ORGANIC LETTERS

2000
Vol. 2, No. 11
1613−1616

A Novel Route to Preussomerins via 2-Arylacetal Anions

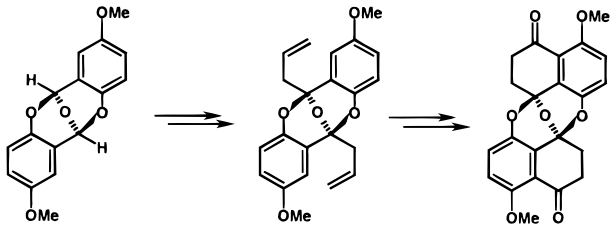
Jacques P. Ragot, Michael E. Prime, Stephen J. Archibald, and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

rjkt1@york.ac.uk

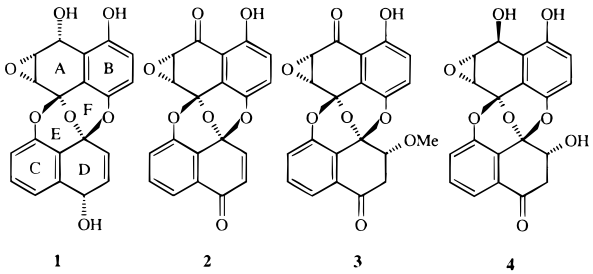
Received March 31, 2000

ABSTRACT



Dimerization of salicylaldehydes provided 6*H*,12*H*-6,12-epoxydibenzo[*b*,*f*][1,5]dioxocins in multigram quantities. Deprotonation–allylation of the benzylic acetals followed by further functionalization of the diallyl derivative and double Friedel–Crafts cyclization gave a novel preussomerin analogue which possessed the full carbon skeleton of the natural products.

The preussomerin family of natural products consists of 10 fungal metabolites.[1] Preussomerin A (**1**) was first isolated from the coprophilous fungus *Preussia isomera* during a study of interspecies competition among dung-inhabiting fungi.[1a] Subsequently, closely related compounds were isolated from the same organism and named preussomerins B−F.[1b] Preussomerin D was also later isolated from endophytic fungus *Hormonema dematioides* recovered from living plant tissue of a coniferous tree.[1c] New additions to this group of natural products came in 1994, when Singh et al. isolated preussomerins G (**2**), H, and I (**3**) from an unidentified



1 **2** **3** **4**

coelomycetes (MF5916).[1d] Most recently a new preussomerin analogue, 3′-*O*-desmethyl-1-epipreussomerin C (**4**), was isolated from cultures of the coprophilous fungus *Sporormiella vexans*.[1e] These 10 preussomerins are characterized by a head to tail trioxabicyclo[3.3.1]nonane bis-acetal nucleus, unique in the natural product kingdom.

Some of these metabolites exhibited significant antifungal and antibacterial properties,[1b] but the main interest concerns their inhibition of Ras farnesyl transferase,[1d] which gives them potential in cancer chemotherapy.[2] We became interested in these natural products as part of our ongoing program to prepare Ras farnesyl transferase inhibitors for biological screening (e.g., manumycin A[3] and palmarumycin CP_1[4]).

Although no synthetic work had been published on the preussomerins when we embarked on this project, Heathcock and Chi[5] recently reported an elegant total synthesis of

(1) (a) Weber, H. A.; Baenziger, N. C.; Gloer, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 6718−6719. (b) Weber, H. A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355−4360. (c) Polishook, J. D.; Dombrowski, A. W.; Tsou, N. N.; Salituro, G. M.; Curotto, J. E. *Mycologia* **1993**, *85*, 62−64. (d) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296−6302. (e) Soman, A. G.; Gloer, J. B.; Koster, B.; Malloch, D. *J. Nat. Prod.* **1999**, *62*, 659−661.

(2) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971−2990.

(3) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526−3527.

(4) Ragot, J. P.; Steeneck, C.; Alcaraz, M.-L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073−1082.

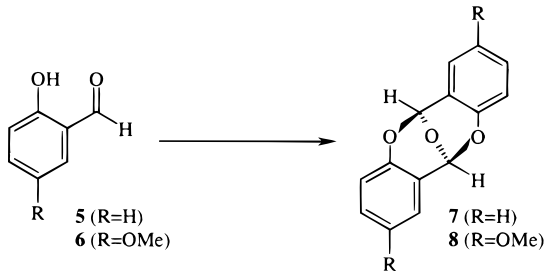
(5) Chi, S.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 3−5.

10.1021/ol005881t CCC: $19.00
Published on Web 05/02/2000

(±)-preussomerins G (**2**) and I (**3**) based on a putative biomimetic approach. In this Letter we describe our own approach toward preussomerins which is based on a novel use of 2-arylacetal anions. We have applied this strategy to construct a novel symmetrical preussomerin analogue containing the full carbon skeleton of the natural products.

Our research commenced with an investigation of ways to form the bis-acetal nucleus of preussomerins. We first tried to dimerize β-hydroxy ketones using a wide range of acidic/dehydrating conditions. This proved unsuccessful, a surprising observation given that β-hydroxy aldehydes readily undergo dimerization. Indeed, the anhydro dimer of *o*-hydroxybenzaldehyde (**5**) (6*H*,12*H*-6,12-epoxydibenzo-[*b*,*f*]-[1,5]dioxocin, **7**) has been known for over a century and many such dimers have been described subsequently.[6] We found the preferred method of dimerization usually employed acetic anhydride as the dehydrating agent and a catalytic amount of sulfuric acid.[6] Thus, **5** gave known dimer **7** in 65% yield on a 20 g scale. Although the novel methoxy anhydro dimer **8** could be obtained from **6** with this procedure (40%), the yield was improved to 96% using pivalic anhydride in place of acetic anhydride (Table 1)

Table 1. Dimerization of β-Hydroxy Aldehydes



substrate	reaction conditions	product	yield (%)[b]
5	Ac_2O, H_2SO_4[a]	**7**	65
6	Ac_2O, H_2SO_4	**8**	40
6	$(^tBuCO)_2O$, H_2SO_4[a]	**8**	96

[a] Reaction carried out on a 20 g scale. [b] After recrystallization

An X-ray crystallographic analysis of a single crystal confirmed the structure of **8** (see Figure 1).

These anhydro dimers possess four of the six rings present in the natural products, and our plan was to use them as starting materials for preussomerins. We therefore needed to replace the hydrogens at both benzylic acetal positions by three-carbon units which could be functionalized and then cyclized on to the aromatic rings to generate rings A and D. Acetal anions are not widely used in synthesis, and only a few examples involving α,α-dialkoxy- or dibenzyloxyacetate anions have been described in the literature.[8] Furthermore,

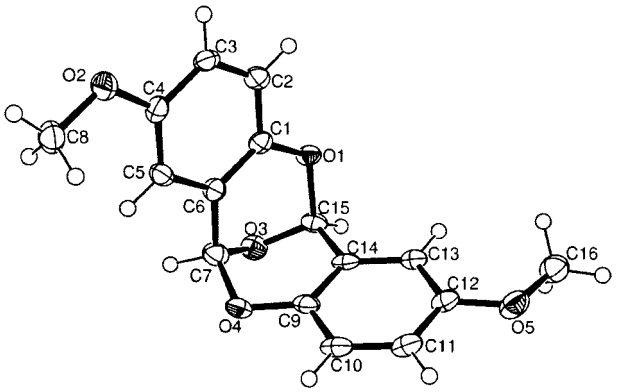
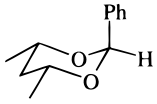
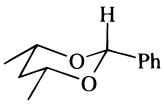


Figure 1. ORTEP[7] plot (50% probability ellipsoids) of the molecular structure of 6*H*,12*H*-2.8-dimethoxy-6,12-epoxydibenzo-[*b*,*f*][1,5]dioxocin (**8**).

it has been reported that α,α-dialkoxyaryl anions are not stable and rearrange in a variety of ways.[9] However, Meyers, Eliel, and co-workers[10] in 1979 published what is, to the best of our knowledge, the only use of 2-arylacetals as acyl anion equivalents. They also showed that the 2-arylacetal proton is removable only if it can occupy an equatorial-like conformation as in **9**; 1,3-dioxanes with axial hydrogens (e.g., **10**) do not undergo proton abstraction.



9



10

These results have been supported[11] by ab initio calculations for α-oxa carbanions carried out by Lehn and Wipff which predicted that an equatorially disposed carbanion (stabilized by the mixing between the carbanion lone pair and the antibonding σ^* orbital of the antiperiplanar O−C bond) should be preferred over the axial carbanion (destabilized by the interaction between the two antiperiplanar occupied lone pairs of the carbanion and the oxygen atom). The acetal protons in the conformationally fixed bis-acetal nucleus are both equatorial, as can be clearly seen from the X-ray structure[12] of anhydro dimer **8** (Figure 1).

We therefore investigated the deprotonation of the anhydro dimers **7** and **8** at the benzylic acetal position. Our results

(6) Kulkarni, V. S.; Hosangadi, B. D. *Synth. Commun.* **1986**, *16*, 191−193 and references therein.

(7) Johnson, C. K. ORTEP, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

(8) (a) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 4551−4554. (b) Neef, G.; Eder, U. *Tetrahedron Lett.* **1977**, 2825−2828. (c) Huet, F.; Pellet, M.; Conia, J. M. *Synthesis* **1979**, 33−34. (d) Adam, W.; Encarnacion, L. A. A. *Chem. Ber.* **1982**, *115*, 2592−2605.

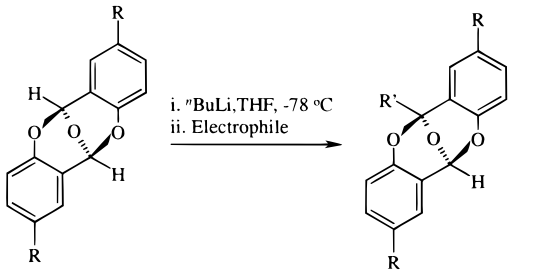
(9) Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2006−2007. (b) Hines, J. N.; Peagram, M. J.; Whitham, G. H.; Wright, M. *Chem. Commun.* **1968**, 1593−1594.

(10) (a) Meyers, A. I.; Campbell, A. L. *Tetrahedron Lett.* **1979**, 4155−4158. (b) Meyers, A. I.; Campbell, A. L.; Abatjoglou, A. G.; Eliel, E. L. *Tetrahedron Lett.* **1979**, 4159−4162.

(11) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498−7505.

(12) Crystallographic data for **8** and **14** can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Table 2. Functionalization of the First Benzylic Acetal Position[a]



substrate	electrophile	product[b]	yield (%)
7	D_2O	**9**	78
7	MeI[c]	**10**	75
7	allyl-Br[c]	**11**	88
8	allyl-Br[c]	**12**	91[d]

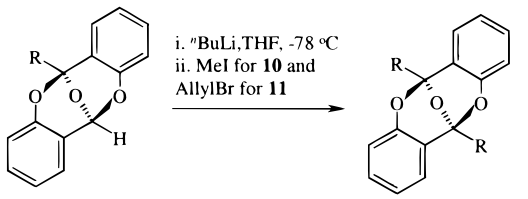
[a] All reactions were carried out using 1.1 equiv of base. [b] All products were fully characterized. [c] Freshly passed through alumina. [d] Three gram scale.

are summarized in Table 2 and showed that deprotonation of **7** occurs smoothly and that the corresponding carbanion can be trapped with D_2O to give **9** or with various carbon electrophiles such as methyl iodide or allyl bromide to give in good yield **10** and **11**, respectively. The allylated adduct **12** was obtained from **8** in 91% yield on a multigram scale.

When **7** or **8** was reacted with 2 equiv of base followed by excess allyl bromide, no dialkylated products were isolated and only **11** and **12** were observed, albeit in lower yields. Sequential allylation was therefore investigated.

Monoalkylated derivatives **10** and **11** were subjected to the same deprotonation/alkylation procedure (Scheme 1), and

Scheme 1. Functionalization at the Second Benzylic Acetal Position



both C_2-symmetric products, **13** and **14**, were obtained. A single crystal of **14** was grown and the structure confirmed by crystallographic studies.[12] The ORTEP representation is shown in Figure 2. It is interesting to note that the general shape of **14** is similar to that of the natural products. Indeed,

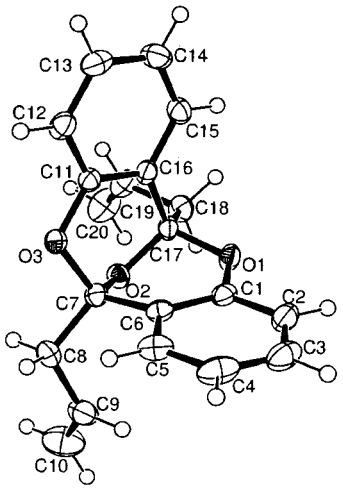


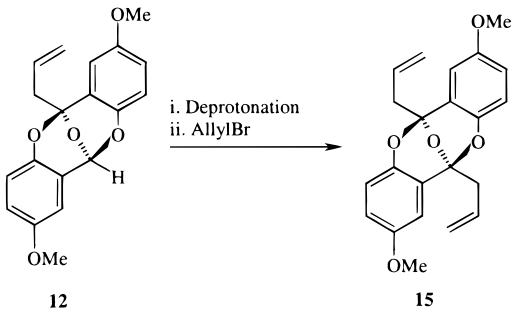
Figure 2. ORTEP[7] plot (50% probability ellipsoids) of the molecular structure of 6*H*,12*H*-6,12-diallyl-6,12-epoxydibenzo[*b*,*f*]-[1,5]dioxocin (**14**).

the two aromatic rings are almost perpendicular to each other with a measured dihedral angle of 83.1° (compared with 77.4° in **1**[1b]).

The yield of the second deprotonation−alkylation was excellent in the case of the methyl derivative but poor when the allyl side chain was present (although significant amounts of starting material were recovered). The lower material balance in the allylation process may result from β-elimination.

The second allylation was optimized using the methoxy derivative **12**, and the results are shown in Table 3. The

Table 3. Optimization of the Second Benzylic Acetal Allylation[a]



deprotonation conditions	recovered **12** (%)[c]	**15** (%)
^{n}BuLi, −78 °C[b]	60	18
^{n}BuLi, TMEDA, −78 °C	68	10
^{s}BuLi, −78 °C	**47**	**52**
^{t}BuLi, −78 °C	53	10

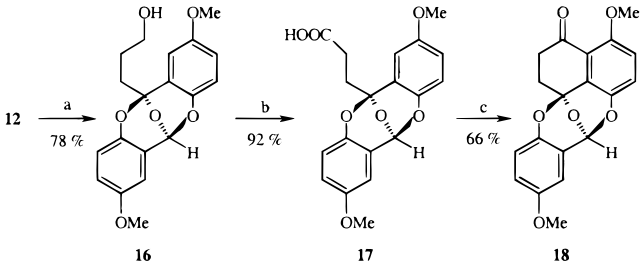
[a] All reactions were carried out in dry THF with 1.1 equiv of base. [b] When the temperature was lowered to −100 °C or the base changed to sodium hexamethyldisilazide, no allylated **15** was isolated and only unreacted **12** was recovered. [c] Recovered starting material.

standard procedure (^{n}BuLi, −78 °C) gave **15** in only 18% yield. When the base was replaced with sodium hexamethyldisilazide or the temperature lowered to −100 °C, no product was formed. While TMEDA addition showed no improvement (10% yield), we were pleased to find that ^{s}BuLi gave a significant improvement, with 52% yield of **15** (99% yield based on recovered starting material). It is possible that the use of ^{s}BuLi suppresses side reactions (such as β-elimination). This result was not improved with ^{t}BuLi where an increasing amount of decomposition could be detected, possibly due to metalation on the aromatic rings.

Having designed a method to alkylate both benzylic acetal positions, we next needed to functionalize the terminal alkenes and effect cyclization onto the aromatic rings, thus forming the hexacyclic structure of the preussomerins.

We developed the chemistry needed on the model system **12** as shown in Scheme 2. Conversion of terminal alkene

Scheme 2. Cyclization on a Model System[a]



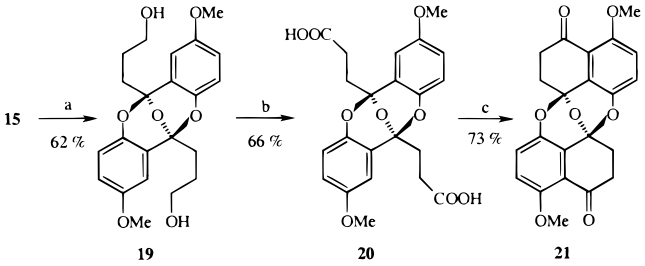
[a] (a) i. 9-BBN, THF, 0 °C, ii. NaOH, H_2O_2; (b) PDC, DMF; (c) i. $(COCl)_2$, cat. DMF, DCM, 0 °C to rt, ii. $AlCl_3$, $PhNO_2$.

12 into primary alcohol **16** proceeded in good yield using 9-BBN followed by oxidative workup. Further oxidation of **16** with pyridinium dichromate in DMF gave acid **17** in excellent yield.

Final ring closure was achieved in two steps: acid **17** was first converted into the corresponding acid chloride using oxalyl chloride and catalytic DMF, and this was reacted in situ with the Lewis acid $AlCl_3$ to effect the intramolecular Friedel−Crafts cyclization. Cyclized ketone **18** was obtained in 66% yield. It is noteworthy that the bis-acetal moiety is compatible with the acidic conditions required for this cyclization. This is a further testimony to the unusual stability of these unique bis-acetals, which has been commented on with the natural products.[1]

Finally, we applied this chemistry to C_2-symmetric dimer **15**, constructing rings A and D simultaneously. Diene **15** was converted into diol **19** with 9-BBN followed by oxidative workup. Diol **19** was oxidized directly to diacid **20** which was converted in situ to the diacid chloride before being subjected to $AlCl_3$. Diketone **21** was thus obtained in 73% yield via a double intramolecular Friedel−Crafts cyclization (Scheme 3).

Scheme 3. Synthesis of the Preussomerin Analogue **21**[a]



[a] (a). i. 9-BBN, THF, 0 °C, ii. NaOH, H_2O_2; (b) PDC, DMF; (c) i. $(COCl)_2$, cat. DMF, DCM, 0 °C to rt, ii. 2 equiv of $AlCl_3$, $PhNO_2$.

Compound **21**, which was fully characterized, contains the complete carbon skeleton and all of the rings A−F found in the natural products: it can thus be considered a novel preussomerin analogue.

In summary, we have developed a new strategy to access preussomerins. The central bis-acetal can be obtained in multigram quantities using dehydrating dimerization of β-hydroxy aldehydes to give anhydro dimers such as **7** or **8**. We have demonstrated that both acetal positions can be sequentially deprotonated and alkylated. Finally we have applied this novel methodology to prepare preussomerin analogue **21**.

We are currently extending this methodology to achieve a total synthesis of the natural product in racemic form and to develop an asymmetric version in order to obtain preussomerins in enantiomerically pure form.

Acknowledgment. We thank the Yorkshire Cancer Research for studentship (J.P.R.) and postdoctoral (M.E.P.) support.

Supporting Information Available: Experimental procedures and analytical data for compounds **12**, **15**, and **21**. This material is available free of charge at http://pubs.acs.org.

OL005881T