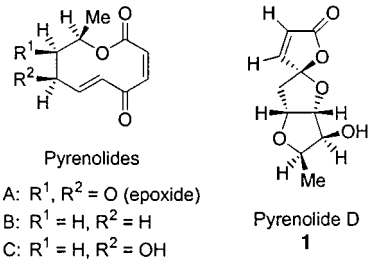
[26] K. Kawamura, M. Shang, O. Wiest, T. P. Fehlner, *Inorg. Chem.* **1998**, *37*, 608.
[27] G. E. Herberich in *Comprehensive Organometallic Chemistry II*, *Vol. 1* (Eds.: E. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**,p. 197.
[28] G. E. Herberich, B. Hessner, G. Huttner, L. Zsolnai, *Angew. Chem.* **1981**, *93*, 471; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 472.
[29] E. D. Jemmis, A. C. Reddy, *Organometallics* **1988**, *7*, 1561.
[30] A. S. Weller, M. Shang, T. P. Fehlner, *Chem. Commun.* **1998**, 1787.

Total Synthesis of (+)-Pyrenolide D**

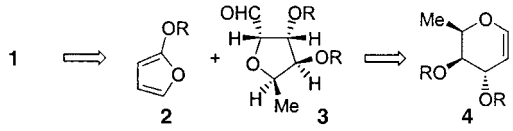
Kenneth M. Engstrom, Mario R. Mendoza, Mauricio Navarro-Villalobos, and David Y. Gin*

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



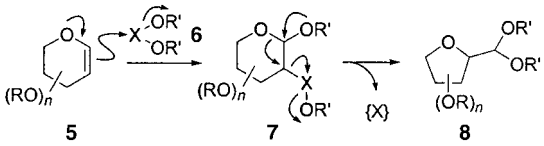
growth-inhibitory and morphogenic activities toward fungi. A fourth metabolite, pyrenolide D (**1**),[2] is structurally distinct from the other members of this family in that it incorporates a highly oxygenated tricyclic spiro-γ-lactone structure related to certain members of the cephalosporolide class 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**.

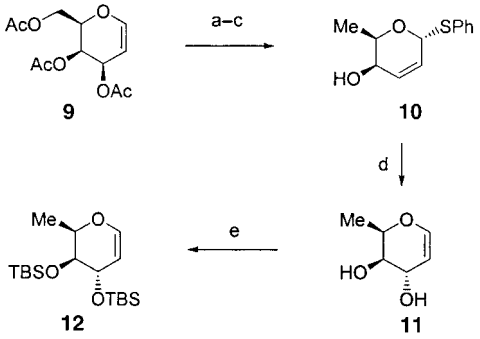
Based on this strategy, the initial synthetic target involved the preparation of 2,3-di-*O*-protected-6-deoxy-D-gulal (**4**) as the desired substrate for the formation of the C-furanoside **3**. The synthesis commenced (Scheme 3) with the preparation of the pseudoglycal **10** from commercially available 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-

[*] Prof. D. Y. Gin, K. M. Engstrom, M. R. Mendoza, Dr. M. Navarro-Villalobos
Department of Chemistry, University of Illinois
Urbana, IL 61801 (USA)
Fax: (+1) 217-244-8024
E-mail: gin@scs.uiuc.edu

[**] This research was supported by the National Institutes of Health, Glaxo Wellcome Inc., the Alfred P. Sloan Foundation, and the Arnold and Mabel Beckman Foundation.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  0044-8249/01/11306-1162 $ 17.50+.50/0

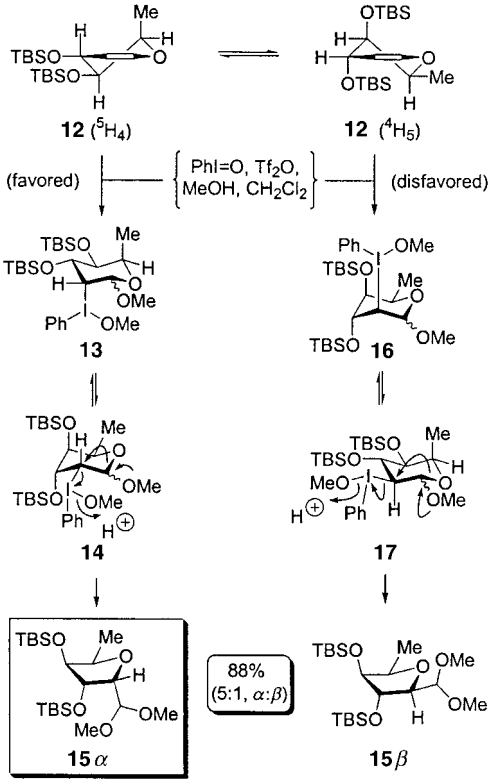


Scheme 3. a) PhSH, $SnCl_4$ (cat.), CH_2Cl_2, $-10\,^{\circ}C$, 84%; b) NaOMe, MeOH, $23\,^{\circ}C$; Bu_2SnO, MeOH, reflux; *p*-toluenesulfonyl chloride, Bu_4NBr, $CHCl_3$, 78%; c) $LiAlH_4$, THF, reflux, 86%; d) *m*-CPBA, CH_2Cl_2, $-40\,^{\circ}C$; Et_2NH, THF, $23\,^{\circ}C$, 89%; e) *tert*-butyldimethylsilyl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

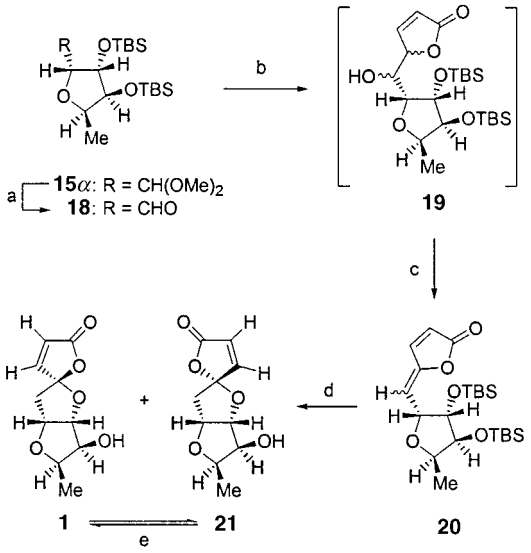
Reports on the direct oxidative ring contraction of glycals have been scarce,[7] with only a few examples of this process proceeding efficiently with stoichiometric quantities of $Tl(NO_3)_3$ as the oxidant. To avoid the use of highly toxic heavy metal salt oxidants, we focused on the use of hypervalent 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



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.

Received: November 30, 2000 [Z16202]

[1] M. Nukina, M. Ikeda, T. Sassa, *Agric. Biol. Chem.* **1980**, *44*, 2761 – 2762.

[2] M. Nukina, H. Hirota, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1158 – 1159.

[3] M. J. Ackland, J. R. Hanson, P. B. Hitchcock, A. H. Ratcliffe, *J. Chem. Soc. Perkin Trans. 1* **1985**, 843 – 847.

[4] a) V. Di Bussolo, Y.-J. Kim, D. Y. Gin, *J. Am. Chem. Soc.* **1998**, *120*, 13515 – 13516; b) V. DiBussolo, J. Liu, L. G. Huffman, Jr., D. Y. Gin, *Angew. Chem.* **2000**, *112*, 210 – 213; *Angew. Chem. Int. Ed.* **2000**, *39*, 204 – 207; c) J.-Y. Kim, V. Di Bussolo, D. Y. Gin, *Org. Lett.* **2001**, *3*, 303 – 306.

[5] R. L. Halcomb, S. H. Boyer, M. D. Wittman, S. H. Olson, D. J. Denhart, K. K. C. Liu, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 5720 – 5749.

[6] a) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4869 – 4876; b) D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147 – 154.

[7] a) A. Kaye, S. Neidle, C. B. Reese, *Tetrahedron Lett.* **1988**, *29*, 1841 – 1844; b) E. Bettelli, P. D'Andrea, S. Mascanzoni, P. Passacantilli, G. Piancatelli, *Carbohydr. Res.* **1998**, *306*, 221 – 230.

[8] a) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, **1992**; b) R. M. Moriarity, O. Prakash, *Org. React.* **1999**, *54*, 273 – 418.

[9] A. Kirschning, *Eur. J. Org. Chem.* **1998**, 2267 – 2274.

[10] A. Kirschning, *Liebigs Ann.* **1995**, 2053 – 2056.

[11] R. M. Moriarty, O. Prakash, M. P. Duncan, R. K. Vaid, N. Rani, *J. Chem. Res. Synop.* **1996**, 432 – 433.

[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

[*] Prof. T. C. W. Mak, Q.-M. Wang
Department of Chemistry
The Chinese University of Hong Kong
Shatin, New Territories, Hong Kong SAR (PR China)
Fax: (+852) 26035057
E-mail: tcwmak@cuhk.edu.hk

[**] Financial support from the Hong Kong Research Grants Council Earmarked Grant (CUHK 4268/00P) is gratefully acknowledged.

  0044-8249/01/11306-1164 $ 17.50+.50/0