591-50-4; ethyl 2-bromovalerate, 615-83-8; benzyl bromide, 100-39-0; 1,1,2-triphenylethanol, 4428-13-1; ethyl acrylate, 140-88-5; ethyl 3-cyclohexylpropanoate, 10094-36-7; formaldehyde, 50-00-0; *O*-benzylhydroxylamine hydrochloride, 2687-43-6.

Supplementary Material Available: Procedures for preparation of *O*-benzylformaldoxime and **5** (2 pages). Ordering information is given on any current masthead page.

Radical Cyclization of Oxime Ethers

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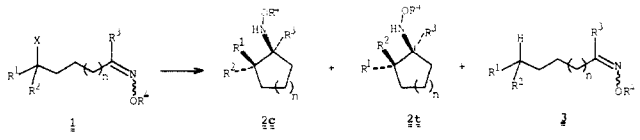
An important feature of the recently developed radical cyclization methods is their tolerance of a high level of functionality in the substrates.[1-3] This ability makes such an approach uniquely suited for the conversion of carbohydrates to carbocyclic derivatives, as elegantly demonstrated by Wilcox[2] and Rajanbabu[3] and their co-workers. A carbonyl group, as the natural unsaturation of a sugar derivative, is reputed to be generally ineffective as a radical acceptor;[4,5] hence in previous approaches a carbon–carbon double bond was incorporated in the precursor. We report here the ready radical cyclization of oxime ethers, easily accessible derivatives in which the electronic character of the carbonyl group is reversed.[6]

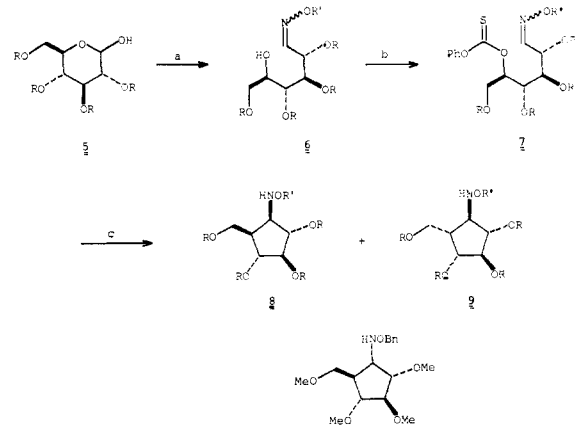
The general reaction investigated is illustrated in eq 1; variations in chain length and in substitution at the radical center and the



(1)

oxime carbon were explored (Table I). With limited exceptions, the *o*-benzyl oxime ethers were employed, and the radical was generated by tin hydride reduction of a phenyl thionocarbonate in benzene or toluene at reflux.[7] We encountered difficulties in preparing tertiary phenyl thionocarbonates; hence for those substrates the corresponding bromides were employed instead.

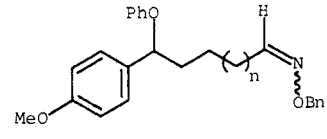
Scheme I



[a] (a) $BnONH_3^+Cl^-$, pyridine/CH_2Cl_2, 21 °C, 4–8 h; or $MeONH_3^+Cl^-$, pyridine/CH_2Cl_2/H_2O, 21 °C, 12–20 h; (b) PhOC(=S)Cl, pyridine, 21 °C, 2–4 h; (c) AIBN, $(n\text{-Bu})_3SnH$, benzene, reflux, 10–14 h.

Cyclization of the simplest member of the series (entries 1 and 2, Table I) proceeds in good yield to give comparable amounts of the cis and trans alkoxyaminocyclopentanes; only about 10% of reduction prior to cyclization is observed. With this cyclization as a benchmark, the varying effects of chain length and substitution can be compared. Lengthening the intervening chain increases the proportion of reduction prior to cyclization, as would be expected (entries 3 and 10, 4 and 11, and 5 and 12). For a given chain length, the aldoximes cyclize more readily than the ketoximes (compare entries 2 and 3 and 9 and 10). In contrast, steric hindrance at the radical center improves the ratio of cyclization to reduction (compare entries 2 and 4 and 9 and 11). Surprisingly, the ratio of cyclization to reduction does not show a significant dependence on concentration (compare entries 1 and 2, 5 and 6, and 12 and 13).

Reaction of the *p*-methoxybenzyl radical (entries 5 and 12) under the standard conditions leads to a greater amount of reduction than seen with the less stabilized dialkyl radicals. A significant byproduct arises from trapping of the benzylic radical with the phenoxy moiety, leading to the phenyl ethers **4**.



Except for the *p*-methoxyphenyl substrates, all of the cyclizations show low stereoselectivity, favoring the cis products in the cyclopentane series and the trans products in the cyclohexanes. These preferences are consistent with the chair-like transition state models proposed by Beckwith.[8] The stereoisomers were assigned from their ^{13}C NMR spectra.[9] The starting materials were obtained and utilized as mixtures of syn and anti oxime isomers. In one experiment (with the methoxime corresponding to the substrate in entry 7), these stereoisomers were separated and subjected separately to the cyclization conditions. However, there

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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.

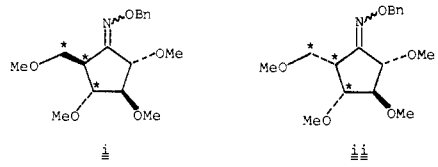
Four stereoisomers can arise in the cyclizations of **7**; however, only **8** and **9** were observed from reaction of the tetrabenzyl ethers **7a** and **7b**; a third, minor isomer **10c** was isolated on cyclization of the tetramethyl derivative **7c**.[10] The stereoselectivity observed in this 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]



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

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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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