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Studies in the aza-Cope reaction: a formal highly enantioselective synthesis of tryprostatin B

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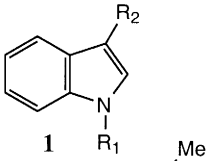
Abstract

The BF_3–Et_2O induced rearrangement of *N*-phthaloyl-1-(3,3-dimethylallyl)-L-tryptophane methyl ester proceeds without significant loss of its optical integrity to provide its 2-(3,3-dimethylallyl) isomer, a key intermediate in the synthesis of tryprostatin B.

Keywords: indoles; sigmatropic rearrangements; enantioselection; natural product.

The protic and Lewis acid catalysed rearrangement of 1-allyl indoles to 2-allyl indole derivatives has been extensively examined as a part of wider studies[1–4] aimed at defining the biosynthetic pathway of echinulin-type mould metabolites. For example, whilst *N*-crotylindole **1a** and $AlCl_3$, in benzene under reflux, gave **2a** (43%),[2] the skatole **1b**[1] in CF_3COOH furnished a mixture (1:1) of **2b** and **3** in a reaction shown to be intramolecular in nature.[2]

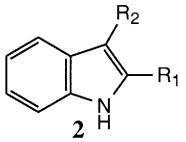


1

a $R_1 = CH_2-CH=C(Me)H$; $R_2 = H$

b $R_1 = CH_2-CH=CMe_2$; $R_2 = Me$

c $R_1 = CH_2-CH=CMe_2$; $R_2 = CH_2-CH_2-NHAc$

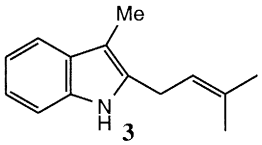


2

a $R_1 = H$; $R_2 = CH(Me)-CH=CH_2$

b $R_1 = CMe_2-CH=CH_2$; $R_2 = Me$

c $R_1 = CH_2-CH=CMe_2$; $R_2 = CH_2-CH_2-NHAc$



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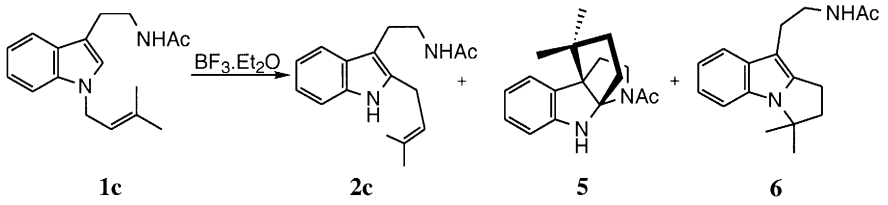
Our interest in the application of pericyclic reactions[5] to the synthesis of biologically active molecules in general, and tryprostatin B[6] (**4a**) in particular, prompted us to undertake a preliminary study† of BF_3–Et_2O induced aza-Cope reaction[7] of 1-(3,3-dimethylallyl)-*N*-acetyltryptamine (**1c**).

From the mixture of products formed in this reaction,‡ three isomeric compounds were isolated and the structures **2c**, **5** and **6** provisionally assigned to them on spectroscopic basis. Exposure of pure **2c** to the Lewis acid converted it into a mixture of **5** and **6** (Scheme 1).



1c **2c** **5** **6**

Scheme 1.

Therefore, the phthaloyl derivative **7a** of 1-(3,3-dimethylallyl)-L-tryptophane methyl ester, wherein the side chain nitrogen is rendered non-nucleophilic, thereby avoiding at least the formation of the compound analogous to **5**, was selected as a potential candidate for the synthesis of **4a**. It was obtained (40%; $[\alpha]_D$ −168) from the known 1-(3,3-dimethylallyl)-L-tryptophane[4] (**8a**) by methylation (CH_2N_2) followed by phthalimidation (phthalic anhydride, Et_3N, DCC, DMAP; 4 days) of the resulting ester. Alternatively[4] it could be obtained (38%; $[\alpha]_D$ −173) from the reaction of **8b** with *N*-carbethoxyphthalimide, neutralisation and methylation (CH_2N_2) of the resultant acid **7b**. Exposure of **7a** in dry CH_2Cl_2 to BF_3–Et_2O,§ free of acid, under carefully defined conditions,¶ afforded **9a** (61%; $[\alpha]_D$ −241), via a process formally involving consecutive [3,3]- and [3,5]-sigmatropic shifts from the presumed cationic species‖ **10**. Since **9a** had been previously converted into tryprostatin B (**4a**) in four steps by Danishefsky et al.,[9] the work described above constitutes, in a formal sense, a highly enantioselective[9] (~95% ee) synthesis of the natural product.

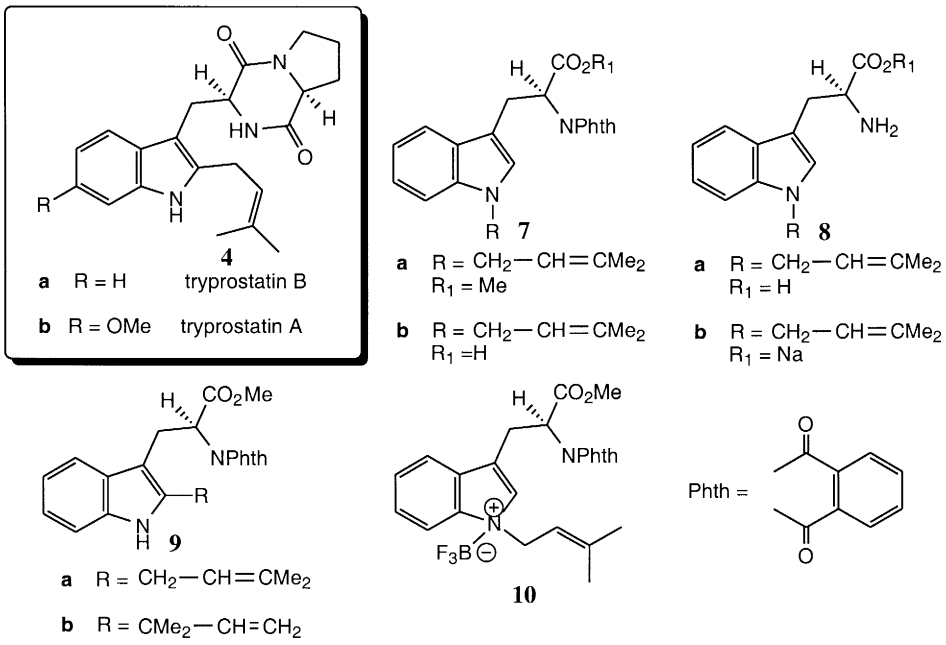
† This work was presented in the 17th International Congress of Heterocyclic Chemistry held in Vienna (Austria) during August 1–6, 1999.

‡ All new compounds gave satisfactory microanalyses or high resolution mass spectra and spectral data. Selected data: **2c**: oil; IR (CH_2Cl_2) 3046, 1671 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.86 (3H, s), 1.76 (3H, s), 1.75 (3H, s). HRMS, M^+ found: 270.17310 $C_{17}H_{22}N_2O$ requires: 270.17320. **5**: oil; IR (CH_2Cl_2) 3411, 3058, 1639 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.99 (3H, s), 1.16 (3H, s), 0.73 (3H, s). HRMS, M^+ found: 270.17284. $C_{17}H_{22}N_2O$ requires: 270.17320. **6**: oil; IR (CH_2Cl_2) 3445, 1671 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.91 (3H, s), 1.62 (6H, s). HRMS, M^+ found: 270.17310. $C_{17}H_{22}N_2O$ requires: 270.17320.

§ Amongst a variety of acid catalysts (CF_3COOH, $ZnCl_2$, $AlCl_3$) examined BF_3–Et_2O was found to be by far the best reagent both in terms of yield obtained and the optical purity of product formed. It is interesting to note that CF_3CO_2H induced greater racemisation of **9a** than $BF_3 \cdot Et_2O$, under similar conditions.

¶ *N*-Phthaloyl-1-(3,3-dimethylallyl)-L-tryptophane methylester [**7a**; 30 mg (0.072 mmol), $[\alpha]_D$ −173, m.p. 93–94°C (Et_2O)] in dry CH_2Cl_2 (3 ml) was treated with $BF_3 \cdot Et_2O$ [215 μl (1.70 mmol)] distilled from CaH_2 at −4°C. The mixture after remaining at the same temperature (18 h) was neutralised with Et_3N, mixed water and extracted with ether. Evaporation of dried (Na_2SO_4) ether solution, under reduced pressure, followed by purification of the residue (ptlc; Et_2O:*n*-hexane 1:1) furnished a yellow oil. Crystallisation (ether-pet. ether) gave **9a** [yellow solid; m.p. 49–50°C, $[\alpha]_D$ −241 (c=0.59, $CHCl_3$); lit.[8] amorphous solid, $[\alpha]_D$ −253 (c=4.0, $CHCl_3$); IR (CH_2Cl_2) 3445, 1747, 1721 cm^{-1}]. The ^1H and ^{13}C NMR spectra were identical with those reported by Danishefsky et al.[8] for the same compound. There was no evidence for the presence of **9b** under these conditions. Prolonged reaction time (40 h) gave a sample of **9a** with diminished $[\alpha]_D$ (−225) and also caused the formation of the compound akin to **6** to occur.

‖ Although it is widely known that simple indoles are protonated largely on C(3), an *N*-protonated species had been proposed as the reactive intermediate in a related rearrangement.[3]



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References

1. Casnati, G.; Marchelli, R.; Pochini, A. *J. Chem. Soc. Perkin Trans. 1* **1974**, 754–757.
2. Inada, S.; Nagai, K.; Takayanagi, Y.; Okazaki, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 833–834.
3. Sammes, P. G.; Weedon, A. C. *J. Chem. Soc. Perkin Trans. 1* **1979**, 3053–3059.
4. Grundon, M. F.; Hamblin, M. R.; Harrison, D. M.; Logue, J. N. D.; Maguire, M.; McGrath, J. A. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1294–1298.
5. Lobo, A. M.; Prabhakar, S. *Pure Appl. Chem.* **1997**, *69*, 547–552.
6. Tryprostatins A (**4b**) and B (**4a**), isolated from *Aspergillus fumigatus* are reported to be cell-cycle progression inhibitors of tsFT210 at the G2/M phase barrier: Cui, C.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382–1384; Cui, C.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534–540; Cui, C.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527–533; Usui, T.; Kondoh, M.; Cui, C.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543–548.
7. For a review on catalysis of Cope rearrangements, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247.
8. Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463–12464.
9. For a recent enantiospecific synthesis of **4a** from a 2-lithioindole and Schöllkopf's chiral auxiliary, see: Zhao, S.; Gan, T.; Yu, P.; Cook, J. M. *Tetrahedron Lett.* **1998**, *39*, 7009–7012.