Total Synthesis of Pterosines B and C via a Photochemical Key Step

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Dedicated to Professor Jochen Mattay on the occasion of his 60th birthday

Abstract: A total synthesis of pterosines B and C is reported. Starting with a fourfold substituted benzene derivative, the introduction of the remaining substituents is mainly based on Sonogashira couplings followed by different transformations of the ethyne moiety. The key step is a photochemical ring-closure of an α-mesyloxy ketone forming the 1-indanone skeleton.

Key words: total synthesis, photochemistry, arenes, ketones

The pterosines constitute a class of sesquiterpene indane derivatives occurring in several plants, e.g. in the bracken fern (*pteridium aquilinium*).[1] Several pterosines have been shown to possess interesting biological activity. Especially due to their cytotoxic[2] and antibacterial[3] activity the pterosines are attractive targets for pharmaceutical applications. In the past years some total syntheses of these compounds have been reported.[4] Despite their seemingly simple structure, the fivefold-substituted aromatic core is a considerable synthetic challenge.

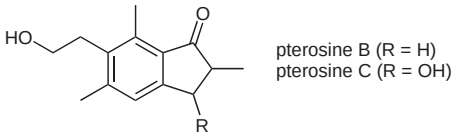
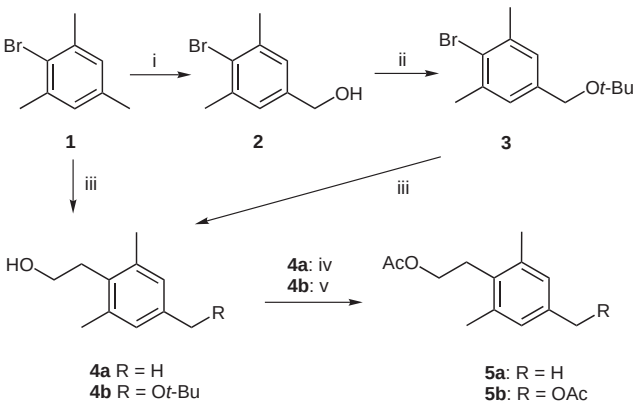


Figure 1

Recently we reported on the photochemical synthesis of some indanones as well as on the mechanism of this reaction.[5] The method rests on an extension of the Norrish–Yang reaction, called spin center shift. To date, this reaction has been successfully applied to the synthesis of cyclopropanes,[6] 1,3-oxazine-4-ones[7] and benzo[*c*]furanes.[5] Herein we wish to describe an application of this photochemical method on the synthesis of pterosines B and C (Figure 1).

Our route commences with the commercially available bromo mesitylene (**1**). After regioselective oxidation of the 4-methyl group,[8] reduction to alcohol **2** and protection with isobutene we obtained *tert*-butyl ether **3** in good yields. The introduction of the C_2 side chain at C-1 proved to be difficult due to the steric hindrance of this position by the two methyl groups. Classic Grignard reaction and halogen–metal exchange with *n*-BuLi gave very low yields of the desired products. These difficulties could be circumvented by using Rieke™ magnesium.[9] Subsequent treatment of the thus obtained Grignard reagent with oxirane afforded the primary alcohol **4b** in very good yields. The same procedure was applied to bromo mesitylene (**1**) giving **4a**. The *tert*-butyl ether protective group in **4b**, necessary for the Grignard reaction, must now be replaced by a relatively acid-stable protective group (vide infra) and we chose acetate esters. Fortunately, deprotection of **4b** and protection of both hydroxy groups could be performed in one step. The alcohol **4a** was protected as the acetate as well (Scheme 1).



Scheme 1 *Reagents and conditions*: i) 1. CrO_3/Ac_2O/HOAc; 2. $LiAlH_4$, 53%; ii) isobutene, $BF_3{\cdot}OEt_2$, 99%; iii) Rieke™-Mg, oxirane (**4a**, 98%; **4b**, 78%); iv) Ac_2O, pyridine, DMAP, 82%; v) Ac_2O, $FeCl_3$, 92%.

An alternative route to **5b** started with 2,6-dimethylphenol (**6**), which was firstly converted into the 4-hydroxy benzoic ester **8** by a Kolbe–Schmidt reaction followed by esterification.[10] Differing from the approach outlined in Scheme 1, the C_2 side chain was introduced by a Sonogashira coupling[11] with trimethylsilyl ethyne and conversion of the acetylenic unit to the acetic acid according to the procedure described by Zweifel giving diacid **10**.[12] Reduction of the carboxyl groups and protection as acetate afforded **5b** (Scheme 2).

The installation of the fifth substituent started with an iodination using the $PhI(OOCCF_3)/I_2$ system described by Muraki et al.[13] Whereas the acetate group turned out to be suitable for the protection of the 2-hydroxyethyl group in all subsequent steps, problems arose with the benzylic

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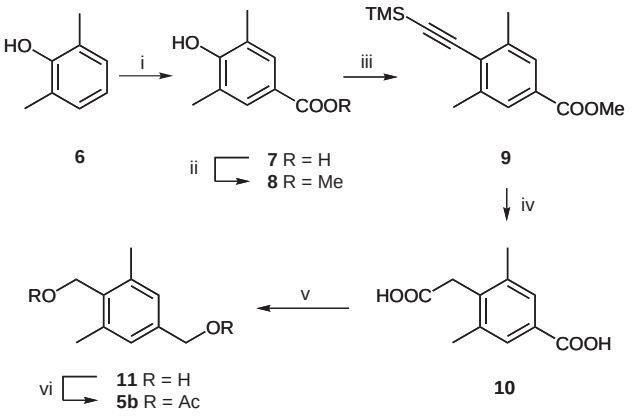
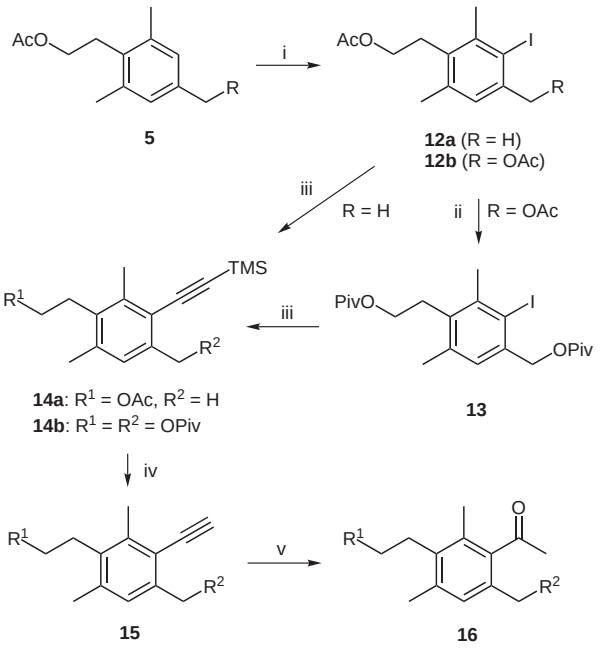


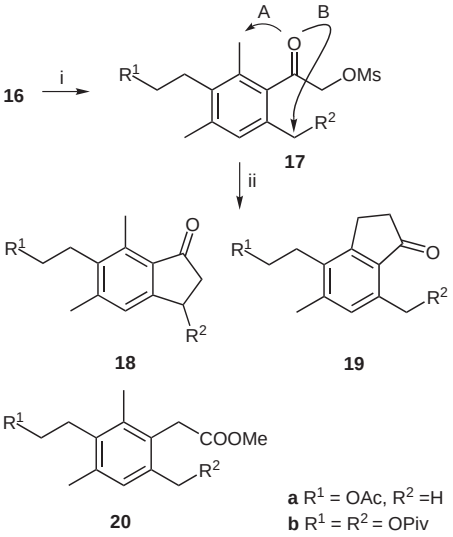
Scheme 2 *Reagents and conditions*: i) 1. NaH; 2. CO_2, 34%; ii) $SOCl_2$, MeOH, 92%; iii) 1. Tf_2O/pyridine, 96%; 2. TMS-ethyne, $Pd(Ph_3P)_2Cl_2$, Et_3N, 92%; iv) 1. BH_3·THF; 2. NaOH, H_2O_2, 44%; v) $LiAlH_4$, 76%; vi Ac_2O, pyridine, DMAP, 96%.

ester moiety in **12b**. Therefore we changed the protective group in **12b** from acetate to pivalate, giving **13**. Both **12a** and **13** underwent a smooth Sonogashira coupling with trimethylsilylethyne to **14a** and **14b**. After removal of the trimethylsilyl group we obtained the acetophenones **16** using a gold-catalyzed hydration (Scheme 3).[14]

The photochemical ring-closure to indanones[5] required the introduction of a leaving group in α-position with respect to the keto group. This was achieved in good yields by treating ketones **16** with PhI(OH)OMs (Scheme 4).[15]



Scheme 3 *Reagents and conditions*: i) I_2/PhI(OOCCF$_3$)$_2$, **12a**: 54%, **12b**: 91%; ii) 1. KOH; 2. PivCl/pyridine, 90%; iii) TMS-ethyne, $Pd(PPh_3)_2Cl_2$, Et_3N, **14a**: 47%, **14b**: 92%; iv) KF, 18-crown-6, **15a**: 96%, **15b**: 66%; v) $Au(PPh_3)CH_3$, TfOH–MeOH–H_2O, **16a**: 72%, **16b**: 77%.



Scheme 4 *Reagents and conditions*: i) PhI(OH)OMs, **17a**: 59%, **17b**: 84%; ii) *hν*; for conditions and yields, see Table 1.

Unfortunately, the irradiation of compounds **17** under various conditions gave the desired 1-indanones **18** only in low yields. In this context the low site selectivity of the initial photochemical hydrogen abstraction by the excited carbonyl group turned out to be the main problem.

In the case of **17a** this comes up to our expectations because the substituents in both *ortho* positions are identical. Admittedly, we were surprised that the undesired 1-indanone **19** was formed in nearly the same amount as **18** from the asymmetric compound **17b** as well. The C–H bond energies of the methylene group (mode B, Scheme 4) should be considerably lower than that of the methyl group (mode A). Obviously, the transition states of both modes are of very early nature and therefore the gradation of the bond energies are not reflected by the site selectivity. If the irradiation was performed in methanol another problem arose. Instead of the expected 1-indanones **18** and **19** we obtained the methyl arylacetates **20** as main products. These compounds were formed in the course of a photo-Favorsky rearrangement, already known from other cases.[16] Even though the preparation of esters **20** was not the objective of this work it should be noted that the described sequence is obviously an interesting method for the introduction of acetic acid moieties into highly substituted aromatic hydrocarbons. The results of the irradiation of **17a** and **17b** are summarized in Table 1. Best yields were achieved with *tert*-butanol as solvent.[17]

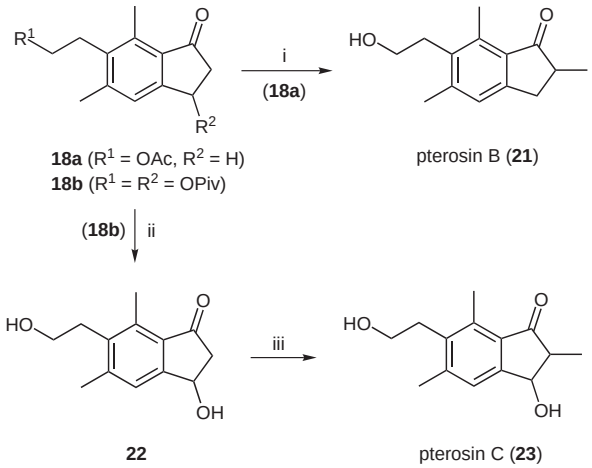
To complete the total synthesis of pterosine B two steps remained. Firstly, the acetate protective group in **18a** had to be cleaved by saponification, which succeeded in very good yields with K_2CO_3/MeOH. The methylation using two equivalents of LDA and MeI gave **21** (pterosine B) with moderate yield.

Table 1 Results of Irradiation of **17a** and **17b**

17	R^1	R^2	Conditions[a]	Yield of **18** (%)	Yield of **19** (%)	Yield of **20** (%)
a	OAc	H	A	9	9	0
			B	0	0	67
			C	17	17	0
b	OPiv	OPiv	A	26	23	0
			B	0	19	68
			C	31	23	0

[a] Conditions: A = 2.0 equiv *N*-methyl imidazole, CH_2Cl_2; B = 2.0 equiv *N*-methyl imidazole, MeOH; C = 2.0 equiv *N*-methyl imidazole, *t*-BuOH.

Application of the same saponification conditions to dipivalate **18a** caused an elimination of water in the sensitive β-hydroxyketone moiety, followed by Michael addition of MeOH. Variation of the reaction conditions (solvent, base) did not solve the problem but caused decomposition of the compound at best. Finally, the diol **22** could be obtained by enzymatic saponification with porcine liver esterase (PLE) in good yields.[18,19] The methylation with LDA/MeI completed the total synthesis of **23** (pterosine C, Scheme 5).



Scheme 5 *Reagents and conditions*: i) 1. K_2CO_3/MeOH, 91%; 2. LDA (2 equiv)/MeI, 43%; ii) PLE/HEPES, 54%; iii) 3 equiv LDA (3 equiv)/MeI, 49%.

In summary, we developed a total synthesis for pterosines B (**21**) and C (**23**), which is based on a photochemical construction of the 1-indanone skeleton. Even though the yields of the photochemical ring-closure were low owing to low site-selectivity, it was in principle demonstrated that this method is suitable for the synthesis of highly substituted aromatic compounds.

Acknowledgment

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(12) (a) Backlund, S. J.; Zweifel, G. *J. Am. Chem. Soc.* **1977**, *99*, 3184. (b) **4-(Carboxymethyl)-3,5-dimethylbenzoic Acid (10).**
Compound **9** (1.00 g, 3.78 mmol) in 10 mL dry THF was cooled to 0 °C and 6.8 mL (6.8 mmol, 1.8 equiv) 1 M BH_3–THF solution was dropped in slowly. After stirring at 0 °C for 2 h a mixture of 10 mL (0.02 mol, 5 equiv) 2 M NaOH and 5 mL (0.06 mol, 15 equiv) aq H_2O_2 solution (30%) was added. After additional stirring for 2 h further 20 mL of 1 M NaOH and 50 mL of Et_2O were added. The phases were separated and the aqueous phase was extracted several times with Et_2O. Then the aqueous phase was acidified to pH 1 with HCl and the product was extracted with several portions of Et_2O. The combined organic phases were dried and evaporated, giving 350 mg (1.68 mmol, 44%) of **10** as a white solid; mp 285 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.29 (s, 6 H, 3,5-Me), 3.65 (s, 2 H, CH_2), 7.59 (s, 2 H, CH_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.8 (3,5-Me), 35.2 (CH_2), 128.5 (CH_{arom}), 128.8, 137.3, 137.9 (C_q), 167.4, 171.8 (COOH). IR (KBr): 2959 (br s), 2923 (s), 2858 (s), 1718 (s), 1667 (s), 1425 (s), 1413 (s), 1303 (s), 1244 (s), 1230 (s), 1182 (m). HRMS (ESI): *m/z* calcd for $C_{11}H_{13}O_4$ [MH^+]: 209.0808. Found: 209.0809.
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(17) **Irradiation of 17a and 17b.**
For solvents, conditions and yields see Table 1. The irradiation was performed in a 500 mL reactor vessel, equipped with a 150 W high-pressure mercury arc lamp (TQ 150, Heraeus) and monitored by TLC. The solvent was removed in vacuo and the residue was purified by flash chromatography.
Analytical Data for 2-(4,6-Dimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl)ethyl Acetate (18a).
Mp 39–41 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, CH_3-acetate), 2.42 (s, 3 H, Me-C_{arom}), 2.60–2.64 (m, 2 H, 2-CH_2), 2.67 (s, 3 H, Me-C_{arom}), 2.94–2.98 (m, 2 H, 3-CH_2), 3.03 (t, J^3 = 7.7 Hz, 2 H, CH_2CH_2O), 4.12 (t, J^3 = 7.7 Hz, 2 H, CH_2CH_2O), 7.10 (s, 1 H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 21.0 (CH_3-C_{arom}), 21.1 (CH_3-acetate), 24.6 (3-CH_2), 27.8 (CH_2CH_2O), 37.1 (2-CH_2), 62.7 (CH_2CH_2O), 125.9 (CH_{arom}), 132.9, 133.8, 137.8, 140.1, 154.6 (C_q), 171.0 (COOR), 207.8 (RCOR).
Analytical Data for 2-{1-[(Pivaloyl)oxy]-4,6-dimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl}ethyl Pivalate (18b).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14, 1.17 (s, 9 H, Piv), 2.46 (s, 3H, Me-C_{arom}), 2.51 (dd, J^3 = 3.0 Hz, J^2 = 18.8 Hz, 1 H, CH_2CH), 2.68 (s, 3 H, Me-C_{arom}), 3.03 (t, J^3 = 7.7 Hz, 2 H, CH_2CH_2O), 3.08 (dd, J^3 = 7.1 Hz, J^2 = 18.8 Hz, 1 H, CH_2CH), 4.10 (t, J^3 = 7.7 Hz, 2 H, CH_2CH_2O), 6.15 (dd, J^3 = 3.0 Hz, J^3 = 7.1 Hz, 1 H, CHOPiv), 7.19 (s, 1 H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.3 (CH_3-C_{arom}), 27.0, 27.1 (CH_3, Piv), 28.0 (CH_2CH_2O), 38.6, 38.6 (C_q, Piv), 44.6 (2-CH_2), 62.3 (CH_2CH_2O), 68.5 (3-CH), 73.2 (CH_2O), 125.4 (CH_{arom}), 132.8, 136.7, 137.5, 145.1, 151.0 (C_q), 178.5, 178.6 (COOR), 202.9 (RCOR). IR (film): 2973 (s), 1717 (vs), 1599 (s), 1478 (s), 1458 (s), 1396 (s), 1281 (s), 1148 (s), 1033 (s), 1010 (s), 984 (m). HRMS (ESI): *m/z* calcd for $C_{23}H_{33}O_5$ [MH^+]: 389.2323; found: 389.2324.
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(19) **Experimental Procedure for 3-Hydroxy-6-(2-hydroxyethyl)-5,7-dimethyl-1-indanone (22).**
To a solution of 65 mg (0.17 mmol) **18b** in 10 mL DMSO was added a mixture of 100 mL 0.01 M aq HEPES buffer solution (pH 7.5, I = 0.1 M NaCl) and 90 mg (2160 units) porcine liver esterase (EC 3.1.1.1, Sigma). The mixture was stirred 2 d at r.t. in which the reaction course was monitored by HPLC analysis (see below). After complete saponification of both ester groups the mixture was treated with 50 mL CH_2Cl_2, filtrated and the phases were separated. The organic phase was dried with $MgSO_4$, evaporated and purified by FCC (CH_2Cl_2–MeOH, 10:1, R_f = 0.39) affording 20.0 mg (90.8 µmol, 54%) **22** as a white solid.
HPLC conditions: column: Eurospher 100 C-18 (Knauer), 5 µm, 250 × 4 mm; mobile phase: gradient MeOH–H_2O (70:30 → 90:10) linear in 20 min, then 90:10 flow: 1 mL/min. peaks: t_R(**22**) = 2.6 min, t_R(**18b**) = 31.9 min.
Mp 143–145 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.34 (dd, J^3 = 3.0 Hz, J^2 = 18.5 Hz, 1 H, CH_2CH), 2.40, 2.56 (s, 3 H, Me-C_{arom}), 2.84 (t, J^3 = 7.5 Hz, 2 H, CH_2CH_2OH), 2.90 (dd, J^3 = 7.0 Hz, J^2 = 18.5 Hz, 1 H, CH_2CH), 3.41–3.46 (m, 2 H, CH_2CH_2OH), 4.78 (t, J^3 = 5.5 Hz, 1 H, CH_2OH), 5.02–5.06 (m, 1 H, 3-CH), 5.57 (d, J^3 = 6.0 Hz, 1 H, OH), 7.31 (s, 1 H, CH_{arom}). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.3, 21.0 (CH_3-C_{arom}), 32.1 (CH_2CH_2OH), 47.7 (2-CH_2), 59.8 (CH_2CH_2OH), 65.6 (3-CH), 125.0 (CH_{arom}), 131.5, 135.6, 137.1, 144.2, 155.6 (C_q), 204.3 (RCOR). IR (KBr): 3391 (br s), 2923 (m), 1687 (vs), 1596 (s), 1408 (m), 1326 (m), 1308 (s), 1260 (m), 1065 (s), 1025 (s), 804 (m). HRMS (ESI): *m/z* calcd for $C_{13}H_{17}O_3$ [MH^+]: 221.1172; found: 221.1173.