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COMMUNICATION

Synthesis of the (–)-TAN-2483B ring system *via* a D-mannose-derived cyclopropane†

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The ring system of the fungal metabolite (–)-TAN-2483B has been synthesised, for the first time, from D-mannose, utilising a cyclopropanation/ring expansion sequence.

Bioactive natural products incorporating the furo[3,4-*b*]pyran-5-one bicyclic system have been isolated from a variety of fungal sources. Fusidilactones A, B, D and E,[1] massarilactones B and D,[2] TAN-2483A and B[3] and waol A[4,5] all contain this ring system. These fungal secondary metabolites display a variety of bioactivities, ranging from antibacterial to anti-tumour properties. To date, only the Snider group has reported the synthesis of members of this family of natural products,[5] namely (–)-TAN-2483A (**1**), massarilactone B and waol A (Fig. 1).[6] These natural products either incorporate a degree of unsaturation across the fused 4a–7a bond (*e.g.* massarilactone B) or possess a *cis*-relationship between H-2 and H-7a (*e.g.* (–)-TAN-2483A, waol A). In contrast to the other members of this family, (–)-TAN-2483B (**2**), isolated from a Japanese filamentous fungus,[3] has a *trans*-relationship between H-2 and H-7a, and was inaccessible through the reported[5] methodology. Herein, we present the first synthesis of the ring system of (–)-TAN-2483B (**2**), accessed from D-mannose through a key cyclopropanation/ring expansion sequence.

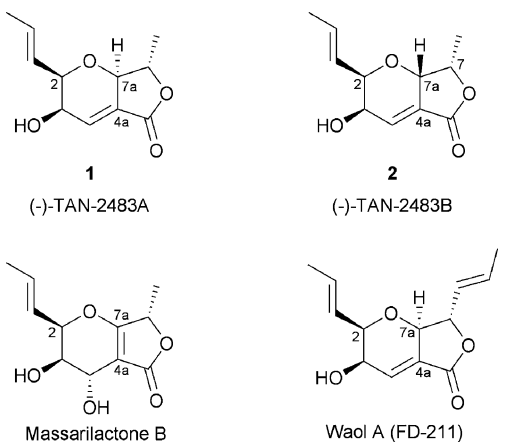
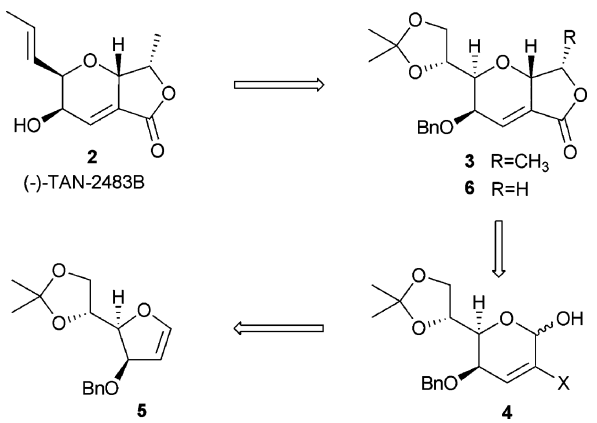


Fig. 1 Selected furo[3,4-*b*]pyran-5-one fungal natural products.

(–)-TAN-2483B possesses multiple chiral centres and several oxygen groups. The stereochemical diversity contained within the carbohydrate chiral pool provided a suitable scaffold for this synthetic endeavour, wherein the ring expansion of a *gem*-dihalocyclopropane[7] fused to a five-membered ring glycal would generate the ring unsaturation. We envisaged that (–)-TAN-2483B could be accessed from furanopyranone **3** (Scheme 1), which in turn could be derived from hemiacetal **4** through Wittig homologation and lactone formation. This substrate could be prepared by *gem*-dihalocyclopropanation of known glycal **5**,[8] followed by silver-promoted ring expansion. The synthesis of a simplified furanopyrone, such as **6**, would provide a proof-of-principle for the proposed approach to the natural product, and is described herein.



Scheme 1 Retrosynthetic analysis of TAN-2483B.

Glycal **5** was prepared from D-mannose using the four-step sequence described by Theodorakis.[8] Initial attempts to cyclopropanate the alkene moiety of **5** with dibromocarbene gave complex mixtures in which the desired cyclopropane was not evident. In contrast, addition of dichlorocarbene to **5** under Mąkosza conditions[9] was a facile process, cleanly yielding a single isomer of cyclopropane **7** (Scheme 2). The propensity of this product to undergo spontaneous ring expansion led to its isolation in variable yields (50–79%) after column chromatography. Ring-expansion of cyclopropane **7** was achieved by treatment with silver acetate and sodium acetate,[10] and provided a mixture of

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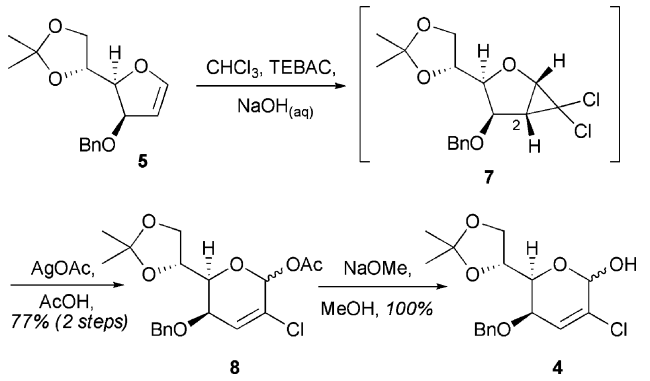
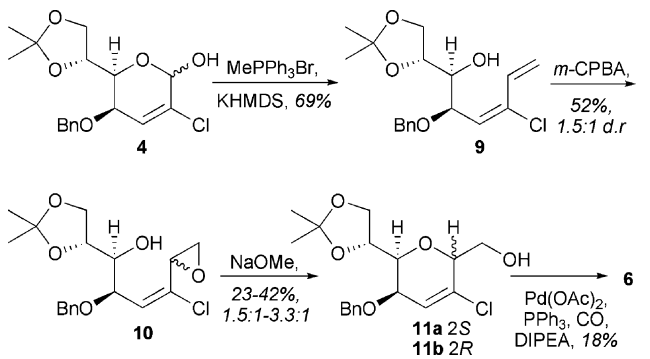


Scheme 2 Synthesis of the pyran ring *via* a cyclopropane.

anomeric acetates **8** (49% combined yield), in addition to the corresponding 3-acetylglycal (16%), formed by acetate attack at C-2 of cyclopropane **7**. Gratifyingly, we found that the desired product (**8**) could be obtained in much higher yield (77% over two steps) by treating the crude cyclopropane **7** with silver acetate in acetic acid.‡ The mixture of acetates was then subjected to methanolysis to afford **4** in a quantitative yield.

Construction of the lactone ring was initiated by Wittig olefination of the masked aldehyde **4** using the ylide derived from methyltriphenylphosphonium bromide, producing diene **9** (Scheme 3). Epoxidation of this diene using Jacobsen's catalyst provided very low conversion, with poor stereoselectivity. Encouragingly, epoxidation with *m*-CPBA produced a mixture of stereoisomers **10** in a 1.5:1 ratio (52% yield). Base-mediated intramolecular epoxide opening of **10** with sodium hydride in DMF was sluggish, affording the product **11** in 23% yield (35% based on recovered starting material) and as a 1.5:1 ratio of epimers, which correlated with the mixture of isomers subjected to this process. Reaction of **10** with methanolic sodium methoxide provided the desired functionalised pyran **11** in a better yield (42%) but as a 3.3:1 mixture of epimers. In this case, the product **11** was accompanied by two by-products, thought to be the seven-membered ring regioisomer and a methyl ether formed by attack of methoxide on the epoxide. The assignment of the major and minor isomers of **11** from these reactions as **11a** and **11b**, respectively, was made after lactone formation (*vide infra*).



Scheme 3 Formation of the TAN-2483B ring system.

The mixture of inseparable alcohols **11a** and **11b** was subjected to a palladium-catalysed carbonylation/lactonisation sequence under an atmosphere of carbon monoxide. This provided the furo[3,4-*b*]pyran-5-one **6**,§ incorporating the bicyclic ring system of (–)-TAN-2483B. Only the desired isomer of **6** was obtained (18% yield), in addition to recovered **11** (63% yield), which was enriched in **11a**. It appears that, surprisingly, the major isomer of the alkenyl chloride, **11a**, is unreactive towards carbonylation under the conditions used. The stereochemical assignment of **6** was based on nOe experiments (Fig. 2). The lack of a significant nOe between H-7a and H-2 provided circumstantial evidence for a *trans*-relationship between H-2 and H-7a across the ring,[11] indicating that the stereochemistry was 7a*S*, as in (–)-TAN-2483B. Future synthetic efforts will initially centre around improving the overall yield of **6** by augmenting the selectivity of the epoxidation and exploring alternative methods for epoxide opening. Our strategy provides suitable functional handles for synthesis of the natural product itself. For instance, removal of the acetonide protecting group in furo[3,4-*b*]pyran-5-one **6**, followed by diol cleavage, Julia–Kocienski olefination and benzyl ether deprotection would produce desmethyl (–)-TAN-2483B. Furthermore, incorporation of the C-7 methyl group, either into an oxidised derivative of alcohol **11** or during the homologation of **4**, would provide the natural product. Our work to these ends will be reported in due course.

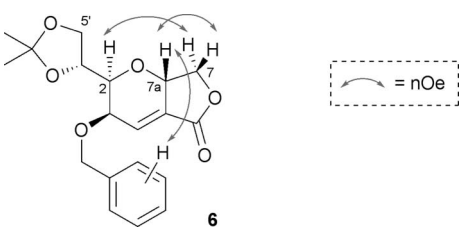


Fig. 2 Key nOe results used in the stereochemical assignment of **6**.

The route described above represents, to our knowledge, the first synthesis of the (–)-TAN-2483B ring system, accessed from D-mannose in 11 steps. This strategy provides scope for inclusion of the functionality present in the natural product.

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Notes and references

‡ **Acetate 8**. Glycal **5** (462 mg, 1.67 mmol) was dissolved in chloroform (3 mL), treated with TEBAC (8 mg, 0.04 mmol), followed by a solution of sodium hydroxide (3.01 g, 75.3 mmol) in water (3.0 mL) and allowed to stir at room temperature for 2.5 hours. The reaction mixture was dissolved in water, then extracted with diethyl ether. The combined ethereal fractions were dried, filtered and concentrated to afford a brown oil. This oil was passed through a plug of silica gel and eluted with 1:5 ethyl acetate/hexanes to afford crude cyclopropane **7** as a yellow oil. This sample was dissolved in acetic acid (17 mL), treated with silver acetate (435 mg, 2.61 mmol), and then stirred at 80 °C for two hours. The solution was filtered through Celite® and eluted with diethyl ether. The reaction mixture was concentrated to provide a yellow oil, which was purified by

column chromatography (1:5 EtOAc/hexanes), affording an inseparable mixture of acetyl pyranoside anomers **8** (495 mg, 77% over two steps, 3:1 ratio) as a pale-yellow oil.

§ **Furo[3,4-*b*]pyran-5-one 6**. A solution of alcohols **11a** and **11b** (40 mg, 0.11 mmol, 2.8:1 ratio) in 1,4-dioxane (3.0 mL) was treated with palladium(II) acetate (10 mg, 0.044 mmol), triphenylphosphine (60 mg, 0.23 mmol) and *N*,*N*-diisopropylethylamine (30 μL, 0.17 mmol), then stirred at reflux under an atmosphere of carbon monoxide for one day. The solution was filtered through a pad of silica, then washed with diethyl ether. The ethereal solution was dried, filtered and concentrated to provide a brown oil. Upon column chromatography (1:3 EtOAc/hexanes), starting material **11** was recovered (3.7:1 ratio, 25 mg, 63%) and bicycle **6** (7 mg, 18%) was obtained as a pale-yellow solid. R_f 0.3 (1:3 EtOAc/hexanes); $[\alpha]_D^{18}$ −142 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (complex m, 5H, Bn), 7.25 (dd, J = 6.1, 3.4 Hz, 1H, H-4), 5.18 (app. td, J = 7.9, 3.0 Hz, 1H, H-7a), 4.64 (d, J = 11.5 Hz, 1H, one of $PhCH_2$), 4.60 (partially obscured dd, J = 8.7, 8.3 Hz, 1H, one of H-7), 4.59 (d, J = 11.5 Hz, 1H, one of $PhCH_2$), 4.42–4.38 (complex m, 2H, H-3 and H-4′), 4.13 (dd, J = 8.6, 6.2 Hz, 1H, one of H-5′), 4.00 (dd, J = 8.8, 7.6 Hz, 1H, one of H-7), 3.96 (dd, J = 8.8, 5.1 Hz, 1H, one of H-5′), 3.38 (dd, J = 8.3, 0.9 Hz, 1H, H-2), 1.38 (s, 6H, $(CH_3)_2C$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (C, C-5), 137.6 (C, Ph), 135.4 (CH, C-4), 133.8 (CH, C-4a), 128.5 (CH, Ph), 128.0 (CH, Ph), 127.8 (CH, Ph), 109.2 (C, $(CH_3)_2C$), 75.7 (CH, C-2), 73.5 (CH, C-4′), 72.0 (CH_2, $PhCH_2$), 71.1 (CH_2, C-7), 70.3 (CH, C-7a), 67.5 (CH_2, C-5′), 67.3 (CH, C-3), 26.9 (CH_3, one of $(CH_3)_2C$), 25.3 (CH_3, one of $(CH_3)_2C$); IR (KBr): 2984, 2923, 2874, 1772, 1377, 1369, 1204, 1108, 1067, 768 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}O_6Na^+$ $[M + Na]^+$ 369.1314, found 369.1308.

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11 Molecular mechanics calculations (see Supporting Information) indicate that the distance between H-2 and H-7a in the undesired epimer, 7a-*epi*-**6**, would be *ca.* 2.38 Å, so a strong nOe signal would be expected. The absence of an nOe implies that the desired isomer, **6**, is formed. This assignment is corroborated by nOe enhancements between H-7a and protons on the top face as drawn: H5′, an aromatic proton of the benzyl group, and the proton attached to C-7 that does not interact with H-2 (the other H-7 displays a weaker nOe with H-7a and a distinct correlation with H-2).