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Exploration of the biomimetic synthesis of indole-diterpene mycotoxins: an unexpected cascade reaction during the attempted synthesis of emindole SB

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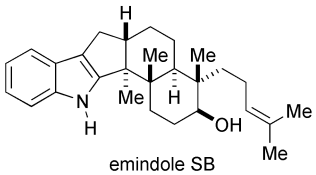
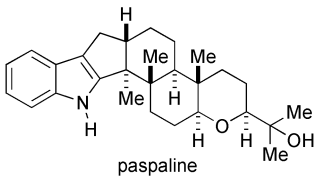
The key step in an attempted biomimetic synthesis of the indole-diterpene mycotoxin emindole SB delivers the pentacyclic compound resulting from 6-*endo* cyclisation instead of the product arising by the 5-*exo* reaction required in the putative biosynthetic pathway.

In recent years, a variety of tremorgenic indole-diterpene alkaloids have been isolated from fungi.[1,2] In many cases, these alkaloids possess significant bioactivity, and some have been implicated as the causative agents for neurological disorders in farm animals. Some of the compounds have been shown to have potent insecticidal activity.[2c,3]

Alkaloids of the family generally possess an indole nucleus connected to a partially or fully cyclised diterpene unit. For example, emindole SB, isolated from the fungus *Emericilla striata*, possesses an indole nucleus fused to a tricyclic diterpene system.[1i] The related compound paspaline contains an additional ring formed by ring closure of the hydroxyl group onto the side-chain alkene.[1a,c] In addition to these simple indole diterpenes,[1] several more complex alkaloids, in which the indole system is adorned with further rings, have been isolated.[2]



emindole SB



paspaline

The fascinating structures of the indole-diterpene mycotoxins combined with the synthetic challenges these compounds present make them very attractive targets for total synthesis. Several members of this family of alkaloids have been synthesised and Smith and co-workers have made several important contributions in this regard.[4]

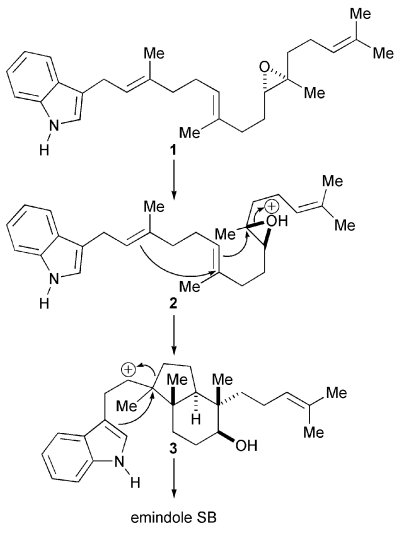
As a prelude to the synthesis of complex indole-diterpene natural products, we embarked on a biomimetic synthesis of emindole SB.[1i] We hoped to synthesise the core structure using a cascade reaction inspired by the putative biosynthetic pathway to this compound (Scheme 1).[1i] A plausible biosynthetic pathway to emindole SB was proposed by Kawai and co-workers and was based on an earlier hypothesis[5] involving an acid-catalysed reaction of the epoxide **1**.[1i] In this pathway, the protonated epoxide **2** undergoes a polyene cyclisation reaction to give the carbocation **3** as a transient intermediate. Subsequent Wagner–Meerwein rearrangement occurs with one-carbon ring-expansion to give a tertiary carbocation which then suffers nucleophilic attack by the indole to give emindole SB.[1i]

To establish the feasibility of the biomimetic cascade reaction, we selected the epoxide **9** as our cyclisation precursor (Scheme 2). The epoxide **9** was designed so that the adjacent vinyl group would facilitate either protic or Lewis acid mediated opening of the epoxide by stabilisation of the incipient positive charge. In addition, the indole nitrogen was protected with a *t*-butyldimethylsilyl group rather than an electron-withdrawing group, in order to retain its nucleophilic character during the cyclisation event.

The synthesis of the epoxide **9** commenced with the protection of farnesol (**4**) as its acetate and subsequent selenium dioxide mediated oxidation, to give the allylic alcohol **5** (Scheme 2).[6] The alcohol **5** was then protected as the tetrahydropyranyl ether and the acetate group was removed to give the alcohol **6** in high yield. The alcohol **6** was converted into the corresponding allylic bromide using standard conditions and the bromide was treated with a *t*-butyldimethylsilyl-protected 3-lithioindole, to deliver the alkylated indole **7** in excellent yield.[7] Removal of the tetrahydropyranyl protecting group and epoxidation of the resulting allylic alcohol using Sharpless asymmetric epoxidation conditions, afforded the epoxide **8**.[8] Oxidation of the alcohol was then performed using Dess–Martin reagent, and the resulting aldehyde was converted into the precursor **9** by standard Wittig methylenation.

Prior to completion of the synthesis, Rainier and Smith reported the synthesis and Lewis acid mediated cyclisation of the epoxide **10** (Scheme 3).[9] Treatment of this epoxide with a stoichiometric amount of boron trifluoride etherate at −40 °C afforded an inseparable mixture of bicyclic products (20% yield), arising from participation of both alkenes in the cyclisation event. Removal of the phenylsulfonyl protecting group provided emindole SA in 8% yield over two steps. Significantly, capture of the final carbocationic intermediate by the indole to form a pentacyclic system was not observed.[9]

The result above suggested that it might not be possible to accomplish the complete cyclisation of our substrate (**9**). However, our precursor differed significantly from that used by Rainier and Smith,[9] and had been designed so that the epoxide



Scheme 1

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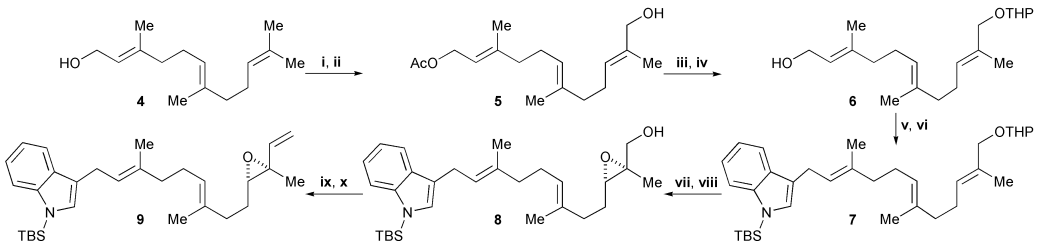
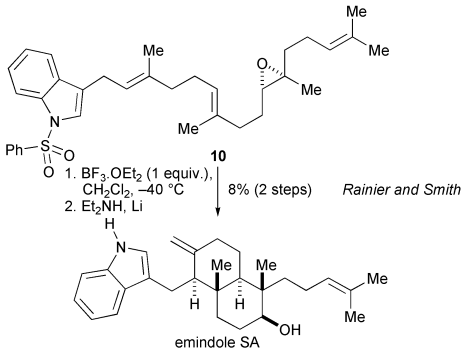


Scheme 2 *Reagents and conditions*: i, Ac_2O, Et_3N, DMAP (5 mol%), CH_2Cl_2, rt (96%); ii, SeO_2 (5 mol%), salicylic acid (10 mol%), *t*-BuOOH (3 equiv.), CH_2Cl_2, rt (46%); iii, dihydropyran (1.5 equiv.), PTSA (5 mol%), CH_2Cl_2, 0 °C; iv, K_2CO_3, MeOH, rt (94% over 2 steps); v, PPh_3, Br_2, Et_3N, CH_2Cl_2, –20 °C; vi, 1-*t*-butyldimethylsilyl-3-bromoindole, *t*-BuLi, THF, −78 °C (83% over 2 steps); vii, PPTS (5 mol%), PTSA (5 mol%), EtOH, rt (80%); viii, Ti(*i*-PrO)$_4$ (5 mol%), diethyl L-(+)-tartrate (7.5 mol%), *t*-BuOOH (2 equiv.), CH_2Cl_2, –20 °C (88%); ix, Dess–Martin reagent, CH_2Cl_2, rt; x, $MePPh_3^+$ Br^- (5 equiv.), NaHMDS (4 equiv.), THF, 0 °C (50% over 2 steps).

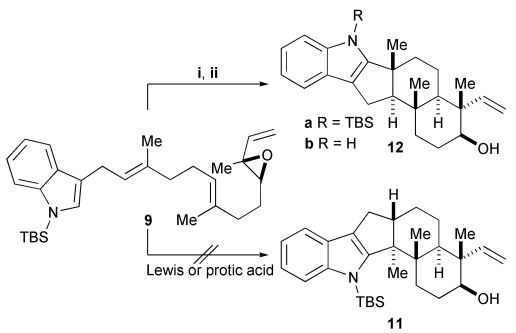


Scheme 3

was activated to ring opening and the indole system was inherently nucleophilic.

It transpired that our substrate does undergo complete cyclisation when exposed to either methylaluminium dichloride or boron trifluoride etherate at –78 °C (Scheme 4). However, neither reaction delivered the compound **11** corresponding to the core of emindole SB. Instead, treatment of the epoxide **9** with methylaluminium dichloride afforded the pentacyclic compound **12a** as a single isomer in 30% yield, whereas the boron trifluoride etherate mediated reaction afforded the desilylated pentacyclic compound **12b** in 33% yield. The cyclisation product **12a** was a crystalline compound and so X-ray crystallography was used to establish the relative configuration of the six stereogenic centres (Fig. 1).†

The successful construction of the pentacyclic compounds **12a** and **12b** by Lewis acid mediated cyclisation of the substrate **9** contrasts with the results obtained by Rainier and Smith upon cyclisation of the related epoxide **10**.[9] In our reaction, three rings, three carbon–carbon bonds and four stereogenic centres were constructed in a highly regioselective and stereoselective manner in a single operation. In addition, the products obtained from our reactions indicate that the second ring is formed by a 6-*endo* cyclisation reaction rather than the 5-*exo* reaction required to mimic the key reaction (**2** → **3**) in the proposed biosynthetic pathway (Scheme 1).[1i] This suggests that the biosynthetic pathway is incorrect or that the 5-*exo* ring-closure event is controlled by a fungal enzyme *in vivo*.



Scheme 4 *Reagents and conditions*: i, $MeAlCl_2$ (1.1 equiv.), CH_2Cl_2, −78 °C (30% **12a**); ii, $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2, −78 °C (33% **12b**).

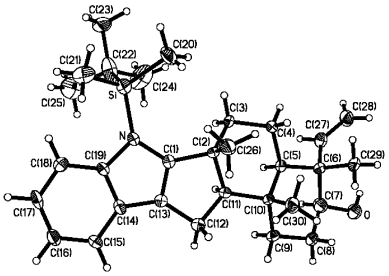


Fig. 1 The X-ray crystal structure of the product **12a** (ellipsoid plot at 30% probability level).

Notes and references

† *Crystallographic data* for **12a**: $C_{30}H_{45}NOSi$, M = 463.76, hexagonal, a = 14.1741(4), c = 75.735(4) Å, U = 8189.4(6) Å^3, T = 150 K, space group P 6_522 (no. 179), Z = 12, μ(Mo-Kα) = 0.11 mm^{-1}, 33782 reflections measured, 6322 unique (R_{int} = 0.10), 4803 were used in all calculations. The final $wR(F^2)$ was 0.26 for all data, $R_1(F)$ was 0.091 for 3301 observed data where $I > 2\sigma(I)$. CCDC 205222. See http://www.rsc.org/suppdata/cc/b3/b302105j/ for crystallographic data in .cif or other electronic format.

1 (*a*) T. Fehr and W. Acklin, *Helv. Chim. Acta*, 1966, **49**, 1907; (*b*) J. P. Springer, J. Clardy, J. M. Wells, R. J. Cole and J. W. Kirksey, *Tetrahedron Lett.*, 1975, 2531; (*c*) J. P. Springer and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 231; (*d*) R. T. Gallagher, J. Finer, J. Clardy, A. Leutwiler, F. Weibel, W. Acklin and D. Arigoni, *Tetrahedron Lett.*, 1980, **21**, 235; (*e*) R. T. Gallagher, J. Clardy and B. J. Wilson, *Tetrahedron Lett.*, 1980, **21**, 239; (*f*) R. J. Cole, J. W. Dorner, J. P. Springer and R. H. Cox, *J. Agric. Food Chem.*, 1981, **29**, 293; (*g*) J. W. Dorner, R. J. Cole, R. H. Cox and B. M. Cunfer, *J. Agric. Food Chem.*, 1984, **32**, 1069; (*h*) K. Nozawa, S. Udagawa, S. Nakajima and K. Kawai, *J. Chem. Soc., Chem. Commun.*, 1987, 1157; (*i*) K. Nozawa, M. Yuyama, S. Nakajima and K. Kawai, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2155.

2 (*a*) A. E. de Jesus, P. S. Steyn, F. R. van Heerden, R. Vleggaar, P. L. Wessels and W. E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1847; (*b*) A. E. de Jesus, P. S. Steyn, F. R. van Heerden, R. Vleggaar, P. L. Wessels and W. E. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1857; (*c*) O. D. Hensens, J. G. Ondeyka, A. W. Dombrowski, D. A. Ostlind and D. L. Zink, *Tetrahedron Lett.*, 1999, **40**, 5455; (*d*) J. G. Ondeyka, K. Byrne, D. Vesey, D. L. Zink, W. L. Shoop, M. A. Goetz and S. B. Singh, *J. Nat. Prod.*, 2003, **66**, 121.

3 P. F. Dowd, R. J. Cole and R. F. Vesonder, *J. Antibiot.*, 1988, **41**, 1868.

4 (*a*) A. B. Smith III and R. Mewshaw, *J. Am. Chem. Soc.*, 1985, **107**, 1769; (*b*) A. B. Smith III and T. L. Leenay, *Tetrahedron Lett.*, 1988, **29**, 2791; (*c*) A. B. Smith III, T. Sunazuka, T. L. Leenay and J. Kingery-Wood, *J. Am. Chem. Soc.*, 1990, **112**, 8197; (*d*) A. B. Smith III, N. Kanoh, H. Ishiyama and R. A. Hartz, *J. Am. Chem. Soc.*, 2000, **122**, 11254.

5 W. Acklin, F. Weibel and D. Arigoni, *Chimica*, 1977, **31**, 63.

6 M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.

7 M. Amat, S. Hadida, S. Sathyanarayana and J. Bosch, *J. Org. Chem.*, 1994, **59**, 10.

8 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.

9 J. D. Rainier and A. B. Smith III, *Tetrahedron Lett.*, 2000, **41**, 9419.