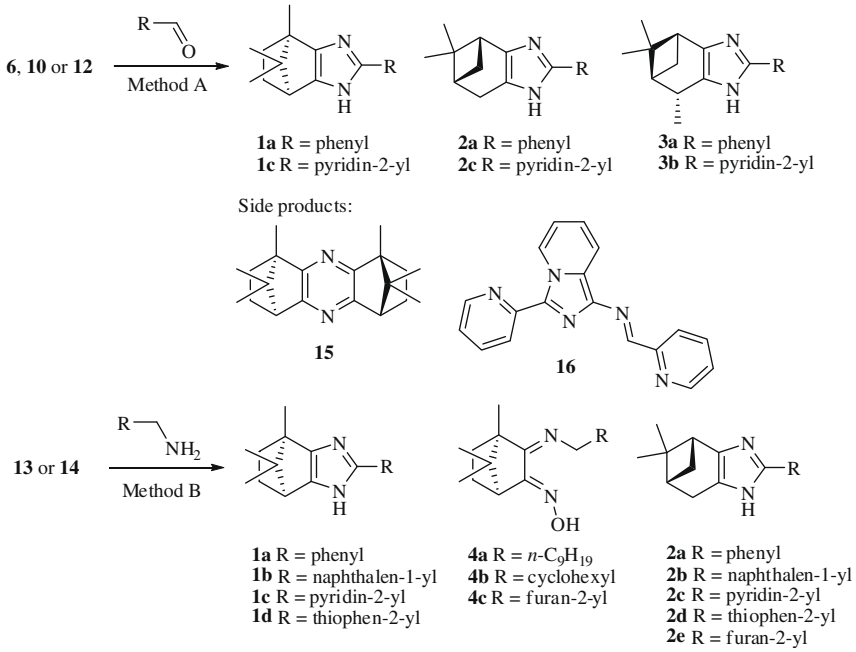
Scheme 1. Synthesis of terpene-derived diketones.

α-Nitrosoketones or α-hydroxyiminoketones may also be applied in the synthesis of imidazoles and, therefore, our further efforts were focused on the nitrosation/oxidation of camphor, nopinone or isopinocampheone. The camphorquinone monoxime **13** could be selectively generated from the camphorquinone **6** by simple treatment with hydroxylamine in ethanol.[27] Conversely, the reaction of the camphor or nopinone with *iso*-amylnitrite[28] afforded the desired monooximes **13** and **14** in a more straightforward manner (Scheme 2). Unfortunately, a similar transformation on isopinocampheone **11** furnished an inseparable mixture of products, where the desired monoxime was not found.



Scheme 2. Camphorquinone and PinDione monoximes.

The initial condensation reaction into an imidazole, using a convenient set of conditions (Method A: benzaldehyde or pyridine-2-carbaldehyde and ammonium acetate in propane-2-ol or DMSO),[17,18] was verified on terpene diketones **6**, **10** and **12**. The desired imidazoles **1a**, **1c**, **2a**, **2c** and **3a–b** bearing phenyl or pyridyl substituents at the 2-position were isolated in moderate yields (Scheme 3, Table 1). The yields attained (7–38%) are substantially lower due to the undesirable formation of bis(terpene)-annulated pyrazine derivatives (e.g., the camphor representative **15**). In the case of pyridine-2-carbaldehyde as the starting aldehyde, another side product was isolated. Its structure was assigned to the substituted imidazo[1,5-*a*]pyridine **16** formed from three molecules of pyridine-2-carbaldehyde. The facile formation of such a product was confirmed by independent treatment of the pyridine-2-carbaldehyde with ammonium acetate. Its formation could be slightly



Scheme 3. Synthesis of the annulated-terepene imidazoles **1–3**.

Table 1
Condensations—methods A/B

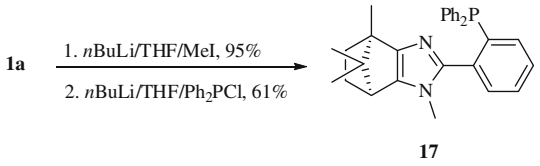
Compd	R	Yield (%) (Method)	$[\alpha]_D^{20}$ (CH_3OH)
1a	Phenyl	A: 38 B: 55	+46.3[a]
1b	Naphthalen-1-yl	B: 52	+41.4[b]
1c	Pyridin-2-yl	A: 10 B: 33	+56.0[a]
1d	Thiophen-2-yl	B: 41	+53.0[b]
2a	Phenyl	A: 32 B: 51	−26.2[a]
2b	Naphthalen-1-yl	B: 50	−21.1[b]
2c	Pyridin-2-yl	A: 8 B: 39	−17.0[a]
2d	Thiophen-2-yl	B: 42	−20.5[b]
2e	Furan-2-yl	B: 41	+33.0[b]
3a	Phenyl	A: 28	+55.0[a]
3b	Pyridin-2-yl	A: 7	+8.0[a]
4a	*n*-Decyl	B: 40	+59.9[b]
4b	Cyclohexyl	B: 52	+72.4[b]
4c	Furan-2-yl	B: 66	+87.8[b]

[a] Concentration *c* is 1.0 g/100 mL.
[b] Concentration *c* is 0.5 g/100 mL.

suppressed by a slow addition of pyridine-2-carbaldehyde into the reaction mixture, using DMSO as a solvent.

Due to the difficulties with the condensation of terpene diketones, we turned our attention to the monoximes **13** and **14**. It is well known that treatment of an α-monoxime with aliphatic amines furnishes 2-substituted imidazoles.[20,29,30] Starting from benzylamine, 1-naphthalenemethylamine, 2-picolylamine, 2-thiophenemethylamine and furfurylamine, we were able to condense monoximes **13** and **14** into imidazoles **1a–d** and **2a–e** (Scheme 3, Table 1). Upon optimization of the reaction conditions, we achieved the best yields conducting the reaction without solvent (neat) under a slight excess of amine (1.5 equiv) at 150 °C (Method B). The yields attained (33–55%) were considerably higher than those for the condensation of diketones **6**, **10** or **12**. Whereas the formation of the side product similar to **16** was suppressed, the pyrazine derivatives remained as side products. A full account on the terpene-pyrazine derivatives formation will be given elsewhere. In the case of *n*-decylamine, cyclohexanemethylamine and furfurylamine as the starting amines and camphor-monoxime **13** as an electrophile, we did not observe the formation of the desired imidazole derivatives at all; 'imino-oximes' **4a–c** were isolated instead. Isolation of such intermediates and the fact that no hints on the mechanism of such a condensation have been given in the literature so far prompted us to investigate the reaction mechanism in more detail. Scheme 4 illustrates our proposed reaction path. The facile formation and structure of 'imino-oxime' derivatives **4** in the first step were confirmed by X-ray analysis (see below) as well as by the recent report by Pedro et al.[7] The amine used in excess in the cyclization reaction may have served as a base, deprotonating either the hydroxy or $-CH_2-$ group. The deprotonation of the hydroxy group (path A) seemed to be more probable than path B. However, as the acidity of the $-CH_2-$ group increases or as the respective C-anion is more stabilized by resonance to the attached R-substituent (R = (hetero)aromate), such deprotonation may take place and path B becomes more feasible. As the amines with aliphatic residues (R = *n*-nonyl and cyclohexyl) or the aromatic furfurylamine do not greatly stabilize such anions (aliphatic ones even destabilize the C-anion by a positive inductive effect), the reaction will terminate at 'imino-oximes' **4** or will not take place at all. This supposition also confirms all other attempted experiments on PinDione monoxime **14,** where we were able to synthesize only furane-2-yl derivative **2e** from the above-mentioned amines. An intramolecular attack of the generated N-anion to the C=N double bond, subsequent elimination of water and a final 2*H*- to 1*H*-imidazole tautomerism most likely lead to the target imidazoles **1a–d**.

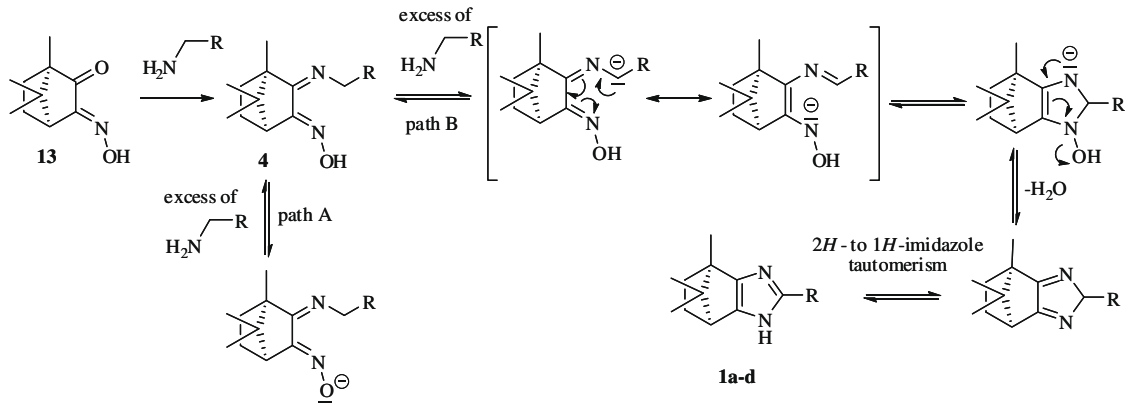
In order to further enhance the complexation ability and explore possible functionalization of the prepared phenyl ligands (series **a**), we attempted to introduce a phosphine chelating functionality at the 2-position. N-Methylation of **1a** using the *n*BuLi/MeI system afforded exclusively only one isomer in 95% yield (*anti*-arrangement of methyl groups). Its direct *ortho*-lithiation and quenching with diphenylphosphinechloride provided the functionalized imidazole **17** in 61% yield (Scheme 5).



Scheme 5. The functionalization of 2-phenylcamphorimidazole **1a**.

Whereas we were unable to grow a suitable crystal for the X-ray analysis of target ligands **1–3** (all attempted crystals for **1a** and **1d** showed heavy disorders), the molecular structures of side products **15** and **16** and intermediate **4b** were also confirmed by crystallography. The structure of **15** has been previously reported.[31,32] Figure 2 shows ORTEP plots of **16** and **4b**. The almost planar molecule **16** packed with parallel layers of molecules separated by 3.5 Å shifted by 1.3 Å along C10–C1 shows typical π–π stacking.

The enantioselectivities of the synthesized ligands were examined in the nitroaldol reaction (Henry reaction[33,34]). Its asymmetric



Scheme 4. Proposed mechanism of the condensation between monoximes and amines (Method B).

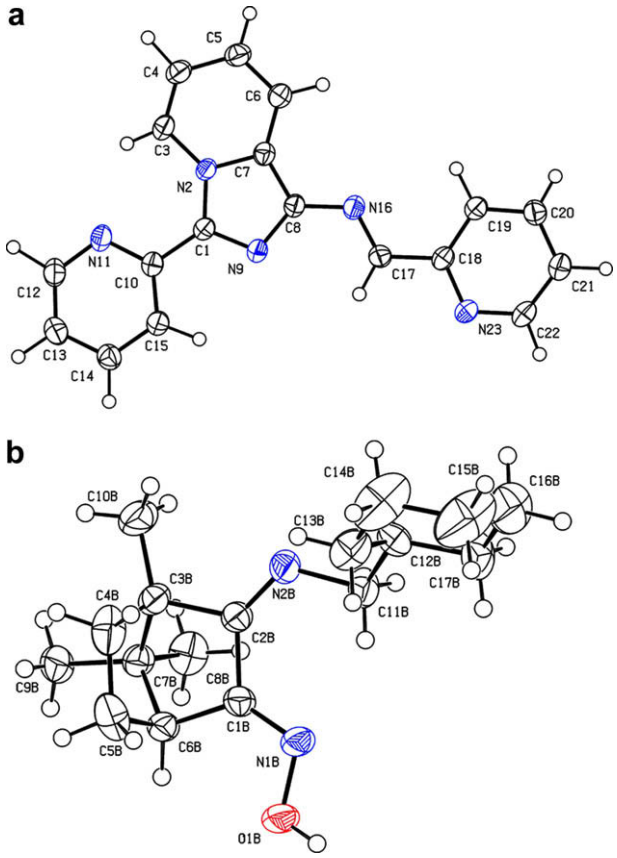
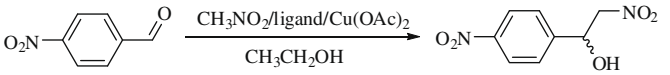


Figure 2. Crystal structures of the side product **16** (a) and 'imino-oxime' **4b** (b) obtained at 173 and 293 K, respectively. Vibrational ellipsoids of the ORTEP plot are shown at the 50% probability level.

version involves a reaction between an aldehyde and a nitroalkane catalyzed by chiral ligands chelating mainly copper (II),[35,7] zinc[36] or rare earth metal salts.[37] This reaction serves as a basic screening of the enantioselectivity, giving a first insight into the catalytic behaviour of the studied ligands. The reactions were carried out at 0.5 M scale with excess of nitromethane (10 equiv) under the conditions given in Ref. 38. The attained yields and enantiomeric excesses (ee's) for ligands **1–3, 17** as well as for 'imino-oximes' **4** are summarized in Table 2. All the optically active compounds prepared were able to catalyze the Henry reaction as bases, affording the desired nitroaldol in isolated yields of 61–98% and reaction times of 24–72 h at 25 °C. Whereas the Henry reaction catalyzed by ligands series **1**, **3**, **4** and **17** afforded the (*S*)-2-nitro-1-(4-nitrophenyl)ethanol, the reaction with ligand series **2** gave the (*R*)-enantiomer. The yields and ees increase within the individual series **1–3**, varying only in the nature of the R-substituent, in a general way—naphthalen-2-yl (**b**), phenyl (**a**), thiophen-2-yl (**d**) and pyridin-2-yl (**c/3b**). The bulkier and uncoordinating substituents such as naphthyl or phenyl most probably prevented access of the copper(II) ion towards the imidazole nitrogens and, as expected, the attained yields and ees were low. On the other hand, from the data in Table 2, it can be clearly seen that the best chemical yields (up to 98%), quick reaction times (24 h) and ees (up to 32%) were achieved by applying the ligands bearing a pyridin-2-yl substituent **1c**, **2c** and **3b**, respectively. These three ligands most probably bind the copper(II) ion by means of the N═C–C═N coordination pocket similar to that known from the 2,2′-bipyridine (bipy)[39] and its related ligands. Hence, the chemical yields and also enantiomeric excesses are higher. N,P-Chelating ligand **17** showed a similar enantioselectivity (29% ee) as that observed for the pyridine derivatives. In addition, 'imino-oximes' **4** were also examined

Table 2
Asymmetric Henry reaction



Ligand	Yield (%)[a]	Reaction time[b] (h)	ee/configuration[c]
1a	76	48	9/(*S*)
1b	62	72	7/(*S*)
1c	98	24	29/(*S*)
1d	86	36	11/(*S*)
2a	89	48	11/(*R*)
2b	73	72	12/(*R*)
2c	96	24	32/(*R*)
2d	81	36	8/(*R*)
2e	61	48	6/(*R*)
3a	72	48	13/(*S*)
3b	85	24	27/(*S*)
17	89	48	29/(*S*)
4a	76	48	21/(*S*)
4b	65	48	16/(*S*)
4c	68	48	18/(*S*)

[a] Isolated yields.
[b] Monitored by TLC (SiO_2; hexane/EtOAc 2:1).
[c] Determined by chiral HPLC analysis on a Daicel Chiracel OB column and simultaneously deduced from [α] values.[35]

in the Henry reaction. The attained yields and ees were even higher than those for target ligands **a**, **b**, **d** and **e**, which were most likely caused by their higher coordination ability given by the presence of imino as well as oxime functionalities.

3. Conclusion

In this work, we have shown the first synthesis of annulated terpene-imidazole derivatives. Starting with terpene diketones and employing two aldehydes, we synthesized six new derivatives in moderate yields. On the other hand, Method B starting with terpene monoximes and amines afforded nine terpene-imidazole derivatives (**1a–d** and **2a–e**) and three 'imino-oximes' **4a–c** in a more straightforward manner and with higher yields. The proposed mechanism of the monoxime and amine condensation—Method B, involves the formation of an 'imino-oxime' **4**, its C-deprotonation, intramolecular attack of the N-nucleophile to the C═N double bond, subsequent elimination of water and finally a 2*H*- to 1*H*-imidazole tautomerism. The electronic effects and the nature of R-substituents strongly affect the entire reaction course. Both methods also furnished terpene-pyrazine derivatives, and in the case of the pyridine-2-carbaldehyde, we observed formation of the side product **16**. The molecular structure of the side products **16** and **4b** has also been confirmed by X-ray analysis. Imidazole **1a** bearing a phenyl ring at the 2-position is capable of N-methylation and *ortho*-lithiation furnishing, after quench with $(Ph)_2PCl$, N,P-chelating ligand **17**. The enantioselective screening of these ligands in the Henry reaction revealed that an N═C–C═N binding pocket similar to that in bipy ligands is crucial. Whereas for the pyridine ligands **1c**, **2c** and **3b,** quick reaction times and enantioselectivities of up to 32% were achieved, the other ligands, except for **17**, showed longer reaction times and lower ees. However, the attained ees resemble those we observed for the similar α-amino acid-derived imidazole ligands.[38]

4. Experimental

4.1. General

Reagents and solvents (reagent grade) were purchased from Aldrich and used as received. THF was freshly distilled from

Na/benzophenone under N_2. The starting diketones **6**, **10** and **12** or monoximes **13** and **14** were synthesized according to the literature procedures (see above). Evaporation and concentration in vacuo were performed at water aspirator pressure. The condensation reactions (method B) were carried out in a glass pressure tube (Aldrich). Column chromatography (CC) was carried out with SiO_2 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminium sheets coated with SiO_2 60 F_{254} obtained from Merck, with visualization by UV lamp (254 or 360 nm). Melting points (mp) were measured on a Büchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 360/500 MHz or 90/125 MHz, respectively, with Bruker AMX 360 or Bruker AVANCE 500 instruments at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Residual solvent signals in the ^1H and ^{13}C NMR spectra were used as an internal reference ($CDCl_3$—7.25 and 77.23, DMSO-d_6—2.55 and 39.51 and CD_3OD—3.31 and 49.15 ppm for ^1H and ^{13}C NMR, respectively). Coupling constants (*J*) are given in Hertz. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet). Protons of the substituents at the 2-position are marked as follows: Ph (Phenyl), Np (naphthalen-1-yl), Py (pyridine-2-yl), Th (thiophen-2-yl), Fur (furan-2-yl), Dec (*n*-decyl) and Chex (cyclohexyl). Additional NMR techniques such as ^1H–^1H COSY, HMBC and HMQC were used for regular signal assignment. Some target imidazoles showed two sets of signals or broad signals in ^1H and ^{13}C NMR spectra as a result of hindered imidazole tautomerism or possible association (may be partially suppressed by adding a drop of TFA).[38] Optical rotation values were measured on a Perkin Elmer 341 instrument, concentration *c* is given in g/100 mL CH_3OH. The mass spectra were measured on GC/MS configuration comprising Agilent Technologies—6890N gas chromatograph (HP-5MS column, length 30 m, I.D. 0.25 mm, film 0.25 μm) equipped with a 5973 Network MS detector (EI 70 eV, mass range 33–550 Da). High resolution FT-MALDI spectra were measured with an IonSpec Ultima Fourier transform (FT) instrument with [(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-eneylidene]malononitrile (DCTB) or 3-hydroxypicolinic acid (3-HPA) as a matrix. The most important signals are reported in *m/z* units with M as the molecular ion. Compounds **4a–c** fragment so easily that the ions corresponding to the neutral loss of water are the base peaks in EI and FT-MALDI (DCTB) mass spectra ($[M-H_2O]^+$ and $[MH-H_2O]^+$). Elemental analyses were performed on EA 1108 Fisons instrument.

4.2. Method A (in *i*PrOH)

Freshly distilled benzaldehyde (9 mL, 80 mmol) was added to a mixture of diketone 6, 10 or 12 (18 mmol) and ammonium acetate (15 g, 0.19 mol) in propan-2-ol (300 mL). The reaction mixture was refluxed for 48 h, after which the solvent was removed in vacuo, the residue taken up in CH_2Cl_2 (200 mL), and washed successively with satd $NaHCO_3$ (aq 100 mL) and brine (100 mL). The organic layer was dried, the solvent evaporated and the crude product purified by CC (SiO_2; EtOAc/hexane 1:1).

4.2.1. (1*R*,7*S*)-1,10,10-Trimethyl-4-phenyl-3,5-diazatricyclo-[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1a

The title compound was synthesized from diketone **6** (3.0 g, 18 mmol). Yield 1.73 g (38%), mp 278–280 °C, $[\alpha]_D^{20} = +46.3$ (*c* 1.0, CH_3OH). ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.89 (s, 6H, 2 × CH_3), 0.93–1.06 (m, 2H, CH_2), 1.26 (s, 3H, CH_3), 1.68–1.76 (m, 1H, CH_2), 1.92–1.99 (m, 1H, CH_2), 2.87 (d, 1H, *J* = 3.6 Hz, CH), 5.42 (br s, 1H, NH), 7.22–7.35 (m, 3H, Ph), 7.85 (d, 2H, *J* = 6.9 Hz, Ph). ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 11.43, 19.37, 20.27, 27.06, 34.07, 49.67, 52.35, 59.93, 124.56, 127.65, 128.3, 128.69, 130.45, 145.82 (1C missing). EI-MS (70 eV) *m/z* (rel. int.): 252 (M^+, 29), 237 (100), 223 (17), 209 (98), 195 (18), 104 (23), 77 (17). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for $[C_{17}H_{21}N_2^+]$ 253.1699; found 253.1693 [MH^+]. Elemental Anal. Calcd for $C_{17}H_{20}N_2$ (252.35): C, 80.91; H, 7.99; N, 11.10. Found: C, 80.88; H, 7.89; N, 11.01.

4.2.2. (1*R*,8*R*)-9,9-Dimethyl-4-phenyl-3,5-diazatricyclo-[6.1.1.0$^{2.6}$]deca-2(6),3-diene 2a

The title compound was synthesized from diketone **10** (2.74 g, 18 mmol). Yield 1.37 g (32%), mp 227–228 °C, $[\alpha]_D^{20} = -26.2$ (*c* 1.0, CH_3OH). ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.70 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.48 (d, 1H, *J* = 9.0 Hz, CH_2), 2.32–2.36 (m, 1H, CH), 2.70–2.81 (m, 3H, CH + CH_2), 2.87 (dd, 1H, *J* = 15.9 Hz, *J* = 3.3 Hz, CH), 7.26 (t, 1H, *J* = 6.6 Hz, Ph), 7.37 (t, 2H, *J* = 7.2 Hz, Ph), 7.79 (d, 2H, *J* = 7.2 Hz, Ph). ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 21.21, 26.46, 26.69, 33.82, 40.81, 41.62, 42.52, 124.26, 127.63, 128.74, 130.33, 131.16, 142.86 (1C missing). EI-MS (70 eV) *m/z* (rel. int.): 238 (M^+, 74), 223 (100), 209 (29), 195 (64), 183 (17), 170 (35), 104 (41), 77 (19). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for $[C_{16}H_{19}N_2^+]$ 239.1543; found 239.1547 [MH^+]. Elemental Anal. Calcd for $C_{16}H_{18}N_2$ (238.33): C, 80.63; H, 7.61; N, 11.75. Found: C, 80.70; H, 7.65; N, 11.74.

4.2.3. (1*S*,7*R*,8*S*)-7,9,9-Trimethyl-4-phenyl-3,5- diazotricyclo-[6.1.1.0$^{2.6}$]deca-2(6),3-diene 3a

The title compound was synthesized from diketone **12** (3.00 g, 18 mmol). Yield 1.27 g (28%), mp 127–130 °C, $[\alpha]_D^{20} = +55.0$ (*c* 1.0, CH_3OH). ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.66 + 0.78 (s, 3H, CH_3), 1.19 + 1.28 (d, 3H, *J* = 7.2 Hz, CH_3), 1.36 + 1.37 (s, 3H, CH_3), 1.47 (d, 1H, *J* = 8.7 Hz, CH_2), 1.99–2.10 + 2.14–2.19 (m, 1H, CH), 2.51–2.55 + 2.68–2.78 (m, 2H, CH_2 + CH), 2.92–2.97 + 3.11–3.19 (m, 1H, CH), 7.20 (t, 1H, *J* = 7.2 Hz, Ph), 7.28 (t, 2H, *J* = 6.9 Hz, Ph), 7.85 (d, 2H, *J* = 6.9 Hz, Ph). ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 17.31, 17.66, 20.80, 23.68, 26.65, 27.35, 30.37, 31.06, 35.27, 36.03, 41.21, 41.47, 42.76, 44.47, 48.57, 49.06, 124.48, 127.28, 128.61, 130.76, 131.78, 143.12 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 252 (M^+, 67), 237 (100), 223 (19), 209 (76), 195 (34), 184 (36), 104 (33), 77 (24). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for $[C_{17}H_{21}N_2^+]$ 253.1699; found 253.1695 [MH^+]. Elemental Anal. Calcd for $C_{17}H_{20}N_2$ (252.35): C, 80.91; H, 7.99; N, 11.10. Found: C, 80.85; H, 7.96; N, 11.04.

4.3. Method A (in DMSO)

Pyridine-2-carbaldehyde (7 mL, 65 mmol) was added dropwise to a mixture of diketone **6**, **10** or **12** (18 mmol) and ammonium acetate (23 g, 0.3 mol) in dry DMSO (150 mL) under N_2 at 100 °C. The reaction mixture was stirred for 4 h at 100 °C and poured into cold aq ammonia (300 mL). The product was extracted with CH_2Cl_2 (300 mL), washed successively with water (3 × 200 mL), the organic layer dried over Na_2SO_4) and the solvent evaporated. The crude product was purified by CC(SiO_2; EtOAc–hexane 1:1) and repeatedly by CC (SiO_2; $CHCl_3$–CH_3OH 100:1).

4.3.1. (1*R*,7*S*)-1,10,10-Trimethyl-4-pyridin-2-yl-3,5-diazatricyclo[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1c

The title compound was synthesized from diketone **6** (3.0 g, 18 mmol). Yield 0.46 g (10%), mp 199–200 °C, $[\alpha]_D^{20} = +56.0$ (*c* 1.0, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.96–1.12 (m, 2H, CH_2), 1.20 + 1.37 (br s, 3H, CH_3), 1.73–1.78 (m, 1H, CH_2), 2.00–2.03 (m, 1H, CH_2), 2.88 (br s, 1H, CH), 7.11 (t, 1H, *J* = 6.0 Hz, Py), 7.67–7.69 (m, 1H, Py), 8.04–8.07 (m, 1H, Py), 8.42 (d, 1H, *J* = 5.0 Hz), 10.62 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.32, 19.17, 20.15,

26.83, 33.92, 49.09, 49.76, 60.25, 117.72, 121.77, 136.70, 136.85, 148.45, 149.12 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 253 (M^+, 30), 238 (100), 210 (84), 196 (12), 105 (11), 77 (10). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for [$C_{16}H_{20}N_3^+$] 254.1652; found 254.1647 [MH^+]. Elemental Anal. Calcd for $C_{16}H_{19}N_3$ (253.34): C, 75.85; H, 7.56; N, 16.59. Found: C, 75.78; H, 7.51; N, 16.61.

4.3.2. (1*R*,8*R*)-9,9-Dimethyl-4-pyridin-2-yl-3,5-diazatricyclo-[6.1.1.0$^{2.6}$]deca-2(6),3-diene 2c

The title compound was synthesized from diketone **10** (2.74 g, 18 mmol). Yield 0.35 g (8%), mp 156–158 °C, $[\alpha]_D^{20} = -17.0$ (*c* 1.0, CH_3OH). ^1H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 0.59 + 0.61 (s, 3H, CH_3), 1.31–1.34 (m, 1H, CH_2), 1.38 (s, 3H, CH_3), 2.28–2.30 (m, 1H, CH), 2.66–2.83 (m, 4H, CH + CH_2), 7.22 (m, 1H, Py), 7.78 (m, 1H, Py), 7.90 (m, 1H, Py), 8.50 (m, 1H, Py), 12.49 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.42, 25.83, 26.77, 28.32, 33.75, 39.85, 41.53, 117.73, 121.83, 136.92, 137.66, 148.57, 149.64 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 239 (M^+, 51), 224 (100), 210 (41), 196 (62), 171 (18), 105 (25), 78 (22). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for [$C_{15}H_{18}N_3^+$] 240.1495; found 240.1500 [MH^+]. Elemental Anal. Calcd for $C_{15}H_{17}N_3$ (239.32): C, 75.28; H, 7.16; N, 17.56. Found: C, 75.27; H, 7.16; N, 17.57.

4.3.3. (1*S*,7*R*,8*S*)-7,9,9-Trimethyl-4-pyridin-2-yl-3,5-diazatricyclo[6.1.1.0$^{2.6}$]deca-2(6),3-diene 3b

The title compound was synthesized from diketone **12** (3.00 g, 18 mmol). Yield 0.32 g (7%), mp 100–101 °C, $[\alpha]_D^{20} = +8.0$ (*c* 1.0, CH_3OH). ^1H NMR (500 MHz, DMSO-d_6, 25 °C): δ = 0.60 + 0.68 (s, 3H, CH_3), 1.28 + 1.38 (d, 3H, *J* = 7.0 Hz, CH_3), 1.42 + 1.44 (s, 3H, CH_3), 1.43–1.49 (m, 1H, CH_2), 2.10–2.12 + 2.25–2.27 (m, 1H, CH), 2.67–2.97 (m, 2H, CH + CH_2), 3.05–3.09 + 3.26–3.28 (m, 1H, CH), 7.20–7.23 (m, 1H, Py), 7.76–7.78 (m, 1H, Py), 7.90–7.92 (m, 1H, Py), 8.50–8.52 (m, 1H, Py). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C): δ = 16.24, 16.64, 20.70, 23.45, 26.00, 26.56, 29.51, 30.11, 31.76, 35.09, 35.08, 41.98, 42.32, 44.21, 47.35, 47.76, 120.85, 124.71, 130.98, 138.54, 139.23, 143.00, 148.72 (1C missing). EI-MS (70 eV) *m/z* (rel. int.): 253 (M^+, 44), 238 (100), 224 (19), 210 (83), 196 (25), 185 (33), 105 (25), 78 (19). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{16}H_{20}N_3^+$] 254.1652; found 254.1652 [MH^+]. Elemental Anal. Calcd for $C_{16}H_{19}N_3$ (253.34): C, 75.85; H, 7.56; N, 16.59. Found: C, 75.79; H, 7.51; N, 16.60.

4.3.4. 3-Pyridin-2-yl-*N*-[(1*E*)-pyridin-2-ylmethylidene]-imidazo[1,5-*a*]pyridin-1-amine 16

The pure title compound was prepared by a 4 h stirring of pyridine-2-carbaldehyde (7 mL, 65 mmol) with ammonium acetate (23 g, 0.3 mol) in DMSO (150 mL) at 100 °C. Yield 4.2 g (65%), mp 184–186 °C. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.75 (t, 1H, *J* = 9.0 Hz), 7.02 (t, 1H, *J* = 9.0 Hz), 7.22–7.25 (m, 1H), 7.30–7.34 (m, 1H), 7.80–7.86 (m, 2H), 8.00 (d, 1H, *J* = 10 Hz), 8.30 (d, 1H, *J* = 8.0 Hz), 8.44 (d, 1H, *J* = 8.0 Hz), 8.67 (d, 1H, *J* = 4.5 Hz), 8.75 (d, 1H, *J* = 4.5 Hz), 9.50 (s, 1H), 9.98 (d, 1H, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 114.62, 118.00, 121.79, 121.85, 122.11, 122.44, 124.20, 126.64, 129.30, 133.68, 136.52, 136.77, 138.57, 148.35, 149.97, 151.13, 154.55, 155.89. HR-FT-MALDI-MS (3-HPA): *m/z* calcd for [$C_{18}H_{14}N_5^+$] 300.1249; found 300.1241 [MH^+]. Elemental Anal. Calcd for $C_{18}H_{13}N_5$ (299.33): C, 72.23; H, 4.38; N, 23.40. Found: C, 72.25; H, 4.39; N, 23.42.

4.4. Method B

A mixture of monoxime **13** or **14** (18 mmol) and amine (27 mmol) was heated in a glass pressure tube for 1 h at 150 °C. The resulting crude product was purified by CC (SiO_2, EtOAc–hexane 2:1).

4.4.1. (1*R*,7*S*)-1,10,10-Trimethyl-4-phenyl-3,5-diazatricyclo-[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1a

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and benzylamine (2.89 g, 27 mmol). Yield 2.50 g (55%). Experimental data are consistent with the derivative **1a** obtained by method A.

4.4.2. (1*R*,7*S*)-1,10,10-Trimethyl-4-naphthalen-2-yl-3,5-diazatricyclo[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1b

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and 1-naphthalenemethylamine (4.24 g, 27 mmol). Yield 2.83 g (52%), mp 204–207 °C, $[\alpha]_D^{20} = +41.4$ (*c* 0.5, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.91 (s, 6H, CH_3), 0.92–0.96 (m, 1H, CH_2), 0.99–1.05 (m, 1H, CH_2), 1.30 (s, 3H, CH_3), 1.70–1.73 (m, 1H, CH_2), 1.94–1.97 (m, 1H, CH_2), 2.86 (d, 1H, *J* = 4.0 Hz, CH), 7.35 (t, 1H, *J* = 7.8 Hz, Np), 7.43–7.46 (m, 2H, Np), 7.54 (d, 1H, *J* = 7.2 Hz, Np), 7.75 (d, 1H, *J* = 8.2 Hz, Np), 7.80–7.83 (m, 1H, Np), 8.65–8.68 (m, 1H, Np). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.60, 19.57, 20.45, 27.24, 34.26, 50.03, 52.45, 59.97, 125.21, 126.16, 126.42, 126.46, 126.84, 128.39, 128.68, 129.18, 131.15, 134.18, 145.74 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 302 (M^+, 43), 287 (95), 273 (15), 259 (100), 245 (10), 154 (10), 127 (11), 106 (12). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{21}H_{23}N_2^+$] 303.1856; found 303.1857 [MH^+]. Elemental Anal. Calcd for $C_{21}H_{22}N_2$ (302.41): C, 83.40; H, 7.33; N, 9.26. Found: C, 83.34; H, 7.32; N, 9.28.

4.4.3. (1*R*,7*S*)-1,10,10-Trimethyl-4-pyridin-2-yl-3,5-diazatricyclo[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1c

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and 2-picolylamine (2.92 g, 27 mmol). Yield 1.50 g (33%). Experimental data are consistent with the derivative **1c** obtained by method A.

4.4.4. (1*R*,7*S*)-1,10,10-Trimethyl-4-thiophen-2-yl-3,5-diazatricyclo[5.2.1.0$^{2.6}$]deca-2(6),3-diene 1d

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and 2-thiophenemethylamine (3.06 g, 27 mmol). Yield 1.91 g (41%), mp 286–289 °C, $[\alpha]_D^{20} = +53.0$ (*c* 0.5, CH_3OH). ^1H NMR (360 MHz, CD_3OD, 25 °C): δ = 0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.95–1.02 (m, 2H, CH_2), 1.77–1.83 (m, 1H, CH_2), 2.00–2.04 (m, 1H, CH_2), 2.84 (d, 1H, *J* = 3.6 Hz, CH), 7.04 (t, 1H, *J* = 5.1 Hz, Th), 7.31 (d, 1H, *J* = 5.1 Hz, Th), 7.35 (d, 1H, *J* = 3.6 Hz, Th). ^{13}C NMR (90 MHz, CD_3OD, 25 °C): δ = 11.65, 19.77, 20.70, 28.08, 35.26, 51.09, 53.51, 60.86, 124.04, 125.71, 128.69, 135.81, 143.32 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 258 (M^+, 42), 243 (95), 229 (20), 215 (100), 201 (21), 121 (18), 106 (19), 91 (10), 77 (12). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{15}H_{19}N_2S^+$] 259.1263; found 259.1260 [MH^+]. Elemental Anal. Calcd for $C_{15}H_{18}N_2S$ (258.38): C, 69.73; H, 7.02; N, 10.84; S, 12.41. Found: C, 69.76; H, 7.05; N, 10.86; S, 12.36.

4.4.5. (1*R*,8*R*)-9,9-Dimethyl-4-phenyl-3,5-diazatricyclo-[6.1.1.0$^{2.6}$]deca-2(6),3-diene 2a

The title compound was synthesized from monoxime **14** (3.01 g, 18 mmol) and benzylamine (2.89 g, 27 mmol). Yield 2.19 g (51%). Experimental data are consistent with the derivative **2a** obtained by method A.

4.4.6. (1*R*,8*R*)-9,9-Dimethyl-4-naphthalen-1-yl-3,5-diazatricyclo[6.1.1.0$^{2.6}$]deca-2(6),3-diene 2b

The title compound was synthesized from monoxime **14** (3.01 g, 18 mmol) and 1-naphthalenemethylamine (4.24 g, 27 mmol). Yield 2.60 g (50%), mp 226–230 °C, $[\alpha]_D^{20} = -21.1$ (*c* 0.5, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.65 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.45 (d, 1H, *J* = 8.9 Hz, CH_2), 2.30–2.33 (m,

1H, CH), 2.68–2.73 (m, 3H, CH + CH_2), 2.83 (dd, 1H, J = 15.7 Hz, J = 3.0 Hz, CH), 7.39 (t, 1H, J = 7.5 Hz, Np), 7.44–7.48 (m, 2H, Np), 7.56 (d, 1H, J = 7.2 Hz, Np), 7.78 (d, 1H, J = 8.2 Hz, Np), 7.82–7.84 (m, 1H, Np), 8.64–8.66 (m, 1H, Np). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.13, 26.41, 26.67, 33.77, 40.75, 41.63, 42.51, 125.29, 126.27, 126.31, 126.39, 126.91, 128.47, 128.62, 128.89, 131.09, 134.18, 142.50 (2C missing). EI-MS (70 eV) *m/z* (rel. int.): 288 (M^+, 89), 273 (100), 259 (48), 245 (45), 207 (40), 154 (39), 127 (31), 77 (22). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{20}H_{21}N_2^+$] 289.1699; found 289.1700 [MH^+]. Elemental Anal. Calcd for $C_{20}H_{20}N_2$ (288.39): C, 83.30; H, 6.99; N, 9.71. Found: C, 83.25; H, 7.05; N, 9.72.

4.4.7. (1*R*,8*R*)-9,9-Dimethyl-4-pyridin-2-yl-3,5-diazatricyclo[6.1.1.0^{2,6}]deca-2(6),3-diene 2c

The title compound was synthesized from monoxime **14** (3.01 g, 18 mmol) and 2-picolylamine (2.92 g, 27 mmol). Yield 1.68 g (39%). Experimental data are consistent with the derivative **2c** obtained by method A.

4.4.8. (1*R*,8*R*)-9,9-Dimethyl-4-thiophen-2-yl-3,5-diazatricyclo[6.1.1.0^{2,6}]deca-2(6),3-diene 2d

The title compound was synthesized from monoxime **14** (3.01 g, 18 mmol) and 2-thiophenemethylamine (3.06 g, 27 mmol). Yield 1.85 g (42%), mp 233–236 °C, $[\alpha]_D^{20} = -20.5$ (c 0.5, CH_3OH). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.68 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.44 (d, 1H, J = 9.2 Hz, CH_2), 2.28–2.31 (m, 1H, CH), 2.68–2.75 (m, 3H, CH + CH_2), 2.81 (dd, 1H, J = 9.2 Hz, 2.5 Hz, CH), 6.96 (t, 1H, J = 5.1 Hz, Th), 7.16 (d, 1H, J = 5.1 Hz, Th), 7.25–7.27 (m, 1H, Th). ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 21.55, 26.78, 27.04, 34.12, 41.10, 41.90, 42.85, 122.29, 124.45, 127.76, 129.02, 131.12, 134.75, 138.98. EI-MS (70 eV) *m/z* (rel. int.): 244 (M^+, 85), 229 (100), 215 (40), 201 (72), 189 (38), 176 (41), 120 (20), 110 (22), 92 (11). HR-FT-MALDI-MS (3-HPA): *m/z* calcd for [$C_{14}H_{17}N_2S^+$] 245.1107; found 245.11.06 [MH^+]. Elemental Anal. Calcd for $C_{14}H_{16}N_2S$ (244.36): C, 68.81; H, 6.60; N, 11.46; S, 13.12. Found: C, 68.90; H, 6.67; N, 11.41; S, 13.08.

4.4.9. (1*R*,8*R*)-4-Furan-2-yl-9,9-dimethyl-3,5-diazatricyclo[6.1.1.0^{2,6}]deca-2(6),3-diene 2e

The title compound was synthesized from monoxime **14** (3.01 g, 18 mmol) and furfurylamine (2.62 g, 27 mmol). Yield 1.68 g (41%), mp 118–123 °C, $[\alpha]_D^{20} = +33.0$ (c 0.5, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.65 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.42 (d, 1H, J = 9.2 Hz, CH_2), 2.29–2.31 (m, 1H, CH), 2.68–2.75 (m, 3H, CH + CH_2), 2.82 (dd, 1H, J = 13.0 Hz, J = 2.9 Hz, CH), 6.38–6.39 (m, 1H, Fur), 6.70 (d, 1H, J = 3.4 Hz, Fur), 7.30–7.31 (m, 1H, Fur), 8.92 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.47, 25.74, 26.91, 34.08, 41.07, 41.84, 42.77, 105.51, 111.94, 127.24, 136.28, 141.47, 146.68 (1C missing). EI-MS (70 eV) *m/z* (rel. int.): 228 (M^+, 96), 213 (100), 199 (42), 185 (53), 173 (34), 160 (40), 120 (19), 94 (20). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{14}H_{17}N_2O^+$] 229.1335; found 229.1332 [MH^+]. Elemental Anal. Calcd for $C_{14}H_{16}N_2O$ (228.29): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.70; H, 7.10; N, 12.29.

4.4.10. (1*S*,4*R*)-3-(Decylimino)-4,7,7-trimethylbicyclo-[2.2.1]heptan-2-one oxime 4a

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and *n*-decylamine (4.24 g, 27 mmol). Yield 2.31 g (40%), oil, $[\alpha]_D^{20} = +59.9$ (c 0.5, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.78 (s, 3H, CH_3), 0.85 (t, 3H, J = 6.6 Hz, Dec $-^{10}CH_3$), 0.90 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.22–1.33 (m, 14H, Dec $-^3CH_2-^9CH_2$), 1.39–1.49 (m, 2H, CH_2), 1.57–1.62 (m, 2H, Dec $-^2CH_2$), 1.68–1.73 (m, 1H, CH_2), 1.88–1.92 (m, 1H, CH_2), 3.22 (d, 1H, J = 4.3 Hz, CH), 3.71–3.77 (m, 1H, Dec $-^1CH_2$), 3.86–3.92 (m, 1H, Dec $-^1CH_2$), 10.62 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.75, 14.32, 18.10, 20.33, 22.89, 24.11, 27.79, 29.60, 29.83, 29.87, 29.95, 30.78, 32.14, 32.59, 45.61, 47.76, 53.83, 55.19, 160.99, 170.29. EI-MS (70 eV) *m/z* (rel. int.): 302 ([$M-H_2O$]$^+$, 26), 287 (100), 273 (12), 259 (100), 190 (11), 159 (12), 146 (10). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{20}H_{35}N_2^+$] 303.2795; found 303.2794 [$MH-H_2O^+$]. Elemental Anal. Calcd for $C_{20}H_{36}N_2O$ (320.28): C, 74.95; H, 11.32; N, 8.74. Found: C, 74.76; H, 11.29; N, 9.16.

4.4.11. (1*S*,4*R*)-3-(Cyclohexylmethylimino)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime 4b

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and cyclohexanemethylamine (3.06 g, 27 mmol). Yield 2.59 g (52%), mp 127–129 °C, $[\alpha]_D^{20} = +72.4$ (c 0.5, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.78 (s, 3H, CH_3), 0.86–0.95 (m, 1H, CH_2), 0.95 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.09–1.14 (m, 1H, CH_2), 1.16–1.26 (m, 2H, Chex), 1.39–1.50 (m, 2H, Chex), 1.61–1.74 (m, 8H, CH_2 + Chex), 1.89–1.95 (m, 1H, CH_2), 3.22 (d, 1H, J = 4.4 Hz, CH), 3.55 (dd, 1H, J = 13.6 Hz, J = 6.4 Hz, CH_2Chex), 3.72 (dd, 1H, J = 13.6 Hz, J = 6.4 Hz, CH_2Chex). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.80, 18.12, 20.37, 24.15, 26.40, 26.95, 31.60, 32.59, 39.79, 45.57, 47.85, 55.16, 60.45, 161.74, 169.48. EI-MS (70 eV) *m/z* (rel. int.): 258 ([$M-H_2O$]$^+$, 23), 243 (100), 229 (13), 215 (94). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{17}H_{27}N_2^+$] 259.2252; found 259.2250 [$MH-H_2O$]$^+$. Elemental Anal. Calcd for $C_{17}H_{28}N_2O$ (276.42): C, 73.87; H, 10.21; N, 10.13. Found: C, 73.73; H, 9.71; N, 10.24.

4.4.12. (1*S*,4*R*)-3-(Furan-2-ylmethylimino)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime 4c

The title compound was synthesized from monoxime **13** (3.26 g, 18 mmol) and furfurylamine (2.62 g, 27 mmol). Yield 3.09 g (66%), mp 142–145 °C, $[\alpha]_D^{20} = +87.8$ (c 0.5, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.80 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.41–1.46 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.71–1.77 (m, 1H, CH_2), 1.91–1.97 (m, 1H, CH_2), 3.22 (d, 1H, J = 4.5 Hz, CH), 4.89 (d, 1H, J = 16.8 Hz, CH_2Fur), 5.04 (d, 1H, J = 16.8 Hz, CH_2Fur), 6.18–6.19 (m, 1H, Fur), 6.29–6.30 (m, 1H, Fur), 7.33–7.34 (m, 1H, Fur), 8.07 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.61, 18.06, 20.42, 24.04, 32.46, 45.89, 47.79, 51.14, 55.40, 106.26, 110.35, 141.66, 154.83, 161.80, 171.46. EI-MS (70 eV) *m/z* (rel. int.): 242 ([$M-H_2O$]$^+$, 38), 227 (100), 213 (14), 199 (95), 185 (14), 121 (15), 106 (15). HR-FT-MALDI-MS (DCTB): *m/z* calcd for [$C_{15}H_{19}N_2O^+$] 243.1492; found 243.1492 [$MH-H_2O$]$^+$. Elemental Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76. Found: C, 69.28; H, 7.81; N, 10.81.

4.5. (1*R*,7*S*)-4-[2-(Diphenylphosphanyl)phenyl]-1,10,10-trimethyl-3,5-diazatricyclo[5.2.1.0^{2,6}]deca-2(6),3-diene 17

n-BuLi (4.15 mL, 6.64 mmol, 1.6 M sol. in hexane) was added to a solution of **1a** (1.676 g, 6.64 mmol) in dry THF (20 mL) under N_2, at 0 °C and the reaction mixture stirred for 10 min. Iodomethane (1 g, 7.2 mmol) was added, the reaction mixture stirred for 1 h at 0 °C and quenched with water. The product was extracted with ether (3 × 50 mL), combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford pure *N*-methyl derivative. Yield 1.68 g (95%), oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.90 (s, 6H, CH_3), 0.98–1.03 (m, 2H, CH_2), 1.36 (s, 3H, CH_3), 1.72–1.77 (m, 1H, CH_2), 1.92–1.96 (m, 1H, CH_2), 2.84 (s, 1H, CH), 3.67 (s, 3H, *N*-CH_3), 7.27–7.30 (m, 1H, Ph), 7.36–7.39 (m, 2H, Ph), 7.56–7.59 (m, 2H, Ph). EI-MS (70 eV) *m/z* (rel. int.): 266 (M^+, 42), 251 (100), 237 (15), 223 (56), 118 (17), 77 (15). *n*-BuLi (1.03 mL, 1.65 mmol, 1.6 M sol. in hexane) was added to a solution of the

N-methyl derivative (399 mg, 1.5 mmol) in dry THF (40 mL) under N_2 and the reaction mixture stirred for 30 min at 0 °C. A solution of Ph_2PCl (350 mg, 1.58 mmol) in THF (2 mL) was added dropwise and stirred for 12 h at 25 °C. NH_4Cl (aq) was added and the reaction mixture extracted with ether (2 × 50 mL), the combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude product was purified by CC (SiO_2; CH_3OH–$CHCl_3$ 1:100). Yield 1.73 g (61%), mp = 192–195 °C, $[\alpha]_D^{20} = +9.0$ (*c* 0.5, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.77 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.81–0.88 (m, 2H, CH_2), 1.25 (s, 3H, CH_3), 1.55–1.62 (m, 1H, CH_2), 1.71–1.76 (m, 1H, CH_2), 2.53 (d, 1H, *J* = 4.9 Hz, CH), 3.35 (s, 3H, *N*-CH_3), 7.34–7.65 (m, 14H, Ph + PPh_2). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 11.32, 18.96, 20.02, 26.29, 32.51, 33.51, 49.38, 52.66, 59.59, 127.91, 128.05, 128.24, 128.37, 131.17, 131.35, 131.46, 131.68, 131.79, 131.97, 133.14, 133.25, 133.85, 133.98, 134.06, 138.95, 144.22. HR-FT-MALDI-MS (3-HPA): *m*/*z* calcd for $[C_{30}H_{32}N_2P^+]$ 451.2225; found 451.2235 $[MH^+]$. Elemental Anal. Calcd for $C_{30}H_{31}N_2P$ (450.55): C, 79.97; H, 6.94; N, 6.22. Found: C, 80.01; H, 6.96; N, 6.24.

4.6. X-ray analysis

The X-ray measurements were carried out on a Bruker Kappa CCD diffractometer equipped with graphite monochromator (MoK_a radiation, λ = 0.71073 Å) and an Oxford Cryostream low-temperature device. Crystallographic data for **16**, $C_{18}H_{13}N_5$, unit cell dimensions from 8359 reflexions at 173 K: monoclinic *C*2/*c*, *a* = 38.0653(2), *b* = 3.8117(10), *c* = 23.905(1) Å, β = 125.422 (2)° (HKL, Scalepack).[40] The structure was solved by direct methods (SIR97[41]). Hydrogen positions were located from a difference Fourier map, non-hydrogen atoms were refined anisotropically, and H-atoms isotropically by full-matrix least-squares analysis with 2585 independent reflexions ($1872 > 2\sigma(I)$) (SHELXL-97[42]). *R*(obs) = 0.060, *wR*(obs) = 0.145.

Crystallographic data for **4b**, $C_{17}H_{28}N_2O$, unit cell dimension from 33268 reflexions at 293 K: *P*212121, *a* = 13.272(2), *b* = 21.560(3), *c* = 22.970(2). The structure was solved by direct methods (SHELXS-97). Hydrogen positions were located from a difference Fourier map, non-hydrogen atoms were refined anisotropically, H-atoms isotropically by full-matrix least-squares analysis with 7843 independent reflexions ($5176 > 2\sigma(I)$) (SHELXL-97). *R*(obs) = 0.076.

CCDC 679056 (**16**) and CCDC 686644 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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