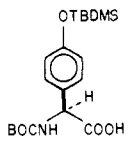

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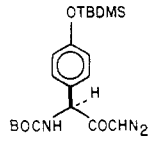

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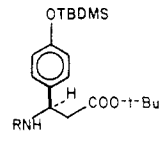
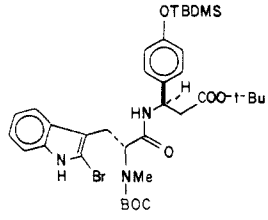


12 R = BOC
13 R = H

(c 1.14, $CHCl_3$), in 61% yield. Selective cleavage of the *N-t*-BOC group in **12** in the presence of the *tert*-butyl ester was realized in ca. 70% overall yield employing *tert*-butyldimethylsilyl triflate (TBDMSOTf) in methylene chloride containing 2,6-lutidine followed by cleavage of the resultant *N-tert*-butyldimethylsilyloxycarbonyl group with potassium carbonate in aqueous methanol–THF(1:1:2).[6]

Coupling (DCC, HBT, THF) of the (*R*)-β-tyrosine derivative **13** with amino acid **9** provided the fully protected dipeptide **14**,



14

$[\alpha]_D$ +27.9° (c 1.88, $CHCl_3$), in 91% yield. Selective cleavage [(a) TBDMSOTf, CH_2Cl_2, 2,6-lutidine; (b) K_2CO_3, H_2O–MeOH–THF, 1:1:2][6] of the *N-t*-BOC group in **14** afforded in 55% yield dipeptide **2**, $[\alpha]_D$ +41.6° (c 2.29, $CHCl_3$).

Construction of the C(1)–C(11) fragment **3** originated with enantiomerically pure (*R*)-(−)-15,[7] $[\alpha]_D$ −60.1° (c 1.38, ether), readily available by resolution of the racemic acid with (−)-α-methylbenzylamine in ether. The absolute configuration of **15** was unambiguously established by single-crystal X-ray analysis of the crystalline ammonium salt.

Iodolactonization of (*R*)-(−)-**15** (Scheme I) followed by reduction and protection of the primary hydroxyl provided **16** in 63% overall yield. Conversion of the secondary hydroxyl into a methoxy methyl ether followed by desilylation and oxidation afforded the corresponding aldehyde which was directly treated with 2-propenylmagnesium bromide. Application of an ortho ester Claisen rearrangement to allylic alcohol **17** generated a rearranged ester which was hydrolyzed and transformed into the *N*-acyloxazolidine **18**, $[\alpha]_D$ +45.3° (c 1.08, $CHCl_3$). Alkylation[8] of the sodium enolate ($NaN(TMS)_2$, THF, −78 °C) of **18** with methyl iodide afforded the desired diastereomer in 71% yield. Removal of the chiral auxiliary employing 3.0 equiv of 2.1 N aqueous potassium hydroxide in methanol gave way to the corresponding carboxylic acid which was converted in a straightforward manner into the pyridinethiol ester **19**, $[\alpha]_D$ +25.6° (c 1.64, $CHCl_3$). Condensation[9] of activated ester **19** with 1.2 equiv of *N*-TMS-Ala-OTMS[10] in tetrahydrofuran (15 h) provided in 91% yield amide **3**, $[\alpha]_D$ −24.5° (c 1.10, $CHCl_3$), thus completing construction of the C(1)–C(11) fragment of jasplakinolide.

Completion of the total synthesis of jasplakinolide required coupling of dipeptide **2** with the C(1)–C(11) segment **3**, which was accomplished with 1.05 equiv of DCC and 1.0 equiv of HBT[11] in tetrahydrofuran. The coupled product **4**, $[\alpha]_D$ +24.4° (c 1.09, $CHCl_3$), was obtained in ca. 50% yield. Conversion of **4** into **1** was realized by the following sequence: (1) cleavage (82%) of the *tert*-butyl ester employing TBDMSOTf (3.0 equiv)/2,6-lutidine (4.0 equiv) in methylene chloride followed by treatment with potassium carbonate (H_2O–MeOH–THF, 1:1:2),[6] (2) deprotection (51%) of the secondary hydroxyl at C(11) with boron trifluoride etherate/ethanedithiol in methylene chloride at 0 °C, (3) macrolactonization (79%) using DCC/DMAP·TFA/DMPA in refluxing chloroform,[12] and (4) desilylation (Bu_4NF, THF, 95%). The synthetic (+)-jasplakinolide, $[\alpha]_D$ +65.6° (c 0.98, CH_2Cl_2), thus obtained was identical ($[\alpha]_D$, TLC, 300 MHz ^1H NMR, CMR, IR, and MS) with an authentic sample of natural material kindly provided by Professor Phillip Crews.

Acknowledgment. Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865) and Rohm and Haas Company is gratefully acknowledged. We are grateful to Peter Ramberg for working out the details for the resolution of unsaturated acid **15**, to Drs. Colin Swithenbank and Zev Lidert (Rohm and Haas) for bringing this important problem to our attention, and to Professor Phillip Crews (University of California, Santa Cruz) for a generous sample of natural jasplakinolide.

Supplementary Material Available: Spectral and analytical data for key intermediates **4**, **9**, and **14** and the acid precursor to **19** (1 page). Ordering information is given on any current masthead page.

(6) Cf. Ohfune, Y.; Sakaitani, M. *Tetrahedron Lett.* **1985**, *26*, 5543.
(7) Cf. Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335.
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(9) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, *1901*.
(10) Venkateswaran, P. S.; Bardos, T. J. *J. Org. Chem.* **1967**, *32*, 1256.
(11) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(12) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

Bis(trimethylstannyl)benzopinacolate-Mediated Intermolecular Free-Radical Carbon–Carbon Bond-Forming Reactions: A New One-Carbon Homologation

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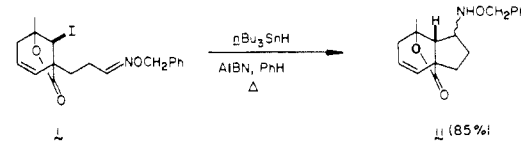
Received August 26, 1987

During the course of a total synthesis underway in our laboratories, a need arose for a synthetic method in which a carbon-centered free radical would couple with a one-carbon addend.[1] A survey of the literature suggested that few such methods existed, the most promising being an interesting nitrile synthesis recently developed by Stork.[2] On the basis of the knowledge that free radicals add intramolecularly to oxime ethers,[3,4] we decided to examine an intermolecular variant of this reaction by using *O*-benzylformaldoxime as an addend. The preliminary results of this study are outlined herein.

We began by examining the reactions shown below. Thus, treatment of 1 equiv of iodocyclohexane with tri-*n*-butyltin hydride

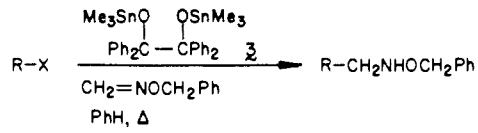
† Alfred P. Sloan Fellow, 1983–1987.
(1) For an overview of intermolecular free-radical addition reactions in organic synthesis, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: New York, 1986.
(2) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.
(3) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, 2821.
(4) (a) Prior to the onset of this study, we demonstrated that i could be converted to a 1:1 mixture of diastereomeric perhydroindans ii (unpublished results with Dr. Balan Chenera). (b) Also, see: Barlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, following paper in this issue.

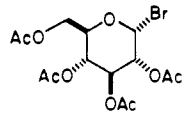
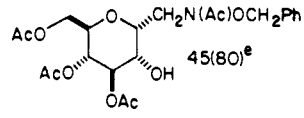
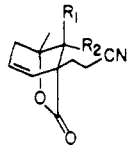
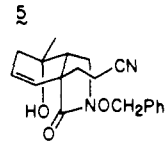


i ii (85%)

0002-7863/88/1510-1631$01.50/0

Chart I. Addition of Radicals to *O*-Benzylformaldoxime[a]

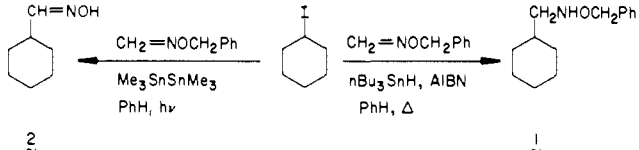


Entry	RX	%Yield RCH_2NHOCH_2Ph[b,c,d]
1	*n*-octyl iodide	77
2	cyclohexyl iodide	76
3	cyclohexyl bromide	56
4	cyclohexyl phenyl selenide	78
5	*t*-butyl bromide	84
6	iodobenzene	67
7	 **4**	 **5** 45(80)[e]
8		

6 R_1 = I R_2 = H — **9** (30)
7 R_1 = C(OH)Ph_2 R_2 = H — **8a** + **8b** (57)[f]
8a R_1 = CH_2NHOCH_2Ph R_2 = H
8b R_1 = H R_2 = CH_2NHOCH_2Ph

[a] All experiments were run in a manner analogous to that described for iodocyclohexane in the text. Unless stated otherwise, the ratio of RX to *O*-benzylformaldoxime to **3** was 1:1:1. [b] Isolated yields. [c] Products gave ^1H NMR, IR, and mass spectra consistent with assigned structures. [d] Yields in parentheses refer to experiments in which 3.0 equiv of *O*-benzylformaldoxime was used. [e] See Supplementary Material for an experimental procedure. [f] Isolated as a 1:1 mixture of diastereomers. The lactone bridge and addend were shown to be cis in one stereoisomer by trimethyltin bromide induced γ-lactam formation.

(1.5 equiv), AIBN (0.05 equiv), and *O*-benzylformaldoxime (10 equiv)[5] in benzene under a variety of conditions gave the addition product **1** in 25% isolated yield at best. Presumably, reduction of the initially formed radical by tin hydride overwhelmed the desired addition.



2 **1**

In an attempt to eliminate reduction of the initially formed radical, we next examined hexamethylditin as a source of stannyl radicals.[7,8] Thus, a benzene solution of iodocyclohexane (1.0 equiv) and hexamethylditin (1.2 equiv) was irradiated through Pyrex until ^1H NMR analysis indicated an absence of starting iodide. Product analysis indicated that cyclohexane carboxaldoxime (**2**) had been generated, presumably via addition of cyclohexyl radicals to *O*-benzylformaldoxime followed by fragmentation and tautomerization of the resulting nitroso compound, but in only 8% yield.[9]

To avoid problems perhaps due to unwanted photochemistry while retaining the attractive nonreducing aspects of hexaalkylditin chemistry, we next examined a little known thermal source of tin radicals. Neumann and co-workers have provided evidence that bis(trimethylstannyl)benzopinacolate (**3**) affords trimethyltin radicals upon warming above 60 °C in benzene.[10] Thus, warming a solution of iodocyclohexane (2.5 mmol), *O*-benzylformaldoxime (2.5 mmol), and **3** (2.5 mmol) in 8 mL of benzene at 75 °C for 4 h followed by an aqueous potassium fluoride workup[11] and chromatography over silica gel gave a 76% yield of **1**.[12] The possible generality of this new free-radical addition reaction is suggested by the examples provided in Chart I. Chart I shows that iodides, bromides, and selenides can be used as radical precursors.[13] Primary, secondary, tertiary, and aryl radicals can be used. Complex radicals also participate reasonably well in this reaction. In the case of glucosyl bromide **4** (entry 7) the α-anomer of the *C*-glycosidic product **5** predomonates.[14] In the case of iodolactone **6** (entry 8), the presumed radical coupling product **7** was obtained in 32% yield along with **8** and **9** when only 1 equiv of *O*-benzylformaldoxime was used.[15,16] The formation of **7** was easily suppressed, however, by increasing the concentration of *O*-benzylformaldoxime relative to **6**. Finally, we note that ethyl 2-bromovalerate failed to give any adduct under the conditions described in Chart I, and benzyl bromide gave an 85% yield of 1,1,2-triphenylethanol.

Aside from representing a potentially useful synthetic method, the aforementioned results suggest that **3** might be a useful reagent for the 1:1 coupling of alkyl halides to other addends. In this regard, we have found that warming equimolar amounts of cyclohexyl iodide, ethyl acrylate, and **3** in benzene followed by an aqueous potassium fluoride workup affords ethyl 3-cyclohexylpropanoate in 83% yield. The synthetic and mechanistic implications of these results are under investigation.[17]

Acknowledgment. We thank the National Science Foundation for their generous support (CHE-8504363), Richard Weisenberger of The Ohio State University Campus Chemical Instrument Center for mass spectral analyses, and Dr. Duane A. Burnett for preliminary studies.

Registry No. 1, 112712-18-2; **2**, 4715-11-1; **3**, 39157-60-3; **4**, 572-09-8; **5**, 112712-19-3; **6**, 99310-22-2; **7**, 112712-20-6; **8a**, 112739-89-6; **8b**, 112712-21-7; **9**, 112712-22-8; i, 112712-25-1; ii, 112712-26-2; *n*-Bu_3SnH, 688-73-3; $Me_3SnSnMe_3$, 661-69-8; $CH_3(CH_2)_8NHOCH_2Ph$, 112712-23-9; $(CH_3)_3CCH_2NHOCH_2Ph$, 112712-24-0; $PhCH_2NHOCH_2Ph$, 4383-24-8; iodocyclohexane, 626-62-0; *O*-benzylformaldoxime, 72399-18-9; *n*-octyl iodide, 629-27-6; cyclohexyl bromide, 108-85-0; cyclohexyl phenyl selenide, 22233-91-6; *tert*-butyl bromide, 507-19-7; iodobenzene,

(5) *O*-Benzylformaldoxime has been used in polar carbon–carbon bond-forming reactions: Ikeda, K.; Yoshinaga, Y.; Achiwa, K.; Sekiya, M. *Chem. Lett.* **1984**, 369. Burnett, D. A.; Hart, D. J.; Liu, J. *J. Org. Chem.* **1986**, *51*, 1929. Basha, A.; Brooks, D. W. *J. Chem. Soc., Chem. Commun.* **1987**, 305. The preparation of this reagent is described in the Supplementary Material.

(6) When an iodide with a higher molecular weight than iodocyclohexane was used, less than 10% of an adduct was obtained, and reduction product was isolated in high yield.

(7) Kuivila, H. G.; Pian, C. H.-C. *Tetrahedron Lett.* **1973**, 2561.

(8) Krusic, P. J.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 846.

(9) Small amounts of cyclohexene were also detected.

(10) Hillgärtner, H.; Neumann, W. P.; Schroeder, B. *Liebigs Ann. Chem.* **1975**, 586.

(11) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

(12) As a prelude to this equipment, we demonstrated that **i** afforded **ii** (see ref 4) in 87% yield with use of these conditions.

(13) The xanthate of cyclohexanol failed to afford **1** under the conditions described herein.

(14) This stereochemical result is consistent with reported observations: Dupuis, J.; Giese, B.; Rüege, D.; Fischer, H.; Korth, H. G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.

(15) The structure of **7** (mp 220–223 °C) was proven by an X-ray crystallographic analysis performed by Dr. Judith Gallucci at The Ohio State University X-ray Crystallographic Facility. Details will be reported elsewhere. When equimolar amounts of **6** and **3** were warmed in benzene, **7** was obtained in 76% yield.

(16) For the differing behavior of **6** upon treatment with *n*Bu_3SnH–AIBN or Me_6Sn_2–*hν*, see: Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409.

(17) Studies conducted since submission of this manuscript suggest that these reactions may be free-radical nonchain processes in which the termination event is a coupling of the adduct radical with a (trimethylstannyloxy)diphenylmethyl radical. We are in the process of testing this hypothesis. We thank Professor Bernd Giese for pointing out the relationship between our mechanistic proposal and a family of radical–radical coupling reactions: Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925.

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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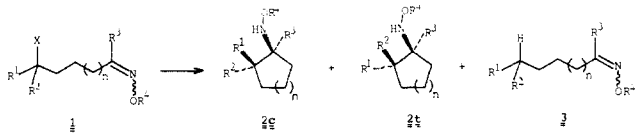
Received September 8, 1987

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]

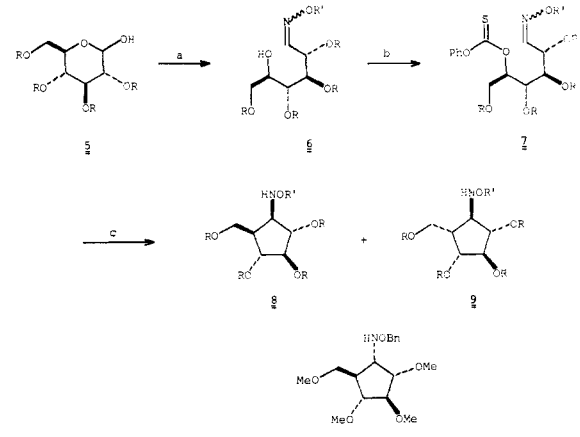
The general reaction investigated is illustrated in eq 1; variations in chain length and in substitution at the radical center and the



(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.

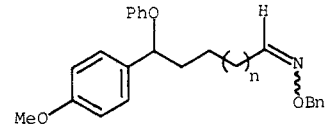
Scheme I



[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

(1) (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3742. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (b) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689, 2693. Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1982**, *23*, 2505. Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (c) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. (d) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620. (e) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (f) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. (g) Beckwith, A. L. J.; Pigou, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 85. (h) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493. (i) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339.

(2) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546. Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102.

(3) Rajanbabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.

(4) Inter alia: Maruyama, K.; Taniuchi, M.; Oka, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 712. Flies, F.; Lalande, R.; Maillard, B. *Tetrahedron Lett.* **1976**, 439.

(5) See, however, a recently reported study which suggests that aldehydes are good radical acceptors: Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484–3486.

(6) The ability of oxime ethers to act as radical acceptors is precedented in the radical cyclization reported by Corey et al. (Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821).

(7) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

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(9) In each instance, the isomers which displayed the higher field resonances for the methine and side-chain carbons were assigned the cis configuration: Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, 2nd ed.; John Wiley & Sons: New York, 1980.

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