102. Enantioselective Synthesis of 3-Azabicyclo[4.3.0]nonane Alkaloids

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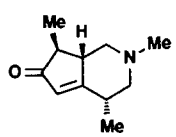
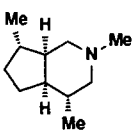
The stereospecific synthesis of the monoterpene alkaloids (–)-α-skytanthine ((–)-**2**), (–)-*N*-demethyl-δ-skytanthine ((–)-**7**), and (+)-epidihydrotecomanine (+)-**4** was achieved from a common intermediate **22**, which in turn was obtained from (1*R*,4*S*,1′*S*)-2-(1′-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene (**10**), *via* a ketene aza-*Claisen* rearrangement. The piperidine derivative (+)-**31**, formally the aza-analogue of (+)-isoiridomyrmecin, was also obtained from the same intermediate **22**.

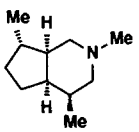
1. Introduction. – The extracts of *Tecoma stans*, a bush common to Latin America, have been used in folk medicine as hypoglycemics [1], and this activity was ascribed to its alkaloid tecomanine ((–)-**1**) [2]. Analogous saturated terpene alkaloids, *i.e.* **2**–**5**, were reported from plants of the genus *Skytanthus* and other *Tecoma* species [3], with varied biological activity [4]. Recently, *Takahashi* and coworkers [5] reported the isolation of the structurally related alkaloid altemicydin (**6**), which presented acaricidal and antitumour activity.



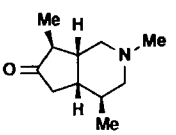
(-)-1



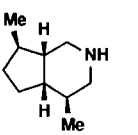
(+)-2



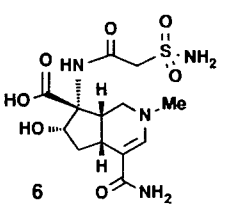
(+)-3



(+)-4



(-)-5



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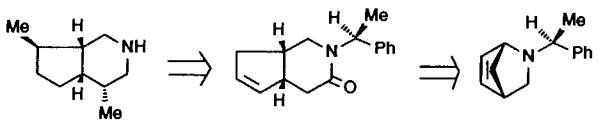
To date, few of these compounds were synthesised as homochiral entities. *Marini-Bettòlo* and his collaborators prepared (+)-α-skytanthine ((+)-**2**) and (+)-δ-skytanthine ((+)-**3**) from iridomyrmecin, nepetalic and nepetalinic acids, and thus established their absolute configurations [6]. *Oppolzer* and *Jacobsen* [7] reported the synthesis of (+)-α-skytanthine ((+)-**2**) and (+)-δ-skytanthine ((+)-**3**) *via* an elegant intramolecular Mg-ene reaction. *Kametani* synthesised (+)-tecomanine ((+)-**1**) [8]. It seemed desirable, however, to design a more flexible yet stereocontrolled route to these compounds and their analogues which would allow ready prediction of the absolute configuration of the

products. We now report the synthesis of (−)-α-skytanthine ((−)-**2**), (+)-epidihydrotecomanine (+)-**4**, and (−)-*N*-demethyl-δ-skytanthine (−)-**7** from a common intermediate **22**, readily obtainable in enantiomerically pure form, using (1-phenylethyl)amine as the original source of chirality. The retrosynthetic rationale for the synthesis is shown in *Scheme 1* for (−)-*N*-demethyl-δ-skytanthine ((−)-**7**). Part of this work already appeared in preliminary communications [9].

Scheme 1. *Retrosynthetic Analysis of the 3-Azabicyclo[4.3.0]nonane Skeleton*



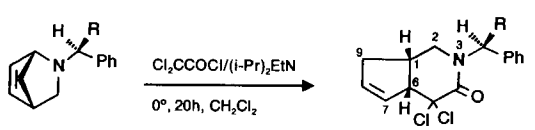
(−)-**7** **17** **10**

2. Results and Discussion. – 2.1. *Aza*-Diels-Alder *Reaction.* It was necessary to obtain the bicyclic starting materials in enantiomerically pure form (see *Scheme 1*). Using the aza-*Diels-Alder* reaction described by *Larsen* and *Grieco* [10], racemic 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**8**) was readily obtained. Attempts at resolving this amine by crystallisation with a variety of chiral acids failed. Samples of enantiomerically pure (+)- and (−)-**8** were obtained by repeated chromatography on an analytical column packed with *Chiracel-OD*. The quantities obtained, however, were insufficient for synthetic purposes.

It was, therefore, envisaged to prepare the enantiomerically pure bicycloheptanes by a diastereoselective aza-*Diels-Alder* reaction, followed by chromatographic purification of the diastereoisomeric adducts. Diastereoselective aza-*Diels-Alder* reactions were described using (1-phenylethyl)amine [10] [11] and amino acids [12] as the sources of chirality. We investigated the use of other commercially available benzylic amines for this reaction [13], but they provided no real advantage for the preparation of large quantities of starting material over the original method described by *Larsen* and *Grieco* [10], who used (1-phenylethyl)amine as the source of chirality. We reported elsewhere on the determination of the absolute configuration of these compounds [13].

2.2. *Ketene Aza*-Claisen *Rearrangement.* Initial studies of the ketene aza-*Claisen* rearrangement were carried out in the racemic series. When *rac*-2-benzyl-2-azabicyclo-[2.2.1]hept-5-ene (**8**) was treated with dichloroketene generated *in situ* from dichloroacetyl chloride with diisopropylethylamine ((i-Pr)$_2$EtN) in CH_2Cl_2 at 0°, 3-benzyl-5,5-dichloro-3-azabicyclo[3.2.0]non-7-en-4-one (**9**) was isolated after 20 h (*Scheme 2*).

Scheme 2. *Aza*-Claisen *Rearrangement*



8 R = H
10 R = Me

9 R = H
11 R = Me

The structure of the rearranged product **9** was secured by NMR spectroscopy (for its dechlorinated parent, see *Exper. Part*). Increasing the temperature reduced the yield of **9** and increased the quantity of tarry side-products. When repeatedly attempting the reaction of **8** with dichloroketene generated *in situ* from Zn and trichloroacetyl chloride, only unreacted starting material was recovered[1]).

The NMR assignments of **9** are obtained by homonuclear decoupling and confirmed by $^{13}C,^{1}H$ correlation experiments. The coupling constant of the protons at the ring junction H–C(1) and H–C(6) of 10.1 Hz is consistent with either a *cis*- or *trans*-ring junction. Evidence for a *cis*-junction is obtained from a difference NOE experiment, in which irradiation at 3.88 ppm (H–C(6)) results in substantial enhancements at 2.79 (H–C(1)), 5.79 (H–C(7)), and to a lesser extent, at 3.28 (H–C(2)) ppm. The coupling constants between H–C(1) and both H–C(2) protons are very similar (6.8 and 7.0 Hz, resp.). This agrees with what is predicted from energy-minimised molecular models[2]) for a boat-chair conformation with the five-membered ring in an '*endo*'-position, where the corresponding torsion angles H–C(1)–C(1)–C(2)–H–C(2) are 56 and 61°, respectively (see below for a discussion of the conformations in these systems).

Similarly, optically active **10** and its diastereoisomer **13** reacted with dichloroketene to azabicyclo[4.3.0]nonenones **11** and **14** in 61 and 52% yield, respectively (see *Schemes 2* and *4*, resp.), the remanent presumably being lost due to a competing *retro-Diels-Alder* process (no other products could be identified).

The *cis*-ring junction in **9**, **11**, and **14** is expected from a concerted [3,3] rearrangement following a transition state with a boat conformation. However, as shown in *Scheme 3*, two alternative mechanisms can be proposed for this reaction. It was previously reported by *Ghosez et al.* [15] that dichloroketene did not react with norbornene. It was not surprising, therefore, that the nucleophilic N-atom of **8**, **10**, and **13** would react with dichloroketene. Conceivably, the resulting zwitterionic intermediate could undergo *retro-Diels-Alder* reaction [16], fragmentations and recombinations [17], and rearrangements [18]. The stereochemical outcome of the reaction points to a concerted [3.3] sigmatropic process. However, ^{1}H-NMR experiments in similar *N*-(arylethyl)-2-azabicyclo[2.2.1]-hept-5-ene systems indicate that the preferred conformation in solution of the benzylic sidechain is as shown in the *endo*-face of the bicyclic system [13]. Thus, the only product obtained would be that deriving from nucleophilic attack at the most hindered face of the aza-norbornene, suggesting that either *a*) the kinetically favoured *exo*-attack is reversible and the intermediate zwitterion **12a** dissociates or rearranges, equilibrating with the *endo*-adduct **12b**, which in turn rearranges leading to product, or *b*) interaction with the double bond and/or the phenyl ring directs the dichloroketene to the *endo*-face, to give **12b** directly, as was observed for phenylselenenyl chloride additions to similar systems [19].

An alternative mechanism could involve a fragmentation of the zwitterion **12a** formed after the kinetically favoured *exo*-attack, into an allyl cation and an amide enolate, in analogy to the acid-catalysed rearrangements reported in similar systems [17a]. Capture of the cation by the enolate C-atom could conceivably yield further products, containing either six- or seven-membered rings. The seven-membered-ring products are expected to

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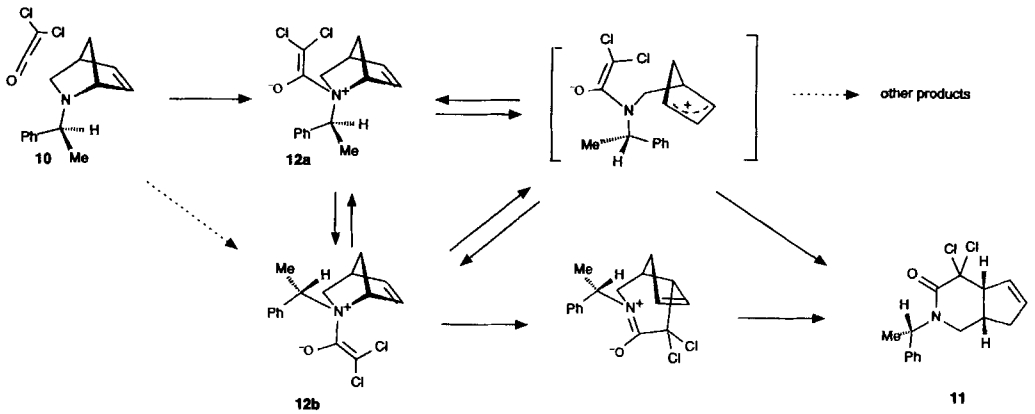
[1]) *Ishida et al.* [14] reported an analogous reaction of allylaziridines and dichloroketene and also found that Zn/trichloroacetyl chloride was unsatisfactory for the reaction. Presumably, coordination of the N-atom with the Zn surface inhibits the reaction.

[2]) Molecular models were constructed using the software in SYBYL 5.4 (*Tripos Associates Inc.*, 1699 S. Hanley Rd., Suite 303, St. Louis, Missouri 63144, USA), and their energy minimised using the MAXIMIN force field, an internal *Sandoz* product based on MM2.

Scheme 3. *Possible Mechanisms for the Aza-*Claisen *Rearrangement*



kinetically disfavoured. By C–C bond rotation, both faces of the allyl cation are available for capture by the enolate, to give, potentially, both *cis*- and *trans*-fused six-membered-ring products. But only *cis*-fused products are observed, as expected for a [3.3] sigmatropic process.

Additional indication for a *Claisen*-like process is provided by the behaviour of the homochiral diastereoisomers **10** and **13**, where the steric strain provided by the benzylic Me group might favour the fragmentation pathway. However, in both cases, the reaction results in complete transfer of chirality to the product, giving only the *cis*-adducts. Although the evidence at present is insufficient to rule out the fragmentation pathway, it is reasonable to assume that the rearrangements here reported proceed by a [3.3] sigmatropic process, accelerated by a number of factors, allowing the reaction to proceed at room temperature. It is conceivable that the actual mechanism of the reaction lies between the two extremes discussed here, and proceeds *via* a substantially polarised transition state.

The aza-*Claisen* rearrangement usually occurs at higher temperatures than those required for the corresponding O-analogues [20]. The rates of the reaction can be substantially lowered *a*) by electron-withdrawing or -donating substituents at the 2- or 5-positions [21], *b*) by introducing a positive charge on the N-atom by protonation [22], quaternisation [23], or complexation with *Lewis* acids [24], *c*) by introducing a negative charge in the system, as in the case of amide-enolate *Claisen* rearrangements [25], *d*) by generating a zwitterionic intermediate [26], and *e*) in the presence of Pd^0 catalysts [27].

Brown et al. [28a] noticed that for a constrained system in a boat conformation, *Cope*-like processes can take place at or below room temperature. This behaviour is also known of 1,2-divinylaziridines, which undergo rapid aza-*Claisen* rearrangements below –20°. Clearly, although the lowest energy conformation is *trans*, inversion of the N-atom allows the *cis*-conformation to occur, presenting an ideal geometry for the rearrangement [29]. Although in both of these cases the driving force for the reaction is the release of ring strain, and the chair transition state is not available for the systems to react, a stereoelectronic factor may contribute to accelerate these rearrangements through the boat transition state [28b].

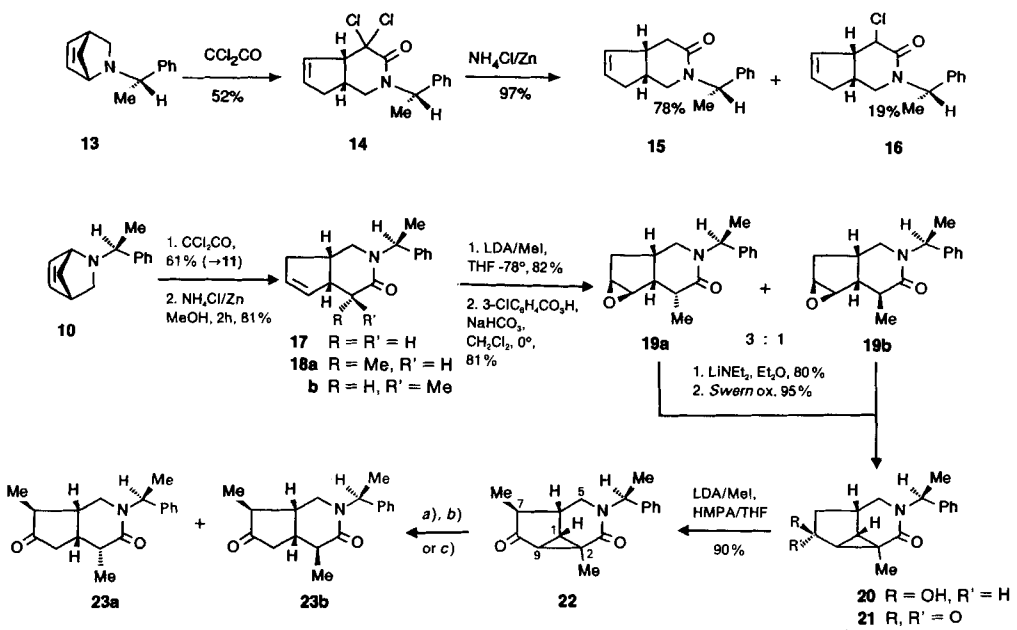
Additionally, the stability of the resulting amide further lowers the activation energy of the process, as in the *Eschenmoser* synthesis of γ,δ-unsaturated β-silylamides [30], and the rearrangement of *O*-allylliminoesters to γ,δ-unsaturated carboxamides [31], however, both of these examples still require high temperatures.

Analogous rearrangements were previously used for the synthesis of bicyclic systems [32]. During the course of our work, the aza-*Claisen* reaction of *rac*-2-benzyl-2-azabi-

cyclo[2.2.1]hept-5-ene (**8**) with diphenyl ketene was reported [33]. In all these cases, the stereochemical outcome is consistent with a [3.3] sigmatropic process. However, a more definitive description of the mechanism of this reaction awaits further experimental evidence.

2.3. *The Tricyclic Intermediate and Its Reductive Opening.* The reduction of the geminal dichloride moiety of **11** was cleanly achieved using Zn/NH_4Cl to yield **17** (*Scheme 4*). At shorter reaction times in the analogous reduction of the diastereoisomer **14**, a monochlorinated species **16** was isolated, indicating the stepwise reduction of the geminal dichloride moiety. At longer reaction times, the reduction was complete for both diastereoisomers, giving **15** and **17**, respectively. Monomethylation of **17** was achieved

Scheme 4. *Synthesis of the Tricyclic Intermediate* **23** *and Its Reductive Opening*



a) Zn, AcOH; isolated yield 73%, **23a**/**23b** 1:2 (by ^{1}H-NMR of the crude product). *b*) SmI_2, THF/DMPU; isolated yield 67%, **23a**/**23b** 1:1 (see *a*)). *c*) Bu_3SnH, benzene; isolated yield 65%, **23a**/**23b** 5:1 (see *a*)).

using the procedure of *Trost* and *Kunz* [34], by addition of the lithium enolate of **17** to MeI. No dimethylation was observed, but two epimeric products **18a** and **18b** (*ca.* 2:1) were formed. A pure sample of **18a** was isolated by HPLC and characterised, but the separation of the isomers was difficult. The mixture **18a**/**18b** was epoxidised with buffered 3-chloroperbenzoic acid give a 3:1 mixture of epoxides **19a** and **19b** which could be readily separated by chromatography.

The gross structure of **18a** follows from its ^{1}H-NMR spectrum, which is fully assigned by homonuclear decoupling experiments. The coupling constants J(1,2ax) and J(1,2eq) are 1.8 and 4.5 Hz, respectively, and J(5,6) is 7.1 Hz. In the ^{1}H-NMR spectrum of **18a**/**18b**, the signals at 1.30, 1.89, 2.40, and 2.88 ppm are clearly resolved, whereas that at 2.10 ppm is partially overlapping with the signal at 2.20 ppm, corresponding to 1 H–C(9) of **18a**. In

a double-resonance experiment, irradiation at 1.30 ppm (*d*, J = 7.4 Hz, Me–C(5) of **18b**) results in a collapse of the signal at 2.10 ppm (*dq*, J = 11.0, 7.4 Hz, H–C(5) of **18b**) to a broad *d*, (J = 11 Hz). Irradiation at 1.89 ppm (*dm*, J = 17 Hz, 1 H–C(9) of **18b**) removes coupling (J = 17 Hz) from the signal at 2.40 ppm (*ddd*, J = 5.0, 10, and 17 Hz, 1 H–C(9) of **18b**). On irradiation of the *dq* at 2.10 ppm (H–C(5) of **18b**), the Me–C(5) *d* of **18b** (1.30 ppm) collapses. The coupling constant J(5,6) can thus be clearly identified as 11 Hz, being compatible with a *trans*-diaxial interaction. In both **18a** and **18b**, Me–C(5) occupies a pseudo-equatorial position. The main product **18a** is, therefore, the (5*R*)- and **18b** the (5*S*)-diastereoisomer.

In analogous fashion, the structures of **19a** and **19b** are readily deduced from their ^{1}H-NMR spectra. For **19b**, J(1,2ax) = 10, J(1,2eq) = 5.8, and J(5,6) = 10 Hz are consistent with a *trans*-diaxial position of bridgehead H–C(1) and H–C(6) and of the corresponding H_{ax}–C(2) and H–C(5), as well as with one *gauche*-interaction between H–C(1) and H_{eq}–C(2). This implies that the conformation of **19b** is an '*exo*'-chair-boat, and thus the configuration at C(5) (*S*). For **19a**, J(1,2ax) and J(1,2eq) are very similar, namely 3.0 and 4.5 Hz. This is expected for an '*endo*'-chair-boat conformation, as discussed above for **9**, indicating that the configuration at C(5) is (*R*).

Each epoxide **19a** and **19b** was treated with lithium diethylamide to yield, as expected, the same intramolecular epoxide-opening product **20** (*Scheme 4*). Thus, for preparative purposes, the mixture **19a**/**19b** was directly converted to **20**. *Swern* oxidation [35] of the tricyclic hydroxy-ketone **20** readily gave the crystalline diketone **21**, which was selectively monomethylated using the procedure of *Callant et al.* [36] to yield the key intermediate **22** as a crystalline solid. As expected, the Me group at C(7) of **22** was on the convex face of the molecule (^{1}H-NMR).

The ^{1}H-NMR spectrum of **22** with a J(6,7) of 2.5 Hz suggests an angle close to 90° between H–C(7) (1.91 ppm) and H–C(6) (2.34 ppm). In fact, from molecular models, the expected angles are either 90° or 35°, depending on the orientation of the Me group. Confirmation of the configuration is obtained from a ROESY experiment, where NOE's can be observed between 1 H–C(5) (2.73 ppm) and H–C(7) (1.91 ppm). Interestingly, the same H–C(5) presents a clear NOE with the benzylic Me–C(1') (1.41 ppm), indicating that this Me group points towards the concave face of the tricycle.

Thus, the rigid tricyclic skeleton of **21** enabled the stereocontrol in the methylation to the key intermediate **22**. To provide again the 3-azabicyclo[4.3.0]nonane skeleton, the cyclopropane moiety of **22** was cleaved by reduction with a variety of reagents, yielding **23a**/**23b** (see *Scheme 4*). The reaction was regioselective, since only cleavage of the 2,9 bond occurred. This parallels a result of *Wenkert* and *Yoder* [37] who established that a dicarbonyl moiety directs the cleavage of a cyclopropane moiety in a similar way as previously shown by *Dauben* and coworkers [38] for the reductive cleavage of carbonyl cyclopropanes: the bond cleaved is that which best overlaps with the π-system of the carbonyl groups.

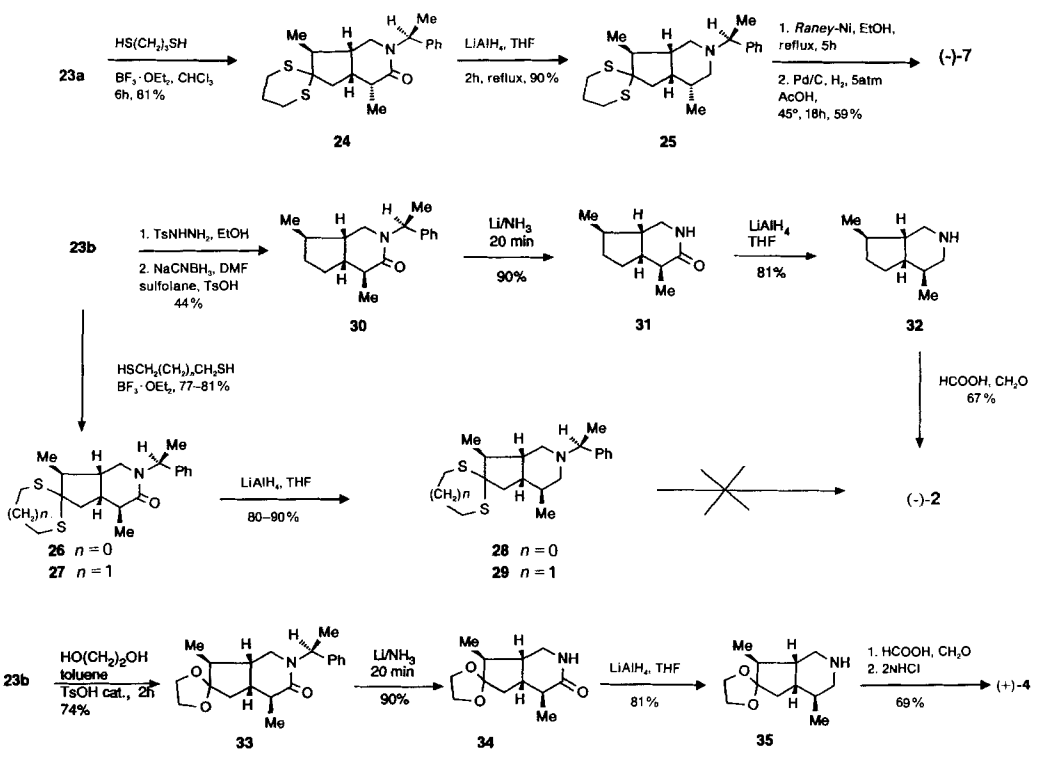
However, regarding the configuration at C(5) substantial differences in the ratio **23a**/**23b** were obtained with different reagents. Subtle effects are known to control the stereochemistry of such reactions [39]. Whereas both SmI_2 in THF and alcohol-free Li/NH_3[3]) gave a practically identical 1:1 proportion of the stereoisomers at C(5), reduction with Zn/AcOH resulted in a ratio of 1:2 for **23a**/**23b**. Formally, in these cases, a two-electron reduction of the cyclopropyl ketone to an enolate carbanion takes place. After the first electron transfer, the ketyl radical generated undergoes a reversible fragmentation to a radical enolate which is either protonated, abstracts a H-atom from a suitable donor, or is further reduced to a dienolate. Protonation of this dienolate controls the steric outcome of the reaction. Presumably, both the Sm and the Li enolate, in the

[3]) On Li/NH_3 treatment of **22**, the 1-phenylethyl group was removed during the cyclopropane cleavage (yield not determined; unpublished results).

absence of a good H-donor, result in a 1:1 equilibrium mixture. The Zn enolate, however, is rapidly protonated by the solvent, thus kinetically trapping the intermediate to give preferentially **23b**. Alternatively, coordination to the surface of the Zn may be responsible for directing the protonation. Reduction with Bu_3SnH inverted the ratio, giving **23a**/**23b** 5:1. In this case, the reaction proceeds as a conjugate addition of the H-atom to the cyclopropyl ketone, with approach of the reagent from the less hindered convex side to give **24a** as the main product. In any case, **23a** and **23b**, containing already all stereogenic centres of the target alkaloids, were cleanly separated by chromatography.

2.4. *Alkaloids (−)-***2**, *(+)-***4**, *and (−)-***7**. To complete the synthesis of (−)-*N*-demethyl-*δ*-skytanthine ((−)-**7**), it was necessary to remove the carbonyl groups at C(4) and C(8) and the *N*-phenylethyl moiety. Thus, treatment of **23a** with propane-1,3-dithiol in $CHCl_3$ in the presence of $BF_3 \cdot OEt_2$ gave dithiane **24** in 81% yield (*Scheme 5*). Reduction with $LiAlH_4$ provided amine **25**, which was converted to (−)-**7** in two steps by reduction with *Raney*-Ni in EtOH [40] followed by hydrogenolysis with Pd/AcOH. The structure of (−)-**7** was established by spectroscopic methods, and confirmed by comparison to an authentic sample from *Tecoma arequipensis*[4]) [3a].

Scheme 5



[4]) Kindly provided by Prof. *F. R. Stermitz* [3a].

Initial attempts to synthesise (−)-α-skytanthine ((−)-**2**) from **23b** paralleled the synthesis of (−)-**7** from **23a**. Thus, **23b** was treated with ethane-1,2-dithiol or propane-1,3-dithiol to give dithiolane **26** and dithiane **27**, respectively (*Scheme 5*). Both **26** and **27** could be reduced with $LiAlH_4$ to the amines **29** and **30**, respectively, but repeated attempts to reduce the thioacetal moieties with *Raney*-Ni failed. As an alternative, treatment of **23b** with (4-toluenesulfono)hydrazide and *in situ* reduction with sodium cyanoborohydride [41] gave **30** in 44% yield. Debenzylation proceeded in 15 min upon reduction with Li/NH_3. The resulting lactam **31**[5]) was then reduced with $LiAlH_4$ (→ **32**) and *N*-methylated by an *Eschweiler-Clarke* procedure to give (−)-**2**. Its structure, determined from spectroscopic parameters, was confirmed by comparison to an authentic sample of the enantiomeric (+)-α-skytanthine[6]) [7].

The oxygenated analogue of (−)-**2**, the dihydrotecomanine (+)-**4**, was obtained from **23b** by protection of the carbonyl group at C(8) as a dioxolane. Thus, treatment of **23b** with ethylene glycol in toluene with catalytic TsOH in a *Dean-Stark* apparatus gave the crystalline dioxolane **33** in 74% yield. After reaction with Li/NH_3 to the crystalline lactam **34** (90% yield) and reduction with $LiAlH_4$ to **35**, deprotection and methylation to (+)-**4** was achieved in one step by treatment with formaldehyde in HCOOH (61% yield from **34**).

2.5. *Conformation of the* cis-*Fused Piperidinones.* In *cis*-fused bicyclo[4.3.0]nonane systems with sp^2 centres in positions 3 and 4, there are two possible chair-boat conformations: the five-membered ring may adopt an '*endor*'- or an '*exo*'-position with respect to the boat. Similar conformations can be observed in the 3-azabicyclo[4.3.0]nonan-4-one systems we have described. This behaviour was studied in the analogous lactones, the iridoids [42] [43]. The corresponding lactams, however, have not been the subject of much attention.

The conformations '*endo*'-chair-boat and '*exo*'-chair-boat of our 3-azabicyclo-[4.3.0]nonan-4-ones can be readily distinguished by ^{1}H-NMR. As mentioned above, for the '*endo*'-chair-boat, the coupling constants between H–C(1) and both H–C(2) are expected to be similar. In contrast, for the '*exo*'-chair-boat, H–C(1) and H_{ax}–C(2) are in an antiperiplanar arrangement, whereas H–C(1) and H_{eq}–C(2) have a *gauche* spatial relationship, thus giving rise to very different coupling constants. The conformational assignments were subsequently confirmed by NOE experiments.

In general, for both the unsubstituted (*e.g.* **15** and **17**) and the 5,5-disubstituted 3-azabicyclo[4.3.0]nonan-4-ones (*e.g.* **11** and **14**), the preferred conformation is a boat-chair, with the five-membered ring in the '*endo*'-position. This is also the case for the 5-α-substituted systems described above (*e.g.* **18a**, **19a**, or **23a**), regardless of the substitution of the five-membered ring. A single β-substituent at C(5) is sufficient to overcome this modest preference, as the substituent at C(5) must adopt a pseudoequatorial position. This constitutes the dominating factor in determining the conformation in the 3-azabicyclo[4.3.0]nonan-4-ones. Thus, the 5-β-substituted compounds in this series, namely **18b**, **19b**, **23b**, **26**–**31**, and **33**–**35**, all exist preferentially in an '*exo*'-chair-boat conformation. Further studies are necessary, however, to establish the size of the barriers to conformational inversion.

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[5]) Lactam **31** is formally the aza-analogue of the iridolactone (+)-isoiridomyrmecin.

[6]) Kindly provided by Prof. *W. Oppolzer* [7].

3. Conclusion. – The induction of all the stereogenic centres in the target alkaloids (−)-**2**, (+)-**4**, and (−)-**7** starting from (*R*)- or (*S*)-1-phenylethylamine was achieved *via* a hetero-*Diels-Alder* reaction followed by the stereospecific ketene aza-*Claisen* rearrangement. The enantiomerically pure tricyclic intermediate **22** allowed a flexible stereocontrolled synthesis of these terpene alkaloids and may be used for the synthesis of related more complex naturally occurring terpene alkaloids. Additionally, the described synthetic route may be used for the stereocontrolled synthesis of novel aza-analogues of known iridoids, such as iridomyrmecin, and of their corresponding epimers, which, although expected to be as ubiquitous as the iridoids themselves on biogenetic grounds, have rarely been reported from natural sources [44].

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Experimental Part

General. Solvents were purchased from *Merck*, BuLi and SmI_2 from *Aldrich*, and the other reagents from *Fluka*. TLC: *Merck* silica gel *60* F_{254} anal. plates, detection by UV, I_2 soln. (I_2 (25 g), KI (20 g), EtOH/H_2O 1:4 (1000 ml)), or *Dragendorff*'s reagent. Flash chromatography (FC): *Merck* silica gel *60* (230–400 mesh), Alox (act. III). Prep. TLC: silica gel *60* F_{254}. M.p.: *Büchi-510* melting-point apparatus; in open capillaries, uncorrected. $[\alpha]_D^{20}$: *Perkin-Elmer-241* polarimeter, 1 ml microcuvette (l = 10 cm). CD (λ, $\Delta\varepsilon$): *Jobin Yvon CD-6*. IR Spectra ($\tilde{\nu}$, cm^{-1}): *Bruker-IFS-66* spectrophotometer. ^1H- and ^{13}C-NMR Spectra (δ, ppm): *Bruker AM 500* (^1H, 500 MHz), *Bruker AMX 400* (^1H, 400 MHz; ^{13}C, 100.62 MHz), *Bruker AM 360* (^1H, 360 MHz; ^{13}C, 90.6 MHz); chemical shifts in ppm rel. to Me_4Si as internal reference; ^{13}C assignments were confirmed with the aid of JMOD and $^{13}C,^1H$ 2 D-correlation experiments, as previously described [13]. MS (*m/z* (%)): *VG-TS-250* spectrometer (EI, 70 eV); *Varian-MAT-212* spectrometer (FAB, 8 keV). Elemental analyses were performed in the analytical service of *Sandoz Ltd.*

Enantiomers of 2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene (**8**). Compound **8** was prepared according to [10]. The enantiomers were separated by automated HPLC on a *Chiracel-OD* column (4 × 250 mm, hexane/i-PrOH/Et_2NH 18:2:0.1, flow rate 1 ml/min, 0.4-ml injection of 1 mg/ml soln. of **8** in hexane). After 415 injections, the pure fractions were pooled and evaporated at r.t./0.02–0.03 Torr: (+)-**8** (51 mg, 31%) and (−)-**8** (48 mg, 29%)). R_f (silica gel, CH_2Cl_2) < 0.01. R_f (silica gel, MeOH/NH_4OH 99:1) 0.37.

(+)-**8**: $[\alpha]_D^{20}$ = +53.5 (c = 0.23, CH_2Cl_2). CD (c = 2.957 mM, MeOH): 197 (+15.5); enant. purity (HPLC) > 99%.

(−)-**8**: $[\alpha]_D^{20}$ = −55.2 (c = 0.21, CH_2Cl_2). CD (c = 2.757 mM, MeOH): 195 (−16.7); enant. purity (HPLC) *ca.* 95%.

(1R,6S*)-3-Benzyl-5,5-dichloro-3-azabicyclo[4.3.0]non-7-en-4-one* (**9**). $(i\text{-}Pr)_2EtN$ (18.5 ml, 98 mmol) was added in 1 portion to a cooled (0°) soln. of **8** (10 g, 54 mmol) in CH_2Cl_2 (150 ml) under Ar. A soln. of dichloroacetyl chloride (10.4 ml, 98 mmol) in CH_2Cl (100 ml) was added dropwise over 4 h and the mixture kept at 0° for 20 h, after which it was washed with H_2O (100 ml), sat. aq. $NaHCO_3$ soln. (150 ml), and brine (100 ml). The org. phase was dried (Na_3SO_4) and evaporated and the brown oil chromatographed (silica gel, *t*-BuOMe/hexane 1:2 to 1:1): **9** (10.8 g, 68%). Colourless crystals. M.p. 106–108° (Et_2O). R_f (silica gel, *t*-BuOMe/hexane 1:2) 0.25. IR (CH_2Cl_2): 3030*w*, 2920*m*, 2850*w*, 1690*s*, 1497*m*, 1412*m*, 1355*m*, 810*m*. ^1H-NMR (360 MHz, $CDCl_3$): 1.97 (*ddddd*, J = 17.2, 2.4, 2.3, 2.1, 1 H–C(9)); 2.60 (*ddddd*, J = 17.2, 9.6, 3.9, 2.3, 1 H–C(9)); 2.79 (*ddddd*, J = 10.1, 9.6, 7.0, 6.8, 2.1, H–C(1)); 3.28 (*dd*, J = 13.2, 6.8, H_{ax}–C(2)); 3.67 (*dd*, J = 13.2, 7.0, H_{eq}–C(2)); 3.88 (br. *d*, J = 10.0, H–C(6)); 4.52 (*d*, J = 14.6, 1 H–C(1′)); 4.75 (*d*, J = 14.6, 1 H–C(1′)); 5.79 (*ddt*, J = 5.8, 2.3, 2.3, H–C(7)); 5.89 (*ddt*, J = 5.8, 2.3, 2.3, H–C(8)); 7.29–7.40 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 33.4 (C(1)); 39.1 (C(9)); 49.6 (C(2)); 51.8 (C(1′)); 60.8 (C(6)); 85.6 (C(5)); 127.5 (arom. C), 127.8 (C(7), arom. C); 128.3 (arom. C); 134.5 (C(8)); 135.7 (arom. C); 163.4 (C(4)). FAB-MS (NOBA): 300 (12), 298 (61), 296 (100, MH^+). EI-MS: 297 (3), 295 (5, M^+), 262 (38), 260 (74), 92 (31), 91 (100). Anal. calc. for $C_{15}H_{15}Cl_2NO$ (296.196): C 60.8, H 5.1, N 4.7, Cl 23.9; found: C 61.0, H 5.1, N 4.7, Cl 24.0.

(1R,6S*)-3-Benzyl-3-azabicyclo[4.3.0]non-7-en-4-one.* NH_4Cl (1.73 g, 32.34 mmol) was added to a soln. of **9** (1.6 g, 5.4 mmol) in dry MeOH (80 ml) cooled at 0°. The resulting soln. was stirred and Zn powder (2.02 g, 54 mmol) added in portions over 30 min. The mixture was allowed to warm to r.t. and stirred 3 h more, after which it

was filtered. The filtrate was evaporated, the residue taken up in CH_2Cl_2 (20 ml), the resulting soln. washed with H_2O (50 ml), dried ($MgSO_4$), and evaporated, and the crude product recrystallised ((i-Pr)$_2$O): colourless crystals (0.9 g; 74%). M.p. 74–75°. IR (CH_2Cl_2): 3030*w*, 2920*m*, 2850*m*, 1650*s*, 1479*m*, 1412*m* (br.), 1355*m*, 1150*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 1.82 (br. *d*, J = 16.8, H_{ax}–C(9)); 2.35 (*dd*, J = 15.0, 7.0, 1 H–C(5)); 2.48–2.62 (*m*, H–C(1), H_{eq}–C(9)); 2.62 (*dd*, J = 15.0, 7.0, 1 H–C(5)); 3.02 (*dd*, J = 13.0, 7.0, 1 H–C(2)); 3.24 (*m*, H–C(6)); 3.27 (*dd*, J = 13.0, 5.1, 1 H–C(2)); 4.57 (*AB*, 2 H–C(1′)); 5.53 (*m*, H–C(7)); 5.61 (*m*, H–C(8)); 7.30 (*m*, 5 arom. H). ^{1}H-NMR (360 MHz, (D_5)pyridine): 1.74 (*ddd*, J = 16.5, 2.2, 2.2, H_{ax}–C(9)); 2.31 (*dd*, J = 14.5, 6.1, H_{eq}–C(5)); 2.32 (*dm*, J = 16.5, H_{ax}–C(5)); 2.90 (*dd*, J = 13.5, 6.1, H_{eq}–C(2)); 3.10 (*m*, H–C(6)); 3.20 (*dd*, J = 13.5, 5.1, H_{ax}–C(2)); 5.48 (*m*, H–C(7)); 5.55 (*m*, H–C(8)); 7.40 (*m*, 5 arom. H). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 35.3 (C(1)); 36.9 (C(9) or C(5)); 37.8 (C(9) or C(5)); 43.3 (C(6)); 50.0 (C(2) or C(1′)); 50.2 (C(2) or C(1′)); 127.3, 128.1, 128.4 (arom. C); 130.1 (C(7)); 132.6 (C(8)); 137.4 (*s*, arom. C); 172.1 (*s*, C(4)). EI-MS: 227 (86, M^+), 136 (37), 107 (28), 91 (100). Anal. calc. for $C_{15}H_{17}NO$ (227.306): C 79.3, H 7.5, N 6.2; found: C 79.1, H 7.7, N 6.1.

*(−)-(1*S*,6*R*,1′*S*)-5,5-Dichloro-3-(1′-phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one* (**11**). As described for **9**, with (i-Pr)$_2$EtN (40 ml, 0.19 mol), **10** (20 g, 0.1 mol), CH_2Cl_2 (300 ml) dichloroacetyl chloride (21 ml, 0.19 mol), and CH_2Cl_2 (100 ml; addition within 8 h; washing with H_2O (200 ml), sat. aq. $NaHCO_3$ (200 ml), and brine (200 ml)). FC (silica gel, *t*-BuOMe/hexane 1:4) gave **11** (19 g, 61%). Low-melting solid M.p. 48–50° (Et_2O). R_f 0.25. $[\alpha]_D^{20} = -67.8$ (c = 0.9, CH_2Cl_2). CD (c = 1.60 mM, MeOH): 194.0 (7.4); 199.5 (2.2); 214.0 (14.8); 238.5 (−5.8). IR (KBr): 1683 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.50 (*d*, J = 6.0, 3 H–C(2′)); 2.15 (*dm*, J = 12.1, 1 H–C(9)); 2.55 (*m*, 1 H–C(9), H–C(1)); 3.15 (*dd*, J = 13.0, 7.3, 1 H–C(2)); 3.25 (*dd*, J = 13.0, 7.0, 1 H–C(2)); 3.88 (*dm*, J = 10.0, H–C(6)); 5.80 (*m*, H–C(7)); 5.91 (*m*, H–C(8), H–C(1′)); 7.29–7.40 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 15.1 (C(2′)); 33.8 (C(1)); 39.1 (C(9)); 44.5 (C(2)); 52.1 (C(1′)); 60.8 (C(6)); 86.3 (C(5)); 127.1 (arom. C); 127.7, 127.8 (C(7), arom. C); 128.2 (arom. C); 134.5 (C(8)); 139.3 (arom. C); 163.6 (C(4)). EI-MS: 309 (3, M^+), 294 (3), 274 (85), 105 (100). Anal. calc. for $C_{16}H_{12}Cl_2NO$ (305.183): C 61.9, H 5.5, N 4.5, Cl 22.9; found: C 61.8, H 5.4, N 4.4, Cl 22.9.

*(−)-(1*R*,6*S*,1′*S*)-5,5-Dichloro-3-(1′-phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one* (**14**). As described for **11**, with (i-Pr)$_2$EtN (1.04 ml, 9.8 mmol) **13** (1 g, 5.0 mmol), and dichloroacetyl choride (2 ml, 9.8 mmol): **14** (800 mg, 52%). M.p. 97° (Et_2O). $[\alpha]_D^{20} = -81.8$ (c = 0.2, MeOH). CD (c = 3.24 mM, MeOH): 226.0 (−1.94). IR (KBr): 1673 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.51 (*m*, 1 H–C(9)); 1.52 (*d*, J = 7.0, 3 H–C(2′)); 2.45 (*ddq*, J = 17.0, 9.7, 2.0, 1 H–C(9)); 2.72 (*m*, H–C(1)); 2.90 (*dd*, J = 13.6, 5.9, 1 H–C(2)); 3.55 (*dd*, J = 13.6, 6.3, 1 H–C(2)); 3.90 (*dm*, J = 10.0, H–C(6)); 5.71 (*m*, H–C(7)); 5.78 (*m*, H–C(8)); 6.00 (*q*, J = 7.0, H–C(1′)); 7.29–7.35 (*m*, 5 arom. H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.9 (C(2′)); 33.6 (C(1)); 39.4 (C(9)); 44.6 (C(2)); 52.0 (C(1′) or C(6)); 61.0 (C(1′) or C(6)); 86.0 (C(5)); 127.6, 127.8 (arom. C); 128.2 (C(7)); 128.4 (arom. C); 134.9 (C(8)); 139.2 (arom. C); 163.3 (C(4)). EI-MS: 309 (4, M^+), 294 (5), 274 (96), 105 (100). Anal. calc. for $C_{16}H_{12}Cl_2NO$ (305.183): C 61.9, H 5.5, Cl 22.9, N 4.5; found: C 62.0, H 5.5, Cl 22.8, N 4.5.

*(−)-(1*S*,6*R*,1′*S*)-3-(1′-Phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one* (**17**). NH_4Cl (3.3 g, 61.97 mmol) was dissolved in a cold (0°) soln. of **11** (3.18 g, 10.25 mmol) in dry MeOH (150 ml) with vigorous stirring. Then Zn powder (6.5 g, 102.5 mmol) was added in portions over 50 min. The mixture was allowed to warm to r.t. and stirred for further 2 h, after which it was filtered. The filtrate was evaporated, the residue taken up in CH_2Cl_2 (50 ml), the resulting soln. washed with H_2O (40 ml), dried (Na_2SO_4), and evaporated, and the crude product purified by FC (silica gel, *t*-BuOMe/hexane 1:1): **17** (2.01 g, 81%). White crystals. R_f 0.2. M.p. 59° (Et_2O/hexane). $[\alpha]_D^{20} = -85.0$ (c = 0.6, CH_2Cl_2). CD (c = 2.09 mM, MeOH): 193.0 (−3.6); 204.0 (6.3); 221.5 (−21.0). IR (KBr): 1652 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.45 (*d*, J = 7.0, 3 H–C(2′)); 1.97 (*dm*, J = 16.5, H_{ax}–C(9)); 2.23 (*dd*, J = 15.0, 9.0, H_{ax}–C(5)); 2.35 (*m*, H–C(1)); 2.50 (*ddq*, J = 16.5, 9.0, 2.8, H_{eq}–C(9)); 2.64 (*dd*, J = 15.0, 6.0, H_{eq}–C(5)); 2.82 (*dd*, J = 13.0, 9.0, H_{ax}–C(2)); 2.95 (*dd*, J = 13.0, 6.0, H_{eq}–C(2)); 3.25 (*m*, H–C(6)); 5.55 (*dq*, J = 6.1, 2.8, H–C(7)); 5.66 (*dq*, J = 6.1, 2.8, H–C(8)); 5.96 (*q*, J = 7.0, H–C(1′)); 7.30 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 16.1 (C(2′)); 35.5 (C(1)); 37.4 (C(9) or C(5)); 37.5 (C(5) or C(9)); 43.2 (C(6)); 44.9 (C(2)); 49.2 (C(1′)); 127.1, 127.2, 128.3 (arom. C); 129.7 (C(7)); 132.7 (C(8)); 140.6 (arom. C); 172.0 (C(4)). EI-MS: 241 (71, M^+), 105 (100). Anal. calc. for $C_{16}H_{19}NO$ (241.333): C 79.6, H 7.9, N 5.8; found: C 79.8, H 7.9, N 5.8.

*(−)-(1*R*,6*S*,1′*S*)-3-(1′-Phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one* (**15**) *and (−)-(1*R*,5*S*,6*S*,1′*S*)-5-Chloro-3-(1′-phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one* (**16**). As described for **17**, from **14** (1 g, 3.22 mmol), Zn (2.11 g, 32.3 mmol), and NH_4Cl (1.03 g, 19.3 mmol): **15** (R_f 0.4; 6.10 mg, 78%) and **16** (R_f 0.3; 170 mg, 19%).

15: $[\alpha]_D^{20} = -59.2$ (c = 0.2, MeOH). CD (c = 3.23 mM, MeOH): 207.0 (−1.25); 220.0 (−2.18). IR (KBr): 1654 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.42 (*dm*, J = 18.0, 1 H–C(9)); 1.51 (*d*, J = 7.2, 3 H–C(2′)); 2.25 (*dd*, J = 13.5, 6.9, 1 H–C(5)); 2.38 (*ddq*, J = 18.0, 11.0, 3.0, 1 H–C(9)); 2.55 (*m*, H–C(1)); 2.60 (*dd*, J = 13.5, 6.0, 1 H–C(5)); 2.87 (*dd*, J = 14.0, 7.0, 1 H–C(2)); 3.11 (*dd*, J = 14.0, 4.9, 1 H–C(2)); 3.20 (*m*, H–C(6)); 5.50 (*m*, H–C(7)); 5.55 (*m*, H–C(8)); 5.98 (*q*, J = 7.2, H–C(1′)); 7.28–7.39 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$):

15.8 (C(2')); 35.5 (C(1)); 37.1 (C(9) or C(5)); 37.5 (C(5) or C(9)); 43.1 (C(6)); 44.9 (C(2)); 49.4 (C(1')); 127.3, 127.5, 128.2 (arom. C); 130.3 (C(7)); 132.3 (C(8)); 140.7 (arom. C); 171.8 (C(4)). EI-MS: 241 (76, M^+), 226 (16), 105 (100).

16: M.p. (*t*-BuOMe/hexane) 112–114°. $[\alpha]_D^{20} = -41.2$ ($c = 0.4$, MeOH). CD ($c = 4.54$ mM, MeOH): 206.5 (−1.37); 221.5 (−1.95). IR (KBr): 1658 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.25 (*dm*, $J = 16.5$, 1 H–C(9)); 1.51 (*d*, $J = 7.3$, 3 H–C(2')); 2.35 (*dd*, $J = 16.5$, 10.5, 1 H–C(9)); 2.63 (*m*, H–C(1)); 3.00 (*dd*, $J = 13.1$, 6.0, 1 H–C(2)); 3.22 (*dd*, $J = 13.1$, 6.2, 1 H–C(2)); 3.56 (*m*, H–C(6)); 4.62 (*d*, $J = 6.0$, H–C(5)); 5.63 (*m*, H–C(7), H–C(8)); 5.97 (*q*, $J = 7.3$, H–C(1')); 7.28–7.35 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 15.6 (C(2')); 34.5 (C(1)); 38.6 (C(9)); 44.1 (C(2)); 50.4 (C(6)); 50.5 (C(1')); 59.5 (C(5)); 127.7 (arom. C); 127.8 (C(7)); 128.3 (arom. C); 133.4 (C(8)); 140.0 (arom. C); 166.8 (C(4)). EI-MS: 275 (12, M^+), 240 (100), 105 (195). Anal. calc. for $C_{16}H_{18}ClNO$ (275.778): C 69.7, H 6.6, N 5.1, Cl 12.9; found: C 69.7, H 6.5, N 5.0, Cl 12.8.

(1S,5R,6R,1'S)- and (1S,5S,6R,1'S)-5-Methyl-3-(1'-phenylethyl)-3-azabicyclo[4.3.0]non-7-en-4-one (**18a** and **18b**, resp.). To a vigorously stirred soln. of $(i\text{-Pr})_2NH$ (1.53 ml, 10.9 mmol) in dry THF (50 ml) under Ar at 0°, 1.6M BuLi (6.22 ml, 9.96 mmol) was added slowly. After 30 min, the soln. was cooled to −79° and a soln. of **17** (2.0 g, 8.3 mmol) in THF (20 ml) added. After 1 h, this mixture was added to MeI (0.69 ml, 11 mmol) in THF (15 ml) at −70°. Then the temp. was slowly raised to r.t. overnight. Sat. NH_4Cl soln. (50 ml) was added, the org. phase washed with H_2O and brine, dried (Na_2SO_4), and evaporated, and the crude product purified by FC (silica gel, *t*-BuOMe/hexane 1:1, R_f 0.30): 1.73 g (82%) of **18a**/**18b** 2:1. A pure sample of **18a** was obtained by HPLC (*LiChrosorb®Si 60*, hexane/AcOEt 1:1, 10 ml/min).

18a: Colourless oil. $[\alpha]_D^{20} = -188.6$ ($c = 0.3$, MeOH). CD ($c = 2.54$ mM, MeOH): 195.0 (−11.6); 206.5 (2.5); 221.5 (−17.6). IR (film): 1655 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.26 (*d*, $J = 7.1$, Me–C(5)); 1.45 (*d*, $J = 7.3$, 3 H–C(2')); 2.20 (*dm*, $J = 13.5$, 1 H–C(9)); 2.54 (*dq*, $J_{gem} = 7.1$, $J(5,6) = 7.1$, H–C(5)); 2.63–2.73 (*m*, H–C(9), H–C(1)); 2.81 (*dd*, $J = 13.0$, 1.8, H_{ax}–C(2)); 2.98 (*dd*, $J = 13.0$, 4.5, H_{eq}–C(2)); 3.21 (*m*, H–C(6)); 5.61 (*dq*, $J = 5.9$, 2.6, H–C(7)); 5.76 (*dq*, $J = 5.9$, 2.6, H–C(8)); 5.97 (*q*, $J = 7.3$, H–C(1')); 7.25–7.35 (*m*, 5 arom. H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 13.5 (*Me*–C(5)); 16.3 (C(2')); 34.2 (C(1)); 38.5 (C(5)); 39.7 (C(9)); 45.5 (C(2)); 49.1 (C(6) or C(1')); 49.6 (C(6) or C(1')); 127.1, 127.2, 128.4 (arom. C); 129.3 (C(7)); 132.0 (C(8)); 140.9 (arom. C); 173.8 (C(4)). EI-MS: 255 (72, M^+), 240 (17), 105 (100).

18b: ^{1}H-NMR (360 MHz, $CDCl_3$; from **18a**/**18b**): 1.30 (*d*, $J = 7.4$, Me–C(5)); 1.45 (*d*, $J = 7.3$, 3 H–C(2')); 1.89 (*dm*, $J = 17.0$, 1 H–C(9)); 2.10 (*dq*, $J = 11.0$, 7.4, H–C(5)); 2.1–2.2 (H–C(1)); 2.40 (*dddd*, $J = 17.0$, 10.0, 5.0, 2.0, 1 H–C(9)); 2.60–2.68 (H–C(1) or H–C(6)); 2.88 (*d*, $J = 10.0$, 11.0, 1 H–C(2)); 2.99 (*dd*, $J = 6.0$, 11.0, 1 H–C(2)); 5.61 (*m*, H–C(7)); 5.76 (*m*, H–C(8)); 5.97 (*q*, $J = 7.3$, H–C(1')); 7.25–7.35 (*m*, 5 arom. H).

(−)-(1S,5R,6R,7R,8S,1'S)- and (−)-(1S,5S,6R,7R,8S,1'S)-7,8-Epoxy-5-methyl-3-(1'-phenylethyl)-3-azabicyclo[4.3.0]nonan-4-one (**19a** and **19b**, resp.). See [45]: A soln. of **18a**/**18b** (3.7 g, 14.6 mmol) in CH_2Cl_2 (10 ml) was added to a cooled (ice-bath), well stirred suspension of 3-chloroperbenzoic acid (3.0 g, 17.6 mmol) and $NaHCO_3$ (1.9 g, 22.9 mmol) in CH_2Cl_2 (40 ml), at a rate such that the temp. was kept between 5 and 10°. After the addition, the mixture was kept at −18° overnight. A 10% Na_2SO_3 soln. (50 ml) was added, the org. layer washed with 5% aq. Na_2CO_3 soln., the combined aq. phase extracted with CH_2Cl_2 (3 × 25 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue chromatographed (silica gel, hexane/*t*-BuOMe 1:1): **19a** (R_f 0.35) and **19b** (R_f 0.40) in 81% combined yield (**19a**/**19b** 3:1).

19a: Colourless oil. $[\alpha]_D^{20} = -128.0$ ($c = 1.0$, CH_2Cl_2). CD ($c = 1.33$ mM, MeOH): 206.5 (−9.7); 221.5 (−28.0). IR (KBr): 1654 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.32 (*d*, $J = 6.8$, Me–C(5)); 1.50 (*d*, $J = 7.3$, 3 H–C(2')); 1.65 (*ddd*, $J_{gem} = 14.0$, $J(9,1) = 7.0$, $J(9,8) = 2.5$, 1 H–C(9)); 2.18 (*dd*, $J_{gem} = 14.0$, $J(9,1) = 8.8$, 1 H–C(9)); 2.31 (*m*, H–C(1)); 2.55 (*dq*, $J = 8.8$, 6.8, H–C(5)); 2.75 (*t*, $J = 8.8$, H–C(6)); 2.83 (*dd*, $J_{gem} = 14.5$, $J(2,1) = 3.0$, H_{eq}–C(2)); 2.92 (*dd*, $J_{gem} = 14.5$, $J(2.1) = 4.5$, H_{ax}–C(2)); 3.44 (*d*, $J = 2.5$, H–C(7)); 3.49 (*t*, $J = 2.5$, H–C(8)); 5.97 (*q*, $J = 7.3$, H–C(1')); 7.25–7.35 (*m*, 5 arom. H). EI-MS: 271 (85, M^+), 256 (27), 180 (27), 105 (100). Anal. calc. for $C_{17}H_{21}NO_2$ (271.359): C 75.2, H 7.8, N 5.2; found: C 74.8, H 8.0, N 5.1.

19b: Solid. M.p. 104–106°. $[\alpha]_D^{20} = -70.9$ ($c = 1.0$, CH_2Cl_2). CD ($c = 1.28$ mM, MeOH): 206.5 (−7.6); 221.0 (−19.7). IR (KBr): 1646 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.38 (*d*, $J = 6.2$, Me–C(5)); 1.44 (*d*, $J = 7.3$, 3 H–C(2')); 1.59 (*d*, $J = 12.0$, 1 H–C(9)); 1.85 (*m*, H–C(1), 1 H–C(9)); 2.03 (*dt*, $J = 10.0$, $J(6,7) = 2.0$, H–C(6)); 2.68 (*dq*, $J = 10.0$, 6.2, H–C(5)); 2.79 (*dd*, $J_{gem} = 13.2$, $J = 5.8$, H_{eq}–C(2)); 2.96 (*dd*, $J_{gem} = 13.2$, $J(1,2) = 10.0$, H_{ax}–C(2)); 3.54 (*m*, H–C(8)); 3.56 (*dd*, $J(7,8) = 2.8$, $J = 2.0$, H–C(7)); 5.92 (*q*, $J = 7.3$, H–C(1')); 7.28–7.32 (*m*, 5 arom. H). FAB-MS (thioglycerol): 272 (66, MH^+), 168 (41), 105 (100). Anal. calc. for $C_{17}H_{21}NO_2$ (271.359): C 75.2, H 7.8, N 5.2; found: C 74.7, H 8.2, N 5.0.

(−)-(1S,2S,6S,8S,9R,1'S)-8-Hydroxy-2-methyl-4-(1'-phenylethyl)-4-azatricyclo[4.3.0.0^{2,9}]nonan-3-one (**20**). To the stirred soln. of Et_2NH (0.11 ml, 0.81 mmol) and Et_2O (4 ml) under Ar in an ice-bath, 1.6M BuLi in hexane (0.6 ml, 0.74 mmol) was added with a syringe. After 10 min stirring, the mixture was allowed to reach r.t. and **19a** (200 mg, 0.74 mmol) in Et_2O (2 ml) added dropwise. The yellow mixture was stirred overnight at r.t., after

which time sat. NH_4Cl soln. (6 ml) was added. The Et_2O phase was separated, the aq. phase extracted with Et_2O (3 × 10 ml), the combined org. phase washed successively with 1N HCl (10 ml), H_2O (10 ml), and sat. $NaHCO_3$ soln, dried (Na_2SO_4), and evaporated, and the crystalline solids recrystallised from Et_2O: **20**. Colourless crystals (180 mg, 80%). M.p. 141–143°. $[\alpha]_D^{20} = -132.0$ ($c = 0.5$, CH_2Cl_2). CD ($c = 1.32$ mM, MeOH): 194.5 (−3.6); 210.0 (+10.7); 225.5 (−15.6). IR (KBr): 1612 (NCO), 3336 (OH). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.32 (*s*, Me–C(2)); 1.43 (*d*, $J = 7.2$, 3 H–C(2′)); 1.54 (*d*, $J = 6.5$, 1 H–C(9)); 1.92 (*ddd*, $J = 14.0$, 7.5, 2.0, H_{eq}–C(7)); 1.97 (*t*, $J = 6.5$, H–C(1)); 2.16 (*m*, H_{ax}–C(7)); 2.53 (*dd*, $J = 12.5$, 3.0, H_{ax}–C(5)); 2.70 (*m*, H–C(6)); 2.85 (*dd*, $J = 12.5$, 2.2, H_{eq}–C(5)); 3.03 (br. *s*, OH); 4.25 (*t*, $J = 6.3$, H–C(8)); 6.11 (*q*, $J = 7.2$, H–C(1′)); 7.20–7.35 (*m*, 5 arom. H). EI-MS: 271 (37, M^+), 254 (50), 167 (51), 152 (47), 105 (100). Anal. calc. for $C_{17}H_{21}NO_2$ (271.359): C 75.2, H 7.8, N 5.2; found: C 74.9, H 8.1, N 5.1.

(−)-(1S,2S,6S,9R,1′S)-2-Methyl-4-(1′-phenylethyl)-4-azatricyclo[4.3.0.0^{2,9}]nonan-3,8-dione (**21**). A soln. of DMSO (2.8 ml, 37.6 mmol) in CH_2Cl_2 (2 ml) was rapidly added under Ar to a cooled (−60°) soln. of oxalyl chloride (1.5 ml, 17.2 mmol) in CH_2Cl_2 (50 ml). After 45 min, a soln. of **20** (1.53 g, 5.6 mmol) in CH_2Cl_2 (10 ml) was added at such a rate that the temp. was kept between −50 and −60°. Then the mixture was stirred for 45 min, Et_3N (5.24 ml) added dropwise while keeping the temp. below −50°, and stirring continued for 5 min. The mixture was allowed to warm to r.t. and H_2O (10 ml) added. The aq. layer was extracted with CH_2Cl_2 (3 × 50 ml), the combined org. extract washed with brine (10 ml), dried (Na_2SO_4), and evaporated, and the crude oil purified by FC (silica gel, AcOEt/hexane 1:1): **21** (1.46 g, 95%). White solid. M.p. 109–111°. $[\alpha]_D^{20} = -55.8$ ($c = 0.5$, CH_2Cl_2). CD ($c = 1.23$ mM, MeOH); 206.5 (27.2); 231.5 (−7.5); 297.5 (−2.9). IR (KBr): 1635 (NCO), 1721 (CO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.42 (*s*, Me–C(2)); 1.42 (*d*, $J = 7.3$, 3 H–C(2′)); 1.90 (*dd*, $J = 18.0$, 2.7, 1 H–C(7)); 2.00 (*d*, $J = 5.5$, H–C(9)); 2.47 (*dd*, $J = 7.0$, 5.5, H–C(1)); 2.65 (*ddd*, $J = 18.0$, 12.0, 1.8, 1 H–C(7)); 2.68 (*dd*, $J = 12.0$, 3.0, 1 H–C(5)); 2.85 (*m*, H–C(6)); 3.10 (*dd*, $J = 12.0$, 2.1, 1 H–C(5)); 6.10 (*q*, $J = 7.3$, H–C(1′)); 7.28–7.39 (*m*, 5 arom. H). FAB-MS (thioglycerol): 270 (76, MH^+), 166 (50), 105 (100). Anal. calc. for $C_{17}H_{19}NO_2$ (269.343): C 75.8, H 7.1, N 5.2; found: C 75.5, H 7.2, N 5.2.

(−)-(1S,2S,6R,7S,9R,1′S)-2,7-Dimethyl-4-(1′-phenylethyl)-4-azatricyclo[4.3.0.0^{2,9}]nonane-3,8-dione (**22**). A soln. of **21** (1.4 g, 5.2 mmol) in THF (8 ml), hexamethylphosphoramide (HMPA; 0.9 ml, 5.2 mmol), and MeI (0.64 ml, 10.4 mmol) were added successively to a soln. of LDA (6.24 mmol) in THF (50 ml) at −80°. The temp. was allowed to reach −30° and then the mixture stirred for 2 h. The reaction was quenched with sat. NH_4Cl soln. (10 ml), the aq. layer extracted with Et_2O (3 × 25 ml), the org. phase dried (Na_2SO_4) and evaporated, and the oil submitted to FC (silica gel, AcOEt/hexane 1:1, R_f 0.6): **22** (1.3 g, 90%). Colourless crystals. M.p. 113°. $[\alpha]_D^{20} = -35.4$ ($c = 0.5$, CH_2Cl_2). CD ($c = 1.23$ mM, MeOH); 207.5 (24.5); 231.0 (−7.7); 302.0 (−1.9). IR (KBr): 1628 (NCO), 1717 (CO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.22 (*d*, $J = 7.9$, Me–C(7)); 1.41 (*d*, $J = 7.5$, 3 H–C(2′)); 1.42 (*s*, Me–C(2)); 1.91 (*dq*, $J = 7.9$, 2.5, H–C(7)); 2.05 (*d*, $J = 5.5$, H–C(9)); 2.34 (*dq*, $J = 7.8$, 2.5, H–C(6)); 2.40 (*dd*, $J = 7.8$, 5.5, H–C(1)); 2.73 (*dd*, $J = 12.2$, 3.0, 1 H–C(5)); 3.09 (*dd*, $J = 12.2$, 2.5, 1 H–C(5)); 6.05 (*q*, $J = 7.5$, H–C(1′)); 7.25–7.40 (*m*, 5 arom. H). FAB-MS (thioglycerol): 284 (50, MH^+), 180 (42), 105 (100). Anal. calc. for $C_{18}H_{21}NO_2$ (203.370): C 76.3, H 7.5, N 4.9; found: C 76.1, H 7.7, H 4.9.

(−)-(1R,5R,6R,9S,1′S)- and (−)-(1R,5S,6R,9S,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)-3-azabicyclo-[4.3.0]nonane-4,8-dione (**23a** and **23b**, resp.). *Procedure a* [37]: A mixture of **22** (311 mg, 1.1 mmol) and Zn (1.7 g) in AcOH (50 ml) was heated to reflux for 20 h. Zn was filtered off, H_2O added, and the mixture extracted with CH_2Cl_2 (3 × 50 ml). FC (silica gel, AcOEt/hexane 3:2) gave **23a** (R_f 0.6; 71 mg, 22%) and **23b** (R_f 0.4; 154 mg, 51%).

23a: Solid. M.p. 87° (AcOEt/pentane). $[\alpha]_D^{20} = -206.7$ ($c = 0.3$, CH_2Cl_2). CD ($c = 1.24$ mM, MeOH): 204.0 (−16.7); 209.5 (−15.2); 220.0 (−28.2). IR (KBr): 1655 (NCO), 1737 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.10 (*d*, $J = 6.0$, Me–C(9)); 1.21 (*d*, $J = 6.0$, Me–C(5)); 1.48 (*d*, $J = 6.3$, 3 H–C(2′)); 2.07 (*ddd*, $J_{gem} = 17.0$, $J(7,6) = 10.0$, $J(7,9) = 2.0$, H_a–C(7)); 2.20 (*m*, H–C(9), H–C(1)); 2.32 (*dd*, $J_{gem} = 17.0$, $J(7,6) = 9.0$, H_b–C(7)); 2.65 (*quint.*, $J = 6.0$, H–C(5)); 2.81 (*dddd*, $J(6,1) = J(6,7a) = 10.0$, $J(6,7b) = 9.0$, $J(6,5) = 6.5$, H–C(6)); 2.95 (*dd*, $J_{gem} = 18.0$, $J(2ax,1) = 2.0$, H_{ax}–C(2)); 3.15 (*dd*, $J_{gem} = 18.0$, $J(2eq,1) = 6.0$, H_{eq}–C(2)); 6.08 (*q*, $J = 6.3$, H–C(1′)); 7.22–7.35 (*m*, 5 arom. H). ^{1}H-NMR (500 MHz, $CDCl_3/C_6D_6$ 3:2): 0.96 (*d*, $J = 7.1$, Me–C(9)); 1.09 (*d*, $J = 7.0$, Me–C(5)); 1.29 (*d*, $J = 7.0$, 3 H–C(2′)); 1.87 (*dddd*, $J(1,6) = 10.0$, $J(1,9) = 7.0$, $J(1,2eq) = 5.2$, $J(1,2ax) = 2.0$, H–C(1)); 1.96 (*ddd*, $J_{gem} = 17.8$, $J(7a,6) = 10.0$, $J(7a,9) = 2.0$, H_a–C(7)); 2.04 (*dq*, $J(9,1) = J(9,Me) = 7.0$, $J(9,7a) = 2.0$, H–C(9)); 2.14 (*dd*, $J_{gem} = 17.8$, $J(7b,6) = 9.0$, H_b–C(7)); 2.34 (*quint.*, $J = 6.5$, H–C(5)); 2.44 (*ddt*, $J(6,1) = J(6,7a) = 10.0$, $J(6,7b) = 9.0$, $J(6,5) = 6.5$, H–C(6)); 2.71 (*dd*, $J_{gem} = 13.5$, $J(2ax,1) = 2.0$, H_{ax}–C(2)); 2.82 (*dd*, $J_{gem} = 13.5$, $J(2eq,1) = 5.2$, H_{eq}–C(2)); 5.72 (*q*, $J = 7.0$, H–C(1′)); 6.80–7.10 (*m*, 5 arom. H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.4 (*Me*–C(5), *Me*–C(9)); 16.5 (C(2′)); 35.2 (C(6)); 38.3 (C(5)); 38.9 (C(7)); 41.1 (C(9) or C(1)); 43.3 (C(2)); 46.2 (C(1) or C(9)); 49.5 (C(1′)); 127.0, 127.1, 128.5, 128.6, 140.5 (arom. C); 173.3 (C(4)); 215.9 (C(8)). EI-MS: 285 (60, M^+), 270 (21), 120 (27), 105 (100). Anal. calc. for $C_{18}H_{23}NO_2$ (285.386): C 75.8, H 8.1, N 4.9; found: C 76.0, H 8.3, N 4.7.

23b: Colourless oil. $[\alpha]_D^{20} = -86.0$ ($c = 1.4$, CH_2Cl_2). CD ($c = 2.18$ mM, MeOH): 205.5 (−6.4); 221.0 (−19.9). IR (film): 1653 (NCO), 1741 (CO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.96 (*d*, $J = 7.0$, Me−C(9)); 1.38 (*d*, $J = 6.1$, Me−C(5)); 1.50 (*d*, $J = 7.2$, 3 H−C(2′)); 1.80 (*m*, $J(1,6) = J(1,9) = J(1,2ax) = 9.5$, $J(1,2eq) = 6.0$, H−C(1)); 2.02 (*m*, $J = 9.5$, 7.2, H−C(9)); 2.18–2.30 (*m*, H−C(5), H−C(6), 1 H−C(7)); 2.52 (*dd*, $J_{gem} = 18.0$, $J(7,6) = 7.9$, 1 H−C(7)); 3.01 (*dd*, $J_{gem} = 13.0$, $J(2ax,1) = 9.5$, H_{ax}−C(2)); 3.25 (*dd*, $J_{gem} = 13.0$, $J(2eq,1) = 6.0$, H_{eq}−C(2)); 6.03 (*q*, $J = 7.2$, H−C(1′)); 7.26–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.1 (*Me*−C(5) or *Me*−C(9)); 14.8 (*Me*−C(9) or *Me*−C(5)); 15.8 (C(2′)); 37.4 (C(6)); 40.9 (C(5)); 41.8 (C(9) or C(1)); 42.7 (C(7)); 43.8 (C(2)); 46.4 (C(1) or C(9)); 50.0 (C(1′)); 127.2, 127.3, 127.5, 140.3 (arom. C); 173.2 (C(4)); 217.3 (C(8)). EI-MS: 285 (74, M^+), 270 (26), 194 (23), 120 (25), 105 (100). Anal. calc. for $C_{18}H_{23}NO_2$ (285.386): C 75.8, H 8.1, N 4.9; found: C 75.3, H 8.0, N 4.8.

Procedure b [46]: To a soln. of **22** (35 mg, 0.12 mmol) in THF/DMPU (3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one) 9:1 (4 ml), SmI_2 (0.1M in THF) was added dropwise at r.t. under Ar, until the purple colour persisted (3 ml). After 5 min, the mixture was quenched with aq. sat. $NaHCO_3$ soln. (1 ml), the aq. layer extracted with Et_2O (3 × 20 ml), the combined org. extract washed with water H_2O and brine, dried (Na_2SO_4), and evaporated, and the residue purified: **23a**/**23b** (23 mg, 67%) 1:1.

Procedure c [47]: To a soln. of **22** (80 mg, 0.27 mmol) in benzene (5 ml) under Ar, Bu_3SnH (0.11 ml, 0.41 mmol) was added over 1 min and AIBN (5 mg, 0.03 mmol) in one portion. The mixture was lowered into a bath preheated to 100° and heated to reflux for 3 h, after which it was cooled and evaporated. The crude product was purified as above: **23a**/**23b** 5:1 (50 mg, 65%).

(−)-(1R,5R,6R,9S,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2″-[1,3]dithiane]-4-one (**24**). Propan-1,3-dithiol (0.05 ml, 0.5 mmol) was added to a soln. of **23a** (100 mg, 0.35 mmol) in $CHCl_3$ (6 ml). After cooling to 0°, $BF_3 \cdot Et_2O$ (0.5 ml) was added. After 6 h, the mixture was washed with 7% aq. KOH soln., water, and brine, the org. phase evaporated, and the residue purified by prep. TLC (silica gel, AcOEt/hexane 2:3): **24** (107 mg, 81%). Oil R_f 0.5. $[\alpha]_D^{20} = -32.3$ ($c = 0.6$, CH_2Cl_2). CD ($c = 2.03$ mM, MeOH): 220.5 (−28.1). IR (film): 1655 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.14 (*d*, $J = 7.0$, Me−C(9)); 1.17 (*d*, $J = 6.5$, Me−C(5)); 1.49 (*d*, $J = 6.9$, 3 H−C(2′)); 1.49 (*dd*, $J = 12.8$, 11.0, 1 H−C(7)); 1.77 (*m*, H−C(9)); 1.85 (*m*, H_{ax}−C(4″)); 2.11 (*m*, H−C(1), H_{eq}−C(4″)); 2.50 (*quint.*, $J = 7.0$, H−C(5)); 2.66–2.77 (*m*, H−C(6), H_{eq}−C(3″), H_{eq}−C(5″)); 2.80 (*m*, 1 H−C(7), 1 H−C(2)); 2.92 (*dd*, $J = 13.8$, 4.3, 1 H−C(2)); 2.99 (*ddd*, $J = 14.1$, 12.1, 2.9, H_{ax}−C(5″)); 3.08 (*ddd*, $J = 14.0$, 12.0, 3.0, H_{eq}−C(3″)); 6.05 (*q*, $J = 6.9$, H−C(1′)); 7.27–7.45 (*m*, 5 arom. H). EI-MS: 375 (45, M^+), 270 (29), 149 (71), 105 (100).

(−)-(1R,5S,6R,9S,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2″-[1,3]dithiolane]-4-one (**26**). As described for **24**, with ethane-1,2-dithiol (0.05 ml, 0.5 mmol), **23b** (100 mg, 0.35 mmol), $CHCl_3$ (6 ml), and $BF_3 \cdot Et_2O$ (0.5 ml): **26** (107 mg, 81%). Solid. R_f 0.5. M.p. 100–102°. $[\alpha]_D^{20} = -58.6$ ($c = 0.9$, CH_2Cl_2). CD ($c = 1.57$ mM, MeOH): 208.0 (−5.7); 222.5 (−16.9); 252.0 (1.2). IR (KBr): 1653 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.90 (*d*, $J = 6.6$, Me−C(9)); 1.19 (*d*, $J = 6.8$, Me−C(5)); 1.43 (*d*, $J = 7.3$, 3 H−C(2′)); 1.40 (*m*, H−C(1)); 1.84 (*dq*, $J = 10.0$, 6.6, H−C(9)); 1.92 (*dd*, $J = 12.5$, 10.2, 1 H−C(7)); 2.00 (*m*, H−C(6)); 2.19 (*m*, H−C(5)); 2.57 (*dd*, $J = 12.5$, 7.3, 1 H−C(7)); 2.85 (*dd*, $J = 13.7$, 10.6, H_{ax}−C(2)); 3.10 (*dd*, $J = 13.7$, 6.0, H_{eq}−C(2)); 3.20–3.30 (*m*, SCH_2CH_2S); 5.95 (*q*, $J = 7.3$, H−C(1′)); 7.27–7.45 (*m*, 5 arom. H). EI-MS: 361 (81, M^+), 105 (100).

(−)-(1R,5S,6R,9S,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2″-[1,3]dithiane]-4-one (**27**). As described for **24**, with propane-1,3-dithiol (0.9 ml, 8.9 mmol), **23b** (1.5 g, 5.3 mmol), $CHCl_3$ (70 ml), and $BF_3 \cdot Et_2O$ (0.5 ml; 36 h): **27** (1.54 g, 77%). Solid. R_f 0.5. M.p. 137–140° (AcOEt/hexane). $[\alpha]_D^{20} = -20.0$ ($c = 0.5$, CH_2Cl_2). CD ($c = 1.68$ mM, MeOH): 202.5 (−10.2); 224.0 (−19.9); 253.5 (0.7). IR (KBr): 1654 and 1643 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.95 (*d*, $J = 6.5$, Me−C(9)); 1.21 (*d*, $J = 6.9$, Me−C(5)); 1.46 (*d*, $J = 7.3$, 3 H−C(2′)); 1.68 (*dd*, $J = 12.6$, 8.7, 1 H−C(7)); 1.70 (*m*, H−C(9)); 1.75 (*m*, H−C(1)); 1.84 (*m*, 1 H−C(4″)); 2.11 (*m*, 1 H−C(4″)); 2.18 (*m*, H−C(6)); 2.23 (*dq*, $J = 10.1$, 6.9, H−C(5)); 2.74 (*m*, H_{eq}−C(5″), H_{eq}−C(3″)); 2.86 (*dd*, $J = 12.8$, 9.5, H_{ax}−C(2)); 3.00 (*ddd*, $J = 14.2$, 12.0, 3.8, H_{ax}−C(3″) or H_{ax}−C(5″)); 3.06–3.15 (*m*, H_{eq}−C(2), 1 H−C(7), H_{ax}−C(5″) or H_{ax}−C(3″)); 5.95 (*q*, $J = 7.3$, H−C(1′)); 7.27–7.35 (*m*, 5 arom. H). EI-MS: 375 (56, M^+), 105 (100).

(+)-(1R,5R,6R,9S,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2″-[1,3]dithiane] (**25**). Under Ar, $LiAlH_4$ (30 mg, 0.8 mmol) was added in 1 portion to a soln. of **24** (107 mg, 0.28 mmol) in THF (4 ml). The mixture was heated to reflux for 2 h, the soln. then allowed to cool to r.t., and aq. sat. Na_2SO_4 soln. (0.8 ml) added. The resulting solid was filtered off and the solvent evaporated: pure **25** (91 mg, 90%). Oil. $[\alpha]_D^{20} = +24.0$ ($c = 1.0$, CH_2Cl_2). CD ($c = 1.36$ mM, MeOH): 193.5 (−15.2); 228.5 (−6.9); 251.5 (1.8). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.81 (*d*, $J = 6.0$, Me−C(9)); 1.15 (*d*, $J = 7.0$, Me−C(5)); 1.34 (*d*, $J = 7.3$, 3 H−C(2′)); 1.83–2.12 (*m*, 8 H); 2.38–2.55 (*m*, 3 H); 2.68–2.78 (*m*, 3 H); 2.96 (*ddd*, $J = 14.0$, 11.0, 3.0, 1 H, H−C(2) or H−C(4)); 3.12 (*ddd*, $J = 14.0$, 3.0, 3.0, 1 H, H−C(2) or H−C(4)); 3.39 (*q*, $J = 7.3$, H−C(1′)); 7.27–7.40 (*m*, 5 arom. H). EI-MS: 361 (8, M^+), 346 (24), 286 (17), 258 (100), 105 (77).

(1R,5S,6S,9S,1'S)-5,9-Dimethyl-3-(1'-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2''-[1,3]dithiolane] (**28**). As described for **25**, from **26**: Oil. CD (c = 2.16 mM, MeOH): 192.5 (−8.5); 248.5 (2.6). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.80 (*d*, J = 6.6, Me–C(5)); 0.90 (*d*, J = 6.8, Me–C(9)); 1.46 (*d*, J = 7.3, 3 H–C(2')); 1.48–1.60 (*m*, H_{ax}–C(4), H–C(6), H–C(5)); 2.00 (*dd*, J = 12.1, 4.0, H_{ax}–C(2)); 2.15 (*m*, H–C(1)); 2.30 (*dd*, J = 13.6, 2.8, 1 H–C(7)); 2.45 (*dq*, J = 11.5, 6.7, H–C(9)); 2.61 (*dd*, J = 13.6, 8.0, 1 H–C(7)); 2.73 (*dm*, J = 12.1, H_{eq}–C(2)); 2.91 (*dm*, J = 11.5, H_{eq}–C(4)); 3.10 (*q*, J = 7.3, H–C(1')); 3.15–3.46 (*m*, SCH_2CH_2S); 7.27–7.45 (*m*, 5 arom. H). EI-MS: 347 (19, M^+), 332 (95), 258 (66), 105 (100).

(−)-(1R,5S,6S,9S,1'S)-5,9-Dimethyl-3-(1'-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2''-[1,3]dithiane] (**29**). As described for **25**, with $LiAlH_4$ (350 mg, 9.2 mmol), **27** (1.44 g, 3.8 mmol), and THF (60 ml). FC (silica gel, AcOEt/hexane 1:3) gave 1.11 g (80%). Oil. R_f 0.6. $[\alpha]_D^{20}$ = −34.8 (c = 0.4, CH_2Cl_2). CD (c = 1.55 mM, MeOH): 193.5 (−11.2); 218.0 (1.7); 232.5 (−2.4); 254.0 (1.1). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.81 (*d*, J = 6.5, Me–C(5)); 1.00 (*d*, J = 7.0, Me–C(9)); 1.32 (*d*, J = 7.3, 3 H–C(2')); 1.55 (*m*, H_{ax}–C(4), H–C(6)); 1.72 (*m*, H–C(5)); 1.83–1.97 (*m*, H–C(1), H_{ax}–C(4'')); 2.02 (*dd*, J = 12.1, 3.9, H_{ax}–C(2)); 2.12 (*m*, H_{eq}–C(4'')); 2.33 (*dd*, J = 14.1, 2.0, 1 H–C(7)); 2.45 (*dq*, J = 14.0, 6.7, H–C(9)); 2.71 (*dm*, J = 12.1, H_{eq}–C(2)); 2.80 (*m*, H_{eq}–C(5''), H_{eq}–C(3''), 1 H–C(7)); 2.91 (*ddd*, J = 11.0, 4.0, 2.0, H_{eq}–C(4)); 2.98 (*ddd*, J = 14.0, 12.1, 3.8, H_{ax}–C(5'')); 3.15 (*ddd*, J = 14.1, 12.1, 3.8, H_{ax}–C(3'')); 3.31 (*q*, J = 7.3, H–C(1')); 7.27–7.35 (*m*, 5 arom. H). EI-MS: 361 (17, M^+), 346 (100), 286 (29), 105 (100).

(−)-(1S,5R,6S,9R)-5,9-Dimethyl-3-azabicyclo[4.3.0]nonane (= *(−)-N-Demethyl-δ-skytanthine*; (−)-**7**). A mixture of **25** (40 mg, 0.11 mmol) and *Raney*-Ni (200 mg, in abs. EtOH (5 ml) was heated to reflux under Ar for 5 h. TLC (AcOEt/hexane 1:1): no **25** left (R_f 0.6), more polar product (R_f 0.5). The *Raney*-Ni was filtered off and the EtOH evaporated. The tarry residue was dissolved in AcOH (40 ml) and hydrogenated over 10% Pd/C (50 mg) in a *Parr* medium-pressure apparatus (70 psi, 45°, 20 h). The mixture was filtered, the filtrate evaporated, the resulting oil taken up in MeOH (1 ml), and oxalic acid (6 mg) added, followed by Et_2O (1 ml) which precipitated the oxalate. The precipitate was filtered off and dissolved in H_2O (0.5 ml), the aq. soln. taken to pH 9–10 by addition of NH_4OH and extracted with CH_2Cl_2 (3 × 2 ml), and the combined extract dried (Na_2SO_4) and evaporated: (−)-**7** (10 mg, 59%). Oil. R_f (AcOEt/hexane 1:1) 0.5. $[\alpha]_D^{20}$ = −22.7 (c = 0.3, $CHCl_3$; [3a]: $[\alpha]_D^{20}$ = −21.5 (c = 7.7, $CHCl_3$)). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.85 (*d*, J = 7.1, Me–C(5)); 0.94 (*d*, J = 7.2, Me–C(9)); 1.13 (*m*, H_{eq}–C(8)); 1.54 (*m*, H_{ax}–C(7), H_{ax}–C(8)); 1.60 (*m*, H–C(1), H–C(9)); 1.70 (br. *s*, NH); 1.88 (*m*, H–C(5)); 1.95 (*m*, H_{eq}–C(7)); 2.17 (*m*, H–C(6)); 2.24 (*t*, J = 12.8, H_{ax}–C(2)); 2.35 (*t*, J = 12.4, H_{ax}–C(4)); 2.69 (*dd*, J = 12.4, 4.1, H_{eq}–C(4)); 2.76 (*dd*, J = 12.8, 6.8, H_{eq}–C(2)). EI-MS: 153 (48, M^+), 138 (40), 44 (100).

(−)-(1R,5S,6R,9S,1'S)-5,9-Dimethyl-3-(1'-phenylethyl)spiro[[3]azabicyclo[4.3.0]nonane-8,2''-[1,3]dioxolane]-4-one (**33**). For 3 h, **23b** (830 mg, 2.9 mmol), ethyleneglycol (0.5 ml, 2.9 mmol), and TsOH (cat.) were heated to reflux in toluene (50 ml). The soln. was made alkaline with aq. sat. $NaHCO_3$ soln., the aq. phase extracted with CH_2Cl_2 (3 × 25 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the oily residue purified by FC (Alox, AcOEt/hexane 1:2): **33** (706 mg, 74%). Solid. R_f 0.4. M.p. 102–104° (Et_2O/hexane). $[\alpha]_D^{20}$ = −102.8 (c = 0.3, CH_2Cl_2). CD (c = 3.0 mM, MeOH): 221.0 (−17.1). IR (KBr): 1655 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.70 (*d*, J = 7.2, Me–C(9)); 1.19 (*d*, J = 6.5, Me–C(5)); 1.48 (*d*, J = 7.3, 3 H–C(2')); 1.48 (*m*, H–C(7)); 1.55 (*m*, H–C(1)); 1.72 (*dq*, J = 9.8, 7.2, H–C(9)); 1.94 (*tt*, J = 11.0, 8.0, H–C(6)); 2.10 (*dd*, J = 12.5, 8.0, 1 H–C(7)); 2.20 (*dq*, J = 11.0, 6.5, H–C(5)); 2.89 (*dd*, J = 13.0, 11.0, H_{ax}–C(2)); 3.11 (*dd*, J = 13.0, 7.0, H_{eq}–C(2)); 3.90 (*s*, OCH_2CH_2O); 5.96 (*q*, J = 7.3, H–C(1')); 7.29–7.35 (*m*, 5 arom. H). FAB-MS (thioglycerol): 330 (100, MH^+). Anal. calc. for $C_{20}H_{27}NO_3$ (329.439): C 72.9, H 8.3, N 4.3; found: C 73.0, H 8.3, N 4.4.

(+)-(1R,5S,6R,9S)-5,9-Dimethylspiro[[3]azabicyclo[4.3.0]nonane-8,2''-[1,3]dioxolane]-4-one (**34**). Li (26 mg, 3.7 mmol) was added to a soln. of **33** (307 mg, 0.93 mmol) in Et_2O/NH_3 1:1 (6 ml). After 15 min, solid NH_4Cl was added carefully to eliminate excess Li. When this reaction was complete, NH_3 was evaporated, the residue taken up in H_2O (20 ml), the aq. layer extracted with Et_2O (3 × 20 ml), the org. extract dried (Na_2SO_4) and evaporated, and the solid recrystallized: **34** (188 mg, 90%). M.p. 210–212° (Et_2O/pentane). $[\alpha]_D^{20}$ = +6.0 (c = 0.5, CH_2Cl_2). CD (c = 5.19 mM, MeOH): 194.5 (−1.2); 214.5 (4.12). IR (KBr): 3254 (NH), 1666 and 1627 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.93 (*d*, J = 7.3, Me–C(9)); 1.12 (*d*, J = 7.2, Me–C(5)); 1.51 (*dd*, J = 12.5, 8.3, 1 H–C(7)); 1.88 (*dq*, J = 9.0, 7.0, H–C(9)); 2.05 (*m*, H–C(6), H–C(1)); 2.15 (*m*, H–C(5), 1 H–C(7)); 3.07 (*ddd*, J = 13.0, 10.0, 2.8, H_{ax}–C(2)); 3.40 (*dt*, J = 13.8, 6.0, H_{eq}–C(2)); 3.95 (*m*, OCH_2CH_2O); 5.98 (br. *s*, NH). FAB-MS (thioglycerol): 226 (100, MH^+), 182 (21). Anal. calc. for $C_{12}H_{19}NO_3$ (225.288): C 64.0, H 8.5, N 6.2; found: C 64.1, H 8.8, N 6.0.

(−)-(1R,5S,6S,9S)-5,9-Dimethylspiro[[3]azabicyclo[4.3.0]nonane-8,2''-[1,3]dioxolane] (**35**). As described for **25**, with $LiAlH_4$ (77 mg, 2.1 mmol), **34** (155 mg, 0.69 mmol), THF (10 ml), and sat. aq. Na_2SO_4 soln. (2 ml): **35** (118 mg, 81%). Oil. $[\alpha]_D^{20}$ = −29.1 (c = 0.7, CH_2Cl_2). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.79 (*d*, J = 6.5, Me–C(5)); 0.90 (*d*, J = 6.8, Me–C(9)); 1.51 (*m*, H–C(6)); 1.47 (*m*, H–C(5)); 1.56 (*m*, H–C(1)); 1.78 (*dd*, J = 14.0, 2.2,

1 H–C(7)); 1.96 (*dd*, J = 14.0, 7.9, 1 H–C(7)); 2.11 (*dd*, J = 12.5, 11.0, H_{ax}–C(4)); 2.20 (*quint.*, J = 6.8, H–C(9)); 2.79 (*dd*, J = 13.0, 4.2, H_{ax}–C(2)); 2.90 (*ddd*, J = 12.5, 3.8, 1.9, H_{eq}–C(4)); 2.98 (*d*, J = 13.0, H_{eq}–C(2)); 3.80–3.97 (*m*, OCH_2CH_2O). EI-MS: 211 (19, M^+), 205 (14), 166 (45), 96 (100).

(+)-(1R,5S,6S,9S)-3,5,9-Trimethyl-3-azabicyclo[4.3.0]nonan-8-one ((+)-**4**). Formaldehyde (37%; 0.62 mmol, 50 µl), formic acid (90%, 0.62 mmol, 26 µl), and **35** (118 mg, 0.56 mmol) were heated at 100° for 1 h. This mixture was taken up in 2N HCl (3 ml) and stirred for 1 h at r.t. The resulting soln. was made alkaline with sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (3 × 10 ml), the org. phase dried (Na_2SO_4) and evaporated, and the oily residue purified by FC (Alox, AcOEt/hexane 1:3): (+)-**4** (57 mg, 61%). Oil. R_f 0.5. $[\alpha]_D^{20}$ = +43.8 (c = 0.8, CH_2Cl_2). CD (c = 9.38 mM, MeOH): 297.0 (1.1). IR (film): 1741 (CO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.88 (*d*, J = 6.8, Me–C(5)); 1.05 (*d*, J = 7.5, Me–C(9)); 1.48 (*m*, H–C(5)); 1.59 (*t*, J = 11.0, H_{ax}–C(4)); 1.66 (*m*, H–C(6)); 1.85 (*m*, H–C(1)); 2.13 (*dd*, J_{gem} = 12.2, J(2ax,1) = 4.0, H_{ax}–C(2)); 2.26 (*s*, MeN); 2.28 (*m*, 2 H–C(7)); 2.49 (*sext.*, J = 7.5, H–C(9)); 2.73 (*ddd*, J_{gem} = 11.0, J(4,5) = 3.5, J(4,2eq) = 2.0, H_{eq}–C(4)); 2.90 (*dt*, J_{gem} = 12.2, J(2,1) = J(2,4eq) = 2.0, H_{eq}–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 12.6 (*Me*–C(5)); 17.3 (*Me*–C(9)); 32.3 (C(5)); 39.0 (C(6)), 40.4 (MeN); 43.0 (C(7)); 43.7 (C(9)); 44.8 (C(1)); 55.6 (C(2)); 62.9 (C(4)); 221.1 (C(8)). EI-MS: 181 (71, M^+), 180 (50), 57 (100).

(−)-(1S,5S,6R,9R,1′S)-5,9-Dimethyl-3-(1′-phenylethyl)-3-azabicyclo[4.3.0]nonan-4-one (**30**). For 2 h, **23b** (1.42 g, 5 mmol) and (4-toluenesulfono)hydrazide (1.16 g, 6.25 mmol) in EtOH (10 ml) were heated to reflux. The EtOH was distilled off and replaced with DMF/sulfolane 1:1 (20 ml). To this soln., cyclohexane (10 ml), TsOH (250 mg), and $NaBH_3CN$ (1.21 g, 20 mmol) were added. With vigorous stirring and under Ar, this mixture was heated at 110° for 6 h. Every 2 h, equal portions $NaBH_3CN$ and TsOH were added. The mixture was diluted with 20 ml of H_2O and extracted with cyclohexane (3 × 20 ml), dried (Na_2SO_4), and evaporated: **30** (596 mg, 44%). Oil. R_f (silica gel, AcOEt/$CHCl_3$ 1:1) 0.5. $[\alpha]_D^{20}$ = −92.0 (c = 0.9, CH_2Cl_2). CD (c = 4.49 mM, MeOH): 198.5 (−4.25); 222.0 (−15.4). IR (film): 1654 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.80 (*d*, J = 6.6, Me–C(9)); 1.10 (*m*, H–C(8)); 1.20 (*d*, J = 6.9, Me–C(5)); 1.22 (*m*, 1 H–C(7)); 1.34 (*m*, H–C(1)); 1.46 (*d*, J = 7.3, 3 H–C(2′)); 1.47 (*m*, H–C(9)); 1.76 (*d*, *quint.*, J = 6.5, 2.8, 1 H–C(8)); 1.92 (*m*, H–C(6)); 2.00 (*m*, 1 H–C(7)); 2.13 (*dq*, J = 10.5, 6.9, H–C(5)); 2.83 (*dd*, J = 13.5, 11.0, H_{ax}–C(2)); 3.45 (*dd*, J = 13.5, 6.0, H_{eq}–C(2)); 5.99 (*q*, J = 7.3, H–C(1′)); 7.27–7.35 (*m*, 5 arom. H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.0 (*Me*–C(9)); 16.0 (C(2′)); 18.5 (*Me*–C(5)); 32.9 (C(7)); 35.4 (C(8)); 39.4 (C(9)); 41.8 (C(5)); 43.4 (C(2)); 44.2 (C(6)); 46.3 (C(1)); 49.8 (C(1′)); 127.1, 128.2, 140.9 (arom. C); 174.6 (C(4)). EI-MS: 272 (50, $[M + 1]^+$), 271 (70, M^+), 256 (31), 180 (55), 105 (100).

(+)-(1S,5S,6R,9R)-5,9-Dimethyl-3-azabicyclo[4.3.0]nonan-4-one (**31**). As described for **34**, from Li (10 mg, **30** (104 mg, 0.38 mmol), Et_2O (3 ml), and NH_3 (2 ml; 20 min). Extraction with CH_2Cl_2. Evaporation gave **31** (60 mg, 100%). Solid. M.p. 164–166° ($CHCl_3$/Et_2O). $[\alpha]_D^{20}$ = +13.1 (c = 0.4, CH_2Cl_2). CD (c = 6.43 mM, MeOH): 221.5 (3.19). IR (KBr): 3246 (NH), 1668 and 1630 (NCO). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.01 (*d*, J = 7.0, Me–C(9)); 1.16 (*d*, J = 7.2, Me–C(5)); 1.19–1.31 (*m*, 2 H–C(8)); 1.65 (*m*, H–C(9)); 1.85 (*m*, H–C(1), 1 H–C(7)); 1.99–2.13 (*m*, 1 H–C(7), H–C(6), H–C(5)); 3.02 (*ddd*, J = 12.0, 10.0, 2.5, H_{ax}–C(2)); 3.38 (*dt*, J = 12.2, 6.0, H_{eq}–C(2)); 5.90 (br. *s*, NH). FAB-MS (thioglycerol): 168 (61, MH^+), 167 (63, M^+), 110 (91), 73 (100). Anal. calc. for $C_{10}H_{17}NO$ (167.251): C 71.8, H 10.3, N 8.4; found: C 71.8, H 10.2, N 8.4.

(1S,5S,6S,9R)-5,9-Dimethyl-3-azabicyclo[4.3.0]nonane (**32**). As described for **25**, with $LiAlH_4$ (187 mg, 4.8 mmol), **31** (270 mg, 1.62 mmol), THF (5 ml), and sat. aq. Na_2SO_4 soln. (2 ml). FC (silica gel, MeOH/$CHCl_3$ 1:1 with 1% NH_4OH, R_f 0.2) gave **32** (200 mg, 81%). Oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (*d*, J = 6.2, Me–C(9)); 0.99 (*d*, J = 6.8, Me–C(5)); 1.23 (*m*, 1 H–C(8)); 1.38 (*m*, H–C(1), H–C(9)); 1.51 (*m*, H–C(6), 1 H–C(7)); 1.75 (*m*, 1 H–C(7)); 1.93 (*m*, 1 H–C(8)); 2.05 (*m*, H–C(5)); 2.22 (*t*, J = 11.2, H_{ax}–C(4)); 2.89 (*dd*, J = 14.1, 5.0, H_{ax}–C(2)); 2.99 (*dd*, J = 11.2, 4.0, H_{eq}–C(4)); 3.05 (br. *d*, J = 14.1, H_{eq}–C(2)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 17.6 (*Me*–C(9)); 19.4 (*Me*–C(5)); 28.0 (C(7)); 32.2 (C(8)); 32.6 (C(9)); 32.9 (C(5)); 44.9 (C(2)); 45.6 (C(6)); 46.6 (C(1)); 52.5 (C(4)). FAB-MS (thioglycerol): 154 (100, MH^+).

(−)-(1S,5S,6S,9R)-3,5,9-Trimethyl-3-azabicyclo[4.3.0]nonane (= *α-Skytanthine*; (−)-**2**). A mixture of **32** (140 mg, 0.91 mmol) with formaldehyde (37%; 1.31 mmol, 107 µl) and formic acid (90%; 1.32 mmol, 56 µl) was heated at 100° for 30 min. Then aq. sat. $NaHCO_3$ soln. (3 ml) was added, the soln. extracted with CH_2Cl_2 (3 × 10 ml), the combined org. extract dried (Na_2SO_4) and evaporated, and the residue purified by FC (silica gel, *t*-BuOMe/MeOH/NH_4OH 95:5:0.5): (−)-**2** (102 mg, 67%). Oil. R_f 0.5. $[\alpha]_D^{20}$ = −75.0 (c = 1.9, CH_2Cl_2; [7]: $[\alpha]_D^{20}$ = +79). ^{1}H-NMR 360 MHz, $CDCl_3$): 0.81 (*d*, J = 6.2, Me–C(9)); 0.96 (*d*, J = 6.8, Me–C(5)); 1.15 (*m*, 1 H–C(8)); 1.38–1.51 (*m*, 1 H–C(7), H–C(1), H–C(9), H–C(6), H_{ax}–C(2)); 1.70 (*m*, 1 H–C(7)); 1.93 (*m*, 1 H–C(8)); 2.22 (*dd*, J = 11.6, 4.0, H_{ax}–C(4)); 2.07 (*m*, H–C(5)); 2.21 (*s*, MeN); 2.65 (*dd*, J = 9.7, 2.0, H_{eq}–C(2)); 2.79 (*dt*, J = 11.6, 1.1, H_{eq}–C(4)). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 170.9 (*Me*–C(9)); 19.5 (*Me*–C(5)); 27.6 (C(7)); 32.2 (C(8)); 33.0 (C(9)); 33.7 (C(5)); 45.0 (MeN); 46.9 (C(6)); 48.3 (C(1)); 55.8 (C(2)); 63.6 (C(4)). EI-MS: 167 (23, M^+), 166 (58), 155 (100).

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