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Total Synthesis of (−)-21-Isopentenylpaxilline

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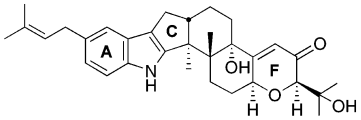
ABSTRACT



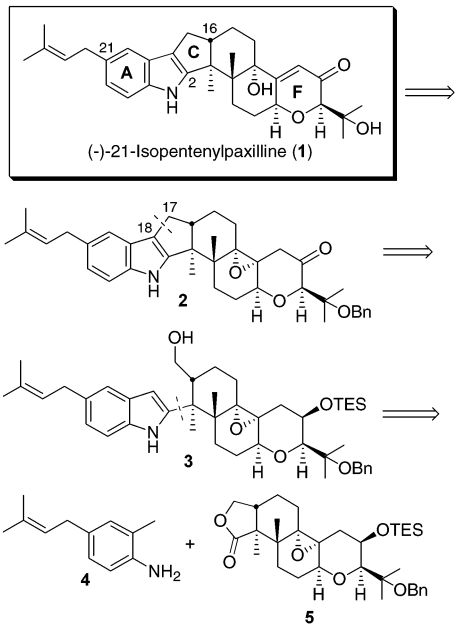
(-)-21-Isopentenylpaxilline (**1**)

The total synthesis of (−)-21-isopentenylpaxilline (1) has been achieved. Key elements of the synthesis include the stereocontrolled construction of the advanced eastern hemisphere (−)-5, a highly efficient union of the eastern and western fragments (−)-5 and 4, respectively, exploiting our 2-substituted indole synthesis, and a new protocol for the construction of ring C.

In 1995, Belofsky and Gloer reported the isolation, structure elucidation, and biological activity of (−)-21-isopentenylpaxilline (**1**),[1] an indole tremorgenic alkaloid derived from the sclerotioid ascostromata of *Eupenicillium shearii* (NRRL3324). Extensive spectroscopic analysis established the complete relative stereochemistry, albeit the absolute stereochemistry remained undefined. Key architectural features include six fused rings, an indole core punctuated at C(21) with an isopentenyl moiety, a fully substituted tetrahydropyran, and six stereogenic centers. Although (−)-21-isopentenylpaxilline (**1**) displays modest antiinsectan activity, the extreme scarcity of **1** has to date precluded comprehensive evaluation of the biological profile. Recently, we embarked on the total synthesis of **1**, as part of a program on the synthesis of bioactive indole diterpenes to provide additional material for further biological evaluation.[2a−g] Herein we disclose the successful conclusion of this synthetic venture.

The synthetic strategy, reminiscent of our recently completed total synthesis of (−)-penitrem D,[2f] is outlined in Scheme 1. To elaborate the γ-hydroxyl-enone functionality that adorns the E and F rings and is required for tremorgenetic activity,[3] we envisioned fragmentation of epoxyketone **2** initiated by ketone enolization. Disconnection of the C(17,-18) σ-bond in ring C then leads to the 2-substituted indole

Scheme 1



3, which in turn would be assembled exploiting the 2-substituted indole synthetic protocol developed in our laboratory

(1) Belofsky, G. N.; Gloer, J. B. *Tetrahedron* **1995**, *51*, 3959. Indole **1** is also referred to as (−)-9-prenylpaxilline.

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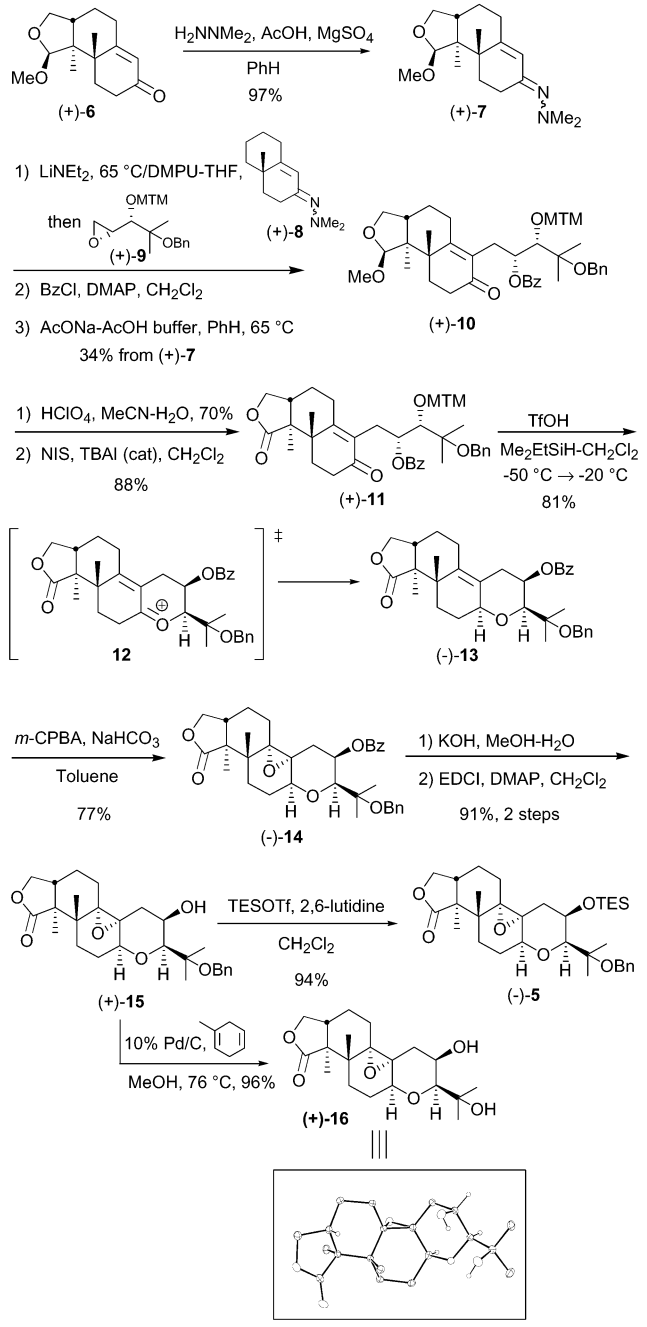
for this purpose.[2g,4] For indole **3**, a western hemisphere aniline (**4**) and a fully elaborated eastern hemisphere lactone (**5**) would be required.[2f,g, 4]

Construction of lactone **5** began with methyl acetal (+)-**6**, an advanced intermediate employed in our (−)-penitrem D synthesis[2f] (Scheme 2). After conversion to hydrazone (+)-**7**, a three-step sequence involving Stork metalloenamine acylation[5] employing epoxide (+)-**9**,[6] in the presence of the equilibration auxiliary (+)-**8**[2f,7] and DMPU,[7] followed in turn by benzoylation of the derived hydroxyl, and hydrolytic removal of the hydrazone furnished enone (+)-**10**.[8] Although the overall yield for this three-step sequence proved to be modest, sufficient material could be prepared to continue the synthesis. Selective hydrolysis of the methyl acetal in the presence of the MTM ether,[9] achieved with $HClO_4$ (4:1 MeOH−H_2O), furnished a mixture of lactols; oxidation with *N*-iodosuccimide (NIS) and tetrabutylammonium iodide (TBAI) led to lactone (+)-**11**. To elaborate the F-ring tetrahydropyran, we envisioned a cascade of reactions, involving removal of the MTM group, cyclization to an intermediate carbocation (e.g., **12**), and capture with hydride. The optimal conditions for this reaction sequence proved to be TfOH in 1:1 Me_2EtSiH−CH_2Cl_2.[10] A similar tactic, employed in our penitrem venture,[2f] was initially developed by Nicolaou for the construction of oxepanes.[11] In this case, the three-step sequence furnishes exclusively *cis*-tetrahydropyran (−)-**13** in 81% yield.[12] Stereoselective epoxidation with *m*-CPBA then afforded (−)-**14**, possessing the desired α-epoxide, requisite for eventual conversion to the γ-hydroxyl-enone in (−)-21-isopentenylpaxilline (**1**). A minor amount of the β-epoxide was also obtained (14%).

At this juncture a protecting group interchange was necessary to permit application of the 2-substituted indole synthesis. To this end, removal of the benzoate (KOH, MeOH/H_2O), followed by treatment with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 to reinstall the lactone moiety that had undergone partial hydrolysis, proceeded in excellent yield (91% for two steps). To confirm the stereochemistry, (+)-**15** was converted via transfer hydrogenation to (+)-**16**; single-crystal X-ray analysis established both the structure and stereochemistry. Silylation of (+)-**15** completed construction of the eastern hemisphere (−)-**5**.

Scheme 2



(2) For related indole-diterpene synthesis, see: (−)-paspaline (a,b), (+)-paspalicine (c,d), (+)-paspalinine (c,d) and (−)-penitrem D (e,f). (a) Smith, A. B., III; Mewshaw, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 1796. (b) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem.* **1989**, *54*, 3449. (c) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (d) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G., Jr.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438. (e) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263. (f) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *114*, 1438. (g) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957.

(3) Dorner, J. W.; Cole, R. J,; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069−1071.

(4) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757.

(5) (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938. (b) Stork, G.; Benaim, J. *Org. Synth.* **1977**, *57*, 69.

(6) Epoxide (+)-**9** was prepared in eight steps and 22% overall yield; see Supporting Information.

(7) Our initial attempt at Stork metalloenamine alkylation of the hydrazone (+)-**7** with (+)-**9** without the auxiliary hydrazone (+)−(**8**) resulted in low yield. Presumably (+)-**8** is required to promote equilibration of the initially quenched kinetic anion. Considerable experimentation led to the observation that DMPU as a cosolvent was required; see Supporting Information.

(8) Best results were obtained with the hydrazone (+)-**7** concentration at 1 M.

(9) Byproducts, comprising ca. 25% of the product mixture, which derived from both acetal and MTM ether hydrolysis, were converted to (−)-**13** in two steps; see Supporting Information.

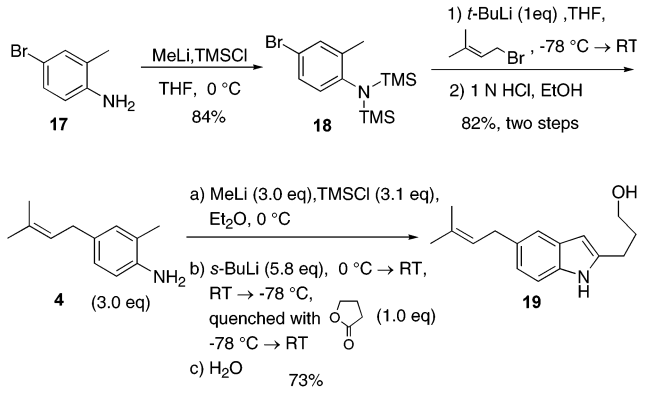
(10) Use of Me_2EtSiH instead of Et_3SiH significantly improved the yield.

(11) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.

(12) NOESY NMR experiments confirmed the cis stereochemistry of pyran (−)-**13**.

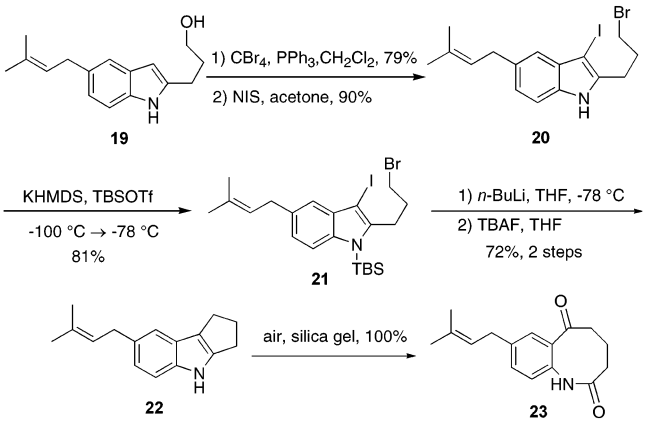
The issue of selective C-ring closure at C(18),[13] was initially addressed with the 2-substitued model indole **19**, available from aniline **4** and butyrolactone, exploiting our indole protocol (Scheme 3). This two-step, one-flask sequence involves generation of the N-TMS aniline, metalation with *s*-BuLi, acylation with butyrolactone, and in situ heteroatom Peterson olefination.[14] Aqueous workup furnished **19** in excellent yield (ca. 73%).

Scheme 3



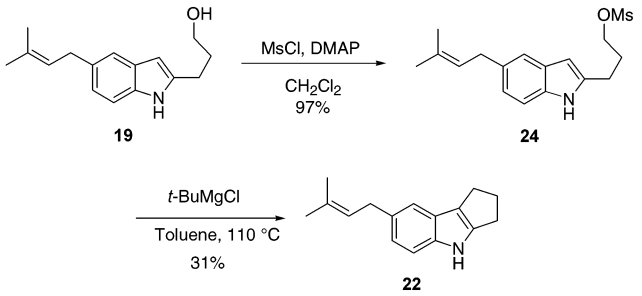
Two tactics for C-ring closure were explored. In the first approach, the primary hydroxyl in **19** (Scheme 4) was converted to the corresponding bromide, followed in turn by treatment with NIS to generate the iodide and protection of the indole nitrogen with a TBS group to provide **21**. Upon lithium−iodide exchange (*n*-BuLi; −78 °C), five-membered ring formation occurred selectively at C(3). Removal of the TMS moiety (TBAF) then provided indole **22** in 72% yield. Interestingly, **22** proved to be highly unstable upon exposure to air and silica gel chromatography. The product, eight-membered ring lactam **23**, was obtained in near quantitative yield.[15]

Scheme 4



The second tactic (Scheme 5), albeit lower yielding with model indole **19**, entailed mesylation followed by treatment with *t*-BuMgCl (1.5 equiv) in toluene at reflux; indole **22** was isolated in an unoptimized yield of 31%.

Scheme 5



With ample quantities of both the western and eastern hemispheres [**4** and (−)-**5**, respectively] in hand, we executed the 2-substituted indole synthesis (Scheme 6). In this case, in situ heteroatom Peterson olefination did not occur. However, heating the intermediate aminoketone in toluene at reflux after workup led to indole ring formation. The excellent yield of (−)-**25** (76%) is a testament to the utility of this indole construction.

Turning to generation of ring C, elaboration of the bromo iodide, corresponding to that employed in the first model study proved to be unworkable.[16] However, mesylation of (−)-**25** followed by treatment of *t*-BuMgCl in toluene at reflux resulted in C ring closure in 73% yield. Removal of the silyl group to provide (−)-**28**, followed by oxidation with concomitant epoxide ring opening employing Ph_3BiCO_3 as an oxidant,[17] furnished enone (+)-**29**. The yield for this critical fragmentation was 69%. Transfer hydrogenation then completed the synthesis of (−)-21-isopentenylpaxilline (**1**).[18] The synthetic material was identical in all respects to the natural material (i.e., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, HRMS, and chiroptic properties), thus confirming both the original structural assignment and defining for the first time the absolute stereochemistry of (−)-21-isopentenylpaxilline (**1**).

(13) There is precedent for five-membered ring closure on nitrogen instead of C-3 with MeMgBr; see: Haseltine, J. N. Ph.D. Thesis, University of Pennsylvania, 1992.

(14) Kruger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132.

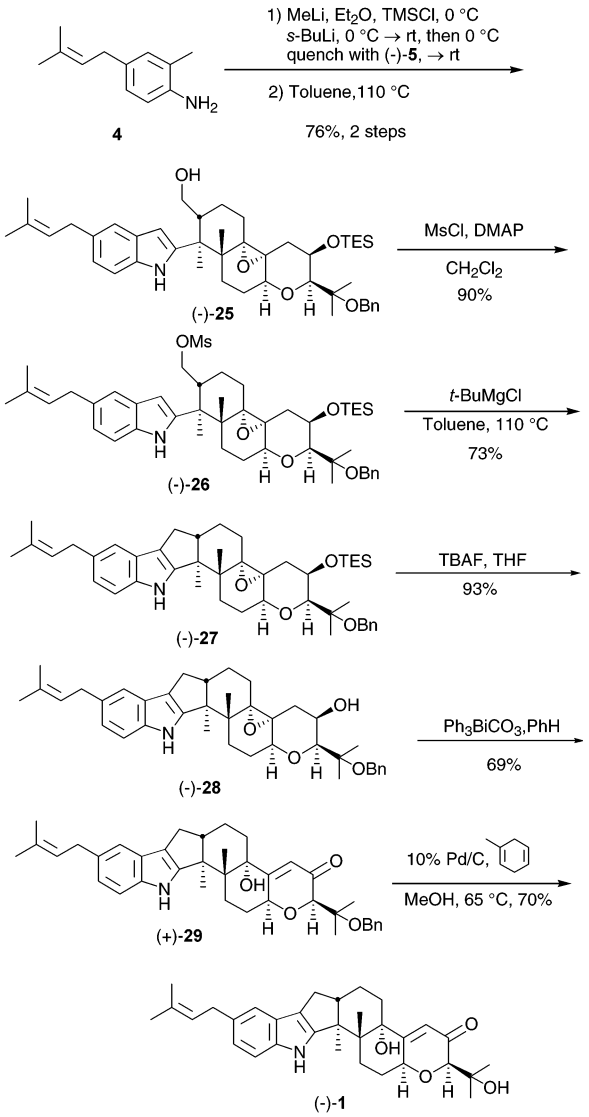
(15) There is precedent for similar facile oxidations in the indole diterpene field. See ref 1 and: Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goets, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809.

(16) Attempted installation of the iodide with NIS led to decompostion.

(17) Barton, D. H. R.; Kitchin, J. P.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *Tetrahedron* **1981**, *37*, 73.

(18) Minor amount (ca. 10%) of the over reduction product was obtained; separation was by HPLC.

Scheme 6



In summary, the first total synthesis of (−)-21-isopentenylpaxilline (**1**) has been achieved. Key elements of the synthesis include the stereocontrolled construction of the advanced eastern hemisphere (−)-**5**, a highly efficient union of the eastern and western fragments (−)-**5** and **4**, respectively, exploiting our 2-substituted indole synthesis, and a new protocol for the construction of ring C.

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Supporting Information Available: Spectroscopic and analytical data for compounds (−)-**1**, **4**, (−)-**5**, (+)-**9**, (+)-**10**, (+)-**11**, (−)-**13**, (−)-**14**, **19**, **20**, **22**, **23**, (−)-**25**, (−)-**26**, (−)-**27**, and (+)-**29** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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