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The first total syntheses of (±)-Preussomerins K and L using 2-arylacetal anion technology

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Abstract—The first syntheses of newly isolated members of the Preussomerin family, Preussomerins K and L, are reported. Key steps include the functionalisation of a 2-arylacetal anion, one-pot Friedel–Crafts cyclisation–deprotection and reductive opening of epoxides.

In recent years, a large number of novel bioactive metabolites have been isolated from fungi, which contain two naphthalene units linked together.[1] Biosynthetically, they all have a common origin, being generated by oxidative coupling via the 1,8-dihydroxynaphthalene (DHN) pathway and late introduction of their individual oxygenation patterns.[2] Most of these metabolites exhibit significant antifungal and antibacterial properties, presumably arising because of interspecies competition among dung-inhabiting fungi. However, the main biological interest concerns their ability to inhibit farnesyl-protein transferase (FTPase) in a highly selective fashion. This enzyme plays a critical role in the post-translational modification of a range of different intracellular proteins. As a result, FTPase inhibitors have great potential in cancer chemotherapy.[3] Among the main representatives of this large group of natural products are the Diepoxins,[4] Palmarumycins,[5] Spiroxins[6] and Preussomerins.[7]

The Preussomerin family of natural products currently consists of 13 members (representative examples are shown in Fig. 1).[7] Preussomerins A–F were the first members of the family to be reported[7a] and Preussomerins G–L are the most recent additions.[7b] From a structural viewpoint, all the Preussomerins possess two naphthalene units linked by three oxygen atoms,

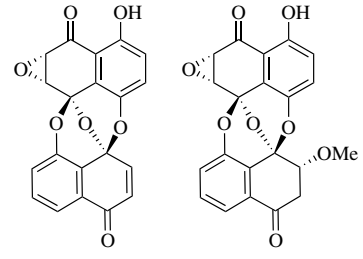

Figure 1. Representative members of the Preussomerin natural products.

generating a bis-spiroacetal system. This remarkable head-to-tail trioxabicyclo[3.3.1]nonane nucleus represents a unique natural product unit and a challenging target for total synthesis.

The first synthesis of a Preussomerin was carried out by Chi and Heathcock, who reported an elegant total synthesis of (±)-Preussomerins G and I.[8] This approach followed a putative biomimetic pathway based on the

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spontaneous oxidative dimerisation of naphthalenediol monoacetals. Further work by Barrett et al., using an oxidative spirocyclisation again as the key step, allowing them to access (−)-Preussomerin G.[9]

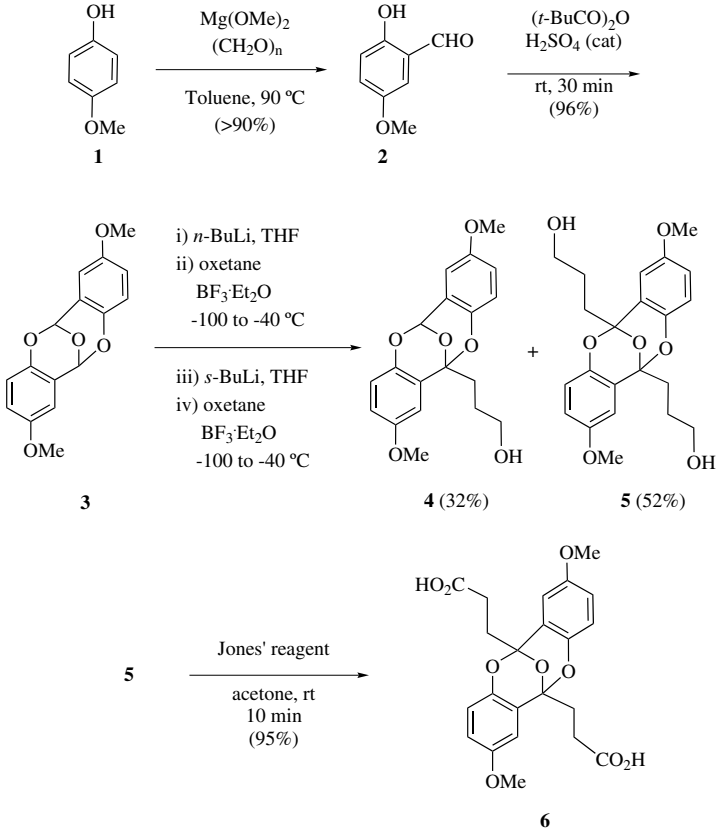
Our interest in the Preussomerins began as part of a programme involving the synthesis of FTPase inhibitors for biological screening (e.g., Manumycin A[10] and Palmarumycin CP1[11]). In this letter we describe the total syntheses of Preussomerin K and L based on a novel non-biomimetic strategy. The route involves formation of the bis-acetal in a single step at the start of the synthesis, with the elaboration of the outer fringes of the molecule at the end. One key step involves the previously reported 2-aryl acetal anion alkylation chemistry,[12] which has now been successfully applied to construct the newer members of the family, Preussomerin K and L, for the first time.

The synthesis started with the inexpensive methoxyphenol **1**. Magnesium methoxide-mediated *ortho*-formylation[13] gave access to large amounts of 5-methoxysalicylaldehyde **2**, which was smoothly dimerised to provide the key bis-acetal **3** in high yield (Scheme 1).[12] Deprotonation of bis-acetal **3** with *n*-BuLi, followed by alkylation with oxetane, provided the unsymmetrical compound **4**. The second alkylation was found to be more difficult, due in part for the need of a stronger base than *n*-BuLi. Under the optimised conditions, both alkylations were conducted in a one-pot manner and the diol **5** could be isolated in 52% yield. Oxidation of diol **5** was achieved by direct Jones oxidation, which provided the diacid **6** in high yield. This sequence represents a considerable improvement of the route originally published by our group.[12]

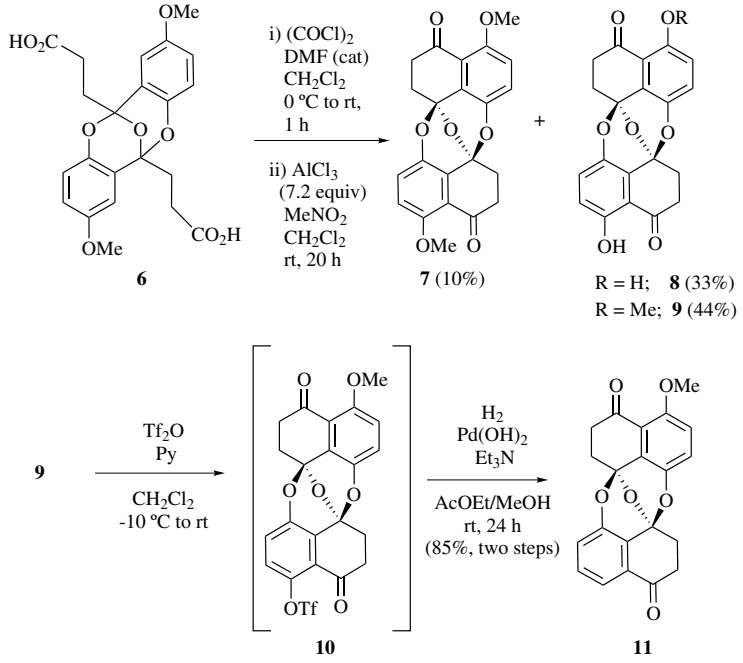
The next key step of the synthesis involved Friedel–Crafts cyclisation of the diacid **6**. After activating the diacid as the acid chloride, treatment with a homogenous solution of $AlCl_3$ in nitromethane produced the Friedel–Crafts adduct **7**. However, if the reaction was allowed to stand for longer in the presence of excess $AlCl_3$, two new compounds, characterised as **8** and **9**, began to appear, indicating that after a rapid cyclisation (less than 1 h to completion), the remaining Lewis acid slowly catalysed the cleavage of the phenolic methoxy groups. All compounds **7**–**9** contain the full Preussomerin skeleton but, additionally, in compound **9** the symmetry has been broken. This one-pot cyclisation–deprotection reaction has been optimised to give a 44% yield of compound **9** (Scheme 2), thereby providing an ideal advanced intermediate for the assault on Preussomerins K and L. It should be noted that compounds **7** and **8** can be recycled to provide additional amounts of **9**.

The deoxygenation of the free phenolic group in **9** was carried out by formation of triflate **10**, which was cleanly reduced by catalytic hydrogenation[14] to provide **11** in good overall yield.

Having established an easily scalable route to **11**, our attention was focused on the introduction of the two

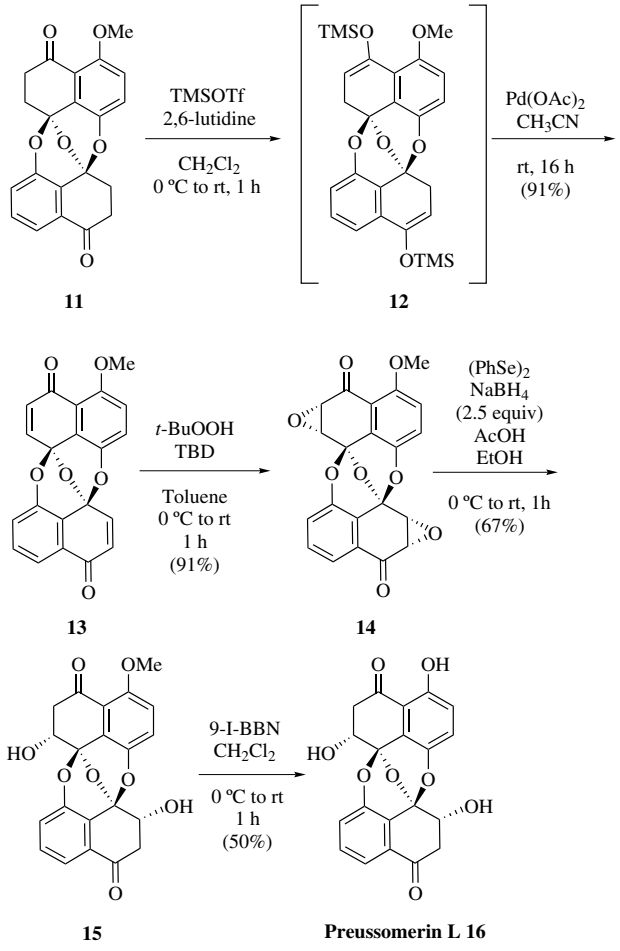


Scheme 1. Early steps of the synthesis.



Scheme 2. Friedel–Crafts acylation–desymmetrisation of the bis-acetal.

conjugated double bonds (Scheme 3). Attempts to carry out the direct conversion of **11** into dienone **13** (benzeneseleninic anhydride,[11] DDQ, IBX,[15] etc.) were unsuccessful. This problem was circumvented by proceeding via the bis-silyl enol ether **12**. Conversion of **12** into dienone **13** was first attempted using IBX complexes.[16] The complex IBX-MPO generated the dienone **13** in 41% yield but the best results were found using Saegusa conditions,[17] giving dienone **13** in 91% yield on treatment with stoichiometric $Pd(OAc)_2$. The use of catalytic Pd was not successful.



Scheme 3. Synthesis of Preussomerin L **16**.

Epoxidation of dienone **13** was carried out using *tert*-butyl hydroperoxide in presence of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (TBD) following our own methodology[18] to yield the bis-α,β-epoxyketone **14** in excellent yield (Scheme 3). It should be noted that the epoxidation proceeded with complete stereoselectivity for the less hindered faces of the dienone **13** giving a single diepoxide. In the next step, selective opening of the diepoxide **14** proved straightforward and the bis-β-hydroxyketone **15** was formed easily in good yields by a regio- and stereoselective organoselenium-mediated process.[19] The X-ray crystallographic analysis of **15** confirmed the structure (Fig. 2),[20] showing it to be exactly in accordance with that of the natural products, with the two aromatic rings almost perpendicular to each other.[7b]

Removal of the methyl of the phenolic ether in **15** was achieved successfully using 9-I-BBN affording the first of the natural products, Preussomerin L **16**.

This route could also be modified to prepare Preussomerin K (Scheme 4). The use of sub-stoichiometric amounts of organoselenium reagent during the reduction of diepoxide **14** generated a mixture of four compounds—the starting material **14**, diol **15** and two new compounds namely **17** and **18**. The most interesting was

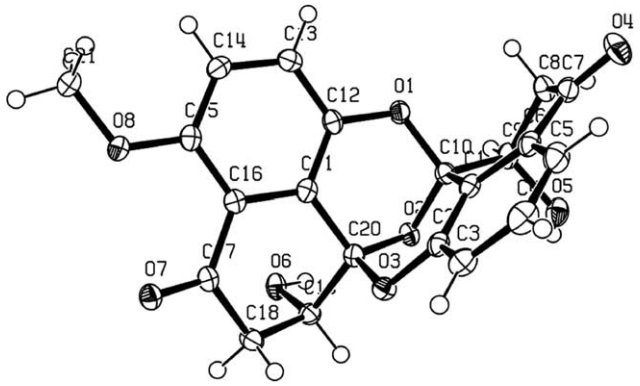


Figure 2. ORTEP drawing of compound **15** (50% probability thermal ellipsoids).[20]

compound **18**, which was easily separated and isolated in 54% yield under the optimised conditions. Unfortunately, attempted deprotection of **18** (9-I-BBN, bromochatecolborane, etc.) resulted in extensive degradation. We circumvented this limitation by using excess boron tribromide, which provided the intermediate bromohydrin **19**. The epoxide was regenerated by basic treatment of **19** affording Preussomerin K **20** (Scheme 4). The data from the synthetic samples of Preussomerin K and L matched those found by analysing authentic samples of the natural compounds kindly provided by Professor K. Krohn.

In summary, we have successfully synthesised the racemic natural products Preussomerin K and L (4% overall yields in both cases) from inexpensive building blocks through the application of a novel non-biomimetic strategy with the functionalisation of a 2-arylacetal anion, one-pot Friedel–Crafts cyclisation–deprotection and reductive opening of epoxides as the key steps of the synthesis. Further studies towards the total synthesis of more members of the Preussomerin family as well as asymmetric approaches are currently under investigation and will be reported in due course.

Acknowledgements

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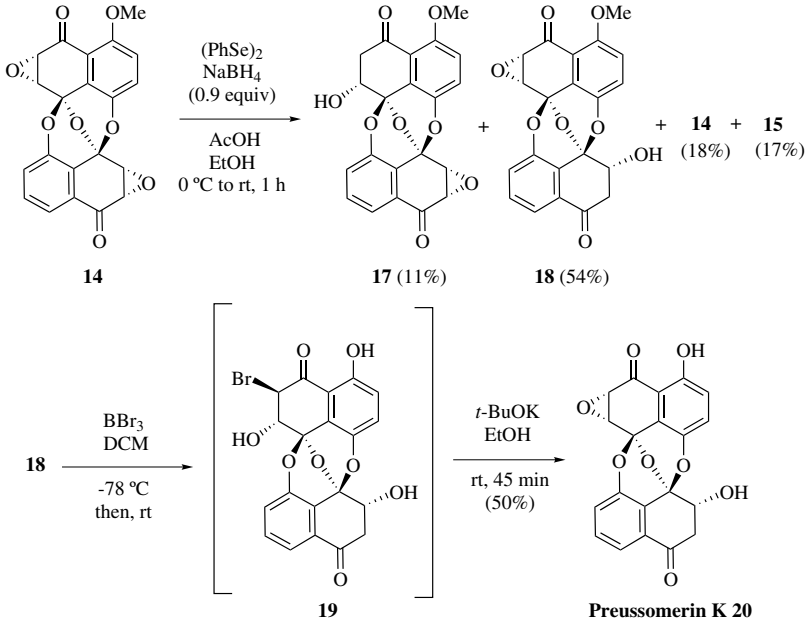
References and notes

1. For a recent review, see Krohn, K. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer: Wien, 2003; Vol. 85, p 1.
2. (a) Bode, H. B.; Wegner, B.; Zeeck, A. *J. Antibiot.* **2000**, *53*, 153; (b) Bode, H. B.; Zeeck, A. *Phytochemistry* **2000**, *55*, 311.
3. (a) Ohkanda, J.; Knowles, D. B.; Blaskovich, M. A.; Sebti, S. M.; Hamilton, A. D. *Curr. Top. Med. Chem.* **2002**, *2*, 303–323; (b) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.
4. (a) Schlingmann, G.; West, R. R.; Milne, L.; Pearce, C. J.; Carter, G. T. *Tetrahedron Lett.* **1993**, *34*, 7225; (b) Schlingmann, G.; Matile, S.; Berova, N.; Nakanishi, K.; Carter, G. T. *Tetrahedron* **1996**, *52*, 435.
5. (a) Krohn, K.; Michel, A.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1099; (b) Krohn, K.; Michel, A.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1093; (c) Krohn, K.; Beckmann, K.; Florke, U.; Aust, H. J.; Draeger, S.; Schulz, B.; Busemanna, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101.
6. McDonald, L. A.; Abbanat, D. R.; Barbieri, L. R.; Bernan, V. S.; Discafani, C. M.; Greenstein, M.; Janota,



Scheme 4. Synthesis of Preussomerin K **20**.

K.; Korshalla, J. D.; Lassota, P.; Tischler, M.; Carter, G. T. *Tetrahedron Lett.* **1999**, *40*, 2489.
7. (a) Weber, H. A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355; (b) Krohn, K.; Flörke, U.; John, M.; Root, N.; Steingröver, K.; Aust, H. J.; Draeger, S.; Schulz, B.; Antus, S.; Simonyi, M.; Zsila, F. *Tetrahedron* **2001**, *57*, 4343, and references cited therein.
8. Chi, S.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 3.
9. Barrett, A. G. M.; Blaney, F.; Campbell, A. D.; Hamprecht, D.; Meyer, T.; White, A. J. P.; Witty, D.; Williams, D. J. *J. Org. Chem.* **2002**, *67*, 2735.
10. Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526.
11. Ragot, J. P.; Steeneck, C.; Alcaraz, M. L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073.
12. Ragot, J. P.; Prime, M. E.; Archibald, S. J.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1613.
13. Aldred, R.; Johnston, R.; Levin, D.; Neilan, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1823.
14. Kozikowski, A. P.; Tückmantel, W.; George, C. *J. Org. Chem.* **2000**, *65*, 5371.
15. (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993; (b) Nicolaou, K. C.; Zhong, Z. L.; Baran, P. S. *J. Am. Chem. Soc.* **2002**, *112*, 7596.
16. Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.
17. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
18. Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R. J. K. *Synlett* **1999**, 795.
19. Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469.
20. Crystallographic data for **16** can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK (ref. CCDC 230613).