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ORIGINAL PAPER

Formation of 3-azabicyclo[3.3.1]non-3-enes: imino amides vs. imino alkenes

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Abstract An effective method for synthesising alkaloid-like compounds containing the 3-azabicyclo[3.3.1]non-3-ene core structure was successfully carried out in a stereoselective manner via the bridged-Ritter reactions. Important optically active 6-alkyl(aryl)amido-4-alkyl(aryl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-enes (imino amides) and 4-alkyl(aryl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]nona-3,6-dienes (imino alkenes) were obtained in one step from (−)-β-pinene and the respective nitriles in the presence of concentrated H_2SO_4. The relative compositions of these products were controlled by varying the reaction conditions. Kinetic studies were conducted to enable a mechanistic understanding of the reaction pathways.

Keywords Bridged-Ritter reactions · Stereoselective reactions · Alkaloid-like compounds · Terpenes · Kinetic studies

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Introduction

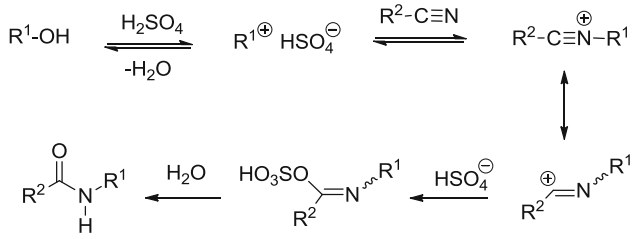
A typical Ritter reaction comprises the reaction of a carbenium ion (usually generated in situ) with a nitrile, and then quenching with water affords an amide product, as shown in Scheme 1. In its widest terms, however, the Ritter reaction is considerably more than this. It encompasses all reactions of a carbenium ion with a nitrile group, followed by subsequent event(s). When viewed in this light, it is seen to be one of the more versatile reactions in organic synthesis [1–9].

One fascinating variant is the bridged-Ritter reaction, examples of which are illustrated in Scheme 2. In such instances, the nitrile reagent essentially clips across a cyclic precursor in a transannular process to yield a cyclic imine (Schiff base) product [10, 11].

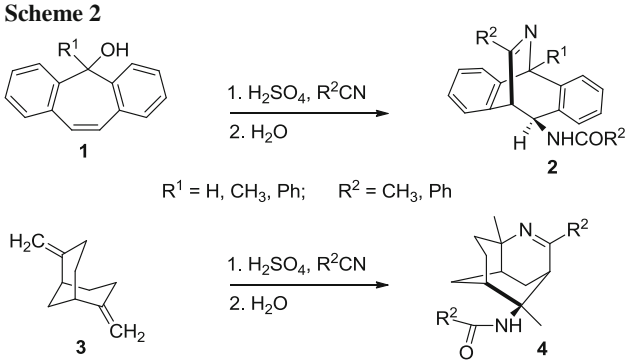
Our earlier work on bridged-Ritter reactions [11–17] clearly established that multi-cyclic imines, such as **2** and **4** chemical scaffolds, can be obtained in a single step from inexpensive starting materials (Scheme 2). For instance, some of these (like **4**) are 3-azabicyclo[3.3.1]non-3-enes, nitrogen-containing molecules that are highly reminiscent of the natural alkaloid derivatives. For this reason, we refer to these compounds as alkaloid-like compounds. The uniqueness of these cyclic compounds lies in their structural similarity to that of the bioactive but rare *Aristotelia* alkaloids (five species are known so far) [18–20]. The 3-azabicyclo[3.3.1]nonane structure can be found in the core structure of known bioactive alkaloids such as (+)-aristolone, (+)-aristoteline, (−)-serratoline, and (+)-aristelone (Fig. 1).

Elegant examples of asymmetric bridged-Ritter reactions were demonstrated by Marschoff [21–23], where (+)-limonene underwent a bridged-Ritter reaction with CH_3CN in the presence of $HClO_4$ to produce an optically active

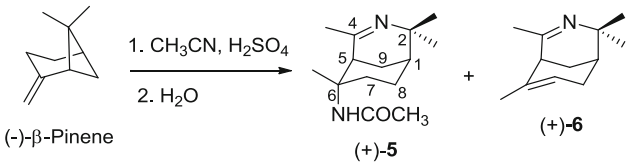
Scheme 1



Scheme 2



Scheme 3



(*1R*,*5R*,*6R*)-6-acetamido-2,2,4,6-tetramethy-3-azabicyclo [3.3.1]non-3-ene. The absolute stereochemistry of this compound was confirmed by X-ray analysis [24] with the reported specific optical rotation $[\alpha]_D^{25} = -144.1°$ (c = 1.3, $CHCl_3$) [25, 26]. Similar asymmetric bridged-Ritter processes also occurred using a variety of other terpenoid substrates [26].

As part of our alkaloid-like drug discovery program, we aim to develop feasible synthetic pathways that allow quick access to alkaloid-like chemical scaffolds that can be used to produce a library of alkaloid-like compounds for drug discovery.

In this article, we describe the detailed stereospecific synthesis of chiral 3-azabicyclo[3.3.1]non-3-enes via the bridged-Ritter reaction conditions, starting from (−)-β-pinene with acetonitrile, chloroacetonitrile, and benzonitrile. We further explore the selectivity outcome of the products under different reaction conditions and investigate the reaction mechanisms based on the study of time-dependent reactive intermediates and products, monitored by GC/MS analyses.

Results and discussion

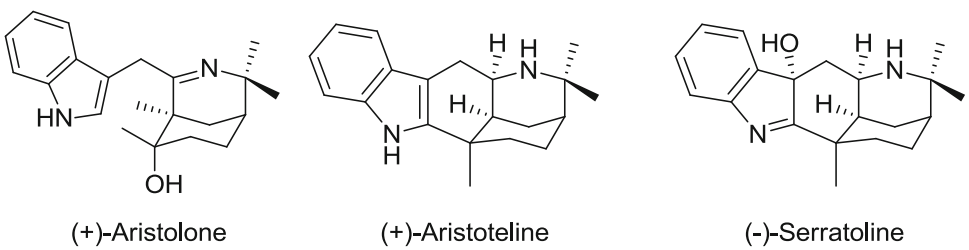
Synthesis of chiral cyclic-imines from (−)-β-pinene and CH_3CN

The use of (−)-β-pinene as the starting material was investigated in our bridged-Ritter reactions. When (−)-β-pinene was treated with acetonitrile, in the presence of concentrated H_2SO_4 [12], optically active imino amide (+)-**5** and imino alkene (+)-**6** were obtained in the ratio of 2.78:1 (Scheme 3). Compound (+)-**5** was obtained in 64 % yield under concentrated H_2SO_4 conditions. This is an improvement of the isolated yield in comparison to the reaction of (−)-β-pinene with CH_3CN, using $HClO_4$ as the protic acid, where the yields were reported to be only between 12 and 36 % [27]. The assignment of configuration of (+)-**5** was deducted on the grounds of chemical path stereospecificity [25] to be (*1S*,*5S*,*6S*) with the expected specific rotation of $[\alpha]_D^{25} = +144.1°$, based on the specific rotation of the corresponding opposite enantiomer [26]. The optical purity of (+)-**5** was directly determined from its observed rotation ($[\alpha]_D^{25} = +108°$) to be 75 % *e.e.*

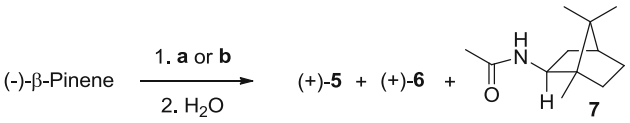
Imino alkene (+)-**6** was also obtained under this study in which concentrated H_2SO_4 was used as an alternative to toxic mercury nitrate as previously reported by Delpech et al. [27, 28] for the synthesis of (±)-**6** from (−)-α-pinene.

The ^{1}H NMR spectrum reveals the alkene proton (H-7) at 5.35 ppm as a complex tdd. The C-6 methyl group appears at 1.80 ppm as a ddd. The ^{13}C NMR spectrum showed two quaternary signals at 167.0 and 134.5, which

Fig. 1 Structures of bioactive *Aristotelia* alkaloids



Scheme 4



a: CH_3CN, H_2SO_4/CH_3CO_2H (1:1), 50 °C, 24 h;
b: CH_3CN, H_2SO_4/CH_3CO_2H (1:10), 0 °C, 30 min, r.t. 23.5 h.

Table 1 Summary of product composition of polar bridging Ritter reactions

Reaction conditions	Composition/%		
	(+)-**5**	(+)-**6**	**7**
a	65	22	10
b	51	11	4

are due to the imine carbon (C-4) and the alkene carbon (C-6), respectively. The optical rotation of compound (+)-**6** was found to be $[\alpha]_D^{25} = +9.1°$ ($c = 0.95$, $CHCl_3$).

Polar solvents, such as acetic acid, were reported to increase the yields in Ritter reactions as they could increase the nucleophilicity of the nitrile and the stability of the carbenium ion [29, 30]. The polar reaction conditions reported by Bishop et al. [11] were adopted for the reaction of (−)-β-pinene and acetonitrile in two attempted methods (**a** and **b**). The conditions and outcome for each reaction are summarised in Scheme 4 and Table 1.

The results of these reaction conditions in method **a** and **b** revealed the formation of (+)-**5** and (+)-**6** in the ratios of 2.95:1 and 5:1. This clearly indicates that the use of acetic acid only provided a modest increase of (+)-**5** over (+)-**6** in method **a**. In the case of method **b**, although the formation of (+)-**5** has somewhat improved over that of (+)-**6**. However, the downside was the reduction of the overall yields of the products. In attempts to optimise the formation of (+)-**5**, we also observed the formation of an unexpected isobornylacetamide **7** in both method **a** and **b**, in 10 and 4 % yields, respectively (Table 1).

The HRMS of **7** reveals the exact mass of 196.16593, which corresponds to $C_{12}H_{22}NO$ ($[M + H]^+$). NMR spectral data of **7** are in agreement to those previously reported in the literature [31]. The optical rotation of compound **7** was found to be $[\alpha]_D^{25} = +20.3°$ ($c = 0.47$, $CHCl_3$). Forster [32, 33] reported the specific optical rotation of (−)-*exo*-*N*-isobornylacetamide [(−)-**7**] to be $[\alpha]_D^{25} = -19.5°$. This stereochemical outcome was confirmed by the work by Zhou et al. [34]. On the basis of the optical rotation of compound **7**, one would infer that this compound is the (+)-*exo*-*N*-isobornylacetamide. The X-ray analysis has revealed that the structure contained two

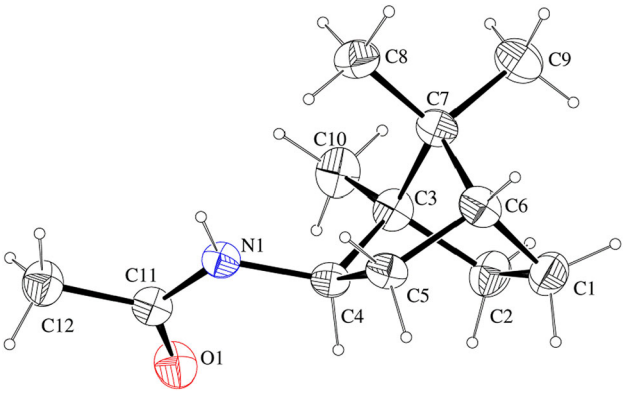


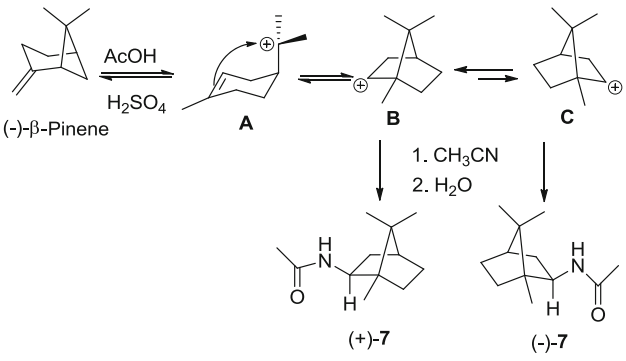
Fig. 2 ORTEP diagram of the structure of compound **7**, showing the relative stereochemistry of the compound

molecules, and they are in the centrosymmetric space group C2/c. This indicates compound **7** is indeed a racemic mixture. The relative stereochemistry of **7** is shown in Fig. 2.

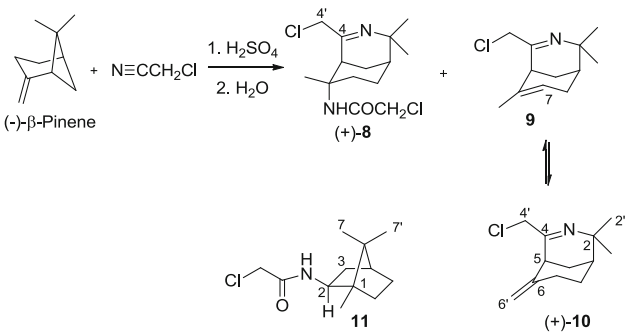
Under Ritter reaction conditions, Carman et al. [31] reported the formation of (±)-*exo*-*N*-isobornylacetamide **7** from the reaction of (+)-camphene with CH_3CN in the presence of H_2SO_4/acetic acid. The racemic formation was further confirmed by Hanzawa et al. [35] on the reaction of chiral (−)-isobornyl acetate with benzonitrile to give the racemic (±)-*exo*-*N*-isobornylbenzamide. The racemisation was explained by the isobornyl carbocation intermediate that underwent the 6,2-hydride shift to form two equal carbocations.

In our case, the formation of compound **7** was unexpected, and its optical rotation contradicts the X-ray analysis. The mechanism in Scheme 5 has been proposed to explain the formation of (±)-**7**. The carbenium ion **A** underwent intermolecular cyclisation to give isobornyl carbocation **B**, which underwent the 6,2-hydride shift to form the minor carbocation intermediate **C**, in a lower proportion than that of **B**. Both intermediates underwent

Scheme 5



Scheme 6



nucleophilic addition with CH_3CN and then quenching with water afforded racemic mixture of **7**.

The bridging Ritter reaction between (−)-β-pinene and chloroacetonitrile

When (−)-β-pinene was treated with chloroacetonitrile, under concentrated H_2SO_4 conditions, optically active imino amide (+)-**8**, imino alkene (+)-**10**, and the isobornylamide **11** were obtained (Scheme 6). The three compounds were isolated by silica column chromatography to give (+)-**8**, (+)-**10**, and **11** in the yields 31, 23, and 19 %, respectively.

The specific rotation of compound (+)-**8** was found to be $[\alpha]_D^{25} = +90.8°$ ($c = 1.06$, $CHCl_3$). The ^{1}H NMR spectrum revealed the presence of the two new CH_2 groups; the group at C-4′ appears as two separate doublets at 4.18 and 4.03 ppm, while the chloroacetamide group ($COCH_2Cl$) as a broad singlet at 4.02 ppm. The carbons of these were also observed in the ^{13}C spectrum at both 49.8 and 43.1 ppm, respectively. Other characteristic features of **8** were also observed, such as the three CH_3 groups at 31.2, 26.5, and 25.9 ppm.

Structure of compound (+)-**10** was fully characterised by spectral analysis. The ^{1}H NMR spectrum showed the two terminal alkene protons (CH_2-6′) to appear as two distinct singlets at 4.86 and 4.78 ppm. These two resonances were confirmed to correlate to the same C-6′ by HSQC. It is noteworthy that the H-5 appears at 3.36 ppm, further downfield than the corresponding proton (2.5 ppm) found in (+)-**6**. ^{13}C NMR analysis confirms all the carbons required. The specific rotation of compound (+)-**10** was found to be $[\alpha]_D^{25} = +49.1°$ ($c = 0.57$, $CHCl_3$).

It is suggested that (+)-**10** was the rearranged product of **9** (Scheme 6). The presence of both compounds was initially observed in the ^{1}H NMR spectrum of the crude mixture. The same sample was further monitored by obtaining its ^{1}H NMR spectra over a period of time. The last ^{1}H NMR spectrum was only shown to contain (+)-**10**. This finding suggests that compound **9** formed in the initial step of the bridged-Ritter reaction. It then underwent double-bond migration over time to form the less constrained (+)-**10** [36].

The identity of isobornyl chloroacetamide **11** was confirmed by spectral analysis. The ^{1}H NMR spectrum revealed the presence of the new CH_2 group as a doublet at 4.04 ppm that was correlated to the ^{13}C peak at 42.9 ppm by HSQC. It also shows H-2 at 3.89 ppm as a complex td. The two methyl groups at C-7′ appear as two singlets at 0.84 and 0.95 ppm, respectively. The third methyl at C-1′ was also observed at 0.84 ppm. The low specific optical rotation of **11** ($[\alpha]_D^{25} = +1.4°$) suggests that racemisation may also occur in the formation of compound **11**, in a similar manner to that of compound **7** (Scheme 5).

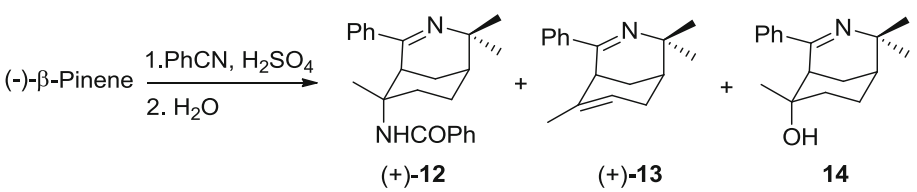
In contrast to its counterpart compound **7**, compound **11** was formed without the use of acetic acid. Despite this, the behaviour of the carbenium ion in chloroacetonitrile allowed for a much larger mole ratio of **11** to form in contrast to **7**.

Bridged Ritter reaction of (−)-β-pinene and PhCN

The reaction of (−)-β-pinene with PhCN under our reaction conditions provided the imino amide (+)-**12** and imino alkene (+)-**13**. The outcome of the reaction revealed that (+)-**12** and (+)-**13** were the major and minor products, in 42 and 24 % yields, respectively (Scheme 7).

The ratio of (+)-**12** and (+)-**13** was reversed by varying the reaction conditions. The cyclic imino alkene (+)-**13** was obtained as the major product (74 %) over the cyclic imino amide (+)-**12** (14 %) when the reaction mixture was left to stand at room temperature overnight without stirring, allowing the PhCN to diffuse slowly into the aqueous layer where the reaction took place. Beside (+)-**12** and (+)-**13**,

Scheme 7



there was also a small trace of compound **14** with molecular mass of $m/z = 257$ as detected by GC/MS of the crude product. Due to its small quantity, it was not possible to isolate compound **14** for a full analysis, after a few attempts had been made.

Kinetic studies

Kinetic studies were undertaken to understand the reaction mechanisms for the formation of (+)-**12**, (+)-**13** by investigating the rate at which intermediates and products formed over time. The reaction was monitored by direct removal of reaction aliquots at a time interval; these were then quenched with water and followed by GC–MS analysis. Figure 3 shows the composition of products (+)-**12** and (+)-**13**, and the intermediate **14** (molecular weight of 257), in each of the GC/MS samples at specific times.

At the 30-min mark, the studies show the amount of (+)-**12** was 17 % and almost equal to that of **14** (16 %), while the concentration of (+)-**13** was at the lowest (4 %). The composition of (+)-**12** and (+)-**13** increases almost in a linear fashion at a similar rate, while that of compound **14** proportionally decreased. The presence of intermediate alcohol **14** in the reaction mixture has provided a plausible reaction pathway, which suggests that the reaction proceeded through the intermediate **E** as shown in Scheme 7. Intermediate **E** came about via the nucleophilic addition of **A** to give the intermediate **D**. **D** further underwent intramolecular cyclisation to form the carbenium ion **E** from which the three compounds (+)-**12**, (+)-**13**, and **14** were derived. This was evidenced by (1) the composition of (+)-**12**, (+)-**13**, and **14** over the reaction time at 0 °C at the 30-min mark (4:1:4) and

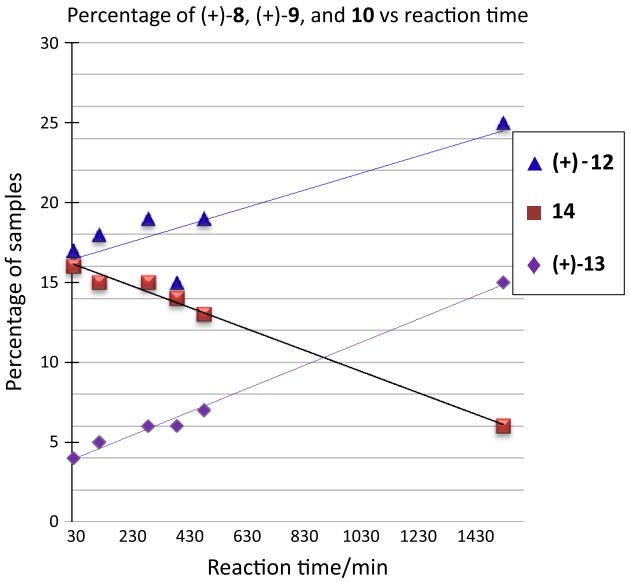
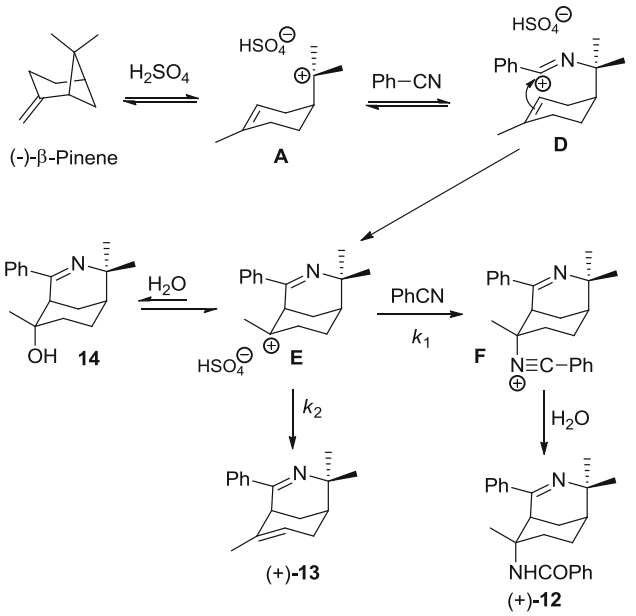


Fig. 3 Reaction profile showing the composition of (+)-**12**, (+)-**13**, and **14** at specific times

Scheme 8



(2) the eventual increase in concentration of (+)-**12** and (+)-**13**, corresponding to the decrease of **14**. The formation of **14** dominated at low temperature. In contrast, at room temperature, the major products were eventually (+)-**12** and (+)-**13**. The data suggest that the transformation of **E** into **14** becomes reversible at moderate temperature, and the rate-determining step (k_1) is the reaction of **E** with another mole of PhCN to form **F** and eventually (+)-**12** (Scheme 8).

Conclusions

This study has led to a better understanding of the chemistry involved in the bridged-Ritter reaction and products that formed. The significance of the bridged-Ritter reaction conditions was determined. It was concluded that (1) a single enantiomer of either cyclic imine amide or imine alkene can be obtained in one step from the reaction of (−)-β-pinene and a nitrile and (2) the yields and the ratios of these products depend on the reaction conditions. It was observed that the stronger acidic conditions provide the highest yields. With more polar conditions, the yields were compromised while allowing for the formation of unexpected the isonorbornyl derivatives. The kinetic studies have allowed a proposed mechanism for the reaction to being uncovered.

Experimental

Reagents and analytical grade solvents were purchased from commercial sources. Progress of reactions was

monitored by TLC analysis, performed on aluminium-backed Merck 60 GF_{254} silica gel or Merck 60 GF_{254} neutral alumina gel with UV detection at 254 nm and/or Dragendorff's reagent. Compounds were purified by column chromatography using Merck flash either neutral alumina or silica gel (40–63 μm). Purity of compounds was determined by ^{1}H NMR and GC/MS. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 500-MHz spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C) in deuterated chloroform ($CDCl_3$), unless otherwise specified. NMR assignments were based on COSY, HSQC, and DEPT experiments. ^{1}H and ^{13}C NMR assignments are based on the numbering system used on the systematic name. Gas chromatographer/mass spectrometer (GC/MS) analysis was carried out on an Agilent 6890 series gas chromatographer coupled to an Agilent 5973 network MS (EI) mass spectrometer. Separation was achieved on a Zebron ZB-5mS (5 % polysilphenylene, 95 % polydimethylsiloxane) capillary column (30 m × 0.25 mm × 0.25 μm). Helium was used as the carrier gas at a flow rate of 1.2 cm^3 min^{-1}. The injection was done by three front inlet washes, three samples pumps, and three post washes. The injection port was in split mode, with a split flow rate of 1.7 cm^3 min^{-1}. The mass spectrometer was operated from 50 to 290 amu, in positive mode, and a solvent delay of 2 min was applied. The following temperature program was used: 50 °C maintained for 2 min, then ramped at 10 °C min^{-1} to 290 °C and held for 4 min. High-resolution mass spectra were obtained on an Agilent 6510 Accurate Mass Q-TOF Mass Spectrometer, equipped with an ESI source.

Bridged Ritter reaction of (−)-β-pinene with CH_3CN

Sulfuric acid (18 M, 4.2 cm^3, 78.7 mmol) was stirred at 0 °C in a flask fitted with a reflux condenser and a drying tube. To the reaction flask was added 21 cm^3 acetonitrile (0.4 mol). A solution of 1.0 g (−)-β-pinene (1.15 cm^3, 7.34 mmol) in 5 cm^3 benzene was added drop-wise, via the condenser, into the reaction mixture. A further 0.5 cm^3 of benzene was used to wash all traces of (−)-β-pinene into the reaction flask. The mixture was stirred at 0 °C for 30 min and then at room temperature for 24 h. Water (30 cm^3) was added into the reaction mixture and stirred for 30 min. The resulting mixture was washed with light petroleum ether, and then the aqueous layer was basified with 2 M solution of sodium hydroxide to pH > 10. The aqueous layer was extracted with chloroform (40 cm^3 × 3). The combined extracts were washed with 50 cm^3 water, dried over anhydrous Na_2CO_3, and filtered. The solvent was removed under reduced pressure to yield green viscous oil as the crude product. The crude product was purified by silica column chromatography using gradient elution from hexane to ethyl acetate/hexane (1:1) to provide (+)-**5**, (+)-**6** in 64 and 23 % yields, respectively.

N-((1S,5S,6S)-2,2,4,6-Tetramethyl-3-azabicyclo[3.3.1]-non-3-en-6-yl)acetamide (**5**, $C_{14}H_{24}N_2O$)

A green wax (1.106 g, 4.67 mmol, 64 % yield); $R_f = 0.73$ (neutral alumina, 10 % ethyl acetate/hexane); $[\alpha]_D^{25} = +108.0°$ ($c = 1$, CH_2Cl_2); IR (film): $\bar{\nu} = 3{,}295$, 3,073, 2,969, 2,935, 1,644, 1,544, 1,460, 1,372, 1,289, 1,210, 1,168, 1,110, 1,037, 894, 752, 665 cm^{-1}; ^{1}H NMR: $\delta = 5.32$ (br s, 1H, NH), 3.17 (br d, $J = 2.0$ Hz, 1H, H-5), 2.09 (s, 3H, CH_3-4′), 1.99 (s, 3H, $COCH_3$), 1.81 (ddd, $J = 2.0$, 2.0, 11.0 Hz, 1H, Ha-9), 1.75 (dd, $J = 2.0$, 2.0 Hz, 1H, H-1), 1.71 (ddd, $J = 2.5$, 14.0 Hz, 1H, Ha-8), 1.57 (ddd, $J = 4.0$, 6.0, 10 Hz, 1H, Hb-9), 1.54 (dd, $J = 4.5$, 8.5 Hz, 1H, Ha-7), 1.47 (s, 3H, CH_3-6′), 1.44 (dd, $J = 4.5$, 7.5 Hz, 1H, Hb-7), 1.40 (ddd, $J = 4.5$, 7.5, 10.0 Hz, 1H, Hb-8), 1.28 (s, 3H, CH_3-2′), 1.15 (s, 3H, CH_3-2′) ppm; ^{13}C NMR: $\delta = 169.8$ (C=O), 166.7 (C-4), 60.4 (C-6), 57.0 (C-2), 55.7 (CH-1), 40.3 (CH-5), 33.2 (CH_2-7), 31.7 (CH_3-4′), 29.8 (CH_3-6′), 24.6 ($COCH_3$), 24.6 (CH_2-9), 24.1 (CH_2-8), 21.1 (CH_3-2′), 14.2 (CH_3-2′) ppm; GC–MS (EI): $R_t = 17.18$ min, *m/z* (%) = 236 (60, M^+), 221 (25), 177 (70), 136 (68); HR-ESI–MS: $[M + H]^+$ found 237.19780, $C_{14}H_{25}N_2O$ requires 237.19669.

(1S,5S)-2,2,4,6-Tetramethyl-3-azabicyclo[3.3.1]nona-3,6-diene (**6**, $C_{12}H_{19}N$)

A yellow oil (0.311 g, 1.76 mmol, 23 % yield); $R_f = 0.61$ (silica, 50 % ethyl acetate/hexane, trace amount of Et_3N); $[\alpha]_D^{25} = +9.07°$ ($c = 0.95$, $CHCl_3$); IR (film): $\bar{\nu} = 2{,}965$, 2,926, 2,870, 1,665, 1,454, 1,359, 1,330, 1,296, 1,253, 1,054, 1,035, 1,018, 884, 821, 799 cm^{-1}; ^{1}H NMR: $\delta = 5.35$ (tdd, $J = 1.5$, 2.5, 3.0 Hz, 1H, H-7), 2.50 (br s, 1H, H-5), 2.22 (ddd, $J = 1.5$, 2.5, 3.0 Hz, 1H, Ha-8), 2.18 (ddd, $J = 2.5$, 5.0, 7.5 Hz, 1H, Hb-8), 2.04 (s, 3H, CH_3-4′), 1.86-1.85 (m, 2H, Ha-9, H-1), 1.80 (ddd, 1.5, 2.5, 5.0 Hz, 3H, CH_3-6′), 1.56 (ddd, $J = 2.5$, 5.0, 11.5 Hz, 1H, Hb-9), 1.20 (s, 3H, CH_3-2′), 1.15 (s, 3H, CH_3-2′) ppm; ^{13}C NMR: $\delta = 167.0$ (C-4), 134.5 (C-6), 122.2 (CH-7), 58.5 (C-2), 40.4 (CH-5), 33.4 (CH-1), 31.8 (CH_3-4′), 28.9 (CH_2-8), 28.2 (CH_3-6), 28.0 (CH_3-2′), 25.5 (CH_2-9), 23.9 (CH_3-2′) ppm; GC–MS (EI): $R_t = 10.95$ min, *m/z* (%) = 177 (15, M^+), 136 (35); HR-ESI–MS: $[M + H]^+$ found 178.15790, $C_{12}H_{20}N$ requires 178.15903.

Bridged-Ritter reaction of (−)-β-pinene with CH_3CN in acetic acid

Method **a**: Sulfuric acid (18 M, 4.5 cm^3) was diluted with 0.5 cm^3 water and stirred in a flask fitted with a reflux condenser and a drying tube at room temperature. To the reaction flask, 21 cm^3 acetonitrile (0.40 mol) was added. A solution of 1.0 g (−)-β-pinene (1.15 cm^3, 7.34 mmol) in 5 cm^3 glacial acetic acid was added drop-wise, via the condenser, into the reaction mixture. A further 0.5 cm^3 of

acetic acid was used to wash all traces of (−)-β-pinene into the reaction flask. The reaction was then heated to ~50 °C for 24 h. The reaction mixture was worked up by the addition of 20 cm^3 water and then basified with 4 M NaOH until pH was >10. The reaction mixture was worked up to give the crude product (1.857 g) and purified as previously described to give 1.121 g **5** (65 %), 0.295 g **6** (22 %), and 0.146 g **7** (10 %). Compound **7** was further purified by recrystallization from hexane to give pale yellow crystals.

Method **b**: (−)-β-pinene (1.46 g, 10.7 mmol) was added to a stirred mixture of 1.5 cm^3 98 % sulfuric acid, 10 cm^3 acetonitrile, and 15 cm^3 glacial acetic acid at 0 °C. The reaction was stirred for 30 min at 0 °C and then overnight at room temperature. The reaction was then worked up to give the crude product (2.174 g), purified as previously described to give 1.292 g **5** (51 %), 0.22 g **6** (11 %), and 0.086 g **7** (4 %).

N-((1S,2S,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)-acetamide (**7**, $C_{12}H_{21}NO$)

A pale yellow solid (58.2 mg, 0.298 mmol, 4 %); m.p.: 125 °C; $R_f = 0.68$ (silica, 50 % ethyl acetate/hexane); $[\alpha]_D^{25} = +20.3°$ ($c = 0.47$, $CHCl_3$); IR (film): $\bar{\nu} = 3{,}314$, 2,955, 2,875, 1,651, 1,547, 1,461, 1,372, 1,330, 1,291 cm^{-1}; ^{1}H NMR: $\delta = 5.35$ (br s, 1H, NH), 3.90 (ddd, $J = 4.5$, 4.5, 9.0 Hz, 1H, H-2), 1.96 (s, 3H, NCOC*H*$_3$), 1.86 (dd, $J = 9.0$, 13.0 Hz, 1H, H-3), 1.73 (dd, $J = 4.0$, 8.0 Hz, 1H, H-4), 1.70 (dddd, $J = 4.0$, 8.0, 12.0, 13.5 Hz, 1H, H-5), 1.56 (ddd, $J = 4.5$, 12.0, 13.0 Hz, 1H, H-3), 1.53 (ddd, $J = 4.0$, 8.5, 8.5 Hz, 1H, H-6), 1.23 (ddd, $J = 4.0$, 9.0, 13.5 Hz, H-6), 1.15 (ddd, $J = 4.0$, 9.5, 13.5 Hz, H-5), 0.90 (s, 3H, CH_3-1′), 0.83 (s, 3H, CH_3-7′), 0.82 (s, 3H, CH_3-7′) ppm; ^{13}C NMR: $\delta = 169.2$ (C=O), 56.8 (CH-2), 48.4 (C-7), 47.10 (C-1), 44.9 (CH-4), 39.2 (CH_2-3), 36.0 (CH_2-6), 27.0 (CH_2-5), 23.6 (CO*C*H$_3$), 20.3 (CH_3-1′), 20.3 (CH_3-7′), 11.7 (CH_3-7′) ppm; GC–MS (EI): $R_t = 14.19$ min, *m/z* (%) = 195 (30, M^+), 180 (10), 136 (40); HR-ESI–MS: $[M + H]^+$ found 196.16593, $C_{12}H_{22}NO$ requires 196.16567.

Bridging Ritter reaction between (−)-β-pinene and chloroacetonitrile

Sulfuric acid (18 M, 4.2 cm^3, 78.7 mmol) was stirred in a flask fitted with a reflux condenser and a drying tube at 0 °C. To the reaction flask, 25 cm^3 chloroacetonitrile (0.40 mol) was added. A solution of 1.0 g (−)-β-pinene (1.15 cm^3, 7.34 mmol) in 5 cm^3 benzene was added dropwise into the reaction mixture, via the condenser. A further 0.50 cm^3 of benzene was used to wash all traces of (−)-β-pinene into the reaction flask. After 30 min the reaction was allowed to reach room temperature and left to run for 2.5 h. The reaction was then quenched by the addition of 30 cm^3 water. The mixture was then basified with 2 M NaOH (until pH > 10). The aqueous layer was washed with petroleum spirits (2×50 cm^3) to remove any remaining pinene before extraction with $CHCl_3$ (2×15 cm^3) and drying with Na_2SO_4.

Within the petroleum spirits fraction, crystals that formed were filtered to give pure (+)-**8** (0.704 g). Petroleum spirits was removed from the filtrate to give a crude mixture (0.390 g) that was analysed by GC/MS to be mainly (+)-**10** and **11** with small quantities of (+)-**8** remaining. The chloroform extraction was also analysed by GC/MS after the solvent had been removed via reduced pressure to show it contained mainly **8**, with small quantities of (+)-**10** and **11**. The two crudes were therefore combined and purified via separation on an alumina column using a mobile phase of 15 % EtOAc and 85 % petroleum spirits. Elution from the column was monitored by TLC, using the same mobile phase, developed in $I_{2(g)}$ atmosphere. This resulted in isolation of a further **8** (0.306 g), as well as 0.511 g **10** and 0.468 g **11**.

2-Chloro-N-[(1S,5S,6S)-4-(chloromethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-en-6-yl]acetamide

(**8**, $C_{14}H_{22}Cl_2N_2O$)

A pale orange solid (1.011 g, 3.32 mmol, 31 %); m.p.: 152 °C; $R_f = 0.18$ (1.5:8.5 EtOAc/petroleum spirits); $[\alpha]_D^{25} = +90.8°$ ($c = 1.06$, $CHCl_3$); IR (neat): $\bar{\nu} = 3{,}280$, 3,098, 2,974, 2,953, 2,898, 2,872, 1,683, 1,653, 1,573, 1,459, 1,432, 1,343, 1,262, 1,107, 972, 890, 806, 725, 706, 692, 660 cm^{-1}; ^{1}H NMR: $\delta = 6.55$ (s, 1H, NH), 4.18 (d, $J = 11.0$ Hz, H1, H-4a') 4.03 (d, $J = 11.0$ Hz, H1, H-4b'), 4.02 (br s, 2H, COC*H*$_2$Cl), 3.41 (br s, 1H, H-5), 1.87 (br m, 1H, H-9a), 1.84-1.81 (m, 1H, H-8a), 1.76-1.70 (m, 3H, H-8b, H-9b, H-1), 1.60 (tt, $J = 4.0$, 14.0 Hz, H, H-7a), 1.46 (s, 3H, CH_3-6′), 1.35 (td, $J = 5.0$, 14.0 Hz, H-7b), 1.32 (s, 3H, CH_3-2′), 1.19 (s, 3H, CH_3-2′) ppm; ^{13}C NMR: $\delta = 165.0$ (C=O), 164.4 (C = N, C-4), 59.2 (C-6), 56.1 (C, C-2), 49.8 (CH_2, C-4′), 43.1 (CH_2, CO*C*H$_2$Cl), 36.9 (CH, C-5), 34.0 (CH, C-1), 32.3 (CH_2, C-7), 31.2 (CH_3, C-2′), 26.5 (CH_3, C-6′), 25.9 (CH_3, C-2′), 24.6 (CH_2, C-9), 24.4 (CH_2, C-8) ppm; GC–MS (EI): $R_t = 20.43$ min, *m/z* (%) = 304, 289 (11), 269 (100), 211 (13), 176 (23); HR-ESI–MS: $[M + H]^+$ found 305.11109, $C_{14}H_{23}Cl_2N_2O$ requires 305.11092.

(1S,5S)-4-(Chloromethyl)-2,2-dimethyl-6-methylene-3-azabicyclo[3.3.1]non-3-ene (**10**, $C_{12}H_{18}ClN$)

A dark brown oily substance (0.511 g, 2.42 mmol, 23 %); $R_f = 0.75$ (1.5:8.5 EtOAc/petroleum spirits); $[\alpha]_D^{25} = +49.1°$ ($c = 0.57$, $CHCl_3$); IR (neat): $\bar{\nu} = 2{,}970$, 2,935, 2,872, 2,209, 1,562, 1,460, 1,382, 1,262, 1,141, 909, 810 cm^{-1}; ^{1}H NMR: $\delta = 4.86$ (s, 1H, H-6a′), 4.78 (s, 1H, H-6b′), 4.13 (d, $J = 12.0$ Hz, 1H, H-4a′), 4.04 (d, $J = 12.0$ Hz, 1H, H-4b′), 3.36 (br s, 1H, H-5), 2.27–2.25 (m, 2H, CH_2-8),

2.01–1.88 (m, 1H, H-7a), 1.82 (s, 3H, CH_3-2′), 1.77 (1H, H1), 1.73–1.63 (1H, H-7b), 1.58–1.53 (2H, CH_2-9), 1.25 (s, 3H, CH_3-2′) ppm; ^{13}C NMR: δ = 164.5 (C-4), 122.3 (C-6), 110.5 (CH_2, C-6′), 60.2 (C-2), 45.0 (CH_2, C-4′), 41.5 (CH, C-5), 35.3 (CH, C-1), 30.9 (CH_3, C-2′), 29.7 (CH_2, C-9), 28.7 (CH_2, C-8), 25.0 (CH_2, C-7), 23.5 (CH_3, C-2′) ppm; GC–MS (EI): R_t = 13.02 min, *m/z* (%) = 211, 196 (6), 176 (100), 93 (44); HR-ESI–MS: $[M + H]^+$ found 212.11262, $C_{12}H_{19}ClN$ requires 212.11278.

2-Chloro-N-((1R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (**11**, $C_{12}H_{20}ClNO$)
A white solid with red flecks (0.468 g, 2.04 mmol, 19 %); m.p.: 70 °C; R_f = 0.51 (1.5:8.5 EtOAc/petroleum spirits); $[\alpha]_D^{25}$ = + 1.4° (*c* = 1.78, $CHCl_3$); IR (neat): $\bar{\nu}$ = 3,324, 2,952, 2,877, 1,654, 1,542, 1,458, 1,393, 1,371, 1,242, 1,032, 931, 793, 680 cm^{-1}; ^{1}H NMR: δ = 6.63 (1H, NH), 4.04 (d, *J* = 4.0 Hz, 2H, $COCH_2Cl$), 3.89 (td, *J* = 5.5, 9.0 Hz, 1H, H-2), 1.88 (dd, *J* = 9.0, 13.0 Hz, 1H, H-3a), 1.78 (t, *J* = 5.0 Hz, 1H, H-4), 1.73 (dddd, *J* = 5.0, 4.0 Hz, 1H, H-5a), 1.64–1.62 (m, 1H, H-3b), 1.59 (dd, *J* = 5.0, 12.0 Hz, 1H, H-6a), 1.30 (ddd, *J* = 4.0, 4.5, 12.0 Hz, 1H, H-6b), 1.18 (ddd, *J* = 2.5, 4.0, 12.0 Hz, 1H, H-5b), 0.95 (s, 3H, CH_3-7′), 0.84 (s, 6H, CH_3-7′, CH_3-1′) ppm; ^{13}C NMR: δ = 164.9 (C=O), 57.0 (CH, C-2), 54.3 (C-7), 51.8 (C-1), 44.9 (CH, C-4), 42.9 (CH_2Cl, C-4′), 38.9 (CH_2, C-3), 35.8 (CH_2, C-6), 27.0 (CH_2, C-5), 20.2 (CH_3, C-7′), 20.1 (CH_3, C-7′), 11.7 (CH_3, C-1′) ppm; GC–MS (EI): R_t = 15.65 min, *m/z* (%) = 229 (2, M^+), 194 (4), 136 (20), 121 (49), 95 (100); HR-ESI–MS: $[M + H]^+$ found 230.12343, $C_{12}H_{21}ClNO$ requires 230.12334.

Bridged Ritter reaction of (−)-β-pinene with PhCN

A mixture of 10 cm^3 PhCN (97 mmol) and 2 cm^3 18 M H_2SO_4 (37 mmol) in round-bottom flask fitted with a condenser and a drying tube was stirred at 0 °C. To the reaction mixture was added drop-wise a solution of 0.94 g (−)-β-pinene (1.1 cm^3, 6.9 mmol) in 8 cm^3 benzene via the condenser. The reaction mixture was stirred at 0 °C for 30 min and then left to stand, without stirring, at room temperature for 24 h. Water (2 cm^3) was added to the reaction flask, followed by 100 cm^3 diethyl ether. The mixture was then set to stir for 10 min. The ether layer was removed and the aqueous layer basified with 4 M NaOH until pH 12. The aqueous layer was then extracted with chloroform (30 cm^3 × 3). The combined extracts were washed with 30 cm^3 saturated NaCl solution, dried over anhydrous Na_2CO_3, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by a neutral aluminium oxide column chromatography (EtOAc/light petroleum, 1:9) to give 0.337 g (+)-**12** (14 %) and 1.193 g (+)-**13** (73 % yield).

The reaction was repeated, and after at 0 °C for 30 min, the reaction was further stirred at RT for 24 h. After the usual workup and purification, the reaction gave 1.03 g (+)-**12** (42 %) and 0.39 g (+)-**13** (24 %).

N-((1S,5S,6S)-2,2,6-Trimethyl-4-phenyl-3-azabicyclo-[3.3.1]non-3-en-6-yl)benzamide (**12**, $C_{24}H_{28}N_2O$)
A yellow solid (1.03 g, 42 %); m.p.: 59 °C; $[\alpha]_D^{25}$ = +147.6° (*c* = 1, CH_2Cl_2); R_f = 0.54 (neutral alumina, 10 % EtOAc/light petroleum); IR (film): $\bar{\nu}$ = 3,300, 2,969, 2,933, 1,641,1,570, 1,525 cm^{-1}; ^{1}H NMR: δ = 7.86 (dd, *J* = 1.5, 7.5 Hz, 2H, 2HAr), 7.77 (dd, *J* = 1.5, 7.5 Hz, 2H, 2HAr), 7.48 (td, *J* = 1.5, 7.5, 7.5 Hz, 1H, HAr), 7.45 (td, *J* = 1.5, 7.5, 7.5 Hz, 1H, 2HAr), 7.34–7.40 (m, 4H, 4HAr), 6.13 (s, 1H, HN), 4.40 (s, 1H, H-5), 2.03 (ddd, *J* = 2.5, 2.5, 13.0 Hz, 1H, H-9), 1.95–1.88 (m, 3H, H-9, 2H-8), 1.76–1.72 (m, 1H, H-1), 1.55–1.52 (m, 2H, 2H-7), 1.41 (s, 3H, CH_3-4′), 1.27 (s, 3H, CH_3-2′), 1.10 (s, 3H, CH_3-2′) ppm; ^{13}C NMR: δ = 167.2 (CO), 165.7 (C-4), 142.2 (C), 135.7 (C), 131.4 (2CH), 129.1 (2CH), 128.7 (2CH), 128.4 (2CH), 127.1 (CH), 126.7 (CH), 58.8 (C-2), 56.6 (C-8), 34.9 (CH-5), 34.3 (CH-1), 33.8 (CH_2-7), 31.6 ($COCH_3$), 27.4 (CH_3-2′), 26.6 (CH_3-2′), 24.9 (CH_2-9), 24.3 (CH_2) ppm; GC–MS (EI): R_t = 27.20 min, *m/z* (%) = 360 (60, M^+), 345 (25), 239 (70), 196 (85); HR-ESI–MS: $[M + H]^+$ found 361.22760, $C_{24}H_{29}N_2O$ requires 361.22744.

(4S,8S)-4,4,8-Trimethyl-2-phenyl-3-azabicyclo-[3.3.1]nona-2,7-diene (**13**, $C_{17}H_{21}N$)
A waxy solid (0.39 g, 24 %); $[\alpha]_D^{25}$ = +33.4° (*c* = 1, CH_2Cl_2); R_f = 0.83 (neutral alumina, 10 % EtOAc/light petroleum); IR (film): $\bar{\nu}$ = 2,965, 2,937, 2,888, 2,834, 1,631, 1,550 cm^{-1}; ^{1}H NMR: δ = 7.76 (dd, *J* = 1.5, 7.5 Hz, 2H, 2HAr), 7.61 (td, *J* = 1.5, 7.5, 7.5 Hz, 1H, HAr), 7.48 (td, *J* = 1.5, 7.5, 7.5 Hz, 2H, 2HAr), 5.32 (dd, 1H, *J* = 1.5, 1.5 Hz, H-7), 3.35 (br s, 1H, H-5), 2.27–2.23 (m, 2H, 2H-8), 2.40–1.96 (m, 2H, Ha-9, H-1), 1.78 (ddd, *J* = 2.0, 2.0, 12.1 Hz, 1H, H-9), 1.42 (qd, *J* = 1.5, 3.5 Hz, 3H, CH_3-6′), 1.32 (s, 3H, CH_3-2), 1.29 (s, 3H, CH_3-2) ppm; ^{13}C NMR: δ = 166.6 (C-4), 140.9 (C-6), 135.1 (C), 132.1 (CH), 129.1 (2CH), 128.2 (2CH), 121.3 (CH-7), 59.5 (C-2), 36.5 (CH-5), 33.8 (CH-1), 31.9 (CH_3-6′), 29.0 (CH_2), 27.7 (CH_3-2′), 25.8 (CH_2), 23.5 (CH_3-2′) ppm; GC–MS (EI): R_t = 17.65 min, *m/z* (%) = 239 (35), 198 (20); HR-ESI–MS: $[M + H]^+$ found 240.17740, $C_{17}H_{22}N$ requires 240.17522.

Kinetic study

A mixture of 10 cm^3 PhCN (97 mmol) and 2 cm^3 18 M H_2SO_4 (37 mmol) was stirred in a round-bottom flask fitted with a condenser and a drying tube at 0 °C. To the reaction mixture was added drop-wise a solution of 0.94 g (−)-β-

Table 2 Numerical details of the solution and refinement of compound **7**

Crystal data	
Chemical formula	$C_{12}H_{21}NO$
M_r	195.30
Crystal system, space group	Monoclinic, *C2/c*
Temperature/K	150
a, *b*, *c*/Å	11.0156(11), 9.7589(11), 21.982(3)
β/°	102.826(12)
V/Å^3	2,304.1(5)
Z	8
Radiation type	Mo *Kα*
μ/mm^{-1}	0.07
Crystal size/mm^3	0.12 × 0.09 × 0.03
Data collection	
Diffractometer	Bruker kappa APEXII CCD Diffractometer
Absorption correction	Multi-scan SADABS (Bruker, 2001)
T_{min}, T_{max}	0.992, 0.998
No. of measured, independent, and observed [$I > 2\sigma(I)$] reflections	16,124, 2,035, 1,541
R_{int}	0.081
$(\sin \theta/\lambda)_{max}$/Å^{-1}	0.595
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.061, 0.183, 1.09
No. of reflections	2,035
No. of parameters	131
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ /e Å^{-3}	0.36, −0.19

pinene (1.1 cm^3, 6.9 mmol) in 8 cm^3 benzene via the condenser. The reaction mixture was stirred at 0 °C for 30 min; an aliquot (0.5 cm^3) of the reaction mixture was taken and transferred into a sample vial that contained 1 cm^3 water. While stirring, the mixture in the sample vial was basified with 4 M NaOH until pH > 10. The aqueous mixture was extracted with $CHCl_3$ (by adding 1–2 cm^3 of $CHCl_3$ while stirring). After the two layers were separated, a small volume of the $CHCl_3$ was removed and set aside and kept at 0 °C for the GC/MS analysis. The process was repeated at the 30-min mark at 0 °C. After the reaction had been allowed to stir at room temperature, the process was repeated at an hour interval for another five aliquots (see the time intervals below).

After the last aliquot (at 5 h and 30 min mark), the reaction mixture was left to stir at room temperature for another 18 h and 30 min. Upon completion, the reaction was worked up following the general procedure. A sample of the crude product was prepared as part of the GC/MS analysis for the kinetic study.

X-ray crystallographic data

Suitable single crystals of compound **7** were selected under the polarizing microscope (Leica M165Z) and were picked up on a MicroMount (MiTeGen, USA) consisting of a thin polymer tip with a wicking aperture. The X-ray diffraction measurements were carried out on a Bruker kappa-II CCD diffractometer at 150 K by using graphite-monochromated Mo-Kα radiation ($\lambda = 0.710723$ Å). The single crystals, mounted on the goniometer using cryo loops for intensity measurements, were coated with paraffin oil and then quickly transferred to the cold stream using an Oxford Cryo stream attachment. Symmetry-related absorption corrections using the program SADABS [37] were applied, and the data were corrected for Lorentz and polarisation effects using Bruker APEX2 software [38]. All structures were solved by direct methods, and the full-matrix least-square refinements were carried out using SHELXL [39]. The non-hydrogen atoms were refined anisotropically. The molecular graphic was generated using Mercury [40]. Key crystallographic data and refinement details are presented in Tables 1 and 2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 960059. The data can be obtained free of charge via http://www.ccdc.cam.ac.uk, by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223/336-033, Tel.: (+44) 1223/336-408.

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