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Studies towards the total synthesis of Sch 56036; isoquinolinone synthesis and the synthesis of phenanthrenes

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Abstract—The isoquinolinone hemisphere of Sch 56036 has been prepared using a modified Pomeranz–Fritsch reaction and the synthesis of the phenanthrene core has been modelled via a Suzuki coupling and subsequent ring closing metathesis.

There is continuing interest in the discovery of novel antifungal agents for the treatment of opportunistic fungal infections in patients, immuno-compromised either through AIDS infection or the use of immuno-suppressant drugs.[1] In the course of the work to discover novel antifungal agents, a polycyclic xanthone, Sch 56036 (**1**, Fig. 1),[2] was isolated from a culture of *Actinoplanes* sp. (SCC 2314) collected on Tarlac in the Philippines. Standard antifungal testing has shown this member of the albofungin family to exhibit high activity against a number of fungal pathogens.

Natural products belonging to the albofungin family have attracted considerable interest over the last 30 years and at least 28 variants on the common polycyclic xanthone core have been discovered, all exhibiting high antibacterial, antifungal or anticancer activity. Two members of the albofungin family have been subjected to total synthetic studies: cervinomycin A_1 (**2**)[3–5] and lysolipin I (**3**, Fig. 2).[6] However, no total syntheses of Sch 56036 have been reported. The common feature of the two most concise and successful cervinomycin A_1 syntheses was the strategy of retrosynthetically dissecting the molecule across the central phenanthrene (ring C, see **1**) system to provide two equivalent sized precursor fragments. The synthesis then either used a

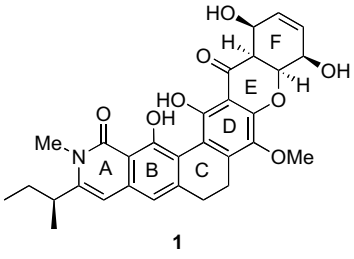

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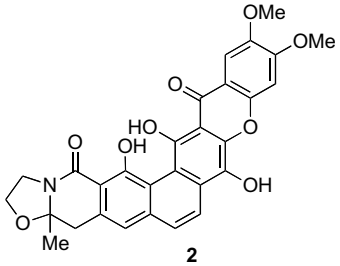
Figure 1.



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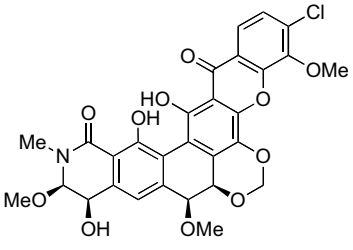

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Figure 2.

Keywords: Sch 56036; Albofungin; Antifungal natural product; Pomeranz–Fritsch reaction; Palladium(0) coupling; Ring closing metathesis; Phenanthrene.
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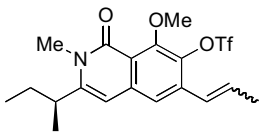

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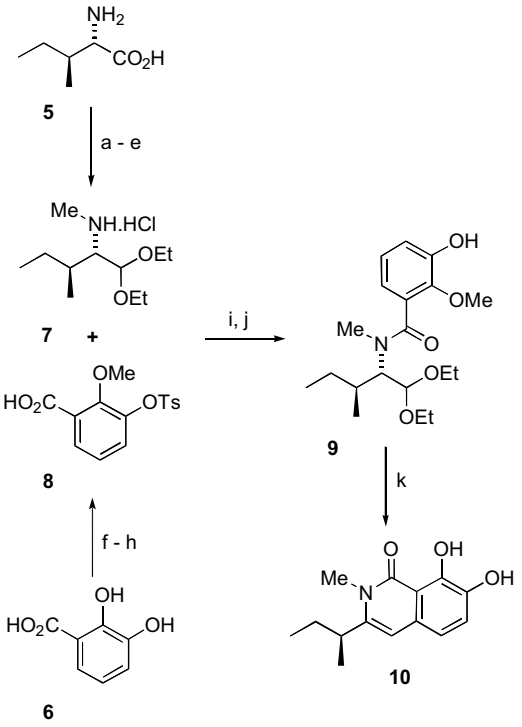
Figure 3.

Wittig reaction[4] or a Heck coupling[3] followed by a low yielding photocyclization reaction to form the central phenanthrene core. This strategy has the advantage of convergence but the low yielding photocyclization seriously constrains the approach. Recognizing the overall utility of these compounds and the underlying strength of late phenanthrene construction, we decided to apply more modern, catalytic methods to the synthesis, with the use of a Suzuki coupling reaction to form the aryl–aryl bond and subsequent ring closing metathesis (RCM) to close the phenanthrene ring.

Initial work was concentrated on the synthesis of the required isoquinoline **4** (Fig. 3) that forms the western hemisphere of Sch 56036. Retrosynthetic analysis of **4** leads, via a modified Pomeranz–Fritsch reaction and amide formation, to a derivative of L-isoleucine and the central aromatic ring. The required isoleucine acetal, **7** (Scheme 1), was synthesized in five steps from commercially available L-isoleucine (**5**)[7] via Boc protection, Weinreb amide formation, *N*-methylation, lithium aluminium hydride reduction of the Weinreb amide to the aldehyde and a one-pot deprotection and ethyl acetal formation to give **7** in an overall yield of 72%. The aromatic acid fragment, **8**, was synthesized over three steps[8] via mono-tosylation of **6**, double methylation and selective saponification to give carboxylic acid **8** in an overall yield of 78%. With the two fragments in hand the required amide was prepared using thionyl chloride and benzotriazole[9] to form the acid chloride from **8**, which was subsequently allowed to condense with amine hydrochloride **7**. Detosylation with potassium hydroxide in aqueous ethanol at reflux gave phenol **9** in a 67% yield from amine hydrochloride **7**.[10]



Scheme 1. Reagents and conditions: (a) Boc_2O, NaOH, dioxane, H_2O, 20 °C, 1 d (100%); (b) MeONHMe, EDCI, *N*-methylmorpholine, CH_2Cl_2, −15 °C, 1 h (100%); (c) MeI, NaH, DMF, 0–20 °C, 2 d (92%); (d) $LiAlH_4$, THF, 0 °C, 35 min (82%); (e) HCl, EtOH, 20 °C, 3.75 h (96%); (f) TsCl, NaOH, Me_2CO, H_2O, 40 °C (100%); (g) MeI, K_2CO_3, Me_2CO, Δ, 15 h (88%); (h) NaOH, Me_2CO, H_2O, Δ, 19.5 h (89%); (i) $SOCl_2$, benzotriazole, Et_3N, CH_2Cl_2, 2.5 h (68%); (j) KOH, EtOH, H_2O, Δ, 17 h (98%); (k) CSA, PhMe, Δ, 22 h (71%).

In parallel with the isoquinolinone **10** synthesis, model studies were carried out on the elaboration of phenanthrenes relevant to the construction of the central ring C. Recently, Iuliano et al. have reported[14] an equivalent process for the elaboration of phenanthrenes using tandem palladium(0) coupling and RCM. In our hands and prior to publication of the Iuliani paper, we examined the model coupling of 2-vinylphenylboronic acid (**12**) with 2-bromostyrene (**13**) under the Fu 'universal' Suzuki coupling conditions.[15] This gave biphenyl **14** in moderate yield (40%). Subsequent RCM using the second generation Grubbs catalyst **11** (Fig. 4) cleanly gave phenanthrene **15**, again in moderate yield (Scheme 2) (50%).[16]

In further studies, a series of *ortho*-substituted triflates **18**[17] were synthesized in reasonable yields (Scheme 3). Attempts at coupling these triflates[18] with boronic acid **12** using the Fu conditions ($Pd(OAc)_2$, PCy_3) were unsuccessful. In contrast, the use of $Pd(PPh_3)_4$ furnished the corresponding biphenyls in good yields.[19,20] Subsequent reaction with catalyst **11** at room temperature proceeded with poor conversion. However, RCM in dichloromethane at reflux gave the phenanthrenes **19** in excellent yields (⩾95%).[21]

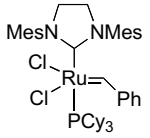


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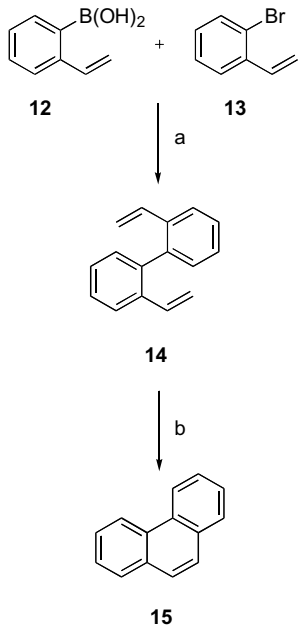
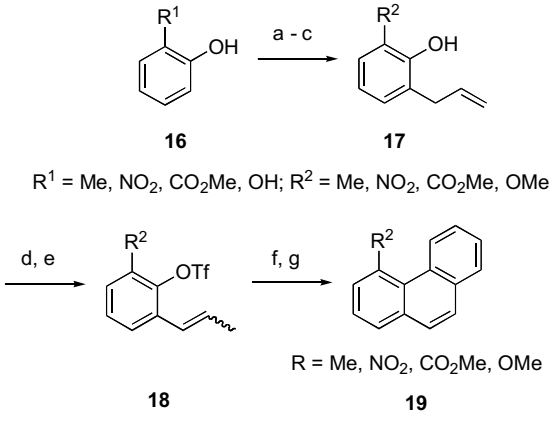
Figure 4.



Scheme 2. Reagents and conditions: (a) $Pd_2(dba)_3$, *t*-$Bu_3PH{\cdot}BF_4$, KF, THF, 20 °C, 18 h (40%); (b) **11** (10 mol %), CH_2Cl_2, 20 °C, 24 h (50%).



Scheme 3. Reagents and conditions: (a) allyl bromide, K_2CO_3, Me_2CO, Δ, 16 h [$R^1 = NO_2$ (85%), CO_2Me (78%), OH (60%)]; (b) ($R^1 = OH$ only) MeI, K_2CO_3, Me_2CO, Δ, 16 h (77%); (c) neat, 210 °C, 3 h, ($R^2 = NO_2$ 170 °C, 45 h) [$R^2 = NO_2$ (76%), CO_2Me (73%), OMe (73%)]; (d) Tf_2O, EtN-*i*-Pr_2, CH_2Cl_2, −78 to 20 °C, 16 h [$R^2 = Me$ (95%), NO_2 (75%), CO_2Me (91%), OMe (93%)]; (e) $RhCl_3$, EtOH, Δ, 3.5 h [$R^2 = Me$ (46%), NO_2 (45%), CO_2Me (52%), OMe (48%)]; (f) **12**, $Pd(PPh_3)_4$, *t*-BuOK, DME, H_2O, Δ, 17 h [$R^2 = Me$ (59%), NO_2 (20%), CO_2Me (54%), OMe (55%)]; (g) **11** (10 mol %), CH_2Cl_2, Δ, 18 h (≥95%).

In summary, we have developed methods for the synthesis of substituted isoquinolinones and *ortho*-substituted phenanthrenes in good yields. Further studies on the synthesis of Sch 56036 (**1**) will be reported in due course.

Acknowledgements

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References and notes

1. Greene, S. I. *Antifungal Drug Ther.* **1990**, *23*, 237.
2. Chu, M.; Truumees, I.; Mierzwa, R.; Terracciano, J.; Patel, M.; Das, P. R.; Puar, M. S.; Chan, T. M. *Tetrahedron Lett.* **1998**, *39*, 7649.
3. Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.
4. Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729.
5. Rao, A. V. R.; Yadav, J. S.; Reddy, K. K.; Upender, V. *Tetrahedron Lett.* **1991**, *32*, 5199.
6. Duthaler, R. O.; Heuberger, C.; Wegmann, U. H.; Scherrer, V. *Chimia* **1985**, *39*, 174.
7. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.
8. King, F. E.; Gilks, J. H.; Partridge, M. W. *J. Chem. Soc.* **1955**, 4206.
9. Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763.
10. Spectroscopic data: Compound **9**: $[\alpha]_D$ −3.09 (*c* 0.905, CH_3OH); IR ($CHCl_3$ film) 3285, 1613, 1469 cm^{-1}; ^1H NMR (d_8-toluene, 500 MHz, 80 °C): δ 0.88 (t, $J = 7.5$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H), 1.07 (t, $J = 7.0$ Hz, 3H), 1.19 (m, 1H), 1.51 (m, 1H), 1.94 (m, 1H), 2.64 (s, 3H), 3.46 (diastereotopic m, 4H), 3.63 (s, 3H), 4.46 (d, $J = 4.1$ Hz, 1H), 4.74 (dd, $J = 10.2$, 4.1 Hz, 1H), 5.63 (s, 1H), 6.66 (dd, $J = 7.5$, 1.9 Hz, 1H), 6.69 (t, $J = 7.6$ Hz, 1H), 6.77 (dd, $J = 7.7$, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.7, 15.2, 15.4, 15.6, 25.4, 32.3, 33.3, 57.3, 61.6, 63.6, 63.8, 103.0, 116.4, 118.3, 120.0, 124.8, 142.8, 149.4, 170.6; MS (ammonia, CI+) *m/z* 354, 308, 103; HRMS calcd for $C_{19}H_{32}NO_5$: 354.2280 (M+H), found: 354.2265 (M+H). Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.56; H, 8.84; N, 3.96. Found: C, 64.49; H, 8.74; N, 3.82.
11. Kaufman, T. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 403.
12. Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. G. *J. Org. Chem.* **1980**, *45*, 1950.
13. Spectroscopic data: Compound **10**: $[\alpha]_D$ +4.61 (*c* 1.09, CH_3OH); IR (neat) 3441, 2966, 1745, 1655, 1593, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 0.97 (t, $J = 7.4$ Hz, 3H), 1.27 (d, $J = 6.7$ Hz, 3H), 1.56 (m, 1H), 1.74 (m, 1H), 2.80 (m, 1H), 3.59 (s, 3H), 5.63 (s, 1H), 6.35 (s, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 13.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.8, 19.9, 29.3, 29.6, 36.4, 104.5, 110.6, 115.0, 122.7, 130.0, 141.1, 145.0, 146.2, 166.5; MS (ammonia, CI+) *m/z* 276 (impurity), 262 (impurity), 248, 232, 218; HRMS calcd for $C_{14}H_{18}NO_3$: 248.1287 (M+H), found: 248.1282. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.91; H, 7.02; N, 5.59.
14. Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711.
15. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
16. The samples of **14** and **15** showed spectroscopic characteristics in agreement with published data; see Acheson, R. M.; Lee, G. C. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2321; Ibrahim, Y. A.; Al-Awadi, N. A.; Kaul, K. *Tetrahedron* **2001**, *57*, 7377.

17. For previous syntheses of the intermediates **17**, see: Houry, S.; Geresh, S.; Shani, A. *Israel J. Chem.* **1973**, *11*, 805; Geresh, S.; Levy, O.; Markovits, Y.; Shani, A. *Tetrahedron* **1975**, *31*, 2803.
18. For a previous synthesis of 2-allyl-6-methoxyphenyl triflate, see: Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
19. Bringmann, G.; Wenzel, M.; Kelly, T. R.; Boyd, M. R.; Gulakowski, R. J.; Kaminsky, R. *Tetrahedron* **1999**, *55*, 1731.
20. Competition between S_NAr attack of hydroxide and palladium catalyzed insertion resulted in low Suzuki coupling yields where $R = NO_2$.
21. For previous syntheses of the phenanthrenes **19**, see: Bachmann, W. E.; Edgerton, R. O. *J. Am. Chem. Soc.* **1940**, *62*, 2219; Dewar, M. J. S.; Warford, E. W. T. *J. Chem. Soc., Abstr.* **1956**, 3570; Dixon, J. A.; Neiswender, D. D., Jr. *J. Org. Chem.* **1960**, *25*, 499; Barnes, R. A.; Hirschler, H. P.; Bluestein, B. R. *J. Am. Chem. Soc.* **1952**, *74*, 32.