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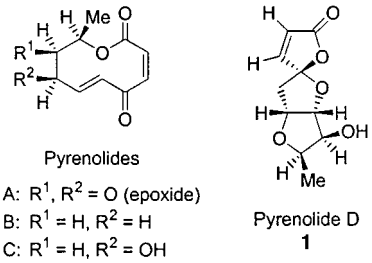
Total Synthesis of (+)-Pyrenolide D**

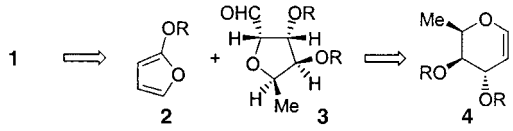
Kenneth M. Engstrom, Mario R. Mendoza, Mauricio Navarro-Villalobos, and David Y. Gin*

The phytogenic fungus *Pyrenophora teres* has been a source of a number of fungal metabolites of interesting and varying biological activities. These metabolites include the pyrenolides A–C,[1] simple macrocyclic lactones that exhibit potent



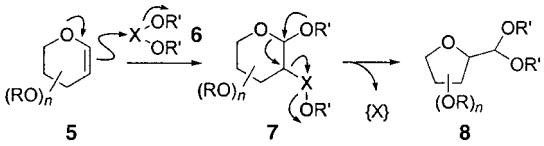
growth-inhibitory and morphogenic activities toward fungi. A fourth metabolite, pyrenolide D (**1**),[2] is structurally distinct from the other members of this family in that it incorporates a highly oxygenated tricyclic spiro-γ-lactone structure related to certain members of the cephalosporolide class of natural products.[3] Moreover, pyrenolide D is further distinguished from the other pyrenolides in that it is not active toward fungi, but rather that it exhibits significant cytotoxic activity toward HL-60 cells. This biological profile, in combination with its densely functionalized polycyclic structure, spawned our efforts to develop a synthetic approach to **1** that would also establish the absolute configuration of the natural product. We report herein the first total synthesis of **1** by a very short sequence. In this context, a method for the efficient construction of highly oxygenated tetrahydrofurans from glycal starting materials is reported.

Initial retrosynthetic disconnection of **1** (Scheme 1) leads back to a 2-alkoxyfuran **2** and the highly oxygenated tetrahydrofurfural derivative **3** as viable synthetic precursors.



Scheme 1. Retrosynthetic analysis.

Although a number of synthetic strategies to prepare **3** can be envisioned through the synthesis and cyclization of acyclic polyol precursors, we reasoned that a more efficient approach might arise from a stereoselective oxidative ring contraction of a glycal substrate such as 6-deoxy-D-gulal (**4**), incorporating three of the four stereocenters within **3**. For such an oxidative ring contraction process to be feasible, an appropriate electrophilic oxidant **6** (Scheme 2) is required. Not only must



Scheme 2. Oxidative ring contraction of glycals.

this reagent efficiently perform an electrophilic activation of the glycal substrate (**5**→**7**), but it must also concomitantly install a potent leaving group at the C2 position of the activated pyranoside intermediate **7**. This would hopefully allow 1,2-migration of the endocyclic C–O bond in a displacement of the C2 leaving group, resulting in a net oxidative ring contraction of the glycal substrate to form the C-furanoside product **8**, an intermediate that directly maps onto the proposed synthetic intermediate **3** (Scheme 1). Given our interest in glycal activation processes,[4] we sought to establish the means to effect the conversion of **5** into **8** as one of the key steps in the synthesis of **1**.

Based on this strategy, the initial synthetic target involved the preparation of 2,3-di-*O*-protected-6-deoxy-D-gulal (**4**) as the desired substrate for the formation of the C-furanoside **3**. The synthesis commenced (Scheme 3) with the preparation of the pseudoglycal **10** from commercially available tri-*O*-acetyl-D-galactal (**9**) through a three-step sequence that included: $SnCl_4$-catalyzed Ferrier-type glycosylation of thiophenol (84%), acetate hydrolysis and selective tosylation of the C6-hydroxy group (78%), and hydride displacement of the C6-sulfonate functionality (86%).[5] Subsequent oxidation of the allylic sulfide in **10** with *m*-chloroperoxybenzoic acid led to the formation of the corresponding anomeric sulfoxide, which underwent an Evans–Mislow [2,3]-sigmatropic rearrangement. Subsequent aminolysis of the sulfenate functionality installed the α-C3-OH group (89%).[6] The resulting 6-deoxy-D-gulal diol **11** was protected as the bis(*tert*-butyldimethylsil-

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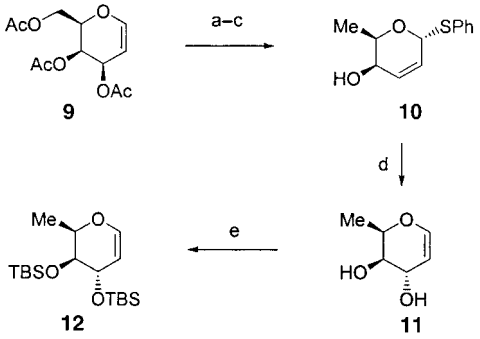
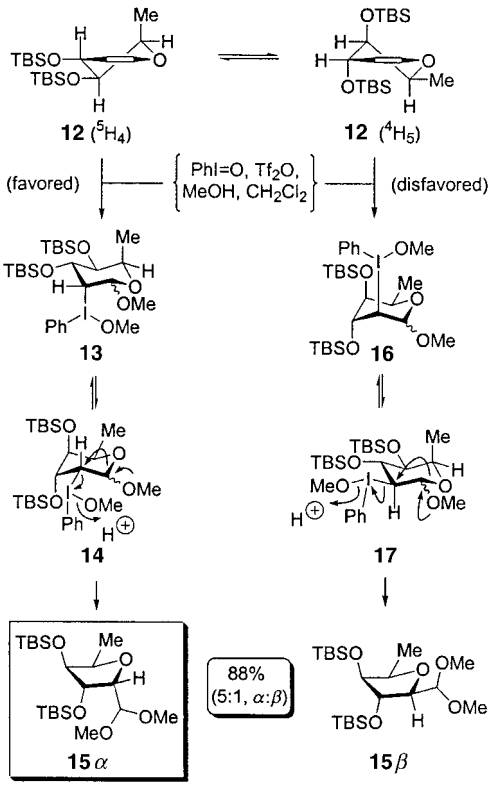


Scheme 3. a) PhSH, $SnCl_4$ (cat.), CH_2Cl_2, $-10\,^{\circ}C$, 84%; b) NaOMe, MeOH, $23\,^{\circ}C$; Bu_2SnO, MeOH, reflux; *p*-toluenesulfonyl chloride, Bu_4NBr, $CHCl_3$, 78%; c) $LiAlH_4$, THF, reflux, 86%; d) *m*-CPBA, CH_2Cl_2, $-40\,^{\circ}C$; Et_2NH, THF, $23\,^{\circ}C$, 89%; e) *tert*-butyldimethylsilyl trifluoromethane sulfonate, 2,4,6-(tri-tert-butylpyridine, DMF, $23\,^{\circ}C$, 76%; TBS = *tert*-butyldimethylsilyl.

yl) ether to afford **12** (76%), the desired glycal precursor for stereoselective oxidative ring contraction.

Reports on the direct oxidative ring contraction of glycals have been scarce,[7] with only a few examples of this process proceeding efficiently with stoichiometric quantities of $Tl(NO_3)_3$ as the oxidant. To avoid the use of highly toxic heavy metal salt oxidants, we focused on the use of hypervalent iodine reagents[8] (i.e., Scheme 2, **6**, X = PhI) to execute this transformation. Studies involving the reaction of hypervalent iodine reagents with glycal substrates have also been limited, except for the pioneering work of Kirschning who employed various I^{III} reagents to effect efficient allylic 3-*O*-oxidations of protected glycals.[9] In their allylic oxidation studies, a few examples were reported in which the action of the Koser reagent (PhI(OH)(OTs)) on a glycal substrate led not only to allylic oxidation, but also to the formation of small quantities of tetrahydrofuran by-products ($\leq 35\%$).[10] Thus, the key challenges in employing I^{III} reagents for glycal oxidative ring contraction in the context of the synthesis of **1** include: 1) the development of a reagent combination that would favor the ring contraction of **12** over the reaction manifold involving C3 oxidation, and 2) the generation of the corresponding C-furanoside **3**, in which the resulting C1-acetal functionality is *cis* to the C3–*O*-substituent, with high stereoselectivity.

After screening a number of hypervalent iodine reagents, we converted the 6-deoxy-D-gulal derivative **12** into the corresponding C-furanoside **15** (Scheme 4) in high yield (88%) by using the reagent combination of iodosylbenzene and trifluoromethane sulfonic (triflic) anhydride (Tf_2O) in a solution of methanol and dichloromethane. In this reaction, dimethoxyiodosylbenzene[11] and triflic acid are presumably generated as the active reagents in situ under anhydrous conditions. The presence of triflic acid is required for efficient ring contraction; the incorporation of an acid scavenger such as 2,4,6-tri-*tert*-butylpyridine rendered the reagent combination unreactive towards **12**.[12] Moreover, the oxidative ring contraction proceeds with good stereoselectivity, yielding a 5:1 mixture of **15** in favor of the desired α-epimer (Scheme 4). Although ^1H NMR spectroscopic analysis of the 6-deoxygulal substrate **12** suggests that it approximates the $^4H_5$ conformation,[13] the half-chair conformational states are dynamic, and it is likely that the observed stereoselective formation of **15*α*** in the ring contraction arises from glycal activation via its $^5H_4$ conformation (i.e., Curtin–Hammett situation, Scheme 4). In this hypothesis, the favored approach of the I^{III} oxidant should occur on the α-face (**12** → **13**), an approach that would not only avoid steric interactions with the C6-methyl group, but would also lead to a chairlike transition state in the activation step to form **13**.[14] Following a conformational chair flip (**13** → **14**) that orients the migrating C1–O bond antiperiplanar to the equatorial C2–I bond, ring contraction would ensue by means of the displacement of iodobenzene with inversion to provide **15*α*** as the major diastereomer. Conversely, β-approach of the oxidant onto **12** ($^4H_5$) would also result in a chairlike transition structure; however, a higher energy transition structure might result as a consequence of a developing *syn*-pentane-like (i.e., 1,3-diaxial) interaction between the C4–O–TBS group and the C2–I^{III} substituent. Following a conformational chair flip (**16** → **17**), ring contraction would lead to the minor diastereomer **15*β***.[15, 16]



Scheme 4. Oxidative ring contraction.

With an efficient synthetic route to the C-furanoside **15*α***, introduction of the butenolide fragment and formation of the spiroketal functionality comprised the remaining steps in the synthesis of **1** (Scheme 5). The dimethyl acetal functionality in the α-epimer of **15** was hydrolyzed in the presence of $TiCl_4$ at $0\,^{\circ}C$. This mild deprotection protocol afforded the tetrahydrofurfural intermediate **18** (88%) without epimerization of the C2 stereocenter and with the TBS protecting groups intact. Addition of commercially available 2-(trimethylsilyloxy)furan to the aldehyde **18** in the presence of $BF_3 \cdot OEt_2$ at $-78\,^{\circ}C$ afforded a diastereomeric mixture of alcohols

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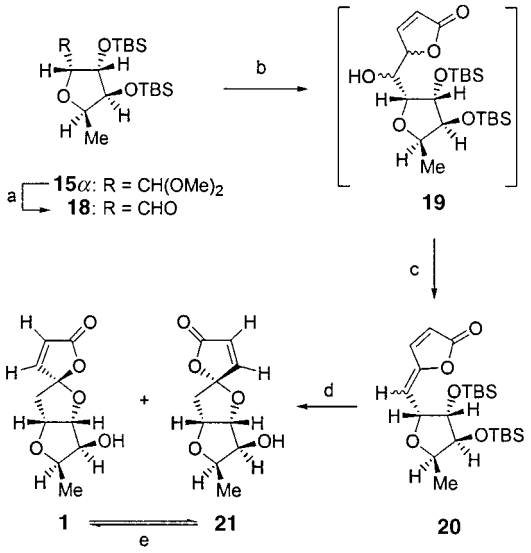

Scheme 5. a) $TiCl_4$, Et_2O, 0 °C, 88 %; b) 2-(trimethylsilyloxy)furan, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C; c) Burgess reagent, PhH, 55 °C, 80 % (two steps); d) 1N $LiOH_{aq}$, 23 °C; 16 % HF_{aq}, 23 °C, 93 % (1:1.4, **1**/**21**); e) 8N HCl_{aq}, THF, 23 °C, quant.

19, which was directly treated with the Burgess dehydrating agent ($MeO_2CNSO_2NEt_3$) to afford the unsaturated γ-lactone **20** (80 %, two steps) as a mixture of stereoisomers (2:1, *E*/*Z*). Formation of the spiroketal functionality and completion of the synthesis proceeded in a two-step, one-pot transformation from **20**, involving initial hydrolysis of the lactone (1N $LiOH_{aq}$), followed by acid-mediated (HF_{aq}) TBS-deprotection and spiroketalization to form a diastereomeric mixture of pyrenolide D (**1**) and its spiroketal epimer **21** in a 1:1.4 ratio (93 % total). Although the thermodynamic distribution of **1** and **21** exhibits essentially no selectivity, separation of the epimers by chromatography is trivial, allowing the quantitative iterative re-equilibration of **21** (8N HCl_{aq}, THF) to enhance the production of the natural product **1**. The spectral data (^1H and ^{13}C NMR, FTIR) of synthetic **1** derived from tri-*O*-acetyl-D-galactal coincide with those reported by Nukina and Hirota ($[\alpha]_D^{23} = +64.3$ ($c = 0.4$, $CHCl_3$), lit.: $[\alpha]_D^{23} = +79.5$ ($c = 0.9$, $CHCl_3$)).

In summary, the first synthesis of pyrenolide D (**1**) is described, involving a short sequence beginning with tri-*O*-acetyl-D-galactal. A key feature in the synthesis includes the efficient formation of highly functionalized tetrahydrofurfural intermediates directly from glycal substrates, by employing the reagent combination of iodosylbenzene and triflic anhydride in a mixture of methanol and dichloromethane. Not only did this process lead to the efficient synthesis and absolute stereochemical assignment of **1**, but it also highlights this oxidative ring contraction strategy as one that holds promise in both natural product and C-nucleoside synthesis.

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[12] It is likely that the triflic acid serves to activate the $PhI(OMe)_2$ reagent generated in situ.
[13] ^1H NMR analysis shows a relatively small H3−H4 proton coupling constant ($J_{3,4} = 2.8$ Hz). This is consistent with previous observations in other pyranosides incorporating vicinal *tert*-butyldimethylsilyl ethers in which *gauche* interactions between the bulky protective groups are minimized. See, for example: a) M. A. Tius, J. Busch-Peterson, *Tetrahedron Lett.* **1994**, *35*, 5181 – 5184; b) W. A. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **1999**, *121*, 3541 – 3542.
[14] This rationale assumes, among other things, that the activation of gulal **12** proceeds irreversibly through a relatively late (i.e., C2-pyramidalized) transition state. For some discussions on the conformational flexibility of glycals, see: a) J. Thiem, P. Ossowski, *J. Carbohydr. Chem.* **1984**, *3*, 287 – 313; b) W. R. Roush, D. P. Sebesta, C. E. Bennett, *Tetrahedron* **1997**, *53*, 8825 – 8836.
[15] The employment of the *tert*-butyldimethylsilyl protecting groups was crucial in achieving the desired stereoselectivity. The use of dibenzyl-D-gulal with the identical oxidative ring contraction procedure led to indiscriminate facial approach of the I^{III} reagent, affording a 1:1 (α/β) mixture of the corresponding tetrahydrofurfural acetals in 82 % yield.
[16] Formation of the minor diastereomer **15*β*** might also arise from the β-approach of the oxidant onto **12** ($^5H_4$), leading to a higher energy twist-boatlike transition state. Following a conformational half-chair flip, ring contraction would lead to the minor diastereomer **15*β***.

Crown-Ether-Directed Assembly of Discrete and One-Dimensional Silver Aggregates Containing Embedded Acetylenediide**

Quan-Ming Wang and Thomas C. W. Mak*

In memory of Daniel Y. Chang

Recent studies have shown that the coordination modes of the acetylide dianion (C_2^{2-}, IUPAC name acetylenediide) can be classified into three categories: 1) linear end-to-end

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