Table I. Tin Hydride Induced Cyclization of Oxime Ethers

	substrate (1)							product ratios[c]		
entry	R^1	R^2	R^3	R^4	X[a]	n	solvent[b] (M)	2c + 2t/3	2c/2t	yield[d] (%)
1	c-C_6H_{11}	H	H	Bn	PTC	1	B (0.01)	87/13	52/48	84
2	c-C_6H_{11}	H	H	Bn	PTC	1	B (0.1)	89/11	52/48	89
3	c-C_6H_{11}	H	Me	Bn	PTC	1	T (0.01)	73/27	69/31	74
4	c-C_6H_{11}	Me	H	Bn	Br	1	B (0.001)	>98/2	78/22	63
5	p-MeOPh	H	H	Bn	PTC	1	B (0.002)	48/9[e]	>98/2	42
6	p-MeOPh	H	H	Bn	PTC	1	B (0.05)	57/18[e]	>98/2	48
7	$BnOCH_2$	H	H	Bn	PTC	1	T (0.2)	83/17	50/50	59
8	$\Sigma SiOCH_2$[f]	H	H	Me	PTC	1	T (0.2)	88/12	51/49	67
9	c-C_6H_{11}	H	H	Bn	PTC	2	T (0.01)	73/27	33/67	71
10	c-C_6H_{11}	H	Me	Bn	PTC	2	B (0.001)	<2/98		
11	c-C_6H_{11}	Me	H	Bn	Br	2	B (0.002)	81/19	33/67	68
12	p-MeOPh	H	H	Bn	PTC	2	B (0.05)	23/33[e]	<2/98	18
13	p-MeOPh	H	H	Bn	PTC	2	B (0.001)	34/<3[e]	<2/98	32

[a] PTC = phenyl thionocarbonate (PhOC(=S)O). [b] Reactions carried out with 3 equiv of n-Bu_3SnH and 0.5 equiv of AIBN at reflux in benzene (B) or toluene (T) at the substrate concentration indicated. [c] Product ratios computed from NMR analysis of product before purification. [d] Yield of purified product (2c + 2t). [e] Phenoxy ether 4 accounts for the remainder of the material (2 + 3 + 4 = 100%). [f] ΣSi = *tert*-butyldimethylsilyl.

Table II. Tin Hydride Induced Cyclization of Glucose-Derived Oxime Ethers[a]

entry	substrate	product ratio (8/9)	yield[b] (%)
1	**7a**	62/38	93
2	**7b**	64/36	88
3	**7c**	60/31[c]	91

[a] Reactions carried out with 2.4 equiv of $(n\text{-}Bu)_3SnH$ and 0.2 equiv of AIBN at reflux in benzene at 0.01 M. [b] Isolated yield of purified product. [c] Product also contained 9% of a third isomer, **10c**.

was not a significant difference in the isomer ratio of the products obtained.

This cyclization method was readily applied to the conversion of a carbohydrate to a carbocycle, as illustrated in Scheme I. The *o*-protected glucose hemiacetals **5** (**a**; R = Bn, **b**; R = Me) were converted directly into the methyl or benzyl oximes, and the hydroxyl released at C-4 subsequently acylated to provide the phenyl thionocarbonates **7a–c** (85–96% yield). Tributyltin hydride induced cyclization of these materials proceeds in high yield and without discernible reduction to the acyclic oximes (Table II), in contrast to those reactions described above.

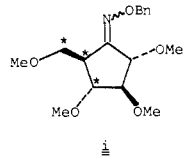
Four stereoisomers can arise in the cyclizations of **7**; however, only **8** and **9** were observed from reaction of the tetrabenzyl ethers **7a** and **7b**; a third, minor isomer **10c** was isolated on cyclization of the tetramethyl derivative **7c**.[10] The stereoselectivity observed in this reaction is very similar to that reported by Rajanbabu for radical cyclization of the closely related vinyl derivative.[3]

Since oxime ethers are readily available derivatives of ketones and aldehydes, the demonstration that they can function as effective radical traps for both intra- as well as intermolecular[11] reactions suggests that they may have useful application in synthesis.

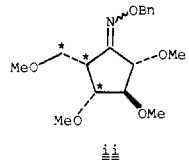
Acknowledgment. This work was supported by a grant from the National Institutes of Health (Grant No. GM-30759).

Supplementary Material Available: Full experimental details for synthesis of the starting materials, chemical transformations, and characterization of the compounds described above (34 pages). Ordering information is given on any current masthead page.

(10) A detailed stereochemical assignment was performed for the tetramethoxy derivatives **8c–10c**. Oxidation of **8c** and **10c** with SO_2Cl_2 affords a mixture of syn and anti oximes i which are clearly distinguishable from the oximes ii obtained from oxidation of **9c**. The cis relationship between the methoxymethyl substituent in oximes ii and the adjacent alkoxy group was revealed by the upfield ^{13}C NMR chemical shifts for the asterisked carbons, in comparison to those for the isomer i. Similarly, ^{13}C NMR was used to demonstrate the cis relationship between the benzyloxyamino and methoxymethyl substituents in **8c** in comparison with **10c**. The configuration of the benzyloxyamino substituent in **9c** is assigned as trans, in agreement with the observations reported by Rajanbabu for a related system.[3]



i



ii

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Total Synthesis of (±)-Pleurotin and (±)-Dihydropleurotin Acid

David J. Hart*[1a] and Horng-Chih Huang[1b]

Department of Chemistry, The Ohio State University Columbus, Ohio 43210

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Pleurotin (**1**) is an antitumor antibiotic which belongs to a family of quinonoid natural products whose pharmacological properties may be triggered by bioreduction.[2] The structure of pleurotin was determined by a combination of degradative and X-ray crystallographic studies,[3-6] and its biosynthesis has been extensively investigated by the Arigoni group.[7,8] This communication describes a total synthesis of this natural product which features a biomimetic end-game, the oxidative conversion of (±)-dihydropleurotin acid (**2**) to (±)-pleurotin (**1**).

Trans perhydroindan **3**, whose synthesis from benzoic acid has been previously described (10 steps in 36% yield), serves as the starting point for this discussion.[9] The conversion of **3** into (±)-pleurotin involved four stages: (i) reduction of the C(6)–O bond with introduction of a carbonyl group at C(9), (ii) construction of the C(9)–C(14) and C(15)–C(17) bonds, (iii) introduction of the C(8) carboxyl group, and (iv) biomimetic construction of the lactone C(14)–O bond.

The first operation was accomplished as outlined in Scheme I. Oxidation of **3** with *m*-chloroperbenzoic acid gave epoxide **4** in 87% yield. Treatment of **4** with lithium diethylamide (2.2 equiv,

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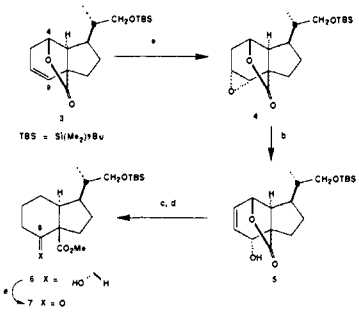
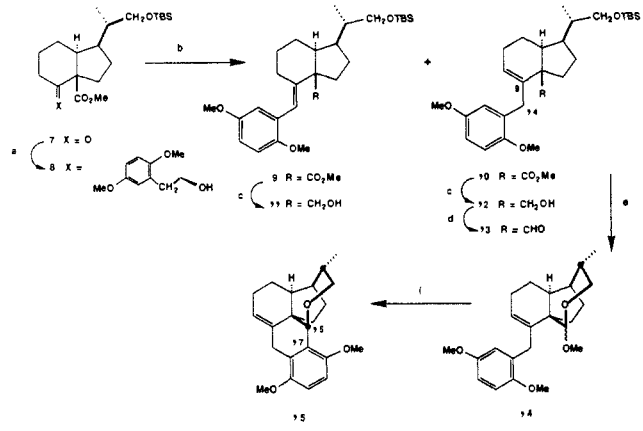
Scheme I[a]



[a] (a) MCPBA, CH_2Cl_2; (b) $LiNEt_2$, Et_2O; (c) Li, $EtNH_2$; (d) CH_2N_2; (e) DMSO, $(COCl)_2$, Et_3N.

Scheme II[a]



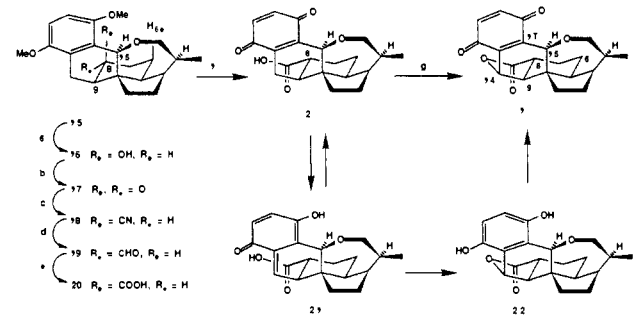
[a] (a) 2,5-Dimethoxyphenylmagnesium chloride, $CeCl_3$, THF; (b) $SOCl_2$, pyridine; (c) $LiAlH_4$, Et_2O; (d) DMSO, $(COCl)_2$, Et_3N; (e) Dowex-50 (H^+), MeOH; (f) $BF_3{\cdot}Et_2O$, $PhCH_3$.

Et_2O, room temperature, 30 min) gave allylic alcohol **5** which was converted to β-hydroxy ester **6** (58% from **4**) upon sequential treatment with excess lithium in ethylamine (room temperature, 1 h) and diazomethane.[10,11] Swern oxidation of **6** gave β-keto ester **7** (88%).[12]

The incipient quinone moiety was grafted to perhydroindan **7** as shown in Scheme II. Treatment of **7** with the reagent derived from 2,5-dimethoxybenzylmagnesium chloride and cerium trichloride gave alcohol **8** (92%)[13] which was dehydrated quantitatively to a mixture of olefins **9** and **10**. Reduction of the crude olefin mixture with lithium aluminum hydride gave alcohols **11** (50%) and **12** (43%) after separation by column chromatography. Oxidation of **12** afforded aldehyde **13** (85%).[12] Treatment of **13** with acidic methanol gave a mixture of diastereomeric acetals **14**, and exposure of **14** to boron trifluoride etherate in toluene gave pentacycle **15** in 52% yield. Although the C(15) stereochemistry was uncertain, we continued the synthesis with the hope that the required stereochemistry had been obtained.[14]

The final two stages of the synthesis are outlined in Scheme III. Thus, hydroboration–oxidation[15] of **15** followed by oxidation[12] of the resulting alcohol **16** (90%) gave ketone **17** (92%). Treatment of **17** with tosylmethylisocyanide and base gave nitrile **18** (75%).[16] The stereochemistry at C(8) of **18** was assigned on

Scheme III[a]



[a] (a) $BH_3{\cdot}THF$; NaOH, H_2O_2; (b) DMSO, $(COCl)_2$, Et_3N; (c) $TsCH_2NC$, KOtBu, DME; (d) i-Bu_2AlH, $PhCH_3$; (e) Ag_2O, NaOH, H_2O; (f) CAN, CH_3CN, H_2O; (g) MnO_2, CH_2Cl_2.

the basis of an 11 Hz coupling constant between H_8 and H_9. In addition, irradiation of H_{15} showed a NOE enhancement of the signals due to H_8 and H_{6a}, establishing the stereochemistry at C(15) for the first time.[17] Nitrile **18** was then converted to aldehyde **19** (93%) and acid **20** (62%) by using conventional procedures.[18-20] Oxidation of **20** with ceric ammonium nitrate gave (±)-dihydropleurotin acid (**2**) in 89% yield, completing a total synthesis of this congener of pleurotin.[8,21,22]

The final step of the synthesis was based on the known behavior of tetraalkyl-*p*-benzoquinones in the presence of nucleophiles[23] and the established last stages of the biosynthesis of pleurotin.[7] Thus, treatment of **2** with manganese dioxide in dichloromethane for 48 h at ambient temperature gave (±)-pleurotin (**1**) in 32% yield along with recovered **2** (33%).[24,25] Although the mechanism of this transformation is uncertain, the pathway shown in Scheme III involving quinone methide **21** and leukopleurotin (**22**) illustrates the chemical relationship between pleurotin and compounds which may be responsible for its biological properties.[2] Attempts to streamline this synthesis and other observations recorded during this study will be reported in due course.

Acknowledgment. We thank the National Science Foundation for their generous support (CHE-8504363) and the Ohio State University Campus Chemical Instrument Center for performing MS and NMR analyses.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of (−)-**1** and (±)-**1** and ^1H NMR spectra of (+)-**2** and (±)-**2** (3 pages). Ordering information is given on any current masthead page.

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(19) Campaigne, E.; LeSuer, W. M. *J. Am. Chem. Soc.* **1948**, *70*, 1555.
(20) Hydroboration–one-carbon homologation procedures would obviously provide a more direct route from **15** to **20**. Several methods are under investigation.
(21) Synthetic (±)-**2** was identical (TLC, MS, IR, 300 MHz ^1H NMR) with material prepared by degradation[4] of authentic pleurotin (**1**).
(22) We thank Professor Arigoni for generously supplying us with a sample of **1** and copies of ref 4, 7, and 8.
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(24) Synthetic (±)-**1** was identical (TLC, MS, IR, 500 MHz ^1H NMR, ^{13}C NMR) with authentic **1**.[22] All intermediates en route to (±)-**1** exhibited IR and ^1H NMR spectra consistent with the assigned structures. ^{13}C NMR spectra were recorded on all compounds except **9**, **10**, **14**, and **2**. Satisfactory combustion analyses (C, H) were obtained for compounds **4**, **5**, **8**, **11**, **15**, **16**, and **17**. Appropriate exact mass data (MS) were recorded for all compounds with the exception of **3**, **6**, **7**, **13**, and **14**, all of which exhibited mass spectral fragmentation patterns in accord with the assigned structures.
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