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Stereoselective synthesis of basiliskamides A and B via Prins cyclisation

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ABSTRACT

A stereoselective and convergent approach to basiliskamides A and B is achieved through our recently developed strategy for the construction of polyketide precursors via Prins cyclisation. The approach mainly relies upon reductive opening of 1-iodomethyl cyclic ethers, Mitsunobu inversion, Takai olefination and Stille coupling along with Prins cyclisation.

Basiliskamides A (**6**) and B (**7**) were co-isolated by Andersen and co-workers in 2002 from the marine bacterium PNG-276 found off the coast of Papua New Guinea.[1] Initial biological studies showed that both basiliskamides A and B showed antifungal activity against *Candida albicans* and *Aspergillus fumigatus*. Basiliskamides A and B are structurally identical in every respect except for the position of the cinnamate ester: C9 in basiliskamide A and C7 in basiliskamide B. The same authors elucidated the structures after rigorous analysis of spectral and comparative data. Recently, Panek and co-workers realised a synthesis via asymmetric crotyl borations thereby providing an absolute proof for the stereostructures of the natural products.[2a] Very recently, during the completion of our synthesis, another synthesis of basiliskamide B was reported by Dias et al.[2b] Inspired by the biological properties and structural similarity to other biologically active natural products, such as crocacins (**1**, **2** and **3**), pironetin (**4**) and YM-47522 (**5**), we investigated the synthesis of basiliskamides A and B via Prins cyclisation.[3] As part of our successful efforts towards the total synthesis of such natural products via Prins cyclisation,[4] we have accomplished a stereoselective total synthesis of the basiliskamides via Prins cyclisation and reductive ring-opening sequence.

In our retrosynthetic analysis (Fig. 1), we envisaged that the core part of the basiliskamides could be easily derived from pyranyl methanol **8** via a Mitsunobu inversion. Pyranyl methanol **8** could be easily constructed via Prins cyclisation, in analogy to our previous approach, from known reagents **9** and **10**.[4]

Our synthesis of basiliskamide A is outlined in Scheme 1. Prins cyclisation between known homoallylic alcohol **9**[4c] and aldehyde **10**[5] in the presence of TFA[4] resulted in the trifluoroacetate salt of **8**, which on treatment with K_2CO_3 in MeOH gave tetrahydropyran diol **8** as the only isolable diastereomer in 50% yield. Though the stereochemical aspects of such Prins cyclisations and structurally similar compounds of **8** have been discussed in detail previously,[3,4] we sought to analyse the products (see later) in this case. Protection of **8** gave TBS ether **11**, and inversion of the secondary hydroxyl group using Mitsunobu's protocol[6] produced pyranol **12** in 68% overall yield. Protection of the inverted alcohol as its TIPS ether and deprotection of the TBS group resulted in pyranyl methanol **13** in 87% yield over two steps. The hydroxyl group in **13** was iodinated using Ph_3P, imidazole and iodine to give **14**, which on reductive ring-opening using Zn in EtOH furnished homoallylic alcohol **15** in 87% yield (2 steps).[4b,h] Esterification of the resulting alcohol with *trans*-cinnamic acid using DCC and DMAP afforded **16** in 90% yield. The terminal olefin group in **16** was selectively subjected to dihydroxylation[7] using AD-mix-α, followed by oxidative cleavage of the resulting diol to reveal the corresponding aldehyde, treatment of which with $CrCl_2$ and CHI_3 gave *trans*-vinyl iodide **17** in 60% yield over the three steps.[8] The remaining formal Stille coupling[2] of **17** with **18** using $PdCl_2(CH_3CN)_2$ produced **19**, which on cleavage of the TIPS ether with HF in pyridine furnished the natural product basiliskamide A **6** in 60% yield over the two steps. The synthetic compound showed spectral and analytical data (^{1}H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$) identical with that of the natural sample.[1,9]

The synthesis of the next target, basiliskamide B **7**, is described in Scheme 2. Although the structures of basiliskamides A and B are only differentiated by the position of the cinnamoyl moiety, it was necessary to start from intermediate **8** to effect an efficient synthesis of **7**. Thus, the 1° hydroxyl group in Prins cyclisation product **8** was protected as the corresponding tosylate using tosyl chloride in

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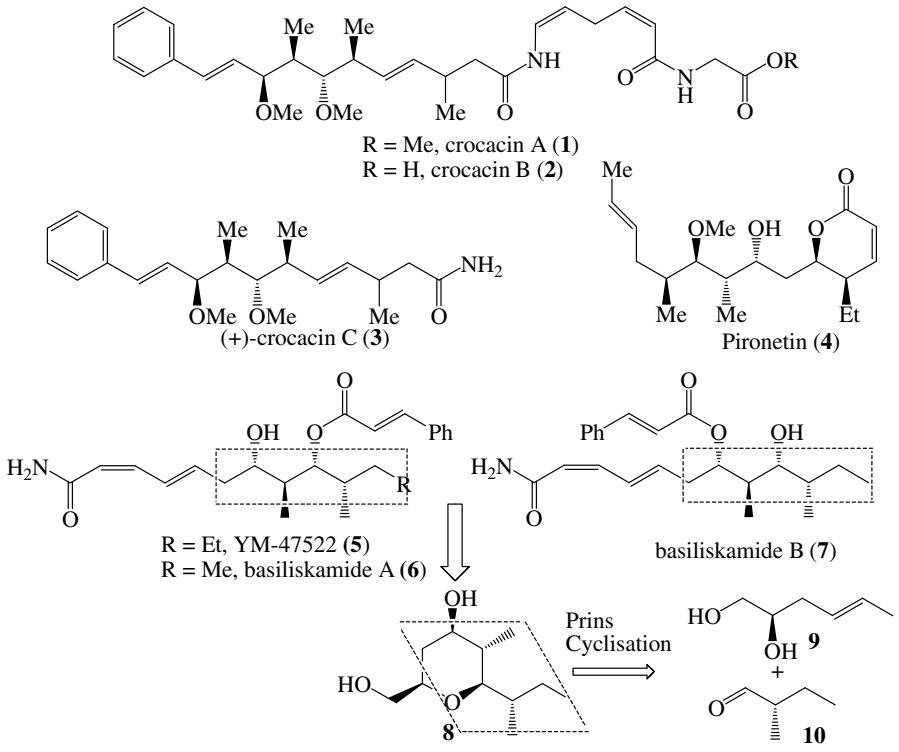
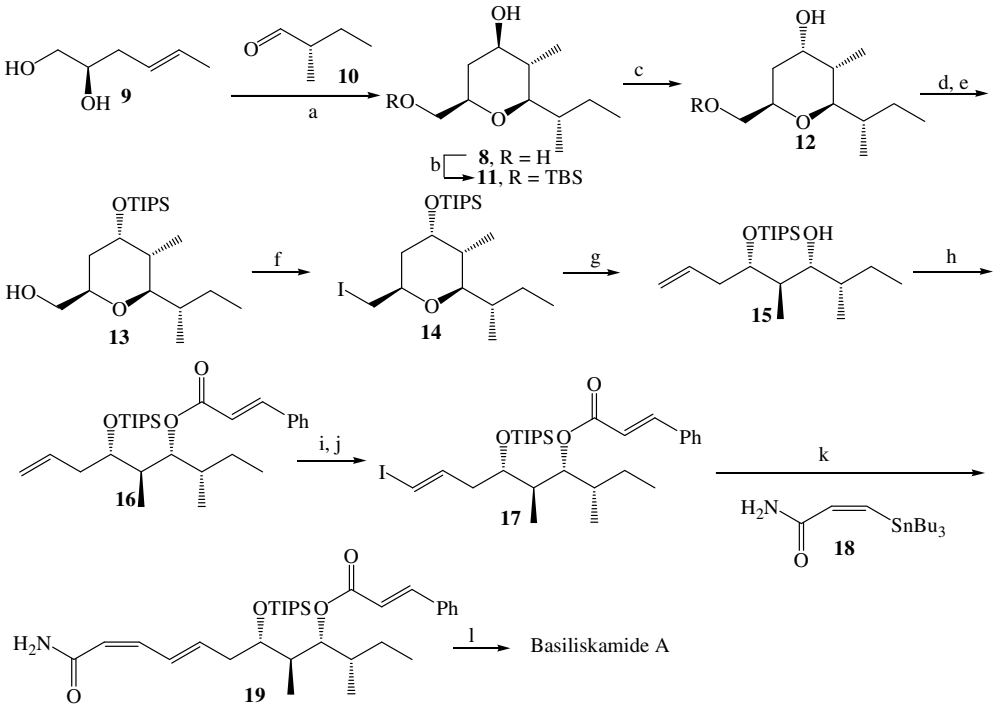
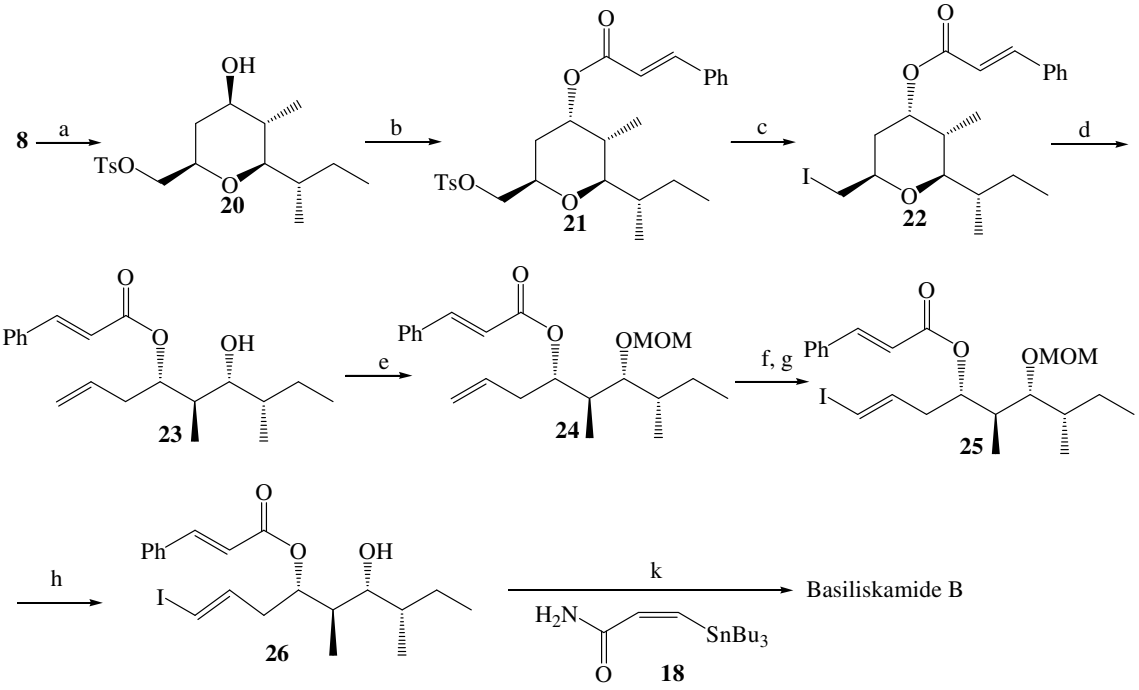


Figure 1.



Scheme 1. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C to rt, 3 h then K_2CO_3, MeOH, rt, 30 min, 50%; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 3 h, 85%; (c) DEAD, *p*-nitrobenzoic acid, Ph_3P, THF, 0 °C to rt, 30 min, then K_2CO_3, MeOH, rt, 30 min, 80%; (d) TIPS(OTf)$_2$, 2,6-lutidine, 0 °C to rt, 6 h, 95%; (e) CSA, MeOH, CH_2Cl_2 (7:1), 0 °C to rt, 10 min, 92%; (f) Ph_3P, imidazole, I_2, benzene, 0 °C to rt, 2 h, 95%; (g) Zn, EtOH, $NaHCO_3$, reflux, 2 h, 92%; (h) *trans*-cinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 90%; (i) (i) AD-mix-α, $CH_3SO_2NH_2$, ^{t}BuOH: H_2O (1:1), 24 h; (ii) $NaIO_4$, THF/H_2O (2:1), 2 h; (j) $CrCl_2$, CHI_3, dioxane/THF (6:1), 12 h, 60% (3 steps); (k) $PdCl_2(CH_3CN)_2$, DMF, rt, 36 h; (l) HF–Py, THF, rt, 12 h, 60% (2 steps).

triethylamine to give **20** in 90% yield. We observed that the ^{1}H NMR specturm of this compound showed clear signals due to H-2 (δ 2.90, dd, 1H, J = 9.8, 1.5 Hz), H-4 (δ 3.32, ddd, J = 12.0, 4.5, 2.2 Hz) and H-5 (δ 1.94, ddd, 1H, J = 13.5, 9.8, 4.5 Hz) with coupling constants consistent with the equatorial disposition of all the substituents on the ring. The 2° hydroxyl group in **20** was inverted



Scheme 2. Reagents and conditions: (a) TsCl, TEA, CH_2Cl_2, 0 °C to rt, 6 h, 90%; (b) DEAD, *trans*-cinnamic acid, Ph_3P, THF, 0 °C to rt, 2 h, 75%; (c) NaI, acetone, reflux, 24 h, 92%; (d) Zn, EtOH, $NaHCO_3$, reflux, 4 h, 85%; (e) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 95%; (f) (i) AD-mix-α, $CH_3SO_2NH_2$, $^tBuOH/H_2O$ (1:1), 24 h, 80%; (ii) $NaIO_4$, THF/H_2O (2:1), rt, 2 h, 95%; (g) $CrCl_2$, CHI_3, dioxane/THF (6:1), 12 h, 83%; (h) BCl_3, CH_2Cl_2, −78 °C, 4 h; (k) $PdCl_2(CH_3CN)_2$, DMF, rt, 24 h, 52% (2 steps).

with *trans*-cinnamic acid, DEAD and Ph_3P to give the cinnamic ester **21** with the required configuration. Next, the tosyl group in **21** was replaced by iodide in the presence of NaI in acetone to yield **22**, which on subsequent reductive elimination using Zn in EtOH gave homoallylic alcohol **23** in 58% yield over 3 steps.[4b,h] Protection of the resulting alcohol as its MOM ether using MOMCl, DIPEA and DMAP gave **24**. Selective hydrolysis of the terminal olefin bond followed by oxidative cleavage produced the corresponding aldehyde, which on iodo olefination gave *trans* olefin **25** in 72% overall yield. Cleavage of the MOM ether in **25** was achieved using BCl_3 in CH_2Cl_2 at −78 °C, and the resulting hydroxy iodo olefin **26** underwent Stille coupling with **18** smoothly to furnish basiliskamide B **7** in 52% yield over the two steps. The synthetic sample was identical in all respects (^1H NMR, ^{13}C NMR, IR, R_f and $[\alpha]_D$) to the naturally isolated compound.[1,9]

In summary, we have described a concise and convergent approach to basiliskamides A and B via a common intermediate using our recently developed synthetic sequence for polyketide precursors. This approach can provide a means for probing the structure–activity relationships of these and other related antifungal agents.

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9. Data for selected compounds. Compound **11**: Colourless liquid; $[\alpha]_D^{20}$ +2.7 (*c* 1.0, $CHCl_3$); R_f = 0.5 (EtOAc/hexane, 1:9); IR (KBr): ν_{max} 3373, 2961, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.61 (dd, 1H, *J* = 10.5, 5.2 Hz), 3.47 (dd, 1H, *J* = 10.5, 5.2 Hz), 3.37–3.24 (m, 2H), 2.91 (dd, 1H, *J* = 9.8, 1.5 Hz), 1.95 (ddd, 1H, *J* = 12.0, 6.0, 4.5 Hz), 1.56–1.12 (m, 5H), 0.92–0.85 (m, 15H), 0.84 (d, 3H, *J* = 6.7 Hz). 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 82.1, 76.1, 74.0, 66.4, 40.8, 37.8, 35.2, 27.1, 25.8, 18.3, 12.5, 12.2, 12.0, −5.3; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{36}O_3Na$ $[M+Na]^+$ 339.2331, found 339.2328. Compound **20**: Yellow oil; $[\alpha]_D^{20}$ +6.8 (*c* 1.05, $CHCl_3$); R_f = 0.5 (EtOAc/hexane, 3:7); IR (KBr): ν_{max} 3407, 2963, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 8.3 Hz), 4.00 (dd, 1H, *J* = 9.8, 6.0 Hz), 3.94 (dd, 1H, *J* = 9.8, 4.5 Hz), 3.62–3.52 (m, 1H), 3.32 (ddd, 1H, *J* = 12.0, 4.5, 2.2 Hz), 2.90 (dd, 1H, *J* = 9.8, 1.5 Hz), 2.49 (s, 3H), 1.94 (ddd, 1H, *J* = 13.5, 9.8, 4.5 Hz), 1.59–1.16 (m, 5H), 0.93 (d, 3H, *J* = 6.7 Hz), 0.87 (t, 3H, *J* = 7.5 Hz), 0.78 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 133.1, 129.8, 127.9, 82.6, 73.5, 72.7, 72.2, 40.6, 37.0, 35.2, 27.0, 21.6, 12.1, 12.0; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{28}O_5NaS$ $[M+Na]^+$ 379.1555, found 379.1548. Compound **6**: White solid; $[\alpha]_D^{20}$ −76 (*c* 0.4, MeOH), lit.[1] $[\alpha]_D^{23}$ −78 (MeOH); R_f = 0.4 (EtOAc/hexane, 9:1); IR (KBr): ν_{max} 3344, 2961, 1672 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.68–7.72 (m, 2H), 7.65 (d, 1H, *J* = 15.5 Hz), 7.38–7.41 (m, 4H), 7.31 (s, 1H),

6.80 (s, 1H), 6.60 (d, 1H, J = 15.5 Hz), 6.30 (t, 1H, J = 11.8 Hz), 5.91 (dt, 1H, J = 14.8, 6.6 Hz), 5.56 (d, 1H, J = 11.1 Hz), 4.92 (m, 1H), 4.57 (d, 1H, J = 5.1 Hz), 3.49 (m, 1H), 2.33–2.24 (m, 1H), 2.08–1.97 (m, 2H), 1.72–1.63 (m, 1H), 1.30–1.02 (m, 2H), 0.96–0.78 (m, 9H); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 167.6, 166.2, 144.7, 140.6, 134.0, 130.5, 129.0, 128.4, 128.2, 119.3, 118.0, 76.2, 69.6, 40.7, 35.6, 34.6, 26.4, 12.8, 11.6, 10.0; HRMS (ESI): m/z calcd for $C_{23}H_{31}NO_4Na$ $[M+Na]^+$ 408.2150, found 408.2170. Compound **7**: White solid; $[\alpha]_D^{20}$ −13 (c 0.8, MeOH), lit.[1] $[\alpha]_D^{23}$ −12 (MeOH); R_f = 0.4 (EtOAc/hexane, 9:1); IR (KBr): ν_{max} 3350, 2962, 1704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.60 (d, J = 15.8 Hz, 1H), 7.50 (dd, J = 15.1, 11.1 Hz, 1H), 7.41–7.38 (m, 3H), 7.34 (s, 1H), 6.85 (s, 1H), 6.58 (d, J = 15.8 Hz, 1H), 6.33 (t, J = 11.1 Hz, 1H), 5.87 (dt, J = 14.4, 7.2 Hz, 1H), 5.57 (d, J = 11.1 Hz, 1H), 5.40 (dt, J = 9.8, 3.2 Hz, 1H), 4.47 (d, 1H, J = 6.5 Hz), 3.26 (m, 1H), 2.64–2.48 (m, 1H), 2.40–2.32 (m, 1H), 1.96–1.88 (m, 1H), 1.42–1.35 (m, 2H), 1.25–1.09 (m, 1H), 0.91–0.80 (m, 6H), 0.75 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75.0 MHz, DMSO-d_6): δ 167.4, 165.4, 143.7, 140.0, 138.0, 134.0, 130.0, 128.8, 128.5, 128.0, 119.6, 118.3, 73.9, 73.0, 36.2, 31.6, 26.5, 11.8, 11.6, 10.3; HRMS (ESI): m/z calcd for $C_{23}H_{31}NO_4Na$ $[M+Na]^+$ 408.2150, found 408.2163.