Studies in sigmatropic rearrangements of *N*-prenylindole derivatives – a formal enantiomerically pure synthesis of tryprostatin B†

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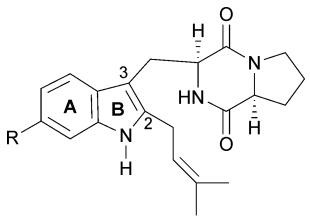
Rearrangement of N^a-prenyl-N^b-acetyltryptamine, induced by $BF_3{\cdot}Et_2O$ at low temperature, leads to a 2-prenyl derivative, and thence to the tricyclic tryptamine **7** and the indoline **8.** Similarly, N^a-prenyl-N^b-phthaloyl-L-tryptophan methyl ester furnished the corresponding 2-prenyl derivative **16**, a known advanced precursor of tryprostatin B. Density functional (B3LYP) calculations for the putative rearrangement transition state for *N*-prenylskatole show that prior coordination of BF_3 to the indolic nitrogen changes the character of the subsequent sigmatropic pericyclic shifts from being entirely covalent to acquiring a significant degree of ionic character. The shifting prenyl group favours the *endo* over the *exo* mode of the transition state by 4.1 kcal mol^{-1}.

Introduction

The cell cycle is a strictly regulated biochemical process by which division into daughter cells occurs.[1] Hence interference by any molecule with this division, which occurs under a universal control mechanism in all eukaryotic cells,[2] can have far-reaching consequences, as for example, in the control of diseases such as cancer. Several alkaloids have been found to possess this property, notably the G2/M mammalian cell cycle inhibitors such as the tryprostatins[3] (**1a**, **1b**) isolated from a marine strain (BM 939) of *Aspergillus fumigatus*, and the related cyclotryprostatin.[4]

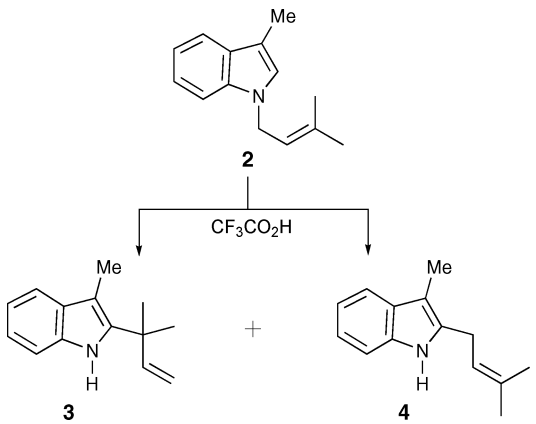


1a: R = OMe; tryprostatin A

1b: R = H; tryprostatin B

Our interest in the application of pericyclic reactions to the synthesis of natural products and other heterocycles[5] had prompted us to apply one such a reaction to an asymmetric synthesis of tryprostatin B[6] (**1b**). Full details pertaining to this work,[7] involving an acid-catalysed rearrangement of an appropriately substituted trytophan, is described herein.

Purely thermal[8] aza-Claisen reactions of some *N*-allyl-3-alkylindoles required high temperatures (450–470 °C) to produce their 2- and 3-allyl indolic derivatives respectively. Subsequent studies had shown that substantial reduction in the activation energy of the reaction can be achieved in the presence of protic or Lewis acids, and that such reactions can be performed at room temperature or lower. Of particular relevance to the present study were the observations of Casnati *et al.*[9a] that the CF_3COOH-catalysed rearrangement of *N*-(3,3-dimethylallyl)skatole (**2**) led, at RT, to a mixture (1 : 1) of **3** and **4** (Scheme 1).



Scheme 1

Results and discussion

From the standpoint of the synthesis of (−)-tryprostatin B (**1b**) starting from an appropriate derivative of indole, the formation of a compound of type **3** is undesirable. Therefore some preliminary experiments were performed with N^a-prenyl-N^b-acetyltryptamine[10] (**6**), readily secured from N^a-acetyltryptamine (**5**) (Scheme 2), as the model compound, to define conditions that favour principally, if not, exclusively, a type **4** compound.

Since the initial results with CF_3COOH or $AlCl_3$ as catalysts were not promising, $BF_3{\cdot}Et_2O$ was next examined to induce the rearrangement of **6**. Systematic variation of substrate *versus* Lewis

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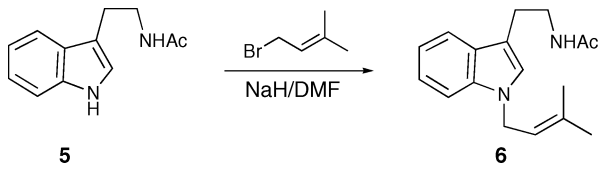
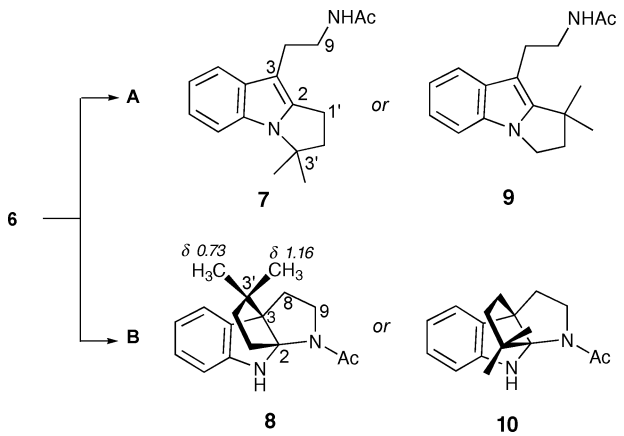


Scheme 2

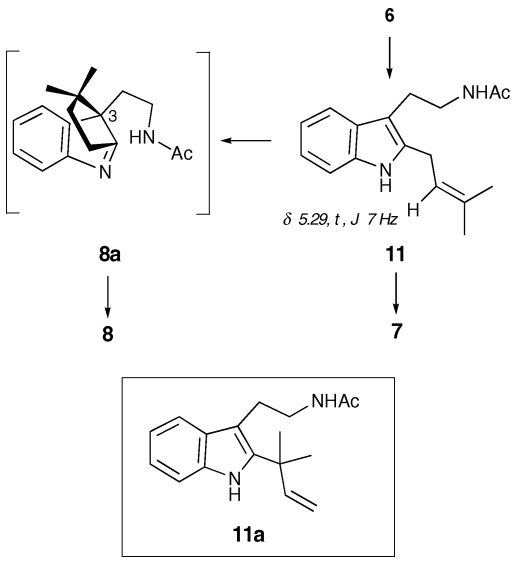
acid concentration led to the definition of experimental conditions whereby it was possible to bring about a chemical reaction without a wealth of products being formed. Thus the reaction carried out at RT (24 h) with **6** and the Lewis acid (12 eq.) yielded two products, **A** and **B**, in 15% and 6% yields respectively. The presence of the NHCO group in **A** was indicated by two IR absorptions at 3445 and 1671 cm^{-1}, and its ^{1}H-NMR spectrum contained a total of 4 aromatic hydrogens (δ_H 7.5–7.0), 8 methylene protons and a geminal dimethyl group (δ_H 1.62, 6H, s). Notable was the absence of the indolic C2 hydrogen, indicating that a rearrangement of **6** had occurred. These data taken in conjunction with its molecular formula $C_{17}H_{22}N_2O$, as determined by exact mass measurement, limited its structure to either **7** or **9** (Scheme 3).



Scheme 3

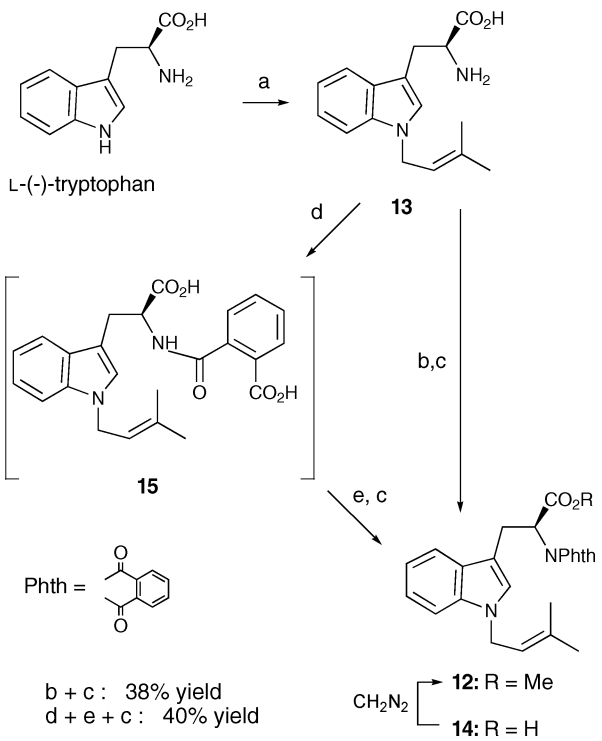
Similarly, the infrared absorptions at 3411 and 1635 cm^{-1} and the ^{1}H-NMR (4H, Ar-H) of compound **B**, analysing for $C_{17}H_{22}N_2O$, were consistent with a bridged hexahydropyrroloindole, **8** or **10** (Scheme 3). Evidence in favour of structure **8** was forthcoming from a bi-dimensional HMBC experiment, which established a correlation between C3 and the hydrogens of the geminal dimethyl groups, two carbons away. When the above reaction was worked up before **7** and/or **8** were detected on the TLC plates, a new isomeric product **11** could be isolated in 23% yield, with the bulk of the starting material remaining unaltered. Its structure was deduced from its ^{1}H-NMR, IR spectra and mass spectra (M^+). Thus the absence of a hydrogen at C2 and the presence of a resonance signal at δ_H 5.29 (1H, t, J = 7 Hz) excluded the alternative product **11a** (Scheme 4).

The observation that pure **11**, on exposure to $BF_3{\cdot}Et_2O$, under similar conditions, was converted into **A** (45%) and **B** (18%), showed that it was the most likely precursor of both these compounds, and excluded the alternative structures **9** and **10**. Having established the feasibility and conditions necessary to bring about the desired rearrangement (**6** → **8**), the phthaloyl



Scheme 4

derivative **12** (Scheme 5), incapable of forming a tetracycle similar to **8**, was chosen for study.



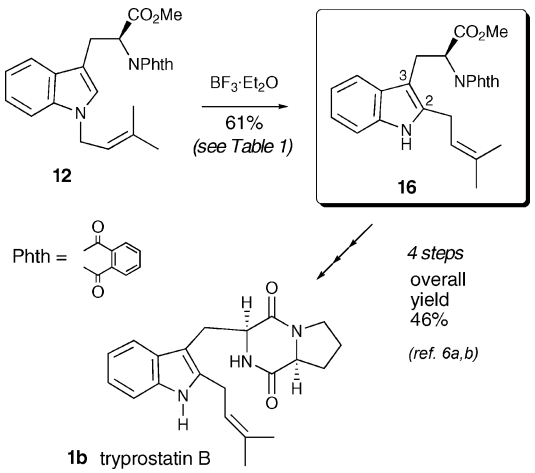
Scheme 5 *Reagents and conditions*: a) Na, liq. NH_3, $Me_2C{=}CHCH_2Br$; b) *N*-carbethoxyphthalimide, NaH; c) CH_2N_2; d) phthalic anhydride; e) DCC, DMAP.

Since attempted prenylation of methyl-N^b-phthaloyl-L-(−)-tryptophan (NaH/DMF/prenyl bromide) could not be achieved without racemisation, the requisite substance was prepared by a literature method.[11] Thus, L-(−)-tryptophan in Na/liq. NH_3 was first prenylated, and the resulting amino acid **13** (mp 196–198 °C; lit.[11] mp 201–202 °C) converted to the phthalimide derivative **14** ($[\alpha]_D$ −174.4, lit.[11] $[\alpha]_D$ −174.5) with *N*-carbethoxyphthalimide.

Methylation of the former with CH_2N_2 provided the N^b-phthalimido ester **12** (79%; $[\alpha]_D$ −173.1; mp 93–94 °C; M^+ 416.17448, $C_{25}H_{24}N_2O_4$ requires 416.17359). Alternatively **12** could be obtained by treatment of **13** with phthalic anhydride and Et_3N, followed by ring closure of resulting phthalamic acid **15** with DMAP and DCC (Scheme 5). Since the singlet due to the OMe group (δ_H 3.78) of the ester **12** was not split on addition of the shift reagent Eu(tfc)$_3$ (a similar treatment of the racemate caused the splitting of the same signal into two, in equal intensity) the substance with $[\alpha]_D$ −173.1 was deemed to be optically pure.

Rearrangement studies

With the key intermediate **12** available in reasonable quantities, a systematic study was undertaken to define optimum conditions which entailed minimum loss of optical purity and maximum chemical conversion during its rearrangement to **16** (Scheme 6).



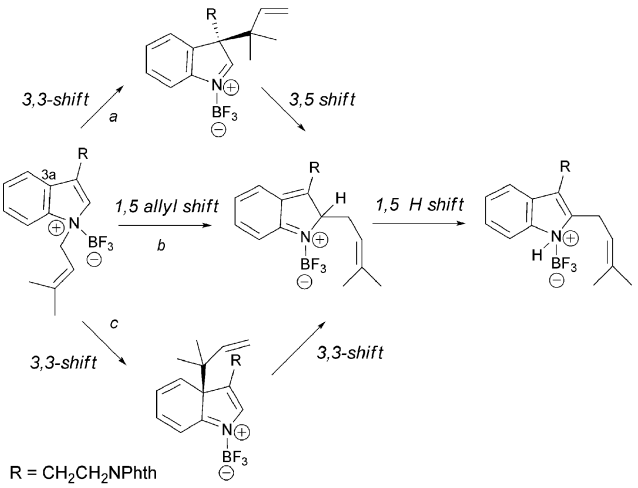
Scheme 6

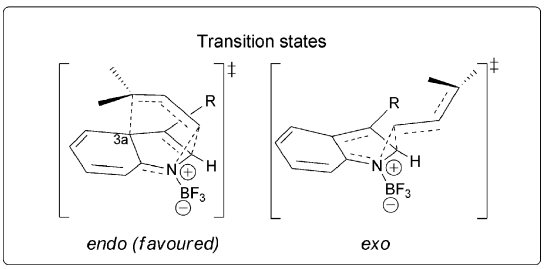
As in the transformation of **6** to **8**, CF_3COOH both as a solvent and as a proton source proved to be less satisfactory, although in one experiment, **16** with an ee of 84% was obtained in 49% yield. More promising results were obtained with $BF_3{\cdot}Et_2O$, as can be seen in Table 1.

It was found that, in general, rearrangements conducted at −4 °C or below with an excess of $BF_3{\cdot}Et_2O$ (a maximum of 36.3 eq.) afforded the desired product **16** (Scheme 6) with $[\alpha]_D$ < −210, *i.e.* ee > 86% based on the value of $[\alpha]_D$ −252, reported by Danishefsky,[6a,b] as that of the enantiomerically pure compound. Fine-tuning of the experimental conditions enabled the highest optical purity (95% ee) to be achieved (Table 1, entry 4, 23.6 eq. of $BF_3{\cdot}Et_2O$ per mole of substrate, −4 °C, 18 h). Under these conditions, **16** was obtained as a pale yellow solid in 61% yield after purification by PTLC [18% from L-(−)-tryptophan]. The spectral data (^{1}H-NMR, ^{13}C-NMR and IR) were in agreement with those reported.[6a,b] Since the conversion of **16** into (−)-tryprostatin B has been reported,[6a,b] the work detailed above constitutes in a formal sense a highly enantiomerically pure synthesis of the same (Scheme 6).

Mechanism

It is interesting to speculate on the mechanism by which conversion of **12** into **16** takes place. If on the basis of the proven intramolecularity of the rearrangement of **2** (as shown by crossover experiments[9b]) the involvement of a discrete ion pair is excluded, three concerted pathways can be envisaged (Scheme 7).





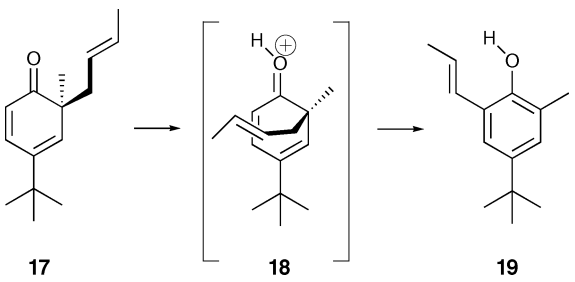
Scheme 7

Table 1 $BF_3{\cdot}Et_2O$-catalysed rearrangement of **12** to **16**

	Starting material **12**					Product **16**		
Entry	Amount/mmol	Eq.	Molar ratio $BF_3{\cdot}Et_2O$/**12**	Temperature/°C	Time/h	Yield (%)	$[\alpha]_D$	ee (%)
1	0.06	1[a]	7.2	RT	15.5	64	−209	83
2	0.048	1[b]	7.2	−4	40	54	−218	86
3	0.048	1[a]	14.8	−4	40	68	−226	89
4	0.072	1[a]	23.6	−4	18	61	−241	95
5	0.048	1[c]	23.6	−4	18	63	−227	90
6	0.048	1[a]	36.3	−14	120	71	−214	84

[a] Molarity 0.024 M, in CH_2Cl_2. [b] Molarity 0.019 M, in CH_2Cl_2. [c] Molarity 0.012 M, in CH_2Cl_2.

Pathway *a* would entail consecutive [3,3]- and [3,5]-rearrangements of the prenyl group from the indole nitrogen–BF_3 complex, followed by a [1,5]-sigmatropic H shift. Excluding the suprafacial 3*s*,5*s* sigmatropic shift,[12] which is forbidden by selection rules, two other pathways are available for the transformation. They are a direct [1,5] shift (pathway *b*) and two consecutive [3,3]-shifts (pathway *c*). Shifts involving allyl groups with retention, unlike similar hydrogen and alkyl transfers,[13a] are relatively rare. Such a possibility was first raised by Miller[13b,c] in connection with the origin of phenolic products from the acid-catalysed rearrangement of linearly conjugated substituted cyclohexadienones (Scheme 8). He noted that substances with terminally substituted allyl groups are reluctant to undergo the normal [3,3]-shifts (leading to inversion) if the centre to which migration occurs bears a bulky substituent. Instead, under these circumstances, it was suggested that a direct [1,5]-allyl shift (retention) could well prevail (**17** → **18** → **19**).



Scheme 8

A more quantitative discrimination between these various alternatives can be made on the basis of density functional (B3LYP) calculations of the putative transition states for *N*-prenylskatole. These show that prior coordination of BF_3 to the indole nitrogen changes the character of the subsequent sigmatropic pericyclic shifts from being entirely covalent to having a significant degree of ionic character, involving an allyl-like carbocation balanced by a F_3B^- anion. π–π-Stacking of the allyl group of the partially coordinated ionic component over the aromatic ring favours an *endo* arrangement (a [3,3]-like shift) of the transition state geometry over an *exo* isomer (a [1,5]- or [1,2]-like shift) by 4.1 kcal mol^{-1} (*cf.* Table 2). The form of the calculated transition mode shows it to 'pivot' about the 3a-position (*cf.* Scheme 7, box), and overall the effect is of a [1,2] N → C migration (Fig. 1).

The barrier (corrected for solvation by dichloromethane) corresponds to a reasonably facile thermal reaction at C3a, thus avoiding the large substituent at C3 in **12**.[14]

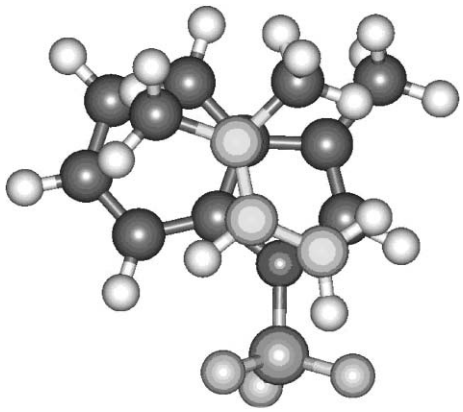


Fig. 1

A similar mechanism can also be invoked to explain the exclusive conversions of the other two substituted tryptamine derivatives **6** and **20** to **11** and **21**,[15] respectively (Scheme 9). Relevant in this context are the results of Sammes *et al.*,[9c] who reported that $BF_3{\cdot}Et_2O$ treatment of the tryptophan derivative **22** gave rise to **23** and **24**. In the light of the arguments presented above, it is suggested that the isomeric structures **25** and **26** could not be excluded for them.

Conclusions

Use of the Lewis acid $BF_3{\cdot}Et_2O$ induces a 1,2-prenyl shift in N^b-phthaloyl-N^a-prenyl-L-tryptophan methyl ester, and leads directly to an advanced synthetic precursor of tryprostatin B. N^b-Acetyl-N^a-prenyltryptamine also furnished a similar rearrangement product. It, however, underwent further reaction involving either the amidic or the indolic nitrogen, to provide indoline **8** and the fused pyrroloindole derivative **7** respectively. The transition state for this pseudo-pericyclic reaction involves a preferred *endo* mode.

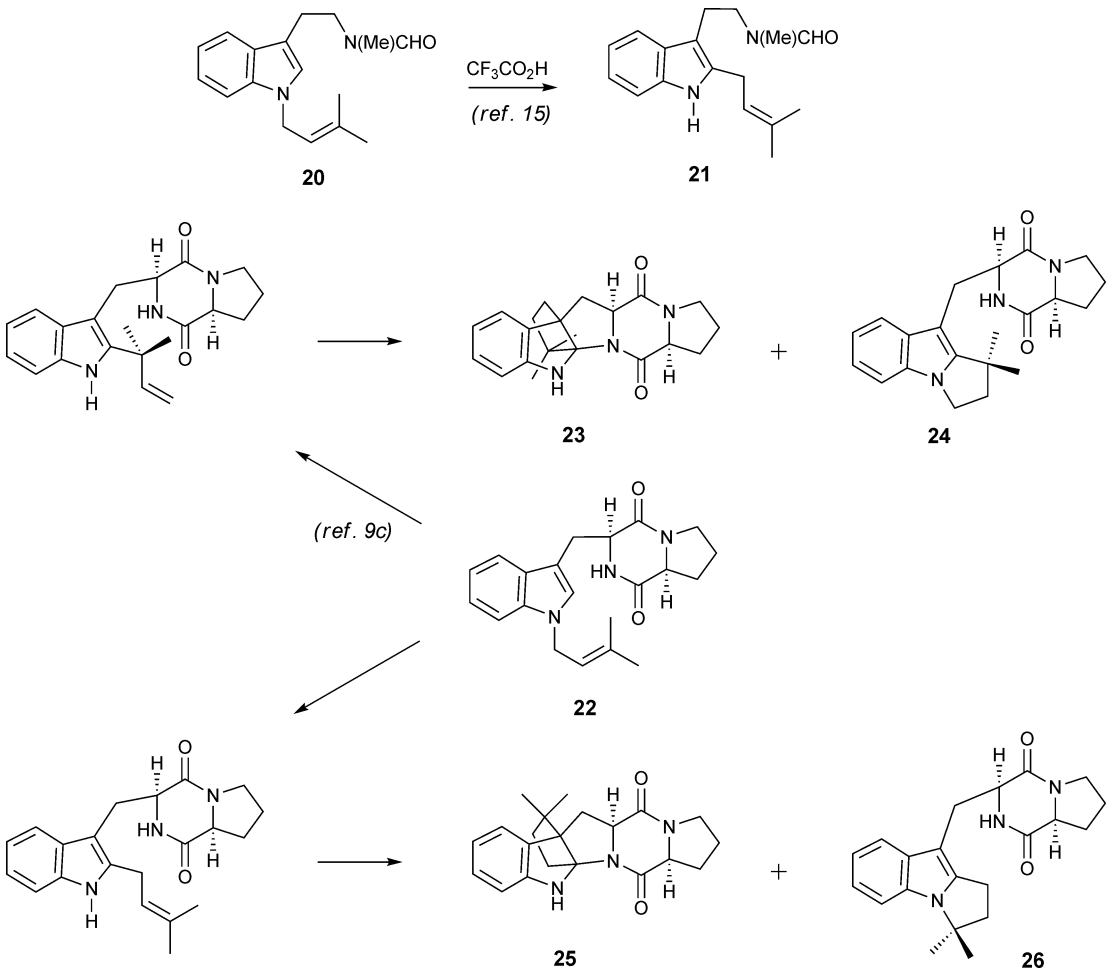
Experimental

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Optical rotations were determined in a Perkin–Elmer 241 MC polarimeter at RT, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Ordinary mass spectra were recorded on a Fisons TRIO 2000 or AEI MS-9 spectrometers. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 400 spectrometer. Chemical shifts are reported relative to

Table 2 B3LYP/6-31G(d) energy calculations for the *endo* and *exo* transition state modes

	Free energy barrier/kcal mol^{-1}	
Mode	B3LYP/6-31G(d)[a]	CPCM[b] solvation model
Endo [1,2]-sigmatropic transition state for N-to-C2 migration	25.8 (ν_i 88 cm^{-1})	19.6
Exo [1,2]-sigmatropic transition state for N-to-C2 migration	29.9 (ν_i 248 cm^{-1})	26.6
ΔE(*endo* − *exo*)	−4.1	−7.0

[a] Free energy barrier, ΔG_{298}, computed from zero-point thermal and entropy corrections to the total energies of reactant and transition state. Geometric coordinates and transition state normal-mode animations are available – see the ESI for this article.† [b] Solvation corrections were applied at the SCRF(CPCM) level (V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995), specifying dichloromethane as solvent.



Scheme 9

tetramethylsilane as the internal reference (δ_H 0.00) for ^{1}H-NMR spectra and to $CDCl_3$ (δ_C 77.00) for ^{13}C-NMR spectra. High-resolution mass spectra were recorded on an AutoSpecQ spectrometer. IR spectra were run on a FT Perkin–Elmer 683 instrument, with absorption frequencies expressed in reciprocal centimetres. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates and PTLC on 0.5 mm thick plates. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). Usual work-up implies drying the water- or brine-washed organic extracts over anhydrous sodium sulfate or magnesium sulfate, followed by filtration and evaporation of the solvent from the filtrate under reduced pressure. Anhydrous solvents were dried as described[16] and freshly distilled.

N^b-Acetyl-*N*^{a}-prenyltryptamine[10] (6)

Mp 63–65 °C (n-hexane); IR (CH_2Cl_2): ν_{max}/cm^{-1} 270 (N–H), 1648 (s, C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.59 (1H, d, J = 7.8 Hz), 7.31 (1H, d, J = 8.2 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.11 (1H, t, J = 7.4 Hz), 6.94 (1H, s), 5.50 (1H, bs, exchangeable with D_2O), 5.37 (1H, t, J = 6.3 Hz), 4.6 (2H, d, J = 6.7 Hz), 3.58 (2H, q, J = 6.4 Hz), 2.96 (2H, t, J = 6.6 Hz), 1.92 (3H, s), 1.82 (3H, t), 1.77 (3H, s); ^{13}C-NMR: δ_C 170.2, 136.5, 136.4, 128.8, 128.7, 128.1, 120.0, 119.0, 111.5, 109.7, 43.9, 39.9, 25.5, 25.1, 23.2, 17.8; HRMS (EI): m/z $C_{17}H_{22}N_2O$ requires 270.17320, found 270.17357.

Rearrangement experiments

N^b-Acetyl-*N*^{a}-prenyltryptamine (**6**) (200 mg, 0.74 mmol) and $BF_3{\cdot}Et_2O$ (1.2 ml, 9.47 mmol) were stirred in an ice-bath until all the starting material had reacted (24 h). Excess $BF_3{\cdot}Et_2O$ was neutralised with Et_3N and the resulting mixture diluted with Et_2O, the organic layer washed with water and dried. Following usual work-up, the products were isolated by PTLC (Et_2O) to furnish compounds **7** and **8**.

Compound 7. Colourless oil (30 mg, 15%); IR (CH_2Cl_2): ν_{max}/cm^{-1} 3445 (N–H), 1671 (s, C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.50 (1H, d, J = 7.5 Hz), 7.40 (1H, d, J = 7.7 Hz), 7.01–7.11 (2H, m), 5.58 (1H, br s, exchangeable with D_2O), 3.53 (2H, m), 2.94 (2H, t, J = 7.3 Hz), 2.89 (2H, t, J = 6.7 Hz), 2.42 (2H, t, J = 7.3 Hz), 1.91 (3H, s), 1.62 (6H, s); ^{13}C-NMR: δ_C 170.1, 141.7, 133.0, 131.3, 120.0, 118.6, 118.4, 109.7, 101.8, 60.8, 43.4, 39.8, 24.5, 23.2, 21.9; HRMS (EI): m/z $C_{17}H_{22}N_2O$ requires 270.17320, found 270.17310.

Compound 8. Colourless oil (11.1 mg, 6%); IR (CH_2Cl_2): ν_{max}/cm^{-1} 3411 (N–H), 1636 (s, C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.06 (1H, t, J = 7.6 Hz), 7.02 (1H, d, J = 7.3 Hz), 6.70 (1H, t, J = 7.3 Hz), 6.46 (1H, d, J = 7.8 Hz), 5.66 (1H, bs, exchangeable with D_2O), 3.63 (1H, m), 3.14–3.21 (1H, m), 2.26–2.36 (3H, m), 2.08 (1H, dd, J_1 = 12.5, J_2 = 5.9 Hz), 1.99 (3H, s), 1.93 (1H, dd, J_1 = 12.3, J_2 = 8.8 Hz), 1.60–1.66 (1H, m), 1.16 (3H, s), 0.73 (3H, s); ^{13}C-NMR: δ_C 169.2, 150.7, 129.5, 128.3, 122.7, 118.0, 108.3, 97.2, 70.4, 49.0, 43.8, 40.3, 36.1, 32.7, 24.0, 23.2, 22.2; HRMS (EI): m/z $C_{17}H_{22}N_2O$ requires 270.17320, found 270.17284.

Isomerisation of 6 to 11

Compound **6** (110 mg, 0.407 mmol) in $BF_3{\cdot}Et_2O$ (0.65 ml, 5.13 mmol) was allowed to stand at 0 °C (1.5 h). Et_3N was then added followed by EtOAc and water. Usual work-up furnished compound **11**: yellow oil (25 mg, 23%); IR: ν_{max}/cm^{-1} 3452 (N–H), 1671 (s, C=O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.17 (1H, s, exchangeable with D_2O), 7.49 (1H, d, J = 7.5 Hz), 7.27 (1H, d, J = 7.8 Hz), 7.04–7.13 (2H, m), 5.65 (1H, bs, exchangeable with D_2O), 5.29 (1H, t, J = 7 Hz), 3.49 (2H, q, J = 6.3 Hz), 3.43 (2H, d, J = 7.0 Hz), 2.99 (2H, t, J = 6.5 Hz), 1.86 (3H, s), 1.76 (3H, s), 1.75 (3H, s); ^{13}C-NMR: δ_C 170.2, 135.4, 134.9, 128.8, 121.3, 120.3, 119.5, 118.0, 110.5, 107.8, 39.9, 25.6, 24.9, 23.9, 23.2, 17.7; HRMS (EI): m/z $C_{17}H_{22}N_2O$ requires 270.17320, found 270.17310.

Isomerisation of 11 to 7 and 8

Exposure of **11** (10 mg, 0.037 mmol) to $BF_3{\cdot}Et_2O$ (56 µl, 0.442 mmol) followed by work-up furnished **7** (4.5 mg, 45%) and **8** (1.8 mg, 18%).

N^a-(3,3-Dimethylallyl)-N^b-phthaloyl-L-tryptophan methyl ester (12)

Method A. N^a-(3,3-Dimethylallyl)-N^b-phthaloyl-L-tryptophan[11] (**14**) (50 mg, 0.12 mmol) in MeOH (10 ml) at 0 °C was treated with an excess of CH_2N_2 in ether. On completion of the reaction (0.5 h), the solvents were removed under reduced pressure and the residue obtained purified by PTLC (Et_2O–n-hexane) to yield the methyl ester **12**: yellow solid (39.3 mg, 79%) on crystallisation (Et_2O); $[a]_D^{25}$ −173.1 (c 0.34, CH_2Cl_2); IR: ν_{max}/cm^{-1} 2964, 2927, 2858, 1745 (s), 1726 (s), 1612; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.75–7.77 (2H, m), 7.66–7.68 (2H, m), 7.60 (1H, d, J = 7.8 Hz), 7.20 (1H, d, J = 8.1 Hz), 7.13 (1H, t, J = 7.4 Hz), 7.04 (1H, t, J = 7.8 Hz), 6.87 (1H, s), 5.25 (1H, t, J = 7.9 Hz), 5.13 (1H, bs), 4.51 (2H, d, J = 6.7 Hz), 3.79 (3H, s), 3.72 (2H, d, J = 7.8 Hz), 1.68 (3H, s), 1.65 (3H, s). The OMe group (δ_H 3.79) remained as a singlet on addition of $Eu(tfc)_3$ (0.5 to 1.0 eq.) to the above solution. ^{13}C-NMR: δ_C 169.9, 167.7, 136.3, 134.1, 132.0, 128.0, 126.0, 123.5, 121.6, 119.9, 119.1, 118.8, 109.6, 109.5, 52.7, 43.8, 25.4, 24.7, 17.7; HRMS (EI): m/z $C_{25}H_{24}N_2O_4$ requires 416.17359, found 416.17448.

Method B. N^a-(3,3-Dimethylallyl)-L-tryptophan[11] (**13**) (130 mg, 0.48 mmol) in MeOH (30 ml) at 0 °C was treated with CH_2N_2 in ether. On completion of the reaction (TLC control) the solvents were removed by a current of N_2. The residue obtained was dissolved in THF (15 ml), and to the resulting solution were added phthalic anhydride (115 mg, 0.78 mmol) and Et_3N (110 ml, 0.79 mmol). The crude phthalamic acid **15** obtained on removal of solvent was dissolved in dry CH_2Cl_2 (15 ml), and the resulting solution treated with DMAP (40 mg, 0.32 mmol) and DCC (200 mg, 0.96 mmol). When the reaction was judged to be complete (TLC control), the solid formed was filtered off. The solvent from the filtrate was evaporated and the resulting residue purified (PTLC; Et_2O–n-hexane, 20%) to give **12**: $[a]_D^{25}$ −168.1 (c 0.11, CH_2Cl_2).

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References

1 H. Lodish, D. Baltimore, A. Berk, S. L. Zipursky, P. Matsudaira and J. Darnell, *Molecular Cell Biology*, Scientific American Books, New York, 1995, p. 1066.
2 (*a*) P. M. Nurse, *Nature*, 1990, **344**, 503–508; (*b*) C. Norbury and P. Nurse, *Annu. Rev. Biochem.*, 1992, **61**, 441–470; (*c*) H. Osada, *J. Antibiot.*, 1998, **51**, 973–982.
3 (*a*) C.-B. Cui, H. Kakeya, G. Okada, R. Onose, M. Ubukata, I. Takahashi, K. Isono and H. Osada, *J. Antibiot.*, 1995, **48**, 1382–1384; (*b*) C.-B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, 1996, **49**, 534–540; (*c*) C.-B. Cui, H. Kakeya, G. Okada, R. Onose and H. Osada, *J. Antibiot.*, 1996, **49**, 527–533; (*d*) T. Usui, M. Kondoh, C.-B. Cui, T. Mayumi and H. Osada, *Biochem. J.*, 1998, **333**, 543–548.
4 C.-B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1997, **53**, 59–72.
5 A. M. Lobo and S. Prabhakar, *Pure Appl. Chem.*, 1997, **69**, 547–552.
6 For other syntheses of tryprostatin B, see: (*a*) K. M. Depew, S. J. Danishefsky, N. Rosen and L. Sepp-Lorenzino, *J. Am. Chem. Soc.*, 1996, **118**, 12463–12464; (*b*) J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11964–11975; (*c*) B. Wang, L. Chen and K. Kim, *Tetrahedron Lett.*, 2001, **42**, 1463–1466; (*d*) S. Zhao, T. Gan, P. Yu and J. M. Cook, *Tetrahedron Lett.*, 1998, **39**, 7009–7012; (*e*) E. Caballero, C. Avendaño and J. C. Menéndez, *J. Org. Chem.*, 2003, **68**, 6944–6951. For tryprostatin A, see:; (*f*) T. Gan and J. M. Cook, *Tetrahedron Lett.*, 1997, **38**, 1301–1304; (*g*) T. Gan, R. Liu, P. Yu, S. Zhao and J. M. Cook, *J. Org. Chem.*, 1997, **62**, 9298–9304; (*h*) C. Ma, X. Liu, X. Li, J. F. Anderson, S. Yu and J. M. Cook, *J. Org. Chem.*, 2001, **66**, 4525–4542.
7 For a preliminary account of the work, see: A. S. Cardoso, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, 2000, **41**, 3611–3613.
8 J. M. Patterson, A. Wu, C. S. Kook and W. T. Smith, *J. Org. Chem.*, 1974, **39**, 486–488.
9 (*a*) G. Casnati and A. Pochini, *J. Chem. Soc., Chem. Commun.*, 1970, 1328–1329; (*b*) G. Casnati, R. Marchelli and A. Pochini, *J. Chem. Soc., Perkin Trans. 1*, 1974, 754–757; (*c*) P. G. Sammes and A. C. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3053–3060.
10 Prepared by the method described for N^a-prenyl-N^b-methoxycarbonyltryptamine: T. Hino, K. Hasumi, H. Yamaguchi, M. Taniguchi and M. Nakagawa, *Chem. Pharm. Bull.*, 1985, **33**, 5202–5206.
11 M. F. Grundon, M. R. Hamblin, D. M. Harrison, J. N. D. Logue, M. Maguire and J. A. McGrath, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1294–1298.
12 For a rare example of such a reaction, see: (*a*) P. J. Battye and D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1986, 1807–1808. Examples of 3,5-shifts (pseudo-pericyclic reactions) involving dienyl esters are

known. The presence of a lone pair of the oxygen atom orthogonal to the p-system is a prerequisite for these rearrangements to occur: (*b*) D. M. Birney, X. Xu and S. Ham, *Angew. Chem., Int. Ed.*, 1999, **38**, 189–193; (*c*) S. Quideau, M. A. Looney, L. Pouysegu, S. Ham and D. M. Birney, *Tetrahedron Lett.*, 1999, **40**, 615–618.
13 (*a*) J. F. Quin, M. E. Bos and W. D. Wulff, *Org. Lett.*, 1999, **1**, 161–164; (*b*) B. Miller, *J. Am. Chem. Soc.*, 1970, **92**, 6252–6259; (*c*) B. Miller, *J. Am. Chem. Soc.*, 1970, **92**, 6246–6252.
14 Avoidance of steric congestion could well be the reason, despite the attendant loss of aromaticity for a reported [3,3]-sigmatropic reaction: A. Bosum and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 558–589.
15 P. Wulff, J. S. Carlé and C. Christophersen, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2895–2898.
16 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, 2nd edn, Pergamon, Oxford, 1980.

