Pyrrolizidine Alkaloids by Intramolecular Palladium-Catalysed Allylic Alkylation: Synthesis of (±)-Isoretronecanol

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An efficient and stereoconvergent approach to 3-substituted hexahydroindol-2-one derivatives by palladium-catalysed intramolecular allylic alkylation has been developed. Subsequently, the straightforward conversion of the hexahydroindol-2-one **7d** into the alkaloid (±)-isoretronecanol has been performed. The synthesis entails 11 steps starting from 1,3-cyclohexadiene, affording the final target in a 29% overall yield.

Introduction

The last few years have witnessed a growing interest in the development of new synthetic methodologies toward pyrrolizidine alkaloids[1] such as isoretronecanol (**1**),[2] laburnine (**2**),[3] and amphorogynine A (**3**)[4,5] (Figure 1).

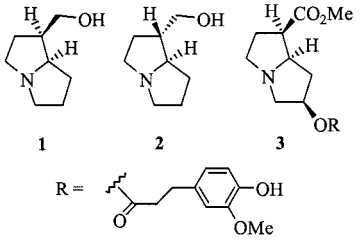
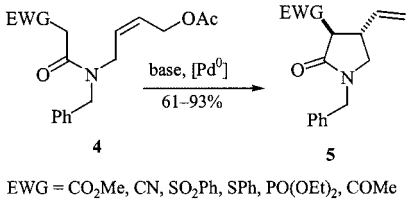


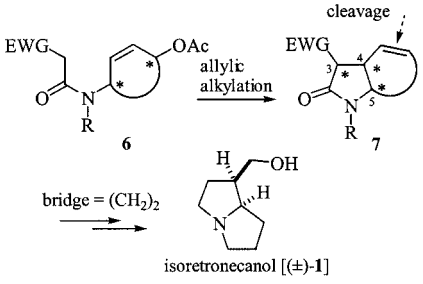
Figure 1. Pyrrolizidine alkaloids: (+)-isoretronecanol (**1**); (+)-laburnine (**2**); amphorogynine A (**3**)

We have previously reported an efficient method for the preparation of *trans*-3,4-disubstituted pyrrolidin-2-ones **5** by palladium-catalysed intramolecular allylic alkylation of the *N*-allylamides **4** (Scheme 1).[6]



Scheme 1

As a logical extension of this study, and in order to obtain synthetically more interesting structures, we decided to direct our investigations toward the cyclisation of alkyl-bridged allylamides **6**, so as to obtain, after cyclisation, bicyclic 3,4,5-trisubstituted pyrrolidone systems **7**.[7] Furthermore, we anticipated that double-bond cleavage of these new bicyclic structures might lead to interesting synthetic applications in the alkaloid field such as, for example, the synthesis of isoretronecanol (**1**) (Scheme 2).



Scheme 2. General strategy toward bicyclic 3,4,5-trisubstituted pyrrolidones and isoretronecanol [(±)-**1**]

Such a variant involves new stereochemical implications that were absent in the previous study. Indeed, in this case,

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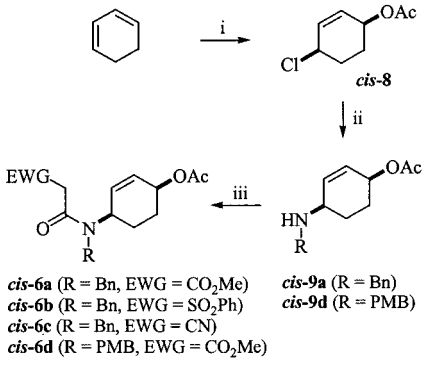
the allylic amine necessary to build up the cyclisation precursor is chiral. As a consequence, the stereogenic units already present on the precursor may govern the diastereoselectivity of the cyclisation. Moreover, the use of enantiopure precursors is conceivable. Accordingly, investigations to obtain bicyclic 3,4,5-trisubstituted pyrrolidone systems **7** were first addressed.

Results and Discussion

Preparation of *cis*- and *trans*-Cyclohexenylamides

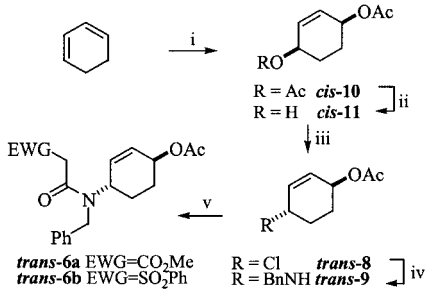
In order to study the key cyclisation step, both the *cis* and *trans* precursors **6** were required. 1,3-Cyclohexadiene was converted into *cis*-4-chloro-2-cyclohexen-1-yl acetate (***cis*-8**) and then into the corresponding *cis*-4-amino-2-cyclohexen-1-yl acetates ***cis*-9a**,**d** by reaction with benzylamine or 4-methoxybenzylamine (PMB-NH_2), according to Bäckvall's procedure.[8,9] Standard treatment of the resulting secondary amines with methyl 3-chloro-3-oxopropionate, (phenylsulfonyl)acetic acid (with DCC and DMAP), or cyanoacetic acid (with DCC and DMAP), gave the 1,4-disubstituted amides ***cis*-6a−d** (Scheme 3).



Scheme 3. Synthesis of the allylamide precursors ***cis*-6a−d**; reagents and conditions: (i) ref.[8], 90%; (ii) ***cis*-9a**: cat. $Pd_2dba_3{\cdot}CHCl_3$, PPh_3, $BnNH_2$, THF, room temp., 12 h, 95%; ***cis*-9d**: PMB-NH_2, cat. $Pd(OAc)_2$, PPh_3, $PhCH_3$, room temp., 10 h, 73%; (iii) ***cis*-6a**: MeO_2CCH_2COCl, NEt_3, CH_2Cl_2, 0 °C, 2 h, 94%; ***cis*-6b**: $PhSO_2CH_2CO_2H$, DCC, DMAP, THF, room temp., 12 h, 93%; ***cis*-6c**: $NCCH_2CO_2H$, DCC, DMAP, THF, room temp., 12 h, 90%; ***cis*-6d**: MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 88%

Accessing the corresponding *trans* analogues ***trans*-6** proved to be more challenging. Indeed, nucleophilic substitution (in the absence of palladium catalyst) of *cis*-4-chloro-2-cyclohexen-1-yl acetate (***cis*-8**) by benzylamine led to an inseparable mixture of the corresponding allylamines ***cis*-9a** and ***trans*-9a** in a 30:70 ratio. An alternative route was therefore devised.

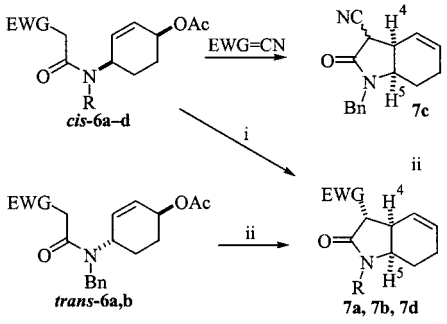
The diacetate ***cis*-10**, in turn obtained from 1,3-cyclohexadiene,[10] was converted into the corresponding monoacetate ***cis*-11** by Zemplén-type methanolysis[11] followed by monoacetylation under controlled conditions. Treatment of ***cis*-11** with NCS/PPh_3 gave *trans*-4-chloro-2-cyclohexen-1-yl acetate (***trans*-8**). Subsequent palladium-catalysed allylic amination in the presence of benzylamine gave the desired allylic amine ***trans*-9**. Finally, standard acylation of the resulting amine with methyl 3-chloro-3-oxopropionate or (phenylsulfonyl)acetic acid (DCC, cat. DMAP) gave the desired amides ***trans*-6a** and ***trans*-6b**, respectively (Scheme 4).



Scheme 4. Synthesis of the allylamide precursors ***trans*-6a**,**b**; reagents and conditions: (i) ref.[8]; (ii) a: NEt_3, $MeOH/H_2O$, room temp., 10 h, 73%; b: Ac_2O, DMAP, Py, CH_2Cl_2, room temp., 17 h, 53%; (iii) NCS, PPh_3, THF, 16 h, 97%; (iv) cat. $Pd_2dba_3{\cdot}CHCl_3$, PPh_3, $BnNH_2$, THF, room temp., 10 h, 87%; (v) ***trans*-6a**: MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 94%; ***trans*-6b**: $PhSO_2CH_2CO_2H$, DCC, THF, room temp., 10 h, 92%

Palladium-Catalysed Cyclisation

With these precursors in hand, attention was turned to the crucial cyclisation step. Gratifyingly, when the *cis* precursors ***cis*-6a**,**b**,**d** were treated with NaH (1.0 equiv.) and added to a DMF solution of the catalytic system [$Pd(OAc)_2$/1,2-bis(diphenylphosphanyl)ethane (dppe)], the expected bicyclic amides **7a**,**b**,**d** were isolated, all in 90% yield (Scheme 5, Method A). Further experiments with ***cis*-6a** showed that a catalytic amount of NaH (0.1 equiv.) was sufficient to effect the cyclisation, with an unchanged 90% yield. In contrast, the absence of NaH totally prevented the cyclisation. In these three cases a single diastereoisomer was formed. The coupling constant values in the ^1H NMR spectrum of the bicyclic products suggest the presence of a *cis* junction between the two rings, and a *trans* disposition be-

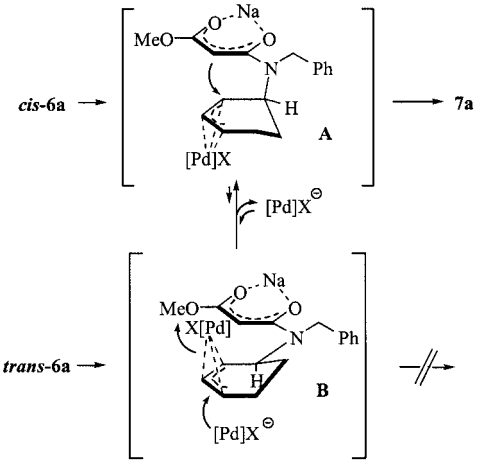


a: R = Bn, EWG = CO_2Me;
b: R = Bn, EWG = SO_2Ph;
c: R = Bn, EWG = CN;
d: R = PMB, EWG = CO_2Me.

Scheme 5. Palladium-catalysed cyclisation of the allylamides ***cis*-6a−d** and ***trans*-6a**,**b**; reagents and conditions: (i) Method A: a: NaH (1.0 equiv.), b: $Pd(OAc)_2$ (1.0 mol %), dppe (2.0 mol %), DMF, 50 °C, 0.5 h, **7a** 90%, **7b** 90%, **7c** 87%, **7d** 90%; (ii) Method B: a: NaH (1.0 equiv.), b: $Pd(OAc)_2$ (5.0 mol %), dppe (10 mol %), DMF, 100 °C, 0.5 h, **7a** 60%, **7b** 73%

tween the electron-withdrawing group (EWG) and the carbon atom of the six-membered ring directly bound to the vicinal position.[12] When the nitrile precursor ***cis*-6c** was submitted to the same conditions as above (Scheme 5, Method A), the expected *cis*-fused bicyclic product **7c** was obtained in 87% yield. However, in this case, a 60:40 inseparable mixture of diastereoisomers was obtained (Scheme 5).

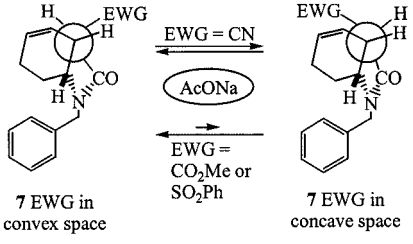
Cyclisation of the precursors ***trans*-6a** and ***trans*-6b** was then addressed. Surprisingly, these transformations required harsher reaction conditions, and afforded the *cis*-fused bicycles **7a** and **7b** as single diastereoisomers. Thus, cyclisation of the *trans*-fused isomers gave the same product as previously obtained from the corresponding *cis*-fused ones, though in somewhat lower yields (Scheme 5, Method B; **7a** 60%, **7b** 73%).



Scheme 7. Stereoconvergence of allylamides ***cis*-6a** and ***trans*-6a**

Plausible Reaction Mechanisms

The different behaviour between ***cis*-6a**,**b**,**d**, and ***cis*-6c** may be accounted for by considering that a base-promoted equilibration of the final products, by the acetate anion liberated in the medium, is likely to take place. As a consequence, while the methoxycarbonyl and phenylsulfonyl derivatives strongly prefer to place these rather bulky groups in the less-congested convex portion of space, location of the small and linear nitrile function is likely to be immaterial in terms of energy differentiation in **7c** (Scheme 6).



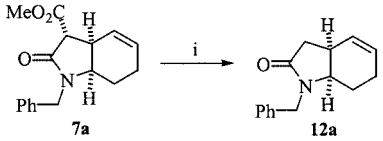
Scheme 6. Isomerisation between epimeric hexahydroindol-2-one derivatives **7**

A mechanistic hypothesis that rationalises the stereoconvergence of ***cis*-6** and ***trans*-6** is depicted in Scheme 7. Addition of the Pd^0 complex to the *cis*-fused allylic acetate is expected to proceed with an inversion mechanism, as originally demonstrated by Hayashi,[13] so as to afford the (η^3-allyl)palladium intermediate **A**. In this complex, the nitrogen substituent occupies a pseudo-axial position and cyclisation can smoothly ensue, again with an inversion mechanism, affording the *cis*-fused adduct **7a**.

On the other hand, cyclisation of the precursor ***trans*-6a** follows a less canonical path. We believe that the ionisation step takes place with the usual inversion mechanism, so as to form the expected η^3-allyl system **B** (Scheme 7). However, in this case, intramolecular addition of the carbanion *anti* to the palladium atom may be a forbidden process, as the pseudo-equatorial C−N bond disposition of the reacting complex is likely to prevent a correct orbital overlap. As a result, the η^3-allyl complex **B** may have enough time to isomerize to complex **A**, the same as obtained from the corresponding *cis*-fused isomer ***cis*-6a**. Although isomerisation of (η^3-allyl)palladium complexes is normally expected to proceed by a π-σ-π mechanism,[14] such a pathway is obviously not available to cyclic systems such as those under consideration. As a consequence, **B**-to-**A** isomerisation appears to take place by a Pd^0-promoted S_N2-type substitution, as first reported by Bäckvall et al.[15] and recently confirmed by Amatore, Jutand, Moreno-Mañas et al.[16]

Interestingly, an analogous behaviour of contrasting reactivity between *cis* and *trans* vicinally substituted six-membered precursors has been reported by Oppolzer[17] and by Bäckvall[18] in alkene- and allene-based carbopalladations, respectively.

In order to stress the effectiveness of our methodology, the synthesis of **12a**, a compound already reported by Ogasawara et al. in enantiopure form,[2p] was undertaken. As expected, simple decarboxylation of **7a** under classical Krapcho conditions[19] led to **12a** in high yield (Scheme 8). Interestingly, our synthetic route to **12a**, though racemic, compares favourably with the already reported one in terms of straightforwardness and efficiency.[20]



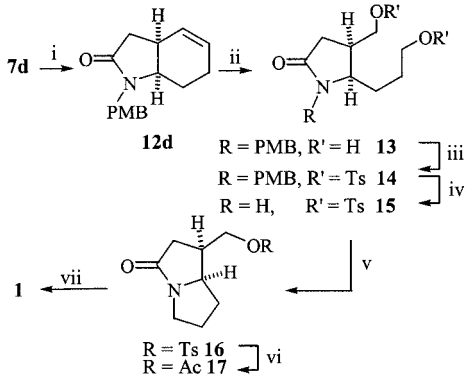
Scheme 8. Decarboxylation of hexahydroindol-2-one **7a**; reagents and conditions: (i) NaCl, wet DMSO, 10 h, 155 °C, 90%

All the above experiments were carried out on racemic substrates. Nonetheless, as the ensemble of transformations **9** → **7** are expected to respect the configurational integrity of the stereogenic carbon atom linked to the nitrogen atom (C-1 in **9**), it can be reasonably anticipated that repetition of the sequence on the enantiopure allylic amine ***cis*-9** or ***trans*-9** should afford the bicyclic compounds **7** with undiminished enantiopurity. Interestingly, Bäckvall et al. have reported that enzymatic desymmetrisation of the *meso*-diacetate **10** allowed preparation of the amine ***cis*-9** in highly enantioenriched form.[21] As a consequence, we have developed an easy and stereoconvergent access to bicyclic 3,4,5-trisubstituted pyrrolidone systems **7**, which is, in principle, directly transposable to enantioenriched substrates.

Synthesis of (±)-Isoretronecanol

The ready availability of the bicyclic amides **7a**−**d** prompted us to exploit the above-described palladium-catalysed cyclisation strategy in a synthetic application. Our choice focused on isoretronecanol (**1**),[2] an alkaloid isolated from *Planchonella* sp.[22] and *Phalaenopsis equestris*.[23]

In this instance, decarboxylation of the PMB-substituted bicyclic amide **7d** under Krapcho's conditions[19] led to the quantitative formation of **12d** (Scheme 9). Subsequent *cis*-dihydroxylation with cat. OsO_4 and Me_3NO in THF/H_2O gave the corresponding diol, which was directly submitted to periodate cleavage. $NaBH_4$ reduction of the thus formed dialdehyde in situ provided diol **13** in a 95% overall yield for the sequence. Judging a selective alcohol functionalisation a difficult and unnecessary (vide infra) task,[2p] diol **13** was then converted into the ditosylate derivative **14** in 82% yield. Oxidative removal of the PMB protecting group with CAN[24] afforded the corresponding secondary amide **15**. Treatment of the latter amide with NaH triggered a clean *5-exo-tet* cyclisation, leading to the pyrrolizidinone **16**. After quantitative tosylate-to-acetate replacement, treatment of the thus formed bicyclic acetoxy amide **17** with $LiAlH_4$ effected concomitant reduction of the ester and amide functions, thereby generating (±)-isoretronecanol (**1**) in 80% yield. This material proved identical in all respects, except optical rotation, with the natural product.[25]



Scheme 9. Conversion of hexahydroindol-2-one **7d** into isoretronecanol [(±)-**1**]; reagents and conditions: (i) NaCl, wet DMSO, 10 h, 155 °C, 99%; (ii) a: cat. OsO_4, $Me_3NO{\cdot}2H_2O$, THF/H_2O (10:1), room temp.; 12 h. b: $NaIO_4$, MeOH, room temp.; 1 h; c: $NaBH_4$, MeOH; 2 h, 95% over 3 steps; (iii) TsCl, NEt_3, DMAP, CH_2Cl_2, room temp.; 5 h, 82%; (iv) CAN, CH_3CN/H_2O, 0 °C, 5 h, 89%; (v): NaH, 0 °C → room temp., 12 h, quant.; (vi) Bu_4NOAc, cat. NaI, THF, 55 °C, 8 h, quant.; (vii) $LiAlH_4$, THF, 66 °C, 2 h, 80%

Conclusion

In summary, we have developed an efficient and stereoconvergent route to 3-substituted hexahydroindol-2-one derivatives featuring a palladium-catalysed intramolecular allylic alkylation as the key step. Further manipulation of the hexahydroindol-2-one **7d** allowed the straightforward conversion of this intermediate into isoretronecanol [(±)-**1**]. The synthesis entails 11 steps starting from 1,3-cyclohexadiene affording the final target in a 29% overall yield. We believe that the above devised methodology extends the synthetic potential of the palladium-catalysed allylation reaction and may be adaptable to the preparation of other related pyrrolizidine derivatives.

Experimental Section

General Remarks: All reactions were conducted under dried nitrogen or argon using oven-dried glassware. For air- and/or water-sensitive reactions, glassware was flame-dried and then allowed to cool under argon or dried nitrogen before use. All solvents were purified and distilled according to standard methods. Chromatographic purifications were conducted using 40−63 μm or 15−40 μm silica gel. All NMR spectra were recorded in $CDCl_3$. Elemental analyses were carried out with accepted tolerance of ±0.3 units on C, H and N. All compounds were isolated as oils unless otherwise stated, and their purities were determined to be > 95% by NMR analysis. IR spectra were recorded with a Perkin−Elmer 1420. Absorption bands are reported in cm^{-1}. NMR spectra were recorded with either a Varian-Gemini 200/50 MHz or a Bruker ARX 400/100 MHz. Chemical shifts (δ) are reported in parts per million (ppm) down-field and high-field from the residual-solvent peak. GC-MS spectra were recorded with a Shimadzu GC-17A and Shimadzu Mass-spectrometer QP-5000.

General Procedure for Acylation with Methyl Chlorocarbonylacetate: NEt_3 (0.681 mL, 4.9 mmol) and methyl chlorocarbonylacetate (0.394 mL, 3.675 mmol) were added dropwise in sequence to a solution of the allylic amine (2.45 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C. After 4 h of stirring at room temp., the mixture was diluted with diethyl ether (50 mL) and water (3 × 20 mL). The collected organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 5:5) to afford the desired product as a yellow oil.

(±)-Methyl 3-{[(1*S*,4*R*)-4-(Acetyloxy)cyclohex-2-en-1-yl](benzyl)-amino}-3-oxopropanoate (*cis*-6a): From ***cis*-9a**[21] (94%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.39−7.18 (m, 5 H), 5.98−5.86 (m, 1 H), 5.78 (d, ^3J = 10.3 Hz, 1 H), 5.32−5.21 (m, 1 H, 70%), 5.11 (m, 1 H), 4.54 (AB system, 2 H, 30%), 4.49 (AB system, 2 H, 70%), 2.02 (s, 3 H, 30%), 1.98 (s, 3 H, 70%), 1.54−1.86 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4, 167.4, 167.2, 166.7, 165.6, 137.9, 137.0, 133.4, 133.1, 128.2, 128.1, 127.8, 127.6, 126.7, 126.3, 126.0, 125.0, 64.4, 63.8, 55.2, 51.7, 51.6, 51.0, 47.3, 46.0, 40.8, 40.7, 26.2, 26.2, 23.1, 21.8, 20.5 ppm. IR (CCl_4): $\tilde{\nu}$ = 2958, 2248, 1721,

1639 cm^{-1}. MS (EI): *m*/*z* (%) = 345 [M^+] (2), 286 (14), 206 (9), 91 (100). $C_{19}H_{23}NO_5$ (345.40): calcd. C 66.07, H 6.71, N 4.06; found C 66.21, H 6.77, N 4.09.

(±)-Methyl 3-{[(1*S*,4*S*)-4-(Acetyloxy)cyclohex-2-en-1-yl](benzyl)amino}-3-oxopropanoate (*trans*-6a): From ***trans*-9**[21] (94%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.16−7.35 (m, 5 H), 5.78 (m, 1 H), 5.62 (m, 1 H), 5.20−5.42 (m, 2 H), 4.51 (AB system, 2 H, 30%), 4.45 (AB system, 2 H, 70%), 3.77 (s, 3 H, 30%), 3.69 (s, 3 H, 70%), 3.61 (s, 2 H, 30%), 1.40−2.21 (m, 4 H), 3.30 (s, 2 H, 70%), 2.03 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.2, 167.7, 167.1, 165.9, 138.0, 137.1, 131.5, 130.8, 128.6, 128.0, 127.2, 126.6, 126.5, 125.3, 68.6, 68.4, 55.5, 52.1, 51.4, 47.4, 46.0, 41.3, 27.7, 27.6, 27.2, 25.6, 20.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3045, 2957, 1730, 1643 cm^{-1}. MS (EI): *m*/*z* (%) = 346 [M^+] (1.2), 286 (11), 106 (53), 91 (78). $C_{19}H_{23}NO_5$ (345.40): calcd. C 66.07, H 6.71, N 4.06; found C 66.18, H 6.83, N 4.12.

(±)-Methyl 3-{[(1*S*,4*R*)-4-(Acetyloxy)cyclohex-2-en-1-yl](4-methoxybenzyl)amino}-3-oxopropanoate (*cis*-6d): From ***cis*-9d**[9] (88%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (d, ^2J = 8.7 Hz, 2 H, 34%), 7.13 (d, ^2J = 8.7 Hz, 2 H, 66%), 6.90 (d, ^2J = 8.7 Hz, 2 H, 34%), 6.83 (d, ^2J = 8.7 Hz, 2 H, 34%), 5.93 (m, 1 H), 5.80 (m, 1 H), 5.23 (m, 1 H, 66%), 5.14 (m, 1 H), 4.67 (AB system, ^2J = 15 Hz, 1 H, 34%), 4.49 (AB system, ^2J = 17.8 Hz, 1 H, 34%), 4.41 (AB system, ^2J = 17.8 Hz, 1 H, 66%), 4.35 (AB system, ^2J = 15 Hz, 34%, 1 H), 4.25 (m, 1 H, 34%), 3.80 (s, 3 H, 66%), 3.78 (s, 3 H, 34%), 3.77 (s, 3 H, 34%), 3.70 (s, 3 H, 66%), 3.60 (s, 2 H, 34%), 3.32 (s, 2 H, 66%), 2.05 (s, 3 H, 34%), 2.01 (s, 3 H, 66%), 1.6−1.8 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 168.4, 167.9, 159.4, 134.3, 129.8, 129.2, 129.0, 128.9, 127.6, 114.8, 114.2, 64.9, 56.6, 56.3, 55.7, 52.8, 52.2, 47.9, 41.9, 27.4, 27.3, 24.1, 22.9, 21.7 ppm. IR (neat): $\tilde{\nu}$ = 1730 cm^{-1}, 1640, 1430. $C_{20}H_{25}NO_6$ (375.42): calcd. C 63.99, H 6.71, N 3.73; found C 64.02, H 6.79, N 3.82.

General Procedure for Acylation by DCC: The acid derivative (0.32 mmol), DCC (79 mg, 0.38 mmol) and a catalytic amount of DMAP (4 mg, 0.032 mmol) were added in sequence to a solution of the allylic amine (0.32 mmol) in dry THF (5 mL). After 15 h of stirring at room temp., a large amount of hexane (7 mL) was added and the resulting suspension was filtered through a Celite® pad. The organic layer was concentrated under reduced pressure and the resulting crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 50:50) to afford the expected product.

(±)-(1*S*,4*R*)-4-{Benzyl[(phenylsulfonyl)acetyl]amino}cyclohex-2-en-1-yl Acetate (*cis*-6b): From ***cis*-9a** (93%): ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.88 (m, 2 H), 7.53 (m, 3 H), 7.16 (m, 5 H), 5.97−5.86 (m, 1 H), 5.74−5.59 (m, 1 H), 5.27−5.16 (m, 1 H), 4.60 (s, 2 H), 4.38 (d, ^3J = 4.92 Hz, 1 H, 75%), 4.31 (d, ^3J = 4.92 Hz, 1 H, 25%), 4.02 (s, 2 H), 2.04 (s, 3 H, 25%), 2.03 (s, 3 H, 75%), 2.00−1.64 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 200 MHz): δ = 170.5, 137.3, 134.3, 133.0, 129.6, 129.3, 129.2, 128.6, 128.4, 127.8, 127.3, 125.6, 65.0, 60.6, 52.1, 47.7, 26.7, 22.5, 21.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3049, 2940, 1727, 1645 cm^{-1}. $C_{23}H_{25}NO_5S$ (427.52): calcd. C 64.62, H 5.89, N 3.28; found C 64.72, H 5.93, N 3.34.

(±)-(1*S*,4*S*)-4-{Benzyl[(phenylsulfonyl)acetyl]amino}cyclohex-2-en-1-yl Acetate (*trans*-6b): From ***trans*-9** (92%). M.p. 32−35 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.86 (m, 2 H), 7.52 (m, 3 H), 7.11 (m, 5 H), 5.78 (m, 1 H), 5.58 (m, 1 H), 5.28 (m, 1 H), 4.63 (s, 2 H), 4.34 (m, 1 H), 4.03 (s, 2 H), 2.04 (s, 3 H, 30%), 2.02 (s, 3 H, 70%), 1.48−2.05 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.5 162.6, 161.6, 138.8, 138.5, 137.6, 136.9, 134.8, 132.8, 132.3, 132.1, 130.7, 130.2, 129.0, 129.0, 128.3, 128.2, 127.6, 126.9, 126.8, 125.4, 68.7, 68.5, 60.5, 60.0, 56.3, 52.0, 47.4, 46.6, 27.9, 27.7, 27.5, 25.8, 21.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3058, 2990, 1727, 1644, 1419, 1247 cm^{-1}. MS (EI): *m*/*z* (%) = 368 (26.3) [M^+ − 59], 141 (12), 77 (81.2). $C_{23}H_{25}NO_5S$ (427.52): calcd. C 64.62, H 5.89, N 3.28; found C 64.64, H 5.87, N 3.21.

(±)-(1*S*,4*R*)-4-[Benzyl(cyanoacetyl)amino]cyclohex-2-en-1-yl Acetate (*cis*-6c): From ***cis*-9a** (90%): ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42−7.20 (m, 5 H), 5.35−5.28 (m, 1 H, 50%), 5.20−5.16 (m, 1 H), 4.72 (AB system, ^2J = 15.4 Hz, 1 H, 25%), 4.54 (AB system, ^2J = 18.2 Hz, 1 H, 75%), 4.49 (AB system, ^2J = 18.2 Hz, 1 H, 75%), 4.43 (AB system, ^2J = 15.4 Hz, 1 H, 25%), 4.30−4.20 (m, 1 H, 20%), 3.90 (AB system, ^2J = 13 Hz, 1 H, 30%), 3.86 (AB system, ^2J = 13 Hz, 1 H, 30%), 3.89 (AB system, ^2J = 18.5 Hz, 1 H, 20%), 3.64 (AB system, ^2J = 18.5 Hz, 1 H, 20%), 3.33 (AB system, ^2J = 19 Hz, 1 H, 50%), 3.29 (AB system, ^2J = 19 Hz, 1 H, 50%), 3.32 (m, 1 H, 30%), 2.08 (s, 3 H, 20%), 2.06 (s, 3 H, 30%), 2.05 (s, 3 H, 50%), 1.58−1.93 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 1710.6, 170.7, 163.5, 162.1, 137.0, 135.8, 133.1, 129.8, 128.8, 128.4, 127.3, 126.1, 125.9, 114.2, 67.6, 65.3, 64.9, 52.8, 52.7, 51.4, 48.3, 27.1, 26.4, 26.2, 25.7, 23.0, 21.57 ppm. IR (neat): $\tilde{\nu}$ = 2980 cm^{-1}, 2280, 1740, 1670, 1450. $C_{18}H_{20}N_2O_3$ (312.37): calcd. C 69.21, H 6.45, N 8.97; found C 69.35, H 6.55, N 9.12.

General Procedure for the [$Pd(OAc)_2$/PPh_3]-Catalysed Intramolecular Allylic Alkylation. Method A: NaH (60% dispersion in mineral oil; 1.36 mmol) was added to a solution of the cyclisation precursor (1.36 mmol) in dry DMF (5 mL) under argon, cooled in a water/ice bath, and the solution was stirred at room temp. for 10 min. In a separate flask, $Pd(OAc)_2$ (0.0136 mmol) and dppe (0.0272 mmol) were dissolved in dry DMF (2 mL). The resulting enolate was then transferred with a cannula under argon pressure to the preformed palladium(0) complex, and the resulting mixture was stirred at 50 °C for 30 min. After cooling at room temp. and dilution with a saturated aqueous solution of NH_4Cl (10 mL), the product was extracted with diethyl ether (3 × 10 mL). The collected organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to afford the expected product of cyclisation as a yellow oil. **Method B:** The cyclisation was performed as reported for Method A, but in the presence of 0.05 equiv. of $Pd(OAc)_2$ and 0.1 equiv. of dppe and heating the reaction mixture at 100 °C for 30 min.

(±)-Methyl (3*R*,3a*R*,7a*R*)-Benzyl-2-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-3-carboxylate (7a): From ***cis*-6a** (Method A, 90%) or from ***trans*-6a** (Method B, 60%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36−7.24 (m, 5 H), 5.86−5.78 (m, 1 H), 5.61−5.54 (m, 1 H), 5.00 (AB system, ^2J = 15 Hz, 1 H), 4.03 (AB system, ^2J = 15 Hz, 1 H), 3.80 (s, 3 H), 3.70−3.61 (m, 1 H), 3.28 (d, ^3J = 7.8 Hz, 1 H), 3.19−3.13 (m, 1 H), 1.98−1.79 (m, 3 H), 1.54−1.39 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.0, 168.3, 135.0, 131.8, 127.6, 126.8, 126.6, 124.67, 53.3, 53.0, 51.6, 43.4, 35.5, 22.9, 20.3 ppm. IR (CCl_4): $\tilde{\nu}$ = 3033, 2937, 2846, 1733, 1680 cm^{-1}. MS (EI): *m*/*z* (%) = 285 [M^+] (100), 226 (85), 146 (91). $C_{17}H_{19}NO_3$ (285.34): calcd. C 71.56, H 6.71, N 4.91; found C 71.48, H 6.63, N 4.79.

(±)-(3*R*,3a*S*,7a*R*)-1-Benzyl-3-(phenylsulfonyl)-1,3,3a,6,7,7a-hexahydro-2*H*-indol-2-one (7b): From ***cis*-6b** (Method A, 90%) or from ***trans*-6b** (Method B, 73%). M.p. 151−153 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 8.00 (m, 2 H), 7.75−7.55 (m, 3 H), 7.40−7.20 (m, 5 H), 5.90 (m, 1 H), 5.65 (m, 1 H), 5.01 (AB system, ^2J = 15.2 Hz, 1 H), 3.95 (AB system, ^2J = 15.2 Hz, 1 H), 3.78 (d, ^3J = 5.4 Hz, 1 H), 3.86−3.75 (m, 1 H), 3.55−3.51 (m, 1 H), 2.00−1.50 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 165.0, 135.4, 134.2, 129.7,

129.5, 129.0, 128.8, 127.8, 127.7, 125.4, 71.2, 53.6, 44.5, 33.9, 23.9, 20.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3008, 2933, 2848, 1691, 1308, 1145 cm^{-1}. MS (NH_3): *m*/*z* (%) = 368 (3) [M^+ + 1], 226 (80), 91 (100), 77 (27). $C_{21}H_{21}NO_3S$ (367.46): calcd. C 68.64, H 5.76, N 3.81; found C 68.70, H 5.93, N 3.62.

(±)-(3*R*/*S*,3a*R*,7a*R*)-1-Benzyl-2-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-3-carbonitrile (7c): From ***cis*-6c** (Method A, 87%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.40−7.10 (m, 5 H), 6.05 (m, 1 H, 40%), 5.92 (m, 1 H, 60%), 5.80−5.65 (m, 1 H), 4.99 (AB system, ^2J = 15.2 Hz, 1 H, 40%), 4.97 (AB system, ^2J = 15.2 Hz, 1 H, 60%), 4.04 (AB system, ^2J = 15.2 Hz, 1 H), 3.69 (d, ^2J = 8.9 Hz, 1 H, 40%), 3.66−3.40 (m, 1 H), 3.30 (d, ^2J = 9.8 Hz, 1 H, 60%), 3.05 (m, 1 H), 2.10−1.50 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 166.4, 165.7, 135.9, 135.8, 131.9, 130.9, 129.3, 129.2, 128.4, 123.9, 122.6, 116.9, 115.8, 54.9, 54.5, 45.4, 45.2, 39.9, 39.5, 38.3, 34.6, 34.3, 25.9, 25.3, 24.1, 23.8, 22.4, 21.1 ppm.

(±)-Methyl (3*R*,3a*R*,7a*R*)-1-(4-Methoxybenzyl)-2-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-3-carboxylate (7d): From ***cis*-6d** (Method A, 90%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.18 (d, ^3J = 8.7 Hz, 2 H), 6.84 (d, ^3J = 8.7 Hz, 2 H), 5.80 (m, 1 H, H_d), 5.55 (m, 1 H), 4.93 (AB system, ^2J = 15.0 Hz, 1 H), 3.96 (AB system, ^2J = 15.0 Hz, 1 H), 3.75 (s, 6 H), 3.62 (m, 1 H), 3.26 (d, ^3J = 7.4 Hz, 1 H,), 3.11 (m, 1 H), 2.1−1.7 (m, 3 H), 1.6−1.4 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.2, 169.4, 159.2, 129.4, 128.8, 128.3, 125.8, 114.1, 53.4, 54.5, 21.5 C_g, 54.1, 52.8, 44.1, 39.7, 24.1 ppm. IR (neat): $\tilde{\nu}$ = 1740 cm^{-1}, 1690, 1520, 1440, 1260 cm^{-1}. MS (EI): *m*/*z* (%) = 315 (17) [M^+], 194 (4), 121 (100). $C_{18}H_{21}NO_4$ (315.37): calcd. C 68.55, H 6.71, N 4.44; found C 68.66, H 6.82, N 4.56.

General Procedure for the Demethoxycarbonylation: Water (0.176 mL, 9.28 mmol, 4 equiv.) and NaCl (177 mg, 3.02 mmol, 1.3 equiv.) were added in sequence to a solution of the methyl ester derivative (2.32 mmol, 1equiv.) in DMSO (5 mL) and the resulting mixture was warmed at the appropriate temperature. The reaction mixture was then cooled to room temp., water (20 mL) was added and the mixture was extracted with chloroform (3 × 15 mL). The collected organic layers were washed with a saturated NaCl aqueous solution (3 × 10 mL), dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude oil was purified by flash chromatography (petroleum ether/ethyl acetate, 55:45) to afford the decarboxylated product as a brown oil.

(±)-(3a*S*,7a*R*)-1-Benzyl-1,3,3a,6,7,7a-hexahydro-2*H*-indol-2-one (12a): From **7a** (90%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37−7.23 (m, 5 H), 5.81−5.77 (m, 1 H), 5.61−5.55 (m, 1 H), 5.03 (AB system, ^2J = 15 Hz, 1 H), 4.00 (AB system, ^2J = 15 Hz, 1 H), 3.98−3.55 (m, 1 H), 2.87−2.76 (m, 1 H), 2.65 (ABX system, ^2J = 16.6, ^3J = 9 Hz, 1 H), 2.27 (ABX system, ^2J = 16.6, ^3J = 7.4 Hz, 1 H), 2.00−1.60 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.4, 136.9, 128.7, 128.0, 127.6, 55.3, 44.0, 37.5, 32.2, 23.7, 21.2 ppm. MS (NH_3): *m*/*z* (%) = 228 (100) [M^+ + 1]. $C_{15}H_{17}NO$ (227.31): calcd. C 79.26, H 7.54, N 6.16; found C 79.46, H 7.79, N 6.19.

(±)-(3a*S*,7a*R*)-1-(4-Methoxybenzyl)-1,3,3a,6,7,7a-hexahydro-2*H*-indol-2-one (12d): From **7d** (99%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.10 (d, ^3J = 8.9 Hz, 2 H), 6.76 (d, ^3J = 8.9 Hz, 2 H), 5.70 (s, 1 H), 5.45 (m, 1 H), 4.86 (AB system, ^2J = 14.8 Hz, 1 H), 3.84 (AB system, ^2J = 14.8 Hz, 1 H), 3.69 (s, 3 H), 3.46 (m, 1 H), 1.9−1.4 (m, 4 H), 2.12 (ABX system, ^2J = 16, ^3J = 6.9 Hz, 1 H), 2.52 (ABX system, ^2J = 16, ^3J = 8.8 Hz, 1 H), 2.67 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 174.3, 158.9, 129.3, 127.6, 114.0, 55.2, 43.3, 37.5, 32.1, 23.6, 21.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1680, 1610, 1510, 1430 cm^{-1}. MS (EI): *m*/*z* (%) = 257 (23) [M^+], 136 (6), 121 (100). $C_{16}H_{19}NO_2$ (257.33): calcd. C 74.68, H 7.44, N 5.44; found C 74.71, H 7.50, N 5.62.

(±)-(4*R*,5*R*)-4-(Hydroxymethyl)-5-(3-hydroxypropyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (13): $Me_3NO{\cdot}2H_2O$ (977 mg, 8.80 mmol) was added portionwise to a solution of **12d** (1.13 g, 4.40 mmol) in THF (40 mL) and distilled water (4 mL). After dissolution of the amine *N*-oxide, OsO_4 (4.5% solution in *i*PrOH, 496 mg, 0.088 mmol) was added and the mixture was stirred at room temp. overnight. A saturated aqueous solution of sodium sulfite (0.5 mL) was added and stirring was continued for 30 min. The reaction mixture was then treated with brine (10 mL) and the organic layer was extracted with a large amount of EtOAc (3 × 50 mL). The collected organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. The resulting crude solid material was used in the next step without further purification. The crude diol (1.29 g) in methanol (20 mL) was treated with $NaIO_4$ (1.04 g, 4.84 mmol, 1.1 equiv.) in one portion and the resulting mixture was stirred at room temp. for 1 h, until appearance of a white suspension. The reaction was monitored by TLC (CH_2Cl_2/MeOH, 95:5). The suspension was filtered through a Celite® pad, the filtrate was cooled to 0 °C and treated portionwise with solid $NaBH_4$ (665 mg, 17.6 mmol, 4.0 equiv.). After 2 h of stirring at room temp., the mixture was cooled again to 0 °C and treated with a saturated aqueous NH_4Cl solution (15 mL). A standard extractive workup with EtOAc (3 × 100 mL) gave, after removal of solvents, a crude material which was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to afford **13** as a colourless oil (1.22 g, 95%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.16 (d, ^3J = 8.4 Hz, 2 H), 6.86 (d, ^3J = 8.4 Hz, 2 H), 4.97 (AB system, ^2J = 14.9 Hz, 1 H), 3.89 (AB system, ^2J = 14.9 Hz, 1 H), 3.81 (s, 3 H), 3.77 (ABX system, ^2J = 10.9, ^3J = 7.4 Hz, 1 H), 3.70 (ABX system, ^2J = 10.9, ^3J = 6.1 Hz, 1 H), 3.61 (m, 2 H), 3.56 (m, 1 H), 2.55 (m, 1 H), 1.58−1.54 (m, 2 H, H_g), 2.44 (ABX system, ^2J = 16.5, ^3J = 8.3 Hz, 1 H), 2.34 (ABX system, ^2J = 16.5, ^3J = 9.0 Hz, 1 H), 1.90 (br. s, 2 H, OH), 1.70−1.66 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 175.4, 160, 130.2, 129.5, 115.0, 63.2, 62.1, 59.0, 56.2, 44.9, 39.5, 35.0, 29.5,25.3 ppm. IR (neat): $\tilde{\nu}$ = 3375, 2930, 1658, 1245 cm^{-1}. $C_{16}H_{23}NO_4$ (293.36): calcd. C 65.51, H 7.90, N 4.77; found C 65.45, H 7.80, N 4.85.

(±)-3-[(2*R*,3*R*)-1-(4-Methoxybenzyl)-3-({[(4-methylphenyl)sulfonyl]-oxy}methyl)-5-oxopyrrolidin-2-yl]propyl 4-Methylbenzenesulfonate (14): NEt_3 (0.85 mL, 6.12 mmol, 4.0 equiv.) and a catalytic amount of DMAP (2 mg, 0.015 mmol) were added in sequence to a solution of **13** (450 mg, 1.53 mmol) in dry CH_2Cl_2 (15 mL). The resulting mixture was cooled to 0 °C and TsCl (877 mg, 4.61 mmol, 3.0 equiv.) was added in one portion. After 15 min of stirring at 0 °C, the mixture was left to warm to room temp. and then stirred for a further 6 h. A saturated aqueous $NaHCO_3$ solution (2 mL) was then added and the mixture was extracted with diethyl ether (3 × 10 mL). After drying with $MgSO_4$ and concentration under reduced pressure, the crude oil was purified by flash chromatography (petroleum ether/ethyl acetate, 3:7) to afford **14** as a colourless oil (755 mg, 82%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (d, ^3J = 7.6 Hz, 2 H), 7.76 (d, ^3J = 7.6 Hz, 2 H), 7.38 (d, ^3J = 7.6 Hz, 4 H), 7.09 (d, ^3J = 8.4 Hz, 2 H), 6.83 (d, ^3J = 8.4 Hz, 2 H), 4.86 (AB system, ^2J = 14.8 Hz, 1 H), 4.01 (m, 2 H), 3.88 (m, 2 H), 3.80 (AB system, ^2J = 14.8 Hz, 1 H), 3.79 (s, 3 H), 2.46 (m, 1 H), 2.63 (m, 1 H), 2.46 (s, 6 H), 2.38 (ABX system, ^2J = 16.8, ^3J = 8.6 Hz, 1 H), 2.13 (ABX system, ^2J = 16.8, ^3J = 9.2 Hz), 1 H, 1.6−1.4 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 197.6, 173.6, 160.1, 146.4, 146.0, 133.8, 133.2, 131.1, 130.9, 130.2, 129.0, 128.8, 115.1,

70.6, 69.2, 58.0, 56.2, 45.1, 36.6, 34.3, 25.9, 25.2, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2940, 1650, 1520, 1460 cm^{-1}.

(±)-3-[(2*R*,3*R*)-3-({[(4-Methylphenyl)sulfonyl]oxy}methyl)-5-oxopyrrolidin-2-yl]propyl 4-Methylbenzenesulfonate (15): $(NH_4)_2Ce(NO)_6$ (2.55 g, 4.66 mmol) was added in one portion to a solution of **14** (700 mg, 1.16 mmol) in a CH_3CN/H_2O (3:1) mixture (12 mL) cooled to 0 °C. After 2 h of stirring, EtOAc (10 mL) and brine (5 mL) were added. The mixture was extracted with a large amount of EtOAc (3 × 50 mL). The collected organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. The crude material was purified by flash chromatography (ethyl acetate/acetone, 9:1) to afford the expected *N*-deprotected pyrrolidone **15** (493 mg, 89%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (m, 4 H), 7.39 (m, 4 H), 7.33 (s, 1 H, NH), 4.03 (m, 4 H), 3.62 (m, 1 H), 2.82 (m, 1 H), 2.47 (s, 6 H), 2.31 (ABX system, ^2J = 16.8, ^3J = 8.6 Hz, 1 H), 2.05 (ABX system, ^2J = 16.8, ^3J = 9.3 Hz, 1 H), 1.71 (m, 1 H), 1.61 (m, 1 H), 1.46 (m, 1 H), 1.29 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 197.6, 146.3, 145.9, 133.6, 133.2, 131.1, 131.0, 128.7, 128.8, 70.9, 69.3, 56.1, 38.1, 27.4, 26.7, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2918, 2850, 1779, 1678, 1358, 1035 cm^{-1}.

(±)-[(1*R*,7a*R*)-3-Oxohexahydro-1*H*-pyrrolizin-1-yl]methyl 4-Methylbenzenesulfonate (16): NaH (33 mg, 0.82 mmol, 60% dispersion in mineral oil) was added in one portion to a cooled solution (0 °C) of the secondary amide precursor **15** (395 mg, 0.82 mmol) in dry THF (16 mL) under argon. The mixture was stirred at room temp. for 12 h, then it was cooled again to 0 °C, and a saturated aqueous NH_4Cl solution (2 mL) was added dropwise. The mixture was extracted with a large amount of EtOAc (3 × 50 mL). The collected organic layers were dried with $MgSO_4$ and the solvents evaporated under reduced pressure. The crude oil was purified by flash chromatography (ethyl acetate/acetone, 8:2) to afford the expected pyrrolizidine derivative **16** (353 mg, quant.). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, ^3J = 8.2 Hz, 2 H), 7.38 (d, ^3J = 8.2 Hz, 2 H), 4.04 (m, 1 H), 3.94 (m, 2 H), 3.46 (m, 1 H), 3.08 (m, 1 H), 2.83 (2H), 2.47 (s, 3 H), 2.1−1.9 (m, 3 H), 1.82 (m, 1 H), 1.38 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 173.6, 146.2, 133.4, 131.0, 128.9, 70.1, 63.9, 41.9, 37.9, 34.3, 26.6, 22.6 ppm. IR (neat): $\tilde{\nu}$ = 2919, 1675, 1011 cm^{-1}. MS (EI): *m*/*z* (%) = 309 (6) [M^+], 185 (2), 124 (18), 91 (32), 70 (100).

(±)-[(1*R*,7a*R*)-3-Oxohexahydro-1*H*-pyrrolizin-1-yl]methyl Acetate (17): nBu_4NOAc (44 mg, 0.15 mmol) and a catalytic amount of NaI were added in sequence to a solution of the tosylate **16** (15 mg, 0.05 mmol) in dry THF (0.5 mL) under argon. The mixture was stirred at room temp. for 12 h, then the solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (EtOAc/acetone, 8:2) to afford **17** as a colourless oil (9 mg, quant.). ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.15 (ABX system, ^2J = 11.2, ^3J = 7.6 Hz, 1 H), 4.03 (m, 1 H), 4.01 (ABX system, ^2J = 11.2, ^3J = 6.6 Hz, 1 H), 3.52 (ABX system, ^2J = 11.7, ^3J = 8.4 Hz, 1 H), 3.11 (ABX system, ^2J = 11.7, ^3J = 3.0 Hz, 1 H), 2.91 (m, 1 H), 2.82 (m, 1 H), 2.26 (m, 1 H), 2.15 (m, 1 H), 2.06 (s, 3 H), 2.02 (m, 1 H), 1.83 (m, 1 H), 1.51 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 173.9, 171.1, 64.3, 63.7, 41.6, 38.0, 33.6, 25.9, 21.2, 27.0 ppm. IR (neat): $\tilde{\nu}$ = 3000, 1770, 1720, 1450, 1280 cm^{-1}. MS (EI): *m*/*z* (%) = 197 (19) [M^+], 155 (4), 124 (14), 70 (100), 43 (86). $C_{10}H_{15}NO_3$ (197.23): calcd. C 60.90, H 7.67, N 7.10; found C 60.93, H 7.79, N 7.21.

(±)-(1*R*,7a*R*)-Hexahydro-1*H*-pyrrolizin-1-ylmethanol [(±)-Isoretronecanol (1)]: Powdered $LiAlH_4$ (38 mg, 0.36 mmol) was added in one portion to a solution of the acetate **17** (9 mg, 0.05 mmol) in dry THF (1 mL) cooled to 0 °C. The reaction mixture was stirred at room temp. for 30 min and at 65 °C for 2 h. It was then allowed to cool to room temp. and treated with wet diethyl ether (1 mL). An aqueous NaOH solution (15% wt, 15 μL) and water (50 μL) were added in sequence and stirring was maintained for a further 30 min. The reaction mixture was then filtered and washed with warm EtOAc (3 × 5 mL). Concentration of the organic layers under reduced pressure gave the pure alkaloid **1** (5.5 mg, 80%). ^1H NMR ($CDCl_3$, D_2O, 400 MHz): δ = 4.70 (HOD), 3.71 (m, 2 H), 3.54 (m, 1 H), 3.11 (m, 1 H), 2.99 (m, 1 H), 2.64 (m, 1 H), 2.52 (m, 1 H), 2.47 (m, 1 H), 1.90 (m, 1 H), 1.82 (m, 1 H), 1.72 (m, 2 H), 1.56 (m, 1 H), 1.43 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 66.6, 64.8, 55.9, 26.3 C, 54.3, 44.5, 27.7, 26.9 ppm. IR (neat): $\tilde{\nu}$ = 3346, 2924, 2854, 1457, 1049 cm^{-1}. MS (EI): *m*/*z* (%) = 141 (11) [M^+], 124 (8), 110 (7), 83 (100).

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