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A Highly Enantioselective Synthesis of (-)-Antirhine by Chemo-Enzymatic Approach

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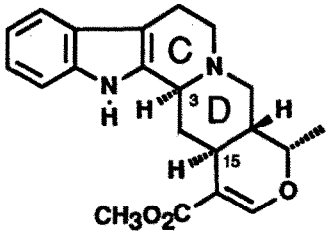
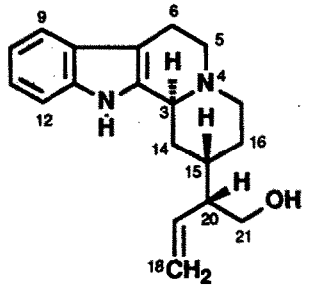
Abstract: (-)-Antirhine **2** was synthesized in an efficient and stereocontrolled fashion from the readily available (1*R*-2*S*)-cyclohexene dimethanol monoacetate **6**. A key step was the regio- and stereoselective Pictet Spengler cyclization of the masked dialdehyde **12** to the indoloquinolizidinone **13**.

The indole alkaloids of class I[1] are formed by the condensation of tryptamine/tryptophane with secologanine and contain the unrearranged carbon skeleton of the monoterpenoid precursor. A common structural feature of such compounds, like (-)-ajmalicine **1**, is a *cis* 3αH, 15αH configuration (the latter being derived from the C-5*S* of secologanine) and a *trans* C/D ring junction. Only in few members of this class, and particularly in (-)-antirhine **2**[2] and its congeners,[3] has a *trans* 3αH, 15βH configuration and a *cis* C/D rings junction been determined.



1

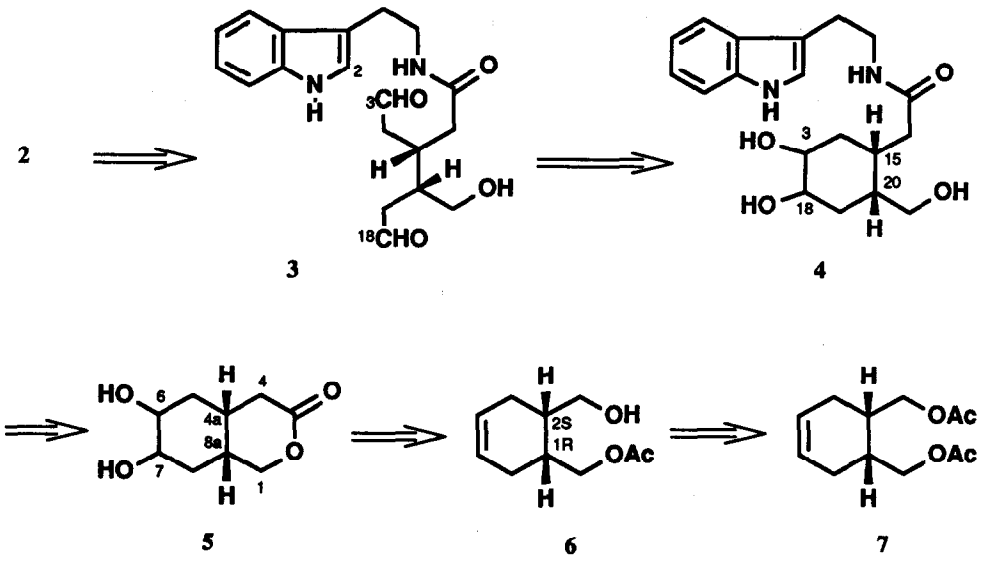


2

In the light of its unique structure, (-)-antirhine **2** has marked potential for total synthesis. The greatest obstacle lies in introducing the required configurations at the stereogenic centers C-3, C-15 and C-20. Since an initial approach to racemic **2** from norcamphor[4], the complete stereocontrol of the C-15 and C-20 stereogenic centers has been achieved only in two syntheses starting from D-mannitol[5] and from secologanine.[6] Starting from natural chirons, two other limited approaches to **2** have been reported[7,8] in which only the chirality at C-15 was controlled.

We report here an expeditious synthesis of **2**[9] with complete control of all stereogenic centers. It

utilizes a chiral starting material readily available by enzymatic methodology and appears to involve a limited number of processing steps. In our retrosynthetic analysis (Scheme 1) we envisioned the C-3 and C-18 of **2** as being equivalent to the aldehyde groups of **3**[10] by Pictet Spengler cyclization and functional group interchange respectively. These aldehydes might be fashioned by oxidative cleavage of the C-3/C-18 bond of the cyclohexane diol **4**, accessible by the condensation of tryptamine with the dihydroxylactone **5**.



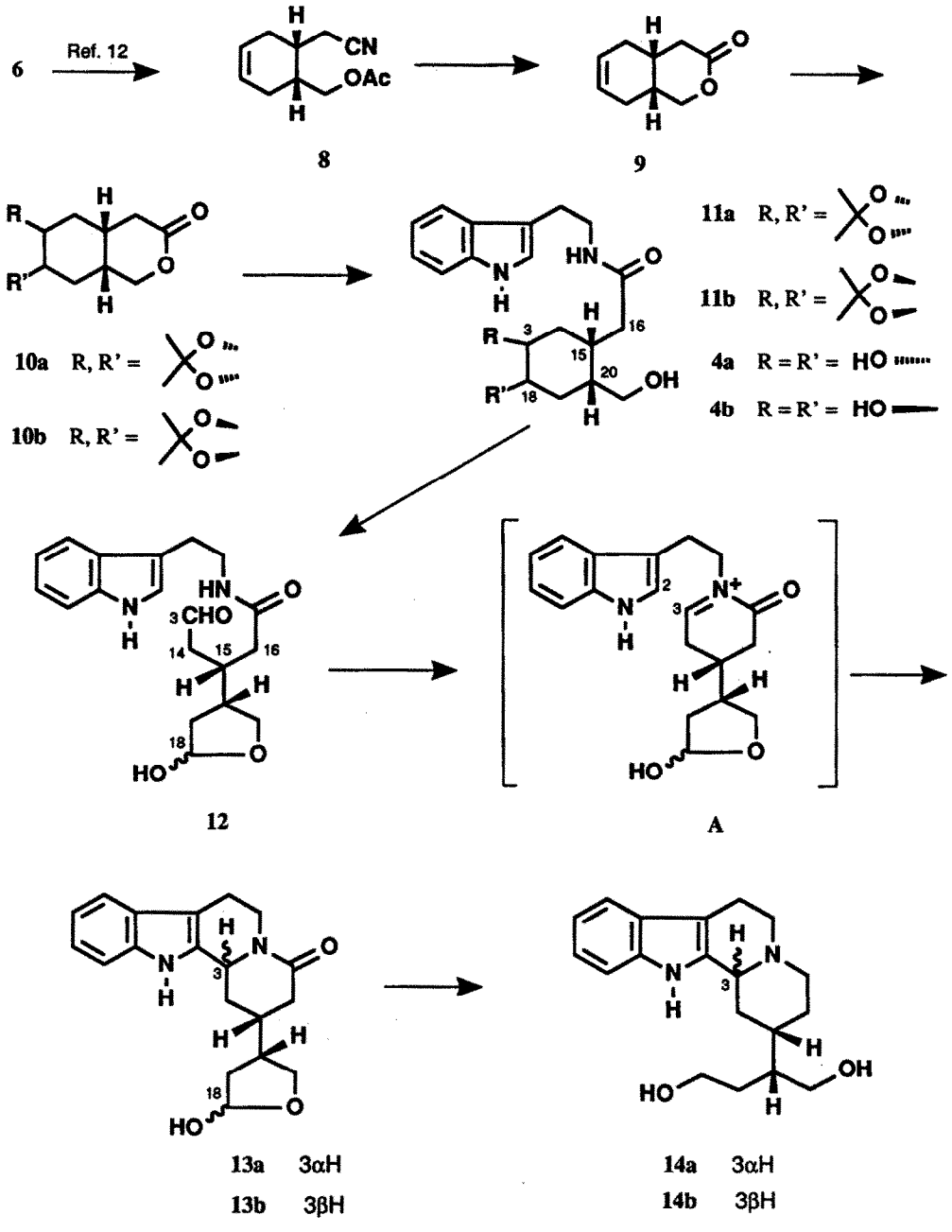
Scheme 1

In order to install the *anti* C-15/C-20 stereochemistry of **2** in the required absolute sense, the chirality at C-4a and C-8a in this lactone must be *R*, as depicted in formula **5**. We achieved **5** by the chain elongation and hydroxylation of the appropriate (-)-1*R*,2*S*-cyclohexene-1,2-dimethanol monoacetate **6**, easily accessible through a well established and very efficient pro(*S*) porcine pancreatic lipase (PPL)-catalyzed desymmetrization of the *meso*-diacetate **7**.[11]

Sequential treatment[12] of **6** (obtained in 95% yield and ee >99%) with CBr_4/Ph_3P; KCN in DMSO at 60°C cleanly afforded the nitrile **8** which upon oxidation by alkaline hydrogen peroxide[13] produced the lactone **9** in 66.5 % overall yield (Scheme 2).

Hydroxylation of **9** with $KMnO_4$ in *t*-BuOH/H_2O in the presence of NaOH[14] gave the rather unstable diol **5** which was immediately protected by reaction with 2,2-dimethoxypropane to afford a 1:5.6 inseparable mixture of the diastereomeric acetonides **10a,b** in 74% yield. The stereochemistry of the acetonides was deduced from a careful inspection of the ^{1}H-NMR and 2D COSY spectrum of the mixture (see Experimental) exploiting the anisotropic deshielding effect of the acetonide oxygen atoms on the protons placed on the same side of that group.

The protected lactones **10a,b** were condensed with tryptamine in refluxing dry *n*-BuOH to give a mixture of amides **11a** and **11b** in 81% yield, partially separable by careful gradient flash chromatography.


6
Ref. 12
CN
OAc
8
9
10a R, R' =
10b R, R' =
11a R, R' =
11b R, R' =
4a R = R' = HO
4b R = R' = HO
12
A
13a 3αH
13b 3βH
14a 3αH
14b 3βH

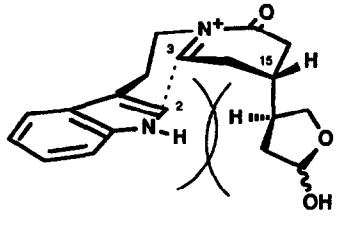
Scheme 2

All 19 carbon atoms of **2** were assembled and both C-15 and C-20 stereocentres were set. As for **10a,b**, the ^{1}H-NMR spectra of **11a** and **11b** revealed their great similarity, but diagnostic differences ascribable to the opposite chirality at the acetonide oxygen bearing carbons were observed in the chemical shift of H-15 (δ 2.10 in **11a**, 2.29 in **11b**), H-20 (δ 1.63 in **11a**, 1.86 in **11b**) and the C-16 methylene protons (δ 2.18 and 2.24 in **11a**, 1.96 and 2.12 in **11b**). Deprotection of the diol function of the **11a,b** mixture under standard conditions proceeded smoothly, delivering the triols **4a,b** in 95% yield, again as a 1:5.6 separable mixture.

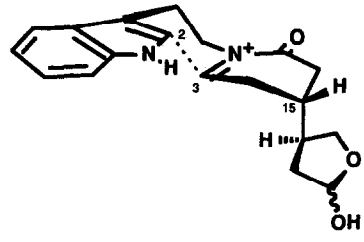
We next turned our attention to explore the two key steps on which our approach was based, namely the oxidative cleavage of the C-3/C-18 bond of **4** and the Pictet Spengler cyclization of the resulting dialdehyde **3** that, if successful, would give the tetracyclic skeleton of antirhine.

The reaction of **4** with sodium periodate in THF/H_2O at 0°C proceeded cleanly to give a c.a. 1.2:1 mixture of the rather unstable epimeric acetals **12**, *via* the intermediacy of the non-isolable dialdehyde **3** which, not surprisingly, underwent a highly favoured (5-*exo*-trig) intramolecular cyclization. The ^{1}H-NMR and 2D COSY spectrum, associated with ^{1}H decoupling studies, of the crude reaction material[15] provided good evidence for **12**, in spite of the marked overlap of some signals. In particular the detection of C-14 methylene protons at δ 2.23 and 2.58 (coupled to the broad triplet of the H-3 aldehyde proton at δ 9.65, J = 1 Hz), and the C-16 methylene protons at δ 2.15 and δ 2.28, which were found connected to the same multiplet centered at δ 2.06 attributable to the methyne H-15, suggested that the aldehyde group at C-18 was involved in the formation of the hydroxytetrahydrofurane ring.

The formation of the indoloquinolizidinone **13** from **12** *via* the intermediacy of acyliminium ion **A** (Pictet Spengler cyclization) was hampered by two problems. The first problem was that the initial nucleophilic attack of the amide nitrogen of **12** could, in principle, involve the latent aldehyde carbon C-18, ultimately giving rise to a regioisomeric seven-membered cyclized product. We felt that this less favoured 7-*exo* trig[16] cyclization could be further inhibited by mild acidic conditions that would prevent the unmasking of C-18 carbonyl, making a reaction *via* the 6-*exo* trig mode predictable. A second problem was the stereochemical outcome of the incipient stereogenic centre C-3 during the second annulation step (**A** → **13**). We envisioned that the initial perpendicular approach to indole C-2 by the electrophilic iminium carbon C-3 in a chair-like six atom array would preferentially involve the transition state A_1 (Figure 1), leading to the correct *anti* relationship of H-3 and H-15 (**13a**; 3*S*, 5*R* configuration).



A_2



A_1

Figure 1

The alternative transition structure A_2, leading to the *cis* relationship between H-3 and H-15 (**13b**), would result in severe steric interference between the indole nucleus and the axial oriented hydroxytetrahydrofurane residue.

As expected the acid promoted cyclization of **12** under kinetically controlled conditions (0.05 M HCl, acetone, 45°C, 15 min) proceeded smoothly with high levels of regio- and stereoselectivity, giving rise to a 85% yield (based on **4**) of an inseparable mixture of 3αH isomer **13a** and 3βH isomer **13b** in a ca. 9:1 ratio, each isomer consisting of a pair of epimers at C-18 in a ca. 7:3 ratio.

Detailed analysis of ^{1}H-NMR and 2D cosy spectrum and ^{13}C-{^{1}H} correlation studies of the mixture **13**, allowed the detection of the H-3α of **13a** at δ 4.88 as a br dd (J = 10.0 and 4.2 Hz) and H-3β of **13b** at δ 4.70 as a br dd (J = 12.5 and 4.0 Hz). Moreover, the complex diastereomeric nature (and relative ratio) of these isomers was confirmed by the appearance of the methylene protons H-21 at δ 4.23, 3.56, δ 4.01, 3.73, δ 4.20, 3.62 and δ 3.98, 3.76 as four pairs of triplets (J = 8.0 Hz) due to the close similarity of geminal and vicinal couplings.

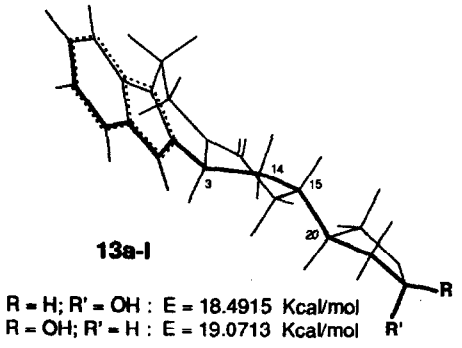
The above assignment of the stereochemistry at C-3 in **13a** and **13b** (four isomers) was supported by force field studies. Extensive molecular mechanics calculations,[17] on Dreiding model structures suggested by NMR and literature data[5,18] and containing the four possible stereochemical arrangements at C-3 and C-18, yielded the minimized conformations **13aI**, **13aII** and **13aIII** for the 3*S*(3αH) epimers and structures **13bI** and **13bII** (Figure 2) for the 3*R*(3βH) epimers, **13aIII** and **13bI** representing the global minima.[19] Other solution conformations gave no appreciable contribution. Comparison of the experimental vicinal coupling constant values between the C-14 methylene protons and H-3 and H-15 of **13a** and **13b**, with those calculated[20] from the above conformations as the average of the corresponding ^{3}J weighted by a Boltzmann distribution, suggested the configuration 3*S*(3αH) for **13a** and hence 3*R*(3βH) for **13b** (Table).

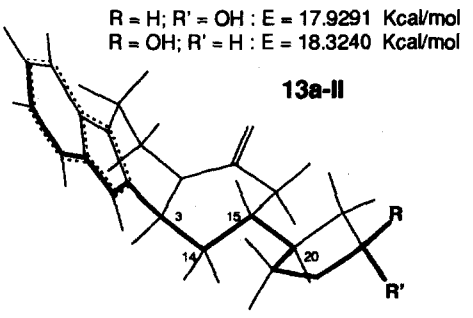
Furthermore, the stereochemistry at C-3 in **13a** was further confirmed by the observation of diagnostic n.O.e. contacts between H-3α and H-20, at δ 2.50 (br dtt) and δ 2.18 (m) in the two C-18 epimers, as predictable from the structures **13aI** and **13aIII**.

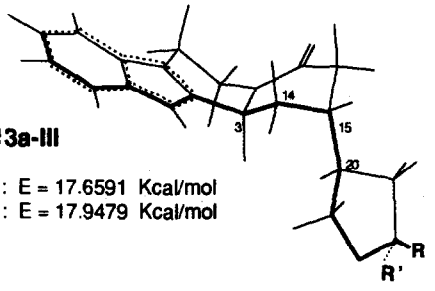
Reduction of the **13a/13b** mixture with LHA in THF at 80°C removed the asymmetry at C-18 and the amide carbonyl, affording the indoloquinolizidines **14a** and **14b** in a 93:7 distribution which compares very closely to that determined earlier for **13**. Compounds **14a** and **14b** were readily separated by chromatography and their stereochemistry defined by making recourse to their diagnostic ^{1}H- and ^{13}C-NMR signals (in comparison with literature data for the major 3αH isomer **14a**)[4,5] and CD spectra profiles.

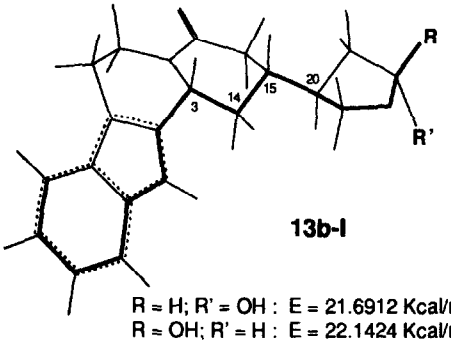
To complete our synthetic plan we first decided to convert pure *cis*-indoloquinolizidine **14a** into (-)-antirhine **2** following the methodology previously described by Takano *et al.*[4] In this protocol (Scheme 3), **14a** was regioselectively selenilated [SeCN(*o*-NO_2)Ph, Bu_3P, THF) to the monoderivative **15** (39.2%) which upon oxidation with *m*-CPBA afforded **2** in 71.9% yield (28.2% from **14a**).

However, as reported recently,[5] the repetition of this sequence led to the isolation of pure (-)-antirhine **2**,[21] but only in 9.1% yield (from **14a**). We found that the selenation of **14a** was very slow and incomplete, giving the selenoderivative **15** in poor yield (26%), probably because of the low solubility of **14a** in THF. Attempts to prepare **15** by changing the reaction conditions were not successful, *e.g.* treating **14a** with [SeCN(*o*-NO_2)Ph]/(*n*-Bu)$_3$P (100% excess) in DMF over extended periods at r.t. produced mainly the bis-selenoderivative **16**.









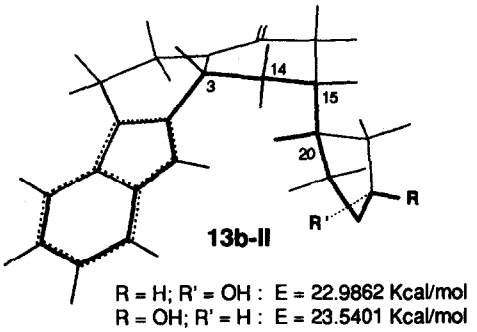
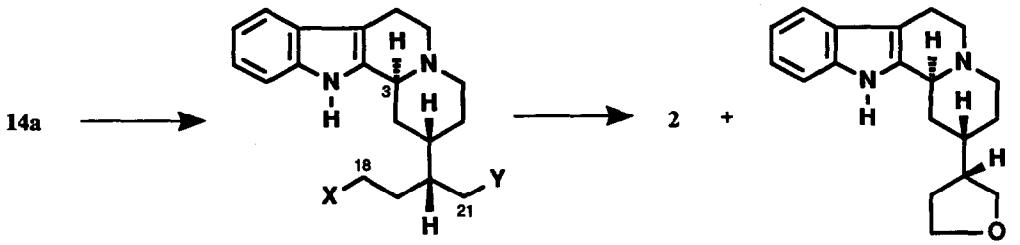


Table. Observed *vs* calculated vicinal coupling costants values (Hz) between H-3, H-14 and H-15.

Protons	**13a** (3α-H)				**13b** (3β-H)			
	R = H; R' = OH		R = OH; R' = H		R = H; R' = OH		R = OH; R' = H	
	J-obs	*J-calc*	*J-obs*	*J-calc*	*J-obs*	*J-calc*	*J-obs*	*J-calc*
H-3/H-14α	4.2	3.82	4.2	3.95	12.5	13.16	12.5	13.34
H-3/H-14β	10.0	9.54	10.0	9.82	4.0	3.69	-	3.84
H-14α/H-15	7.5	6.71	7.2	6.30	12.5	13.40	12.5	13.64
H-14β/H-15	3.5	2.80	3.0	2.47	1.8	2.50	-	2.52



15 X = Se(o-NO_2)Ph, Y = OH

16 X = Y = Se(o-NO_2)Ph

17 X = SeO_2(o-NO_2)Ph, Y = OH

18 X = SeO(o-NO_2)Ph, Y = OH

Scheme 3

In our hands the oxidation of **15** with m-CPBA produced only a moderate yield of **2** (35%), the major product being the till now unreported tetrahydrofurane derivative **19** (38%). After experimentation it was supposed that the cyclized product **19** was probably formed by an intramolecular attack of C-21 oxygen at C-18 in the selenonyl intermediate **17**,[22] itself derived by an overoxidation[23] of a relatively stable selenoxide intermediate **18**.

Attempts to prevent the formation of **19** by changing the oxidant to $NaIO_4$ followed by treatment of the resulting intermediate material in THF at 40° C in the presence of Et_3N, failed to give appreciable results and **2** was isolated in 40% yield along with **19** in the minor extent of 31%.

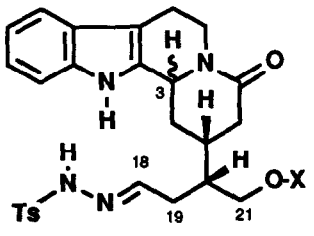
Although we were unable to fully account for the discrepancy between our results and previous reports, we clearly needed to develop an alternative regioselective route for introducing the required double bond at C-18. To this end we prepared the N-tosylhydrazones **20a,b** from **13a,b** and examined the reactivity toward base-induced decomposition (Bamford-Stevens type reaction).

The N-tosylhydrazone **20a** was obtained as a colourless crystalline solid, contaminated by its inseparable epimer **20b**[24] (ca. 5 - 10%) in 86% yield as a 1:3 mixture of *syn* and *anti* isomers at C(18)=N double bond. The impossibility of separating these isomers prevented a complete analysis of this material by high-field ^{1}H-NMR, and only the signals of **20a** (*syn*:*anti*) could be assigned by interpretation of a 2D COSY experiment. In particular, the signal (minor intensity) at δ 6.78 (t, J = 5.2 Hz) was due to the H-18 in the *syn* isomer of **20a** and that at δ 7.32 (m) to the same proton in the *anti* isomer.

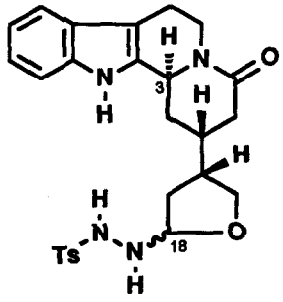
An interesting feature of ^{1}H-NMR spectra of **20a** was the appearance, after a short period of time (ca. 30 min) at r.t. of two sets of mutually coupled signals at δ 8.57 (exch. D_2O, d, J 3.2 Hz), 4.96 (exch. D_2O, dd, J 6.5 and 3.2 Hz), 4.55 (br q, J 6.5 Hz) and δ 8.52 (exch. D_2O, d, J 3.2 Hz), 5.08 (exch. D_2O, dd, J 7.2 and 3.2 Hz), 4.52 (br dt, J 7.2 and 6.5 Hz) respectively, that were assigned to the Ts-NH-NH-C(18)H moiety in the two C-18 epimers **21** (ca. 1:1) derived from the partial intramolecular cyclization of **20a**. A similar ring chain tautomerization process of hydrazones has been reported.[25]

The high propensity of **20a** towards intramolecular cyclization and the relative steric hindrance of the C-19 methylene protons proved to be a complicating factor in its use in synthesis. When the mixture **20a,b** was subjected to the Shapiro reaction[26] (*n*-BuLi, THF-TMEDA, -78° C to room temperature) the substitution products **22a,b**[24] and **23a,b**[24] were isolated in 43 and 24% yield respectively, together with trace amounts of alkene **24a,b**.[24] In addition, compound **23** was formed in 43% yield as the only isolable product when NaH in dry toluene[27] was used to decompose the N-tosylhydrazone **20**.

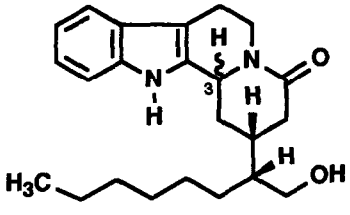
Although the optimum conditions for the above reactions have not yet been determined, it was clear that the abstraction of the α-proton H-19 was so slow that both intra- and intermolecular nucleophilic substitution compete extremely effectively with elimination.[28] Therefore, in order to prevent the formation of substitution products it was necessary to block the hydroxyl group at C-21 of **20**, and to use a non-nucleophilic base in the subsequent aprotic Bamford-Stevens reaction.



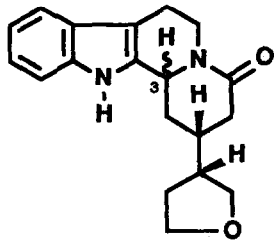
20a 3αH, X = H
20b 3βH, X = H
25a 3αH, X = SiTBDM
25b 3βH, X = SiTBDM



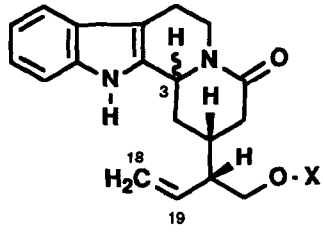
21



22a 3αH
22b 3βH



23a 3αH
23b 3βH



24a 3αH, X = H
24b 3βH, X = H
26a 3αH, X = SiTBDM
26b 3βH, X = SiTBDM

Thus when the readily accessible O-SiTBDM N-tosylhydrazones **25a,b**[24] (ca. 19:1 by ^{1}H-NMR) were subjected to the action of NaH in dry toluene, according to the method described by Piers *et al*,[27] the olefin **26a,b**[24] was cleanly produced in 70% yield as an unseparable mixture of 3αH:3βH epimers in ca. 19:1 ratio (^{1}H NMR).

As mentioned before for the products in this series, only the major epimer 3αH **26a** could be fully

characterized by spectroscopic data. In particular the terminal methylene group of **26a** was confirmed by the appearance of a triplet (δ 116.9) in the vinylic region of the ^{13}C NMR spectrum. Further, appropriate resonances of the vinylic protons H-18 [δ 5.71(dt, J = 17.0 and 9.8 Hz)] and H-19 [δ 5.14(dd, J = 9.8 and 1.8 Hz); δ 5.09(dd, J = 17.0 and 1.8 Hz)] were observed in the 300 MHz ^1H NMR spectrum.

In order to complete the synthetic approach, **26a,b** was finally reduced with LAH in dry THF at reflux. Acidic work-up of the resulting material cleanly afforded (-)-antirhine **2**[21] in 77 % yield (13.2 % from **6**) and (+)-C_3-epi-antirhine in 6 % yield.[29]

In summary the potential of **6** as a synthon for the enantiosynthesis of the unique Corynanthe-type indole alkaloid variant (-)-antirhine **2** was demonstrated. The extension of this methodology for the synthesis of other monoterpenoid indole alkaloid variants, will be the subject of a forthcoming communication from these laboratories.

EXPERIMENTAL

IR spectra were recorded on Perkin-Elmer 681 spectrometer for chloroform solutions unless otherwise stated. UV spectra on a Perkin-Elmer 554 for methanol solutions. ^1H-NMR and ^{13}C-NMR spectra were recorded on Bruker WP-80 (^1H, 80 MHz; ^{13}C, 20.1 MHz), Varian XL-200 (^1H, 200 MHz; ^{13}C, 50.2 MHz) and Bruker AC-300 (^1H, 300 MHz,; ^{13}C, 75.4 MHz) spectrometers. HR, EI and FAB mass spectra in the positive mode were determined on VG 70-70 EQ-HF instrument equipped with its standard sources. Optical rotations were determined on Perkin-Elmer 241 polarimeter for chloroform solutions. CD spectra were recorded on a JASCO J 500 spectropolarimeter for solutions in chloroform. Flash chromatography (FC) was carried out using Merck Kieselgel 60, 230-400 mesh. T.l.c. were performed on 0.25 mm thick layers of silica gel GF_{254} (Merck) on glass plates. R_F (solvent system) of products is given.

(1*R*,2*S*)-4-Cyclohexene dimethanol monoacetate (6). This compound was prepared as previously described[11,12] from **7** in 95% yield, e.e. >99%. $[\alpha]_D^{25}$: -18.98° (*c* 4.04).

(1*R*,2*R*)-1-Methanol-2-acetonitrile-4-cyclohexene acetate (8). Prepared starting from **6** in 77.3% yield as previously described.[12] $[\alpha]_D^{25}$: -8.46° (*c* 5.05).

(4a*R*,8a*R*)-1,4,4a,5,8,8a-Hexahydro-3*H*-2-benzopyran-3-one (9). To a well stirred mixture of nitrile **8** (2.44g, 12.6 mmol) and 20% sodium hydroxide (aq) (19 mL) was slowly added, with cooling, 35% H_2O_2 (15.2 mL). An exothermic reaction occured with evolution of oxygen. After stirring at 60°C for 15 min, MeOH (34 mL) was slowly added and stirring was continued at the same temperature for an additional 2 h. After cooling, the resulting mixture was poured into ice water (200 mL), acidified to pH ca. 1 with 17% hydrochloric acid (aq) and extracted with dichloromethane (3 x 30 mL). The combined organic extract was washed with water, 5% $NaHCO_3$ (aq), dried (Na_2SO_4), and concentrated *in vacuo* to give a residue, which was subjected to FC (Et_2O/*n*-hexane, 4:1) to yield 1.65 g (86%) of lactone **9** as colorless oil. R_F(Et_2O/*n*-hexane, 4:1): 0.29; IR: 2900 and 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.46 (m, 2H, H-6 and H-7), 4.33 (dd, 1H, J = 11.0 and 4.3 Hz, H-1), 4.26 (dd, 1H, J = 11.0 and 5.5 Hz, H-1'), 2.57 (dd, 1H, J = 18.0 and 5.8 Hz, H-4), 2.44 (dd, 1H, J = 18.0 and 7.1 Hz, H-4'), 2.33 (m, 1H, H-4a); ^{13}C NMR(50.2 MHz, $CDCl_3$): δ 170.7 (C-3), 124.6 and 124.1 (C-6 and C-7), 72.2 (C-1), 33.8 (C-4), 29.6 and 28.5 (C-4a and C-8a), 28.5 (C-5), 24.0 (C-8); MS (EI) *m/e* (relative intensity): 152 (M^+, 12), 110 (58), 92 (83), 79 (100); HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0839; $[\alpha]_D^{25}$: 5.39° (*c* 2.0).

(4a*R*,8a*R*)-1,4,4a,5,6,7,8,8a-Octahydro-6,7-dihydroxy-6,7-O-isopropylidene-3*H*-2-benzopyran-3-one (10). A solution of 4.3 g (27.3 mmol) of potassium permanganate and 1.13 g (28.2 mmol) of sodium hydroxide in 170 mL of water, cooled to 0°C, was added quickly with vigorous stirring to a cold mixture (5°C) of *t*-BuOH/H_2O (4.5:1) (265 mL) containing 4.0 g (26.3 mmol) of **9**. After 10 min 3% $NaHSO_3$ (aq) was added to ensure complete reduction of the permanganate. The precipitate of MnO_2 was filtered through a layer of Celite® and the resultant solution was concentrated *in vacuo* and continuously extracted with Et_2O for 48 h. The ether solution was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*

and the residual oil dissolved in dry dichloromethane (160 mL). To the resulting solution was then added, under stirring, 2,2-dimethoxy-propane (29 mL, 263 mmol) and PTSA (53 mg, 0.34 mmol). The reaction was complete after 2 h (as indicated by TLC) and subsequently quenched by washing with saturated $NaHCO_3$ (aq). The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residual oil was purified by FC (Et_2O/EtOAc, 9:1) to yield lactone **10** (4.4 g, 74% yield) as an inseparable mixture of two diastereoisomers **10a** and **10b** (1:5.6 ratio from 300 MHz ^1H NMR). Colorless oil; R_F(Et_2O/EtOAc, 9:1): 0.22; IR: 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.39 (dt, 1H, J = 7.8 and 2.3 Hz, H-7), 4.36(dt, 1H, J = 7.8 and 2.2 Hz, H-6), 4.25 (dd, 1H, J = 11.5 and 4.9 Hz, H-1β), 4.05 (dd, J = 11.5 and 7.3 Hz, H-1α, minor), 3.89 (dd, J = 11.5 and 6.8 Hz, H-1α, major), 2.57 (m, 1H, H-4β), 2.45 (br, dddd, J = 12.0, 6.6, 6.0 and 4.6 Hz, H-4a, major), 2.36 (br, dddd, J = 12.2, 6.8, 4.9 and 4.4 Hz, H-8a, major), 2.23 (dd, J = 15.0 and 9.6 Hz, H-4α, minor), 2.18 (m, H-4a, minor), 2.15 (dd, J = 14.0 and 6.6 Hz, H-4α, major), 2.06 (br, dq, J = 7.3 and 5.0 Hz, H-8a, minor), 1.80 (ddd, J = 14.2, 4.6 and 2.2 Hz, H-5β, major), 1.76 (ddd, J = 14.2, 4.4 and 2.3 Hz, H-8β, major), 1.55 (m, 2H, 2H-8, minor), 1.41 (s, 3H, CH_3), 1.35 (ddd, J = 14.2, 12.2 and 2.3 Hz, H-8α, major), 1.30 (m, 2H, 2H-5, minor), 1.29 (s, 3H, CH_3), 1.27 (ddd, J = 14.2, 12.0 and 2.2 Hz, H-5α, major); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.4 (C-3), 107.9 (C-9, minor), 107.2 (C-9, major), 73.0 (C-6 and C-7, minor), 71.8 (C-6 and C-7, major), 70.4 (C-1, major), 70.2 (C-1, minor), 34.4 (C-4), 30.9 (C-5), 26.4 (C-8), 26.0 ($2CH_3$), 23.7 and 23.0 (C-4a and C-8a); MS (EI) *m/e* (relative intensity): 226 (M^+, 5), 210 (100), 169 (20), 151 (9), 105 (55); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1208.

Compounds 11a,b. Lactone **10** (2.51g, 11.1 mmol) was dissolved in *n*-BuOH (5.5 mL), tryptamine (2.66 g, 16.65 mmol) was added and the reaction mixture was kept at reflux for 8 h. The solvent was removed *in vacuo* and the residue was purified by gradient flash chromatography ($CHCl_3$/MeOH, 15.6:1 to 7.3:1) to give 171 mg (4%) of **11a**, 2,7 g (63%) of a 1:6.6 mixture of **11a** and **11b** and 600 mg (14%) of **11b**.
Compound **11a**: amorphous solid; R_F($CHCl_3$/MeOH, 9:1): 0.40; IR: 3480, 3435, 3370 and 1655 cm^{-1}; UV λ_{max} (log ε): 289 (3.77), 280 (3.88) and 274 (sh) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C) δ 10.68 [br, s, 1H, N(1)H], 7.61 [t, 1H, J = 5.5 Hz, N(4)H], 7.52 (br, d, 1H, J = 7.6 Hz, H-9), 7.36 (br, d, 1H, J = 7.6 Hz, H-12), 7.14 (d, 1H, J = 2.0 Hz, H-2), 7.08 (dt, 1H, J = 1.2 and 7.6 Hz, H-11), 6.99 (dt, 1H, J = 1.2 and 7.6 Hz, H-10), 4.26 (t, 1H, J = 5.2 Hz, OH), 4.05 (m, 2H, H-3 andH-18), 3.44 and 3.38(2 x ddd, 2H, J = 11.5, 8.0 and 5.2 Hz, 2H-21), 3.32 (dt, 2H, J = 7.2 and 5.5 Hz, 2H-5), 2.86 (t, 2H, J = 7.2 Hz, 2H-6), 2.24 and 2.18 (2 x dd, 2H, J = 13.6 and 7.0 Hz, 2H-16), 2.10 (m, 1H, H-15), 1.63 (m, 1H, H-20), 1.78-1.58 (m, 4H, H-14 and H-19), 1.42 and 1.25 (2 x s, 6H, $2CH_3$); ^{13}C NMR (75.4 MHz, Py-d_5): δ 173.3 (C-17), 137.8 (C-13), 128.3 (C-8), 123.5 (C-2), 121.9 (C-11), 119.2 (C-9 and C-10), 113.3 (C-7), 107.8 (C-22), 74.3 (C-3 and C-18), 63.9 (C-21), 40.8 (C-5), 39.9 (C-15), 37.7 (C-16), 32.0 (C-19), 31.1 (C-20), 29.2 (C-14), 28.9 (CH_3), 26.7 (CH_3), 26.4 (C-6); MS (EI) *m/e* (relative intensity): 386 (M^+, 23), 371 (26), 238 (20), 211 (34), 169 (13), 144 (100); $[\alpha]_D^{25}$: +2.42° (*c* 1.96). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.35; H, 7.83; N, 7.25. Found: C, 68.42; H, 7.92; N, 7.19.
Compound **11b**: amorphous solid; R_F($CHCl_3$/MeOH, 9:1): 0.38; IR: 3480, 3440, 3360 and 1650 cm^{-1}; UV λ_{max} (log ε): 287 (3.78), 282 (3.88) and 272 (sh) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.68 [br, s, 1H, N(1)H], 7.78 [br, t, 1H, J = 5.5 Hz, N(4)H], 7.56 (br, d, 1H, J = 7.1 Hz, H-9), 7.36 (br, d, 1H, J = 7.1 Hz, H-12), 7.15 (d, 1H, J = 2.5 Hz, H-2), 7.09 (dt, 1H, J = 1.2 and 7.1Hz, H-11), 7.01 (dt, 1H, J = 1.2 and 7.1 Hz, H-10), 4.29 (t, 1H, J = 5.2 Hz), 4.18 (m, 2H, H-3 and H-18), 3.39 and 3.31 (2 x ddd, 2H, J = 11.5, 8.0 and 5.2 Hz, 2H-21), 3.38 (dt, 2H, J = 5.5 and 7.2 Hz, H-5), 2.84 (t, 2H, J = 7.2 Hz, H-6), 2.29 (m, 1H, H-15), 2.12 (dd, 1H, J = 14.0 and 5.8 Hz, H-16), 1.96 (dd, 1H, J = 14.0 and 9.2 Hz, H-16'), 1.86 (m, 1H, H-20), 1.72 (dt, 1H, J = 14.0 and 4.5 Hz, H-19β), 1.70 (m, 1H, H-14α), 1.65 (m, 1H, H-19α), 1.59 (dt, 1H, J = 13.9 and 4.0 Hz, H-14β), 1.42 and 1.26 (2 x s, 6H, $2CH_3$); ^{13}C NMR (75.4 MHz, Py-d_5): δ 173.1 (C-17), 137.8 (C-13), 128.3 (C-8), 123.5 (C-2), 121.9 (C-11), 119.2 (C-9 and C-10), 113.3 (C-7), 112.1 (C-12), 107.8 (C-22), 73.2 and 73.1 (C-3 and C-18), 62.9 (C-21), 40.8 (C-5), 38.1 (C-15), 37.0 (C-16), 32.8 (C-19), 31.7 (C-20), 29.2 (C-14), 28.9 (CH_3), 26.7 (CH_3), 26.4 (C-6); MS (EI) *m/e* (relative intensity): 386 (M^+, 9), 371 (10), 311 (5), 244 (15), 211 (16), 188 (16), 144 (100); $[\alpha]_D^{25}$: -4.68° (*c* 1.58). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.35; H, 7.83; N, 7.25. Found: C, 68.40; H, 7.77; N, 7.22.

Compounds 4a,b. To a solution of **11a/11b** (1:5.6) (3.47 g, 9.0 mmol) in MeOH/H_2O 1:1.5 (100 mL) was added PPTS (270 mg, 1.1 mmol), and the mixture was mantained at 45°C for 2 h. Upon cooling, the reaction mixture was quenched with saturated $NaHCO_3$(aq), and the methanol was removed in vacuo. The resulting cloudy solution was extracted with EtOAc (3 x 20 mL). The organic solution was washed with saturated NaCl(aq), dried over Na_2SO_4, and concentrated *in vacuo*. FC [$CHCl_3$/MeOH/NH_3(*d* 0.88), 40:10:1] led to 448 mg (14%) of **4a** and 2.51 g (80.7%) of **4b**.
Compound **4a**: colourless foam; R_F [$CHCl_3$/MeOH/NH_3(*d* 0.88), 40:10:1]: 0.38; IR (KBr): 3700-3100 (broad) and 1645 cm^{-1}; UV λ_{max} (log ε): 289 (3.70), 280 (3.89) and 273 (sh) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.67 [br, s, 1H, N(1)H], 7.73 (br, t, 1H, J = 5.5 Hz, N(4)H], 7.55 (br, d, 1H, J = 7.5 Hz, H-9), 7.36 (br, d, 1H, J = 7.5 Hz, H-12), 7.14 (d, 1H, J = 2.2 Hz, H-2), 7.08 (dt, 1H, J = 1.2 and 7.5 Hz,

H-11), 6.99 (dt, 1H, J = 1.2 and 7.5 Hz, H-10), 4.37 (br, d, 1H, J = 4.0 Hz, CHOH), 4.36 (t, 1H, J = 5.1 Hz, CH_2OH), 4.18 (br, d, 1H, J = 4.0Hz, CHOH), 3.56 (m, 2H, H-3 and 2H-18), 3.38 (m, 2H, 2H-21), 3.36 (dt, 2H, J = 5.5 and 7.5 Hz, 2H-5), 2.83 (t, 2H, J = 7.5 Hz, 2H-6), 2.25 (dd, 1H, J = 13.8 and 6.6 Hz, H-16), 2.19 (dd, 1H, J = 13.8 and 8.9 Hz, H-16'), 2.09 (m, 1H, H-15), 1.69 (dt, 1H, J = 13.2 and 7.1 Hz, H-14α), 1.64 (m, 1H, H-20), 1.61 (dt, 1H, J = 12.5 and 7.5 Hz, H-19α), 1.50 (br, dt, 1H, J = 12.5 and 4.0 Hz, H-19β), 1.41 (br, dt, 1H, J = 13.2 and 3.9 Hz, H-14β); ^{13}C NMR (75.4 MHz, Py-d_5): δ 174.3 (C-17), 137.5 (C-13), 128.3 (C-8), 123.6 (C-2), 121.6 (C-11), 119.0 (C-9 and C-10), 112.9 (C-7), 112.0 (C-12), 71.0 and 70.6 (C-3 and C-18), 64.1 (C-21), 40.8 (C-5), 38.2 (C-16), 33.2 (C-19), 31.8 (C-14), 30.1 (C-20), 26.1 (C-6); MS (EI) *m/e* (relative intensity): 346 (M^+, 11), 328 (29), 310 (6), 237 (42), 204 (38), 186 (37), 160 (100); $[\alpha]_D^{25}$: -4.57° (*c* 1.28). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.86; H, 7.57; N, 8.09. Found: C, 68.77; H, 7.51; N, 8.13.
Compound **4b**: off-white powder of indefinite m.p.; R_F [$CHCl_3$/MeOH/NH_3(*d* 0.88), 40:10:1]: 0.25 IR (KBr): 3700-3100 (broad) and 1640 cm^{-1}; UV λ_{max} (log ε): 287 (3.67), 281 (3.81) and 272 (sh) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.66 [br s, 1H, N(1)H], 7.76 [t, J = 5.6 Hz, N(4)H], 7.56 (br, d, 1H, J = 7.5 Hz, H-9), 7.36 (br, d, 1H, J = 7.5 Hz, H-12), 7.15 (d, 1H, J = 2.2 Hz, H-2), 7.09 (dt, 1H, J = 1.3 and 7.5 Hz, H-11), 7.00 (dt, 1H, J = 1.3 and 7.5 Hz, H-10), 4.25 (t, 1H, J = 5.1 Hz, CH_2OH), 3.94 (m, 2H, 2CHOH), 3.68 (m, 2H, H-3 and H-18), 3.35 (dt, 2H, J = 5.6 and 7.5 Hz, 2H-5), 3.34 and 3.25 (2ddd, 2H, J = 10.8, 6.9 and 5.1 Hz, 2H-21), 2.84 (t, 2H, J = 7.5 Hz, 2H-6), 2.32 (m, 1H, H-15), 2.09 (dd, 1H, J = 14.2 and 6.1 Hz, H-16), 1.98 (dd, 1H, J = 14.2 and 9.0 Hz, H-16'), 1.92 (m, 1H, H-20), 1.61 (ddd, 1H, J = 13.0, 6.5 and 3.8 Hz, H-19β), 1.60 (ddd, 1H, J = 14.0, 6.0 and 4.0 Hz, H-14β), 1.44 (ddd, 1H, J = 13.0, 10.2 and 3.5 Hz, H-19α), 1.39 (ddd, 1H, J = 14.0, 9.5 and 3.2 Hz, H-14α); ^{13}C NMR (75.4 MHz, Py-d_5): δ 174.1 (C-17), 137.5 (C-13), 128.3 (C-8), 123.4 (C-2), 121.6 (C-11), 119.0 (C-9 and C-10), 112.9 (C-7), 112.0 (C-12), 68.9 and 68.8 (C-3 and C-18), 63.2 (C-21), 40.8 (C-5), 37.5 (C-16), 36.4 (C-15), 33.8 (C-19), 31.8 (C-14), 31.0 (C-20), 26.1 (C-6); MS (EI) *m/e* (relative intensity): 346 (M^+, 10), 328 (14), 308 (9), 237 (51), 204 (6), 198 (29), 186 (8), 150 (100); $[\alpha]_D^{25}$: +2.36° (*c* 1.59). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.86; H, 7.57; N, 8.09. Found: C, 65.96; H, 7.59; N, 8.11.

Compound 12. To a stirred solution of the triols **4a/4b** (1:5.6 mixture of diasteroisomers) (2.65g, 7.66 mmol) in H_2O/THF 7:3 (250 mL) at 5°C was added sodium metaperiodate (1.83g, 8.33 mmol) in water (20 mL), and the solution was stirred for 1 h at 5°C. The resulting cloudy solution was filtered, saturated with NaCl and extracted with EtOAc (3 x 30 mL). The combined extract was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give crude **12**[15] (2.64g) as inseparable mixture of C-18 epimers (ca. 1.2:1 ratio from 300 MHz ^1H NMR) which was not further purified but used directly in the next stage.
Compound **12**: pale yellow gum; IR: 3460, 2720, 1720 and 1635 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.78 [br, s, 1H, N(1)H], 9.65 (br, t, J = 1.0 Hz, H-3), 7.96 [t, J = 5.5 Hz, N(4)H, major], 7.92 [t, J = 5.5 Hz, N(4)H, minor], 7.54 (br, d, 1H, J = 7.2 Hz, H-9), 7.34 (br, d, 1H, J = 7.2 Hz, H-12), 7.15 (d, 1H, J = 2.4 Hz, H-2), 7.08 (dt, 1H, J = 1.2 and 7.2 Hz, H-11), 6.99 (dt, 1H, J = 1.2 and 7.2 Hz, H-10), 6.34 (d, J = 6.0 Hz, OH, major), 5.99 (d, J = 3.8 Hz, OH, minor), 5.31 (ddd, J = 10.0, 6.0 and 4.8 Hz, H-18, major), 5.01 (ddd, J = 4.9, 3.8 and 2.0 Hz, H-18, minor), 3.42 (t, J = 7.8 Hz, H-21, minor), 3.41 (m, 2H, 2H-21, major), 3.33 (dt, 2H, J = 5.5 and 7.5 Hz, 2H-5), 3.21 (t, J = 7.8 Hz, H-21', minor), 2.82 (t, 2H, J = 7.5 Hz, 2H-6), 2.58 (br, dd, 1H, J = 17.5 and 4.2 Hz, H-14), 2.28 (dd, 1H, J = 16.0 and 4.5 Hz, H-16), 2.23(br, d, 1H, J = 17.5 Hz, H-14'), 2.15 (br, dd, 1H, J = 16.0 and 6.8 Hz, H-16'), 2.06 (m, 1H, H-15), 1.84 (m, 1H, H-20), 1.61 (m, 1H, H-19), 1.31 (m, 1H, H-19'); MS (FAB$^+$) *m/e* 345 (MH^+).

Compounds 13a,b. A solution of the crude **12**[15] (1.07g, 2.86 mmol) in acetone (156 mL) and 2N aqueous HCl (4 mL) was stirred at 45°C. After 15 min the solution was cooled to 5°C, neutralized with Et_3N and evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL), and the solution was washed with brine and then dried over anhydrous sodium sulfate. FC ($CHCl_3$/MeOH, 9:1) of the crude material afforded the indoloquinolizidinone **13** (858 mg, 92%) as an inseparable mixture of C-3 epimers **13a/13b** (ca. 9:1) each consisting of a pair of epimers at C-18 (ca. 7:3 ratio from 300 MHz ^1H NMR).
13a/13b: colorless solid; R_F ($CHCl_3$/MeOH, 9:1): 0.28; IR 3690, 3610, 3470 and 1635 cm^{-1}; UV λ_{max} (log ε): 289 (3.73), 280 (3.93) and 272 (sh) nm; MS (EI) *m/e* (relative intensity): 326 (M^+, 11), 308 (21), 280 (15), 237 (100), 209 (8); HRMS calcd for $C_{19}H_{22}N_2O_3$ 326.1630, found 326.1630.
Compound **13a**: ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 9.70 [br, s, N(1)H, minor], 9.66 [br, s, N(1)H, major], 7.37 (br, d, 1H, J = 7.5 Hz, H-9), 7.24 (dd, 1H, J = 1.2 and 7.5 Hz, H-12), 7.05 (dt, 1H, J = 1.2 and 7.5 Hz, H-11), 6.98 (dt, 1H, J = 1.2 and 7.5 Hz, H-10), 5.49 (br, dd, J = 8.4 and 4.8 Hz, H-18, minor), 5.46 (br, d, J = 5.2 Hz, H-18, major), 5.08 (m, H-5β, minor), 4.98 (m, H-5β, major), 4.88 (br, dd, 1H, J = 10.0 and 4.2 Hz, H-3), 4.59 (br, s, OH, minor), 4.52 (br, s, OH, major), 4.23 (t, J = 8.0 Hz, H-21, major), 4.01 (t, J = 8.0 Hz, H-21, minor), 3.73 (t, J = 8.0 Hz, H-21', minor), 3.56 (t, J = 8.0 Hz, H-21', major), 2.92 (ddd, J = 13.1, 12.0 and 5.5 Hz, H-6β, major), 2.86 (br, dt, J = 2.5 and 12.0 Hz, H-5α, major), 2.65 (br, dd, 1H, J = 13.1 and 12.0 Hz, H-6α), 2.50 (br, dtt, J = 7.1, 8.0 and 10.2 Hz, H-20, major), 2.47 (dd, 1H, J = 16.8 and 4.9

Hz, H-16), 2.26 (m, H-19, minor), 2.22 (dd, 1H, J = 16.8 and 8.0 Hz, H-16'), 2.18 (m, H-20, minor), 2.10 (m, 2H, 2H-14), 2.02 (br, dd, J = 12.2 and 7.1 Hz, H-19, major), 1.88 (ddddd, J = 10.0, 8.0, 7.2, 4.9 and 3.0 Hz, H-15, minor), 1.69 (ddddd, J = 10.2, 8.0, 7.5, 4.9 and 3.5 Hz, H-15, major), 1.53 (ddd, J = 12.2, 10.2 and 5.2 Hz, H-19', major), 1.50 (ddd, J = 12.2, 8.4 and 3.5 Hz, H-19', minor); ^{13}C NMR (20.1 MHz, Py-d_5): δ 168.9 (C-17), 137.3 (C-13), 135.0 (C-2), 127.9 (C-8), 121.8 (C-11), 119.5 (C-10), 118.4 (C-9), 11.8 (C-12), 109.4 (C-7), 99.2 (C-18, minor), 98.8 (C-18, major), 70.6 (C-21, major), 69.6 (C-21, minor), 53.2 (C-3, major), 52.9 (C-3, minor), 42.8 (C-20, minor), 41.8 (C-5), 40.8 (C-20, major), 38.9 (C-19, minor), 38.8 (C-19, major), 38.1 (C-16), 34.4 (C-15, major), 33.9 (C-15, minor), 32.2 (C-14, minor), 32.0 (C-14, major), 21.3 (C-6).

Compound **13b**: ^{1}H NMR (300 MHz, DMSO-d_6, 50°C): *i.a.* δ 9.85 [br, s, N(1)-H, minor], 9.51 [br, s, N(1)-H], 5.46 (br, d, J = 5.2 Hz, H-18, major), 4.70 (br, dd, 1H, J = 12.5 and 4.0 Hz, H-3), 4.20 (t, J = 8.0 Hz, H-21, major), 3.98 (t, J = 8.0 Hz, H-21, minor), 3.76 (t, J = 8.0 Hz, H-21', minor), 3.62 (t, J = 8.0 Hz, H-21', major), 2.45 (m, H-20, major), 2.42 (ddd, J = 12.5, 4.0 and 1.8 Hz, H-14β, major), 2.08 (m, H-20, minor), 1.62 (m, H-15, major), 1.44 (br, q, J = 12.5 Hz, H-14α, minor), 1.42 (br, q, J = 12.5 Hz, H-14α, major); ^{13}C NMR (20.1 MHz, Py-d_5) *i.a.* δ 168.3 (C-17, major), 137.6 (C-13), 127.6 (C-8), 108.4 (C-7), 99.2 (C-18, minor), 98.8 (C-18, major), 70.1 (C-21, major), 69.8 (C-21, minor), 54.4 (C-3, major), 54.1 (C-3, minor), 42.8 (C-20, minor), 40.8 (C-20, major), 32.9 (C-14, major).

Compounds 14a,b. Compound **13** (652 mg, 2.0 mmol) in anhydrous THF (10 mL) was added in portions to a stirring suspension of $LiAlH_4$ (273 mg, 7.2 mmol) in anhydrous THF (5 mL) at 0°C under nitrogen over 15 min. The reaction mixture was allowed to come to room temperature and then boiled 2 h under reflux with stirring. It was cooled to 0°C and then successively treated with water (10 mL), 15% aqueous NaOH (1 mL), and $CHCl_3$ (10 mL). The organic layer was filtered off, and the white residue was washed with $CHCl_3$ (4 x 15 mL). The combined organic filtrates were dried (Na_2SO_4), concentrated under reduced pressure and the residue thus obtained was purified by FC ($CHCl_3$/MeOH, 7:3) to give 456 mg (73%) of **14a** and 34 mg (5.5%) of **14b**.

Compound **14a**: white crystals from MeOH; m.p. = 216-218°C (Lit.,[4] m.p. = 215-218°C, Lit.,[5] m.p. = 208-215°C); R_F ($CHCl_3$/MeOH, 7:3): 0.22; IR (KBr): 3600-300 (broad) cm^{-1}; UV λ_{max} (log ε): 289 (3.39), 278 (3.55) and 272 (sh) nm; ^{1}H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.61 [br, s, 1H, N(1)H], 7.36 (dd, 1H, J = 7.5 and 1.5 Hz, H-9), 7.31 (dd, 1H, J = 7.5 and 1.5 Hz, H-12), 7.02 (dt, 1H, J = 1.5 and 7.5 Hz, H-11), 6.95 (dt, 1H, J = 1.5 and 7.5 Hz, H-10), 4.30 (t, 1H, J = 5.1 Hz, OH), 4.26 (t, 1H, J = 5.1 Hz, OH), 3.97 (br, t, 1H, J = 4.8 Hz, H-3), 3.50 (m, 4H, 2H-18 and 2H-21), 3.08 (m, 1H, H-5β), 2.87 (ddd, 1H, J = 14.5, 11.2 and 2 Hz, H-6β), 2.83 (m, 1H, H-5α), 2.68 (ddd, 1H, J = 11.7, 8.2 and 3.8 Hz, H-16), 2.56 (ddd, 1H, J = 11.7, 9.8 and 3.0 Hz, H-16'), 2.49 (br, d, 1H, J = 14.5 Hz, H-6α), 1.93 (m, 2H, 2H-14), 1.45 (m, 1H, H-15); ^{13}C NMR (20.1 MHz, Py-d_5): δ 137.6 (C-13), 132.8 (C-2), 128.8 (C-8), 121.6 (C-11), 119.8 (C-10), 118.3 (C-9), 112.0 (C-12), 106.6 (C-7), 62.6 (C-18), 60.7 (C-21), 55.7 (C-3), 51.8 (C-5), 47.3 (C-17), 41.3 and 32.0 (C-15 and C-20), 32.8 (C-19), 31.4 (C-14), 27.5 (C-16), 19.1 (C-6); MS (EI) *m/e* (relative intensity): 314 (M^+, 77), 313 (100), 225 (96); CD λ (Δε): 295 (+0.80), 265 (+1.27).

Compound **14b**: colourless glass which did not crystallize; R_F ($CHCl_3$/MeOH, 7:3): 0.41; IR (KBr): 3240, 2840 and 2780 cm^{-1}; UV λ_{max} (log ε): 288 (3.20), 280 (3.31) and 273 (sh) nm; ^{1}H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.69 [br, s, 1H, N(1)H], 7.36 (br, d, J = 7.5 Hz, H-9), 7.30 (br, d, J = 7.5 Hz, H-12), 7.02 (br, t, J = 7.5 Hz, H-11), 6.95 (br, d, J = 7.5 Hz, H-10), 4.38 (br, s, 2H, 2OH), 3.50 (m, 4H, 2H-18 and 2H-21), 3.18 (dd, 1H, J = 11.5 and 1.5 Hz, H-3), 3.00 (br, dd, 1H, J = 11.5 and 5.5 Hz, H-5), 2.97 (br, d, 1H, J = 13.0 Hz, H-17), 2.81 (dddd, 1H, J = 13.8, 11.5, 5.5 and 1.8 Hz, H-6), 2.59 (br, dd, 1H, J = 13.8 and 4.0 Hz, H-6'), 2.47 (dt, 1H, J = 4.0 and 11.5 Hz, H-5'), 2.33 (td, 1H, J = 13.0 and 2.7 Hz, H-17'), 2.23 (br, dd, J = 12.5 and 3.6 Hz, H-14β), 1.71 (tq, 1H, J = 12.5 and 3.6 Hz, H-15), 1.63 (br, d, 1H, J = 13.0 Hz, H-16), 1.41 (m, 1H, H-16'), 1.20 (td, 1H, J = 12.5 and 11.5 Hz, H-14α); MS (EI) *m/e* (relative intensity): 314 (M^+, 90), 313 (100), 225 (70); CD λ (Δε): 292 (-0.30), 288 (-0.37), 268 (-0.35), 232 (-0.51). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.57; H, 8.34; N, 8.91. Found: C, 72.71; H, 8.36; N, 8.87.

Compound 15. Tri-*n*-butylphosphine (207 mg, 1.02 mmol) was injected dropwise over 5 min into a magnetically stirred suspension of **14a** (268 mg, 0.85 mmol) and 2-nitrophenylselenocyanate (231 mg, 1.02 mmol) in dry THF (10 mL) under nitrogen. After 12 h at room temperature, a substantial amount of **14a** remained (t.l.c.). More 2-nitrophenylselenocyanate (113 mg, 0.5 mmol) and tri-*n*-butylphosphine (101 mg, 0.5 mmol) were added and, after a further 4 h at room temperature, the solvent was removed *in vacuo*. FC of the yellow residue with $CHCl_3$/MeOH (17:3) as eluant yielded the *selenide* **15** (110 mg, 26%).

Compound **15**: yellow amorphous solid; R_F [$CHCl_3$/MeOH/NH_3(*d* 0.88), 85:15:1]: 0.41; IR: 3470, 3280 and 1590 cm^{-1}; UV λ_{max} (log ε): 288, 278, 270 and 256 nm; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 [br, s, 1H, N(1)H], 8.25 (br, d, 1H, J = 8.0 Hz, *o*-NO_2-ArH), 7.76 (br, d, 1H, J = 8.0 Hz, *m*-NO_2-ArH), 7.67 (br, t, 1H, J = 8.0 Hz, *p*-NO_2-ArH), 7.47 (br, t, 1H, J = 8.0 Hz, *m*-NO_2-ArH), 7.39 (br, d, 1H, J = 7.5 Hz, H-9), 7.34 (br, d, 1H, J = 7.5 Hz, H-12), 7.05 (br, t, 1H, J = 7.5 Hz, H-11), 6.97 (br, t, 1H, J = 7.5 Hz, H-10), 4.42 (br, s, 1H,

OH), 4.18 (br, d, 1H, J = 5.5 Hz, H-3), 3.67 (dd, 1H, J = 11.0 and 4.4 Hz, H-21), 3.58 (dd, 1H, J = 11.0 and 5.4 Hz, H-21'), 3.23-3.10 (m, 2H, 2H-18), 2.98 (m, 1H, H-5), 2.92 (br, t, 1H, J = 12.5 Hz, H-6), 2.75 (m, 2H, 2H-17), 2.60 (br, d, J = 12.5 Hz, H-6'), 2.08 (m, 2H, 2H-14); MS (FAB$^+$): 499 (MH^+), 401 (MH^+-H_2O).

Oxidation of 15. To a cooled (0°C) stirred solution of the *selenide* **15** (97 mg, 0,19 mmol) in MeOH/H_2O, 4.5:1 (10 mL) was added portionwise a solution of sodium metaperiodate (43 mg, 0.2 mmol) in water (2 mL). After being stirred for 1 h at 0°C, the mixture was poured onto saturated $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure and the residue thus obtained was taken into THF (10 mL) in the presence of Et_3N (4 mL). After stirring for 1.5 h at 40°C, the solvent was removed *in vacuo* and the yellow residue was subjected to FC ($CHCl_3$/MeOH, 17:3) to yield 18 mg (31%) of **19** and 23 mg (40%) of (-)-antirhine **2**.
Compound **19**: pale yellow foam; R_F [$CHCl_3$/MeOH/NH_3(*d* 0.88), 85:15:1]: 0.34; IR: 3480 cm^{-1}; UV λ_{max} (log ϵ): 289 (3.17), 279 (3.26) and 273 (sh) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.74 [br, s, 1H, N(1)-H], 7.39 (br, d, 1H, J = 7.5 Hz, H-9), 7.33 (br, d, 1H, J = 7.5 Hz, H-12), 7.06 (br, t, 1H, J = 7.5 Hz, H-11), 6.97 (br, t, 1H, J = 7.5 Hz, H-10), 4.08 (br, m, 1H, H-3), 3.99 (t, 1H, J = 8.0 Hz, H-21), 3.78 (dt, 1H, J = 8.4 and 3.6 Hz, H-18), 3.67 (q, 1H, J = 8.4 Hz, H-18'), 3.42 (t, 1H, J = 8.0 Hz, H-21'), 3.19 (m, 1H, H-5), 2.92 (m, 2H, H-5' and H-6), 2.82 (m, 2H, 2H-17), 2.63 (br, d, 1H, J = 12.0 Hz, H-6'), 2.32 (br, quint., 1H, J = 8.0 Hz, H-20), 2.04 (m, 1H, H-16), 1.97 (br, t, 2H, J = 4.8 Hz, 2H-14), 1.81 (m, 1H, H-15), 1.55 (m, 1H, H-16'); MS (EI) *m/e* (relative intensity): 296 (M^+, 91), 295 (100), 225 (34). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.98; H, 8.17; N, 9.46. Found: C, 76.85; H, 8.16; N, 9.44.
(-)-Antirhine **2**[21]: white crystals from $CHCl_3$; m.p. = 108-112°C, (Lit.,[2]: m.p. = 112-114°C); IR: 3470 and 3270 cm^{-1}; UV λ_{max} (log ϵ): 288 (3.70), 278 (3.72) and 272 (sh) nm; ^1H NMR (300 MHz, acetone-d_6, 30°C): δ 9.91 [br, s, 1H, N(1)-H], 7.39 (br, d, 1H, J = 7.5 Hz, H-9), 7.30 (br, d, 1H, J = 7.5 Hz, H-12), 7.03 (br, t, 1H, J = 7.5 Hz, H-11), 6.97 (br, t, 1H, J = 7.5 Hz, H-10), 5.71 (ddd, 1H, J = 16.6, 10.2 and 8.7 Hz, H-19), 5.09 (br, dd, 1H, J = 10.2 and 2.0 Hz, H-18), 5.07 (br, dd, 1H, J = 16.6 and 2.0 Hz, H-18'), 3.94 (br, m, 1H, H-3), 3.71 (dd, 1H, J = 10.2 and 5.0 Hz, H-21), 3.62 (dd, 1H, J = 10.2 and 5.5 Hz, H-21'), 3.11 (br, dd, 1H, J = 12.4 and 5.0 Hz, H-5β), 2.93 (dddd, 1H, J = 14.2, 12.4, 5.2 and 2.5 Hz, H-6β), 2.84 (dt, 1H, J = 5.2 and 12.4 Hz, H-5α), 2.72 (ddd, 1H, J = 12.5, 7.0 and 3.8 Hz, H-17), 2.59 (ddd, 1H, J = 12.5, 8.0 and 3.0 Hz, H-17'), 2.55 (br, dd, 1H, J = 14.2 and 5.0 Hz, H-6α), 2.33 (m, 1H, H-20), 2.12 (ddd, 1H, J = 13.0, 7.4 and 3.7 Hz, H-14), 2.02 (ddd, 1H, J = 13.0, 7.5 and 3.5 Hz, H-14'), 1.69 (m, 1H, H-15); ^{13}C NMR (75.4 MHz, acetone-d_6, 30°C): δ 145.4 (C-19), 125.9 (C-11), 124.0 (C-10), 122.9 (C-9), 121.5 (C-18), 116.3 (C-12), 68.7 (C-21), 60.2 (C-3), 57.8 (C-5), 54.3 (C-20), 53.5 (C-17), 37.2 (C-14), 37.1 (C-15), 33.7 (C-16), 24.8 (C-6); $[\alpha]_D^{25}$: -1.96° (*c* 0.25), {Lit.,[2] $[\alpha]_D^{25}$: -2° (*c* 0.23)}; CD λ (Δε): 293 (+0.94), 268 (+1.44), 233 (+5.87), 218 (-6.61), [Lit.,[7] CD λ (Δε): 293 (+0.96), 265 (+1.44).

Compounds 20a,b. To 1.3 g (4.0 mmol) of **13** (mixture of diastereoisomers) in 120 mL of MeOH/AcOH 3:1 was added 1.49 g (8.0 mmol, 2 equiv) of *p*-toluenesulfonylhydrazine. After the mixture was stirred for 1 h, the solvent was removed on a rotary evaporator and the solid residue was taken into dichloromethane (100 mL). The dichloromethane solution was washed successively with 3% $NaHCO_3$ (aq), water, and brine and dried over anhydrous $MgSO_4$. The crude product was flash chromatographed ($CHCl_3$/MeOH, 9:1) to afford 1.7g (86%) of *N-tosylhydrazone* **20a** (as an 1:3 inseparable mixture of *syn:anti* isomers) contaminated by its C-3 epimers **20b** (5-10%), (300 MHz ^1H NMR).
Compound **20a**: colourless solid; R_F ($CHCl_3$/MeOH, 9:1): 0.32; IR: 3680, 3470, 1670 and 1635 cm^{-1}; UV λ_{max} (log ϵ): 289 (3.28), 280 (sh), 273 (3.55) nm; ^1H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.81 [br, s, 1H, N(1)H], 10.75 (s, 1H, SO_2NH), 7.63 (d, 2H, J = 7.8 Hz, 2*o*-SO_2-ArH), 7.38 (br, d, 1H, J = 7.5 Hz, H-9), 7.33 (br, d, 1H, J = 7.5 Hz, H-12), 7.32 (d, 2H, J = 7.8 Hz, 2*m*-SO_2-ArH), 7.32 (m, H-18, *anti*), 7.07 (br, t, 1H, J = 7.5 Hz, H-11), 6.99 (br, t, 1H, J = 7.5 Hz, H-10), 6.78 (t, J = 5.2 Hz, H-18, *syn*), 4.89 (br, t, 1H, J = 5.5 Hz, H-3), 4.77 (dd, 1H, J = 12.0 and 4.8 Hz, H-5β), 4.42 (t, 1H, J = 5.0 Hz, OH), 3.38 and 3.31 (2 x dt, 2H, J = 12.0 and 5.0 Hz, 2H-21), 2.90 (dt, 1H, J = 5.1 and 12.0 Hz, H-5α), 2.75 (dddd, 1H, J = 13.8, 12.0, 4.8 and 2.2 Hz, H-6β), 2.63 (br, dd, 1H, J = 13.8 and 5.1 Hz, H-6α), 2.41 (s, $ArCH_3$, *syn*), 2.39 (s, $ArCH_3$, *anti*), 2.25 (m, 1H, H-20), 1.68 (m, 1H, H-15); MS (FAB$^+$): 495 (MH^+). Anal. Calcd for $C_{26}H_{30}N_4O_4S$: C, 63.13; H, 6.12; N, 11.33. Found: C, 63.24; H, 6.15; N, 11.31.

Reaction of *N-tosylhydrazone* (20a,b) with *n*-BuLi. A stirred solution of a 19:1 mixture of *N-tosylhydrazones* **20a** and **20b** (*vide supra*) (1.7 g, 3.44 mmol) in THF/TMEDA 4:1 (60 mL) was cooled to -78°C and treated, while under nitrogen, with 4 equiv. of *n*-butyllitium (11.5 mL of 1.2 *M* in hexane). The deep red solution was stirred at -78°C for 30 min and allowed to warm to room temperature. After 40 min, 5% aqueous NH_4Cl (20 mL) was introduced to the cooled (0°C) solution. The resulting mixture was stirred 15 min prior to extraction with EtOAc (3 x 20 mL). The combined organic extract was washed successively with 1 *N* HCl (aq), water, 5% aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated

in vacuo. The residue material was subjected to FC ($CHCl_3$/MeOH, 24:1) to afford **23a** (256 mg, 24%), **22a** (540 mg, 43%) and 32 mg (3%) of a product to which was tentatively assigned the structure **24a** each of them contaminated by its inseparable C-3 epimer **23b**, **22b** and **24b** respectively (*ca.* 5-10 % by ^{1}H NMR).
Compound **23a**: colourless amorphous solid; R_F ($CHCl_3$/MeOH, 9:1): 0.50; IR: 3470 and 1635 cm^{-1}; UV λ_{max} (log ϵ): 290 (3.24), 282 (3.33) and 271 (sh) nm; ^{1}H NMR (80 MHz, $CDCl_3$): δ 8.33 [br, s, 1H, N(1)-H], 7.58-6.93 (m, 4H, 4Ar-H), 4.98 (m, 1H, H-3), 4.85 (m, 1H, H-5), 4.02 (t,1H, J = 7.8 Hz, H-21), 3.82 (m, 2H, 2H-18), 3.45 (t, 1H, J = 7.8 Hz, H-21'); MS (FAB^+): 311 (MH^+). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.51; H, 7.15; N, 9.03. Found: C, 73.62; H, 7.18; N, 8.97.
Compound **22a**: colourless gum; R_F ($CHCl_3$MeOH, 9:1): 0.46; IR: 3470, 3310 and 1630 cm^{-1}; UV λ_{max} (log ϵ): 289 (3.43), 280 (3.70) and 273 (sh) nm; ^{1}H NMR (300 MHz, DMSO-d_6, 50°C): δ 10.81 [br,s, 1H, N(1)-H], 7.39 (br, d, 1H, J = 7.7 Hz, H-9), 7.34 (br, d, 1H, J = 7.7 Hz, H-12), 7.07 (br, t, 1H, J = 7.7 Hz, H-11), 6.98 (br, t, 1H, J = 7.7 Hz, H-10), 4.94 (m, 1H, H-3), 4.79 (dd, 1H, J = 12.0 and 4.8 Hz, H-5β), 4.29 (t, 1H, J = 4.9 Hz, OH), 3.44 (br, t, 2H, J = 5.0 Hz, 2H-21), 2.90 (dt, 1H, J = 5.1 and 12.0, H-5α), 2.76 (dddd, 1H, J = 14.5, 12.0, 4.8 and 2.2 Hz, H-6β), 2.62 (br, dd, J = 14.5 and 5.1 Hz, H-6α), 2.29 (dt, 1H, J = 14.2 and 4.1 Hz, H-14), 2.25 (br, d, 2H, J = 8.0 Hz, 2H-16), 2.17 (ddd, 1H, J = 14.2, 9.8 and 5.8 Hz, H-14'), 1.78 (m, 1H, H-15), 1.38 (m, 1H, H-20), 0.88 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR (20.1 MHz, $CDCl_3$): δ 170.8 (C-17), 136.2 (C-13), 133.7 (C-2), 127.1 (C-8), 121.7 (C-11), 119.4 (C-10), 118.0 (C-9), 111.2 (C-12), 109.4 (C-7), 62.1 (C-21), 53.8 (C-5), 43.5 (C-20), 42.5 (C-5), 36.7 (C-16), 31.7 (C-14), 30.8 (C-15), 29.7 (C-19), 28.2 (C-18), 21.4 (C-6); MS (FAB^+): 369 (MH^+); HRMS calcd for $C_{23}H_{32}N_2O_2$ 368.2464, found 368.2462.
Compound **24a**: colourless foam; R_F ($CHCl_3$MeOH, 9:1): 0.21; IR: 3475, 3320 and 1640 cm^{-1}; UV λ_{max}: 290, 279 and 270 nm; ^{1}H NMR (80 MHz, DMSO-d_6): δ 10.74 [br, s, 1H, N(1)-H], 7.45-6.90 (m, 4H, 4Ar-H), 4.88 (m,1H, H-3), 5.69 (br, dt, 1H, J = 16.4 and 8.5 Hz, H-19), 5.20-5.05 (m, 2H, 2H-18), 4.33 (t, 1H, J = 5.1 Hz, OH), 3.44 (m, 2H, 2H-21); MS (FAB^+): 311 (MH^+).

Reaction of *N-tosylhydrazone* (20a,b) with Sodium hydride. A stirred suspension of a 19:1 mixture of *N-tosylhydrazones* **20a** and **20b** (*vide supra*)(198 mg, 0.4 mmol) in dry toluene (15 mL) was treated with sodium hydride (10.7 mmol, 320 mg of a 80% dispersion in mineral oil, freed of oil by washing three times with *n*-pentane), and the resulting mixture was refluxed under an atmosphere of argon for 1 h. The reaction mixture was cooled to room temperature, excess base was destroyed by the **cautious** addition of water, and the resulting mixture was partitioned between EtOAc (20 mL) and aqueous ammonium chloride. The aqueous phase was extracted once more with EtOAc and the combined extract was washed with brine, dried (Na_2SO_4), and concentrated. The remaining oil was subjected to FC ($CHCl_3$/MeOH, 24:1) to afford 54 mg (43%) of the cyclized product **23a,b** identical to that isolated from the previous reaction.

Compounds 25a,b. To a solution of a 19:1 mixture of *N-tosylhydrazones* **20a** and **20b** (*vide supra*) (890 mg, 1.8 mmol) and (*i*-Pr)$_2$NEt (Hunig base) (520 μL, 3.04 mmol) in dry DMF (2.5 mL) at 25°C under an atmosphere of nitrogen, was added TBDMSiCl (405 mg, 2.7 mmol). After 3 h the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The EtOAc fractions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford an oil. Purification by FC ($CHCl_3$/MeOH, 19:1) afforded 963 mg (88%) of *protected N-tosylhydrazone* **25a** and its inseparable C-3 epimer **25b** (5 - 10% by 200 MHz ^{1}H NMR).
Compound **25a**: colourless glass; R_F ($CHCl_3$/MeOH, 19:1): 0.38; IR: 3690, 3472, 1670 and 1630 cm^{-1}; UV λ_{max} (log ϵ): 291 (3.30), 283 (sh) and 275 (3.77) nm; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20 [br, s, 1H, N(1)H], 8.01 (br, s, 1H, SO_2NH), 7.72 (d, 2H, J = 7.8 Hz, 2*o*-SO_2-ArH), 7.46 (br, d, 1H, J = 7.0 Hz, H-9), 7.43 (br, d, 1H, J = 7.0 Hz, H-12), 7.31 (m, H-18, *anti*), 7.26 (d, 2H, J = 7.8 Hz, 2*m*-SO_2-ArH), 7.17 (br, t, 1H, J = 7.0 Hz, H-11), 7.09 (br, t, 1H, J = 7.0 Hz, H-10), 4.95 (dd, 1H, J = 12.0 and 5.0 Hz, H-5β), 4.87 (m, 1H, H-3), 3.54 (m, 2H, 2H-21), 2.93 (dt, 1H, J = 12.0 and 5.0 Hz, H-5α), 2.72 (m, 1H, H-6), 2.64 (br, dd, 1H, J = 13.5 and 5.0, H-6'), 2.41 (s, 3H, $ArCH_3$), 2.08 (m, 1H, H-20), 1.72 (m, 1H, H-15), 0.83 (s, 9H, $3CH_3$), 0.06 (s, 6H, $2SiCH_3$); MS (FAB^+): 609 (MH^+). Anal. Calcd for $C_{32}H_{44}N_4O_4SSi$: C, 63.13; H, 7.29; N, 9.21. Found: C, 63.24; H, 7.33; N, 9.15.

Compounds 26a,b. According to the similar method described for **20**, treatment of a *ca.* 19:1 mixture of **25a** and **25b** (*vide supra*)(830 mg, 1.37 mmol) with NaH (879 mg, 36.6 mmol) in dry toluene (100 mL) gave, after FC (EtOAc/*n*-hexane, 9:1), 406 mg (70%) of **26a** contaminated by a *ca.* 5-10% of its inseparable C-3 epimer **26b** (^{1}H NMR, 300 MHz).
Compound **26a**: amorphous colourless solid; R_F ($CHCl_3$MeOH, 97:3): 0.43; IR: 3470 and 1630 cm^{-1}; UV λ_{max} (log ϵ): 289 (3.20), 281 (sh), 279 (3.44) and 274 (sh) nm; ^{1}H NMR(300 MHz, DMSO-d_6, 50°C): δ 10.80 [br, s, 1H, N(1)H], 7.39 (br, d, 1H, J = 7,4 Hz, H-9), 7.34 (br, d, 1H, J = 7.4 Hz, H-12), 7.07 (br, t, 1H, J = 7.4 Hz, H-11), 6.98 (br, t, 1H, J = 7.4 Hz, H-10), 5.71 (dt, 1H, J = 17.0 and 9.8 Hz, H-19), 5.14 (dd, 1H, J = 9.8 and 1.8 Hz, H18), 5.09 (dd, 1H, J = 17.0 and 1.8 Hz, H-18'), 4.96 (br, t, 1H, J = 5.5 Hz, H-3), 4.79 (dd, 1H, J = 12.0 and 4.5 Hz, H-5β), 3.71 (dd, 1H, J = 10.0 and 5.1 Hz, H-21), 3.63 (dd, 1H, J = 10.0 and 6.0 Hz,

H-21'), 2.89 (dt, 1H, J = 12.0 and 5.1 Hz, H-5α), 2.72 (dddd, 1H, J = 13.5, 12.0, 4.5 and 2.2 Hz, H-6β), 2.62 (br, dd, 1H, J = 13.5 and 5.1 Hz, H-6α), 2.29 (m, 1H, H-20), 2.27 (m, 1H, H-14), 2.19 (ddd, 1H, J = 14.5, 8.5 and 3.5 Hz, H-14'), 1.90 (m, 1H, H-15), 0.82 (s, 9H, $3CH_3$), 0.02 (s, 6H, $2SiCH_3$); ^{13}C NMR (75.4 MHz, APT, DMSO-d_6, 50°C): δ 168.3 (C-17), 137.6 (C-19), 136.2 (C-13), 134.4 (C-2), 126.5 (C-8), 120.6 (C-11), 118.3 (C10), 117.3 (C-9), 116.9 (C-18), 110.9 (C-12), 107.9 (C-9), 63.5 (C-21), 52.2 (C-3), 48.8 (C-20), 40.6 (C-5), 35.3 (C-16), 30.0 (C-14), 29.2 (C-15), 25.4 (5 x CH_3), 20.3 (C-6); MS (FAB^+): 425 (MH^+); HRMS calcd for $C_{25}H_{36}N_2O_2Si$ 424.2546, found 424.2546.

Reduction and deprotection of 26a,b. To a stirred mixture of $LiAlH_4$ (76 mg, 2.0 mmol) in THF (5 mL) was added a solution of a *ca.* 19:1 mixture of **26a** and **26b** (*vide supra*) (730 mg, 1.72 mmol) also in THF (10 mL) at 0°C under nitrogen. The reaction mixture was allowed to come to room temperature and then boiled 45 min under reflux with stirring. It was cooled to 0°C and then successively treated with water (10 mL), 15% aqueous NaOH (1 mL) and $CHCl_3$ (10 mL). The organic layer was filtered off, and the white residue was washed with $CHCl_3$ (4 x 10 mL). The combined organic filtrates were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil, which was subsequently dissolved in 3% aqueous H_3PO_4 (100 mL). The resulting mixture was stirred at room temperature for 30 min, after which it was neutralized with 5% aqueous $NaHCO_3$ and extracted four times with 10 mL portions of $CHCl_3$. The organic layers were combined, dried (Na_2SO_4), concentrated under reduced pressure to give a residue which was purified by FC ($CHCl_3$/MeOH, 17:3) to yield 392 mg (77%) of (-)-antirhine **2**[21] (identical to that isolated from the oxidation of **15**) and 31 mg (6%) of (+)-3-epi-antirhine.[29]

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