Polymer-Supported Synthesis of Cyclic Ethers: Electrophilic Cyclization of Tetrahydrofuroisoxazolines

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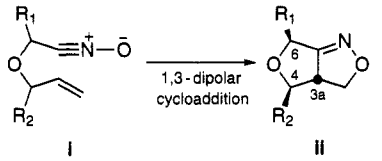
The polymer-supported synthesis of cyclic ethers has been achieved using an intramolecular 1,3-dipolar cycloaddition/electrophilic cyclization sequence. The five-step reaction scheme converts heptadienols to cyclic ethers in 21–49% overall yield from polymer-supported nitroolefin. The heptadienols were varied with a Ph, CH_3, and H group in the allylic position to give the accordingly substituted cyclic ethers. The 1,3-dipolar cycloaddition sets three stereocenters in the tetrahydrofuroisoxazoline, and the electrophilic cyclization establishes a fourth stereocenter in the cyclic ether. The degree of functionalization at the nitroolefin stage was determined by reduction to the primary amine and quantification with ninhydrin. The *cis* cyclic ether is the predominant stereoisomer from the electrophilic cyclization process. This latter step is specific for removal of only the desired cyclic ether from the polymer support.

Introduction

In the preceding paper,[1] we presented a five-step, polymer-supported reaction sequence for the synthesis of 2,5-disubstituted tetrahydrofurans. The desired cyclic ether product is obtained exclusively as byproducts of the sequence are not cleaved from the polymer support. We have extended this 1,3-dipolar cycloaddition/electrophilic cyclization sequence to an *intramolecular* variant which yields cyclic ethers with four stereogenic centers,[2] and here we describe application of a polymer-supported strategy to this synthetic sequence.

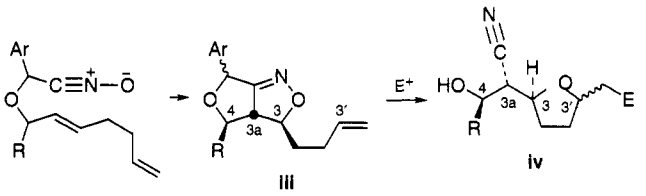
The intramolecular 1,3-dipolar cycloaddition of a nitrile oxide to a substituted double bond affords a novel heterocycle with excellent stereoselectivity. For example, Hassner and Murthy have found that nitrile oxide **i** (R_1 = CH_3 or Ph; R_2 = H) delivers heterocycle **ii** (C6-H *trans* to C3a-H) selectively. These results have been rationalized by examining the stereochemistry of the resulting tetrahydrofuroisoxazoline[3] and by using product-based MM2 calculations.[4] In related studies, Kurth et al.[5] have found that moving the alkyl substituent from C6 to C4 (i.e., R_1 = H; R_2 = CH_3 or Ph) results in complete diastereofacial selectivity; in each case, only the *trans* isomer (C4-H *trans* to C3a-H) was detected. Apparently a C4 stereogenic center exerts greater control than a C6 stereogenic center in these intramolecular 1,3-dipolar cycloadditions.

When the C=C of **i** is 1,2-disubstitued, the resulting heterocycle has an additional stereogenic center at C3 which should be subject to control by manipulating the



I II

geometry of the now internal double bond. It appeared to us that using this strategy to incorporate a 3-butenyl group at C3 (cf. **iii**) would set the stage for an electrophilic cyclization reaction (**iii** → **iv**) to deliver cyclic ether **iv** by concomitant unraveling of the tetrahydrofuroisoxazoline moiety.



III iv

This final transformation immolates the C6 stereogenic center, exposes latent hydroxyl and cyano functional groups, and sets an additional stereogenic center in the cyclic ether. To be congruous with our solution phase studies, the polymer-supported studies reported here utilized an electron-donating group at C6 (Ar = polymer-bound 4-(benzyloxy)phenyl) in order to stabilize the positive charge which develops at this position in the electrophilic cyclization step.

Results and Discussion

Attachment of an electron-donating aryl group to the polymer support was accomplished by linking an anisaldehyde unit to Merrifield's resin. Thus, the phenoxide (anisaldehyde + NaOH in DMSO) was added to chloromethylated polystyrene to provide polymer-supported (benzyloxy)benzaldehyde **1**. Resin **1** exhibits a strong carbonyl IR absorbance at 1698 cm^{-1} and an aldehyde C–H stretch at 2725 cm^{-1}.

Two methods for the conversion of **1** to polymer-supported β-nitrostyrene **3** were investigated. The first method, a two-step process, was effected by nitroaldol condensation (CH_3NO_2, Et_3N) in a THF/ethanol mixed

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(1) (a) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* 1995, *60*, xxx, preceding manuscript in this issue. (b) See Experimental Section of ref 1a for general experimental information.

(2) Beebe, X.; Chiappari, C. L.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1993**, *58*, 7320.

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(4) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277.

(5) Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259.

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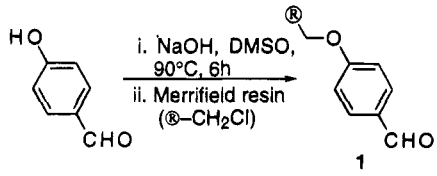

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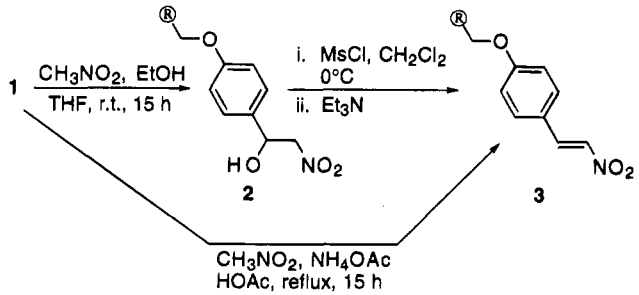
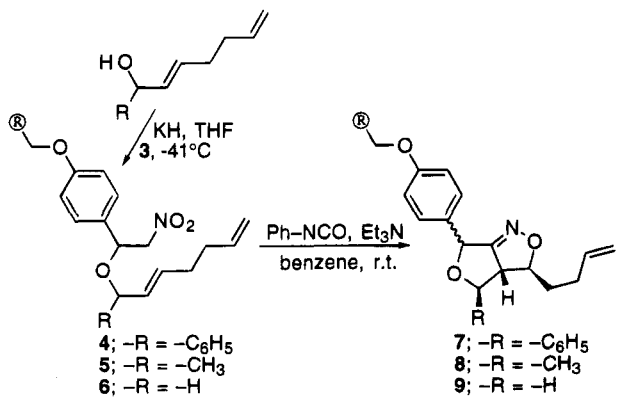
solvent to give polymer-supported nitro alcohol **2** (nitro IR absorbances at 1555 and 1375 cm^{-1}). Nitro alcohol **2** was then dehydrated to β-nitrostyrene **3** by sequential addition of methanesulfonyl chloride and triethylamine[6] (IR absorbances at 1340 and 1629 cm^{-1}). This two-step method is somewhat deficient because a small carbonyl peak is still present in the IR spectrum after the nitroaldol condensation; an indication that the nitroaldol reaction does not go to completion or that **3** (and/or **2**) suffers a retro-aldol reaction.

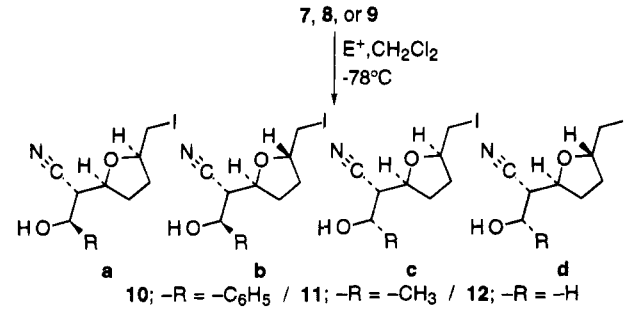


The second method employed nitromethane and glacial acetic acid with catalytic ammonium acetate[7] to effect nitroaldol and dehydration as a one-step process. As these solvents do not swell the polymer support, the reaction was not expected to proceed with appreciable yield. However, to our surprise, this one-step conversion delivered bright yellow **3** which was spectroscopically identical to the product of the two-step method but with no remaining carbonyl present in the IR spectrum. This proved to be the preferred route to **3**.



Subsequent Michael addition of dienol alkoxides to **3** gave the polymer-supported nitro ethers **4**, **5**, and **6**.[8] The progress of each addition reaction was monitored by FT-IR. For example, Figure 1 shows FT-IR spectra for the converison of **4** from **3**; note that the nitroolefin C=C absorbance at 1630 cm^{-1} and the nitro absorbance at 1350 cm^{-1} decrease in intensity while nitro absorbances at 1375 and 1555 cm^{-1} increase in intensity over reaction times of 5 min, 1 h, 2 h, and finally 3 h.

Table 1. Yields and Stereoselectivities for Polymer-Supported Synthesis of Cyclic Ethers 10, 11, and 12



R	compd	electrophile	yield (mmol/g P–S), %	% yield[a]	a:b:c:d
C_6H_5	**10**	ICl	0.069	46	69:31:–:–[b]
C_6H_5	**10**	ICl	0.066	44	69:31:–:–[b]
C_6H_5	**10**	IBr	0.071	47	80:21:–:–[b]
C_6H_5	**10**	IBr[d]	0.065	43	72:28:–:–[b]
C_6H_5	**10**	NIS	0.042	28	72:28:–:–[b]
C_6H_5	**10**	IBr[e]	0.037	25	82:18:–:–[b]
C_6H_5	**10**	IBr[f]	0.074	49	80:20:–:–[b]
CH_3	**11**	ICl	0.052	35	48:38:10:4[c]
CH_3	**11**	IBr	0.041	27	62:18:11:9[c]
H	**12**	IBr	0.031	21	80:20:–:–[b]

[a] Calculated overall yield from **3** based on 0.15 mequiv of β-nitrostyrene/g of polymer. [b] Ratio determined by ^1H NMR integration of H-1′. [c] Ratio determined by capillary GLC of the crude reaction mixture. [d] Reaction solvent toluene. [e] Used 0.5 mmol of dienol/g of polymer support. [f] Used 5 mmol dienol/g polymer support.

These Michael addition reactions must be quenched with acetic acid. When quenched with aqueous hydrochloric acid, the unconjugated nitro absorbances are weaker in intensity in the IR spectrum. This may reflect the fact that acetic acid is better able to permeate the polymer support than aqueous hydrochloric acid; if the nitronate anion is not properly quenched, it can undergo retro-Michael reaction to regenerate the nitrostyrene moiety.

Nitro ethers **4**–**6** were then subjected to phenyl isocyanate mediated dehydration[9] to the polymer-supported nitrile oxide intermediates which undergo concomitant intramolecular 1,3-dipolar cycloaddition to give the polymer-supported tetrahydrofuroisoxazolines **7**–**9**. These reactions were monitored by a decrease in the intensity of the unconjugated nitro absorbances in the IR spectrum, and after 2 days, no further peak reduction was observed and the reactions were worked up. Electrophilic cyclization of the resulting heterocycles yielded solely the desired cyclic ethers. The overall yields from polymer-supported nitrostyrene **3** as well as the stereoselectivities of the electrophilic cyclization are given in Table 1, and as noted, the electrophile was varied to determine if the yield and *cis*:*trans* ratio (i.e., 2,5-relative stereochemistry) could be improved.

The best yield of tetrahydrofuran derivative **10** (47%) was obtained using iodine monobromide[10] in dichloromethane which gave a *cis*:*trans* ratio of 4:1. This yield is nearly identical to the 46% overall yield of **10** obtained in solution phase studies. In these reactions, 2 mmol of

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(9) (a) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474. (b) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *62*, 5339.
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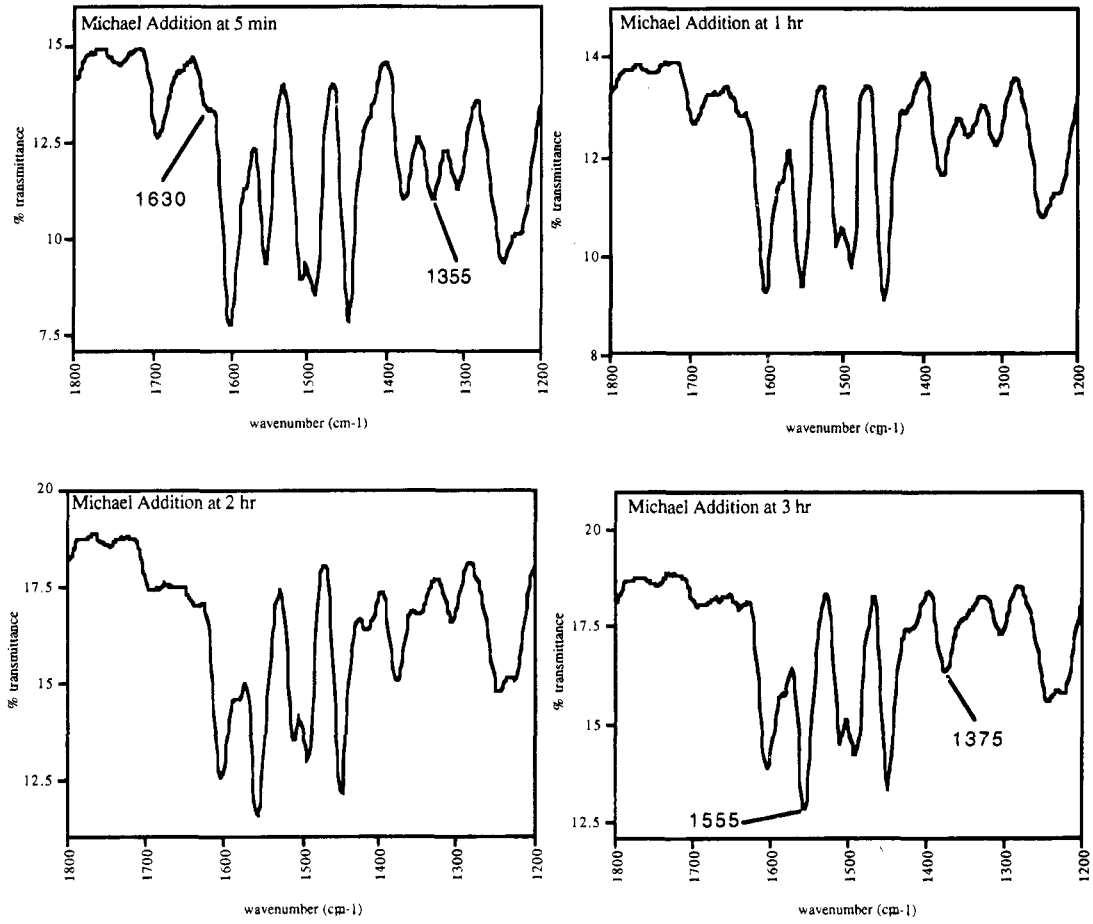


Figure 1. IR spectra of polymer-supported synthesis of **4** from **3**.

dienol were used per gram of polymer-supported nitrostyrene in the Michael addition. When the number of equivalents was increased to 5 mmol of dienol per gram of polymer support, the yield of **10** increased to 49%. When the number of equivalents was decreased to 0.5 mmol of dienol per gram of polymer support, the yield of **10** decreased to 25%. Iodine monobromide gave better *cis*:*trans* ratios throughout the R = Ph, CH_3, H series, and there was essentially no difference in *cis*:*trans* ratios for iodine monochloride versus *N*-iodosuccinimide. When toluene was used instead of dichloromethane, the *cis*:*trans* product ratio decreased.

The electrophilic cyclization of **8** yielded cyclic ethers **11a**, **11b**, **11c**, and **11d** in a 35% overall yield, which may be compared to the 34% overall yield of **11** obtained in solution phase studies. This cyclic ether ratio gives the diastereofacial selectivity of the nitrile oxide in the 1,3-dipolar cycloaddition; it can be seen that the selectivity is about 5:1 α:β, a ratio comparable to the 4.6:1 α:β selectivity observed in solution phase. *Cis*:*trans* product ratios in the cyclizations of these compounds are also interesting as the C4-α tetrahydrofuroisoxazoline gives *cis*:*trans* ratios of 1.3:1 for ICl and 3.4:1 for IBr. On the other hand, the C4-β tetrahydrofuroisoxazoline gives *cis*:*trans* ratios of 2.5:1 for ICl and 1.2:1 for IBr. These are comparable to the stereoselectivities seen in solution phase studies. These data indicate that the relative stereochemistry at C4 partially directs the *cis*:*trans* selectivity in the electrophilic cyclization and is a result of the C4 stereocenter controlling the transition-state conformations of the reaction. The envelope of the furan ring in the heterocycle presumably shifts to minimize a C4–C3 pseudodiaxial interaction, thus moderating the energies of the corresponding transition states. The relative energies of the endo and exo electrophilic attacks are probably closer, resulting in a lower *cis*:*trans* ratio of the cyclic ethers. The overall yield for the polymer-supported synthesis of cyclic ether **12** was 21%, as compared to the solution phase synthesis, which gave **12** in an overall yield of 29%.

A variety of electrophiles were investigated for the cyclization of **7** to determine if the electrophile exerted any effect on the *cis*:*trans* ratio of the cyclic ethers. These included $PdCl_2$, phenylsulfuryl chloride, phenylselenyl bromide, phenylselenyl chloride, Nicholas' cation, and mercuric chloride. Unfortunately, none of these electrophiles effected the cyclization. The crude materials effected obtained from these reactions, while not fully characterized, showed no nitrile absorbances in their IR spectra, indicating that no cyclization had taken place.

The benefits in separation and isolation associated with polymer-supported syntheses are demonstrated by the ^{1}H NMR of the crude product directly upon removal from the polymer support (Figure 2). The bottom ^{1}H NMR spectrum is the crude product, and the top two spectra are the separated *cis* (**10a**) and *trans* (**10b**) diastereomers as indicated. Close examination of these spectra demonstrates that each peak in the crude ^{1}H NMR spectrum can be accounted for in the spectra of the two purified stereoisomers.

It is also noteworthy that the polymer-supported aldehyde is regenerated in the electrophilic cyclization step, but only to a limited extent. The IR spectra of the initial polymer **1** and the polymer after one complete reaction cycle are shown in Figure 3 (the aldehyde carbonyl stretch appears at 1698 cm^{-1}).

Cyclic ethers were also formed from Merrifield's peptide resin without an electron-donating aryl group (i.e.,

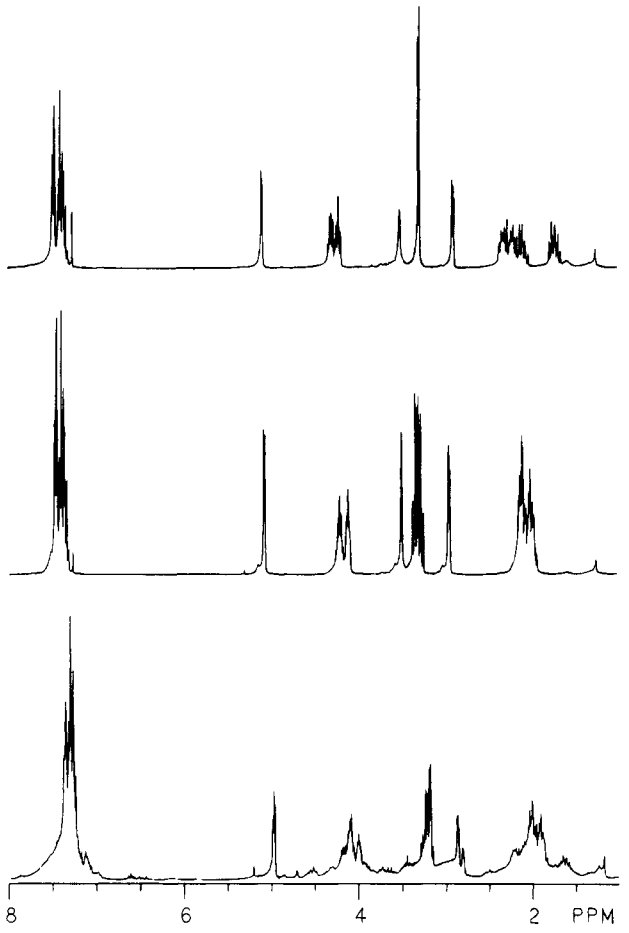
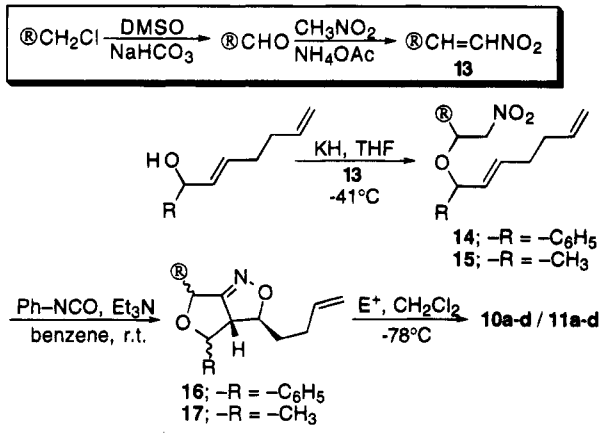


Figure 2. ^{1}H NMR spectra of crude **10a/10b** (bottom), pure **10a** (middle), and pure **10b** (top).

Table 2. Yield and Stereoselectivity of Cyclic Ethers Starting from 13 (®CHO)

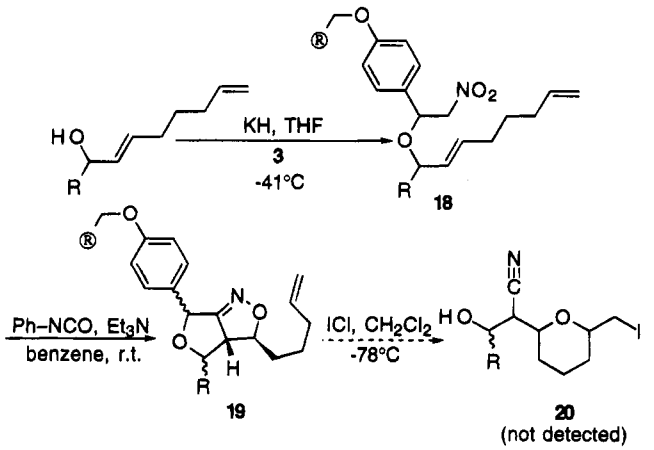


R	compd	electrophile	yield (mmol/g P–S), %	% yield[a]	a:b:c:d
Ph	**10**	IBr	0.074	49	81:19:–:–[b]
CH_3	**11**	ICl	0.070	47	54:32:8:6[c]
CH_3	**11**	IBr	0.038	25	65:15:11:9[c]

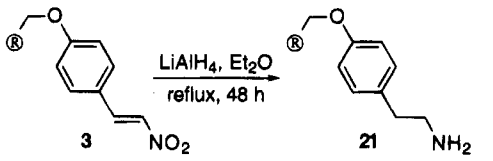
[a] Calculated overall yield from **13** based on 0.15 mequiv of β-nitrostyrene/g of polymer. [b] Ratio determined by ^{1}H NMR integration of H-1′. [c] Ratio determined by capillary GLC of the crude reaction mixture.

starting with polymer-supported nitroolefin **13**). The yields and stereoselectivities for these reactions are presented in Table 2 and are very similar to those obtained starting with polymer-supported aldehyde **1**. The electron-donating aryl group in **1** increases the yield of the electrophilic cyclization reaction, but the tetrahydrofuroisoxazoline intermediate appears to be less stable. Thus, the effects appear to offset one another.

Polymer-supported 4-pentenyl analogue **19** was synthesized from resin **3** in the hope that tetrahydropyrans could be prepared by this polymer-supported sequence. However, while IR data indicate that transformations **3** → **18** → **19** worked, all attempts to cyclize **19** resulted in none of the desired cyclic ether product (**20**) being liberated form the polymer support.



To determine the overall yield of cyclic ether formation for comparison with the conventional solution phase sequence, the degree of functionalization of the polymer-supported β-nitrostyrene (**3**) was quantified. This was accomplished by reducing the β-nitrostyrene with lithium aluminum hydride in refluxing ether to give polymer-supported primary amine **21**.[11] A quantitative ninhydrin test for amines gave a value of 0.15 mequiv per gram of polymer support as the degree of functionalization of the polymer-supported primary amine.[12]



Cis and *trans* stereochemical assignments for the 2,5-disubstituted cyclic ethers proved to be nontrivial. Although separable by HPLC, NOE studies on all of the diastereomers in a variety of solvents proved unrevealing. This situation may be due to the terminal hydroxyl hydrogen bonding with the cyclic ether oxygen, resulting in a 6-membered ring. In the resulting conformation, the ring protons at C2 and C5 are quite distant from one another in both the *cis* and *trans* diastereomers.

The solution to this dilemma involved a combination of X-ray crystallographic and ^{1}H NMR chemical shift data. While phenyl-substituted tetrahydrofurans **10a** and **10b** were crystalline, the crystals proved to be unsuitable for X-ray crystallography. Therefore, the iodomethyl group of each diastereomer (**10a** and **10b**) was reduced by tributyltin hydride, yeilding **22** and **23**, respectively.[13] These reduced compounds were also

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(12) (a) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147. (b) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

(13) (a) Gagnaire, D.; Monzeglio, P. *Bull. Soc. Chim. Fr.* **1965**, 474. (b) Katagiri, K.; Tori, K.; Kimura, Y. *J. Med. Chem.* **1967**, *10*, 1149.

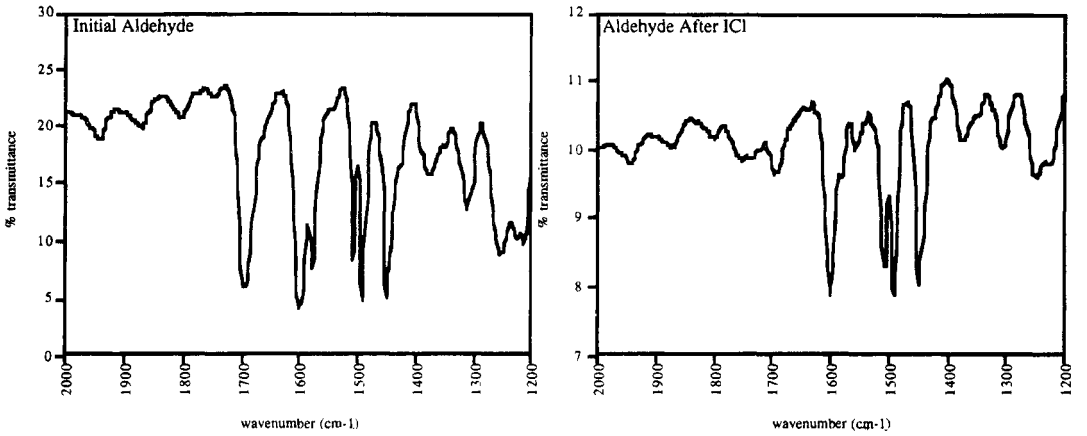


Figure 3. IR spectra of polymer before (left) and after (right) reaction sequence.

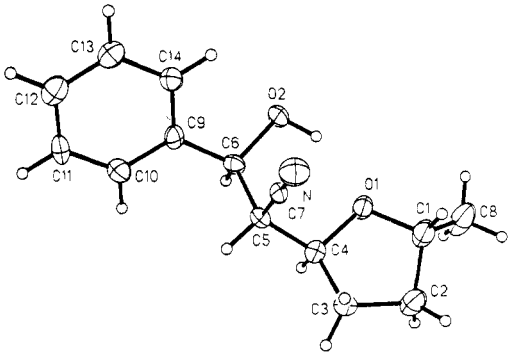
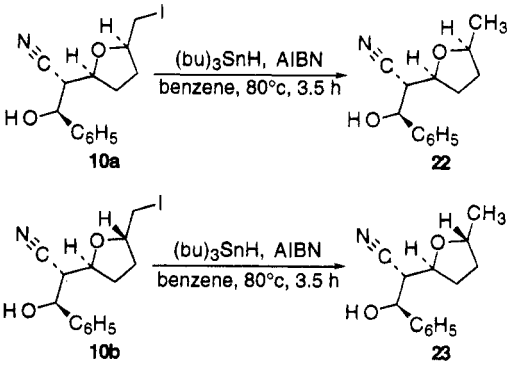


Figure 4. X-ray crystal structure of **23**.

crystalline, and an unambiguous stereochemical assignment for **23** was made by single-crystal X-ray diffraction analysis.[14] The crystal structure (Figure 4) shows that the *minor* diastereomer formed in the cyclization process has a 2,5-*trans* configuration.



Since the only unambiguous stereochemical assignment available was from tetrahydrofuran **23**, a spectroscopic correlation was necessary to assign the correct stereochemistry for all the other diastereomeric cyclic ethers. This was possible by comparing the ^{1}H NMR spectra of the various compounds where a significant and reliable difference for all major diastereomers compared to all minor diastereomers is evident for the four methylene ring protons. These signals appear as two multiplets, each with an integration of 2H, for the major diastereomers. In contrast, all minor diastereomers show three or four different multiplet signals for these same ring methylene protons. These data are presented in Table 3 and shown in Figures 5 and 6. Another important benchmark is the signal multiplicity for the iodomethyl group. In the minor diastereomers, the methylene appears as an apparent doublet, while in the major diastereomers each methylene proton appears as a doublet of doublets (dd). Chromatographic similarities are also evident, with each minor diastereomer eluting before the corresponding major diastereomer in HPLC separations.

Table 3. ^{1}H NMR Chemical Shifts of Tetrahydrofuran H3 and H4

	δ (mult, integral)	
compd	major	minor
10	2.00 (m, 2H) 2.12 (m, 2H)	1.73 (m, 1H) 2.13 (m, 1H) 2.21(m, 1H) 2.32 (m, 1H)
11	1.99 (m, 2H) 2.16 (m, 2H)	1.73 (m, 1H) 2.09 (m, 1H) 2.31 (m, 2H)
12	1.99 (m, 2H) 2.16 (m, 2H)	1.75 (ddt,1H) 2.04 (ddt, 1H) 2.30 (m, 2H)

Table 4. ^{1}H NMR Chemical Shifts of Tetrahydrofuran H2 and H5

	δ (mult, integral)	
compd	major H2; H5	minor H2; H5
10	4.11 (m, 1H); 4.20 (m, 1H)	4.21 (m, 1H); 4.29 (m, 1H)
11	4.18(m, 2H); 4.32 (m, 1H)	4.25 (ddt, 1H); 4.36 (ddd, 1H)
12	4.13 (m, 1H); 4.23 (m, 1H)	4.21 (ddt, 1H); 4.34 (ddd, 1H)

Other data which contributed to determining whether the 2,5-substitution pattern on the tetrahydrofuran ring was *cis* or *trans* were the relative ^{1}H NMR chemical shifts of the ring hydrogens at C2 and C5.[15] In the major diastereomers (**10a**, **11a**, and **12a**), these ring protons appear at consistently lower chemical shift than in the ^{1}H NMR of the minor diastereomers (**10b**, **11b**, and **12b**). These data are presented in Table 4. This information provides conclusive evidence that the major diastereomers from the electrophilic cyclization of these tetrahydrofuroisoxazolines are 2,5-*cis* substituted and the minor diastereomers are 2,5-*trans* substituted.

Conclusion

A polymer-supported intramolecular 1,3-dipolar addition/electrophilic cyclization sequence for the synthesis

(14) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(15) (a) Walkup, R. D.; Mosher, M. D. *Tetrahedron* **1993**, *49*, 9285. (b) Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* 1976, *21*, 1821.

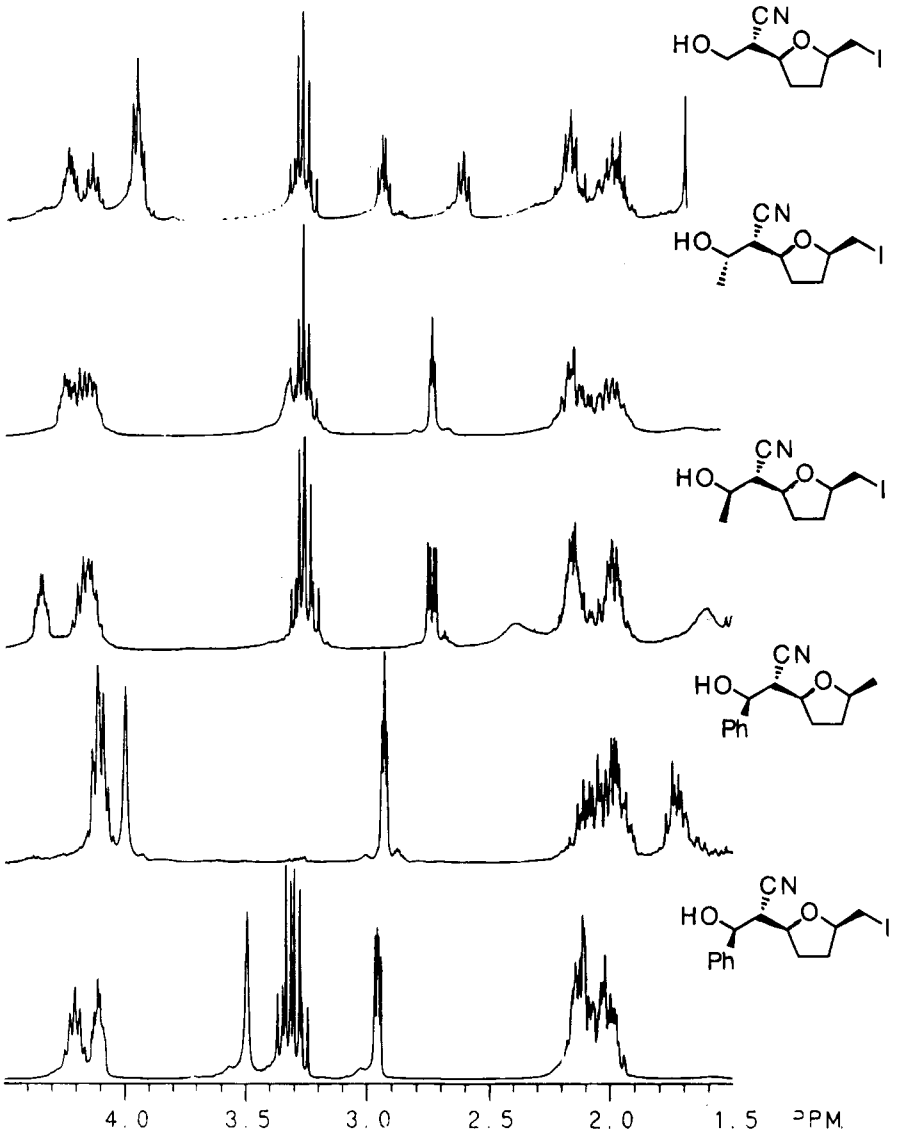


Figure 5. ^{1}H NMR comparison of cyclic ether major diastereomers.

of cyclic ethers from hepta-2,5-dien-1-ols *via* tetrahydrofuroisoxazoline has been developed. The variety of reactions, solvents, and temperatures utilized reflect the versatility of multistep polymer-supported synthesis applied to the formation of organic target molecules. The most important benefit of polymer-supported synthesis used in these reaction sequences is the ease of separation and isolation of the targeted cyclic ethers. The electrophilic cyclization is specific for the formation of the cyclic ethers, and any side products remain attached to the polymer support.

Experimental Section[1b]

Polymer-Supported *p*-Benzyl(oxy) Aldehyde 1. To a solution of 2.26 g (56.5 mmol) of NaOH in 80 mL of DMSO was added 6.16 g (50.4 mmol) of *p*-hydroxybenzaldehyde in 15 mL of DMSO. The resulting red alkoxide solution was stirred for 30 min and then added dropwise to a solution of 18.5 g of Merrifield's peptide resin in 40 mL of DMSO. The reaction mixture was warmed to 90 °C and stirred for 6 h. Workup yielded 19.85 g of **1** as a white solid [FTIR (KBr pellet) 2725 (CHO) and 1698 cm^{-1} (HC=O)].

Polymer-Supported *p*-Benzyl(oxy)-*p*-phenyl-2-nitroethan-1-ol 2. To 20.1 g of **1** were added 21.7 mL of nitromethane, 23.4 mL of ethanol, 20 mL of THF, and 5.5 mL of triethylamine. The reaction was stirred at rt for 17 h. Workup provided **2** [FTIR (KBr Pellet) (OH), 1555 (NO_2), 1375 cm^{-1} (NO_2)].

Polymer-Supported *p*-Benzyl(oxy)-β-nitrostyrene 3 from 2. To a mixture of 20.1 g of **2** and 40 mL of dichloromethane was added 3.1 mL (40 mmol) of methanesulfonyl chloride dropwise. The reaction was stirred at room temperature for 10 min and then placed in an ice bath, and 11.15 mL (80 mmol) of triethylamine was added dropwise. The polymer support slowly turned bright yellow in color, and the reaction was stirred for an additional 15 min. Workup gave **3** as a bright yellow solid [FITR (KBr pellet) 1629 cm^{-1} (C=CNO_2) and 1340 cm^{-1} (C=CNO_2)].

Polymer-Supported *p*-Benzyl(oxy)-β-nitrostyrene 3 from 1. To a solution of 5.02 g of **1** in 25 mL of nitromethane was added 1.00 g (13.00 mmol) of ammonium acetate followed by 25 mL of glacial acetic acid. The reaction mixture was refluxed for 3 h. Workup yielded **3** as a yellow solid [FTIR (KBr pellet) 1629 (C=CNO_2) and 1340 cm^{-1} (C=CNO_2)].

Polymer-Supported 1-[(1-Phenyl-2,6-heptadienyl)oxy]-2-nitroethyl-*p*-benzyl(oxy)benzene 4. Potassium hydride (1.36 g, 35% in mineral oil, 11.86 mmol) was washed with (4 × 20 mL) hexane, dried under a stream of argon, and resuspended in 10 mL of THF. To this mixture was added 1.91 g (10.15 mmol) of 1-phenyl-2,6-heptadien-1-ol in 5 mL of THF, and the resulting alkoxide was added by cannula into a cooled (−44 °C) mixture of 4.91 g of **3b** in 25 mL of THF. After 3 h, the reaction was quenched with 55 mL of 1 M acetic acid and upon workup gave **4** as a yellow solid [FTIR (KBr pellet) 1559 (NO_2) and 1376 cm^{-1} (NO_2)].

Polymer-Supported 1-[(1-Methyl-2,6-heptadienyl)oxy]-2-nitroethyl-*p*-benzyl(oxy)benzene 5. Sodium hydride (0.17

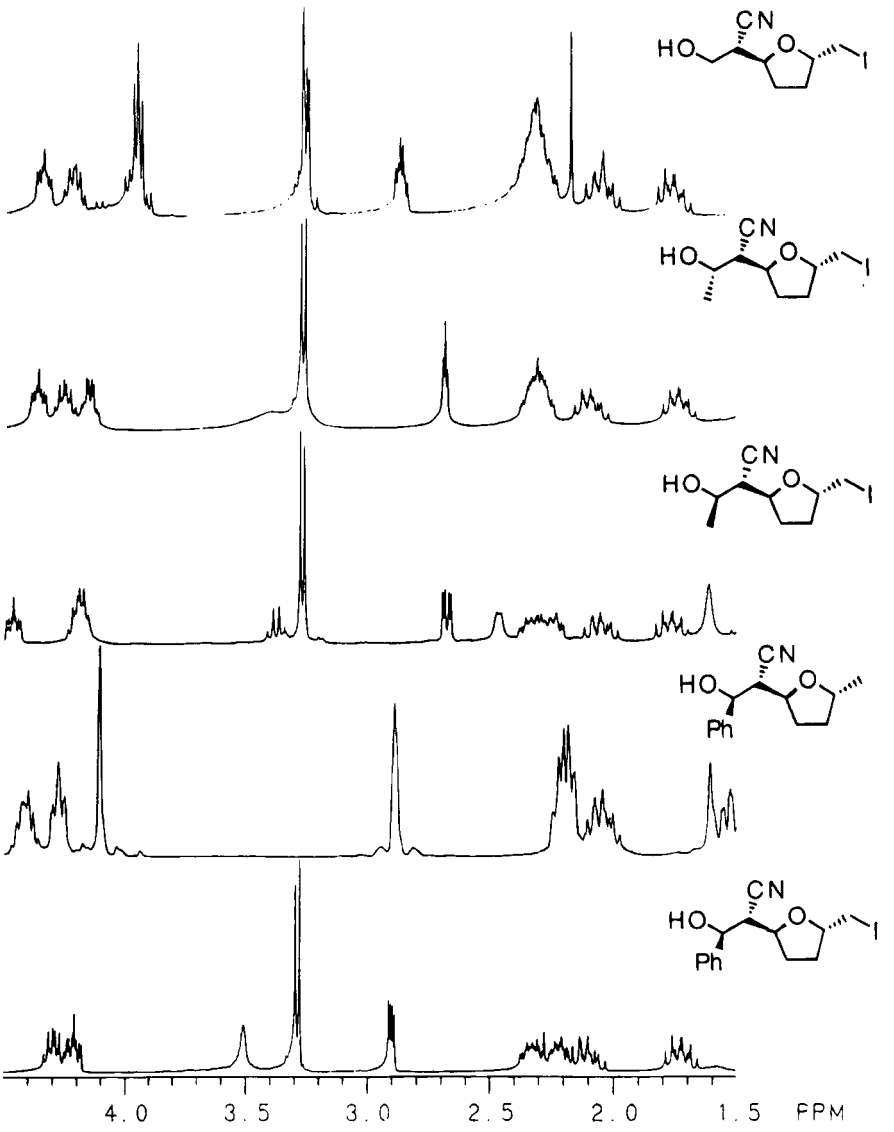


Figure 6. ^{1}H NMR comparison of cyclic ether minor diastereomers.

g, 60% in mineral oil, 4.0 mmol) was suspended in 5 mL of THF. To this mixture was added 440 mg (3.50 mmol) of 1-methyl-2,6-heptadien-1-ol in 5 mL of THF, and the resulting alkoxide was stirred for 1.5 h and then added by cannula into a cooled (−41 °C) mixture of 3.18 g of **3b** in 16 mL of THF. After 20 h, the reaction had reached 20 °C, was quenched with 20 mL of 1 M acetic acid, and upon workup gave 3.26 g of **5** as a yellow solid [FTIR (KBr pellet) 1559 (NO_2) and 1376 cm^{-1} (NO_2)].

Polymer-Supported 1-[(2,6-Heptadienyl)oxy]-2-nitroethyl-*p*-benzyl(oxy)benzene 6. Potassium hydride (809 mg, 35% in mineral oil, 7.07 mmol) was suspended in 5 mL of THF. To this mixture was added 676 mg (6.02 mmol) of 2,6-heptadien-1-ol in 10 mL of THF, and the resulting alkoxide was added by cannula with an additional 10 mL of THF into a cooled (−41 °C) mixture of 2.81 g of **3b** in 15 mL of THF. After 20 h, the reaction had reached room temperature and was quenched with 50 mL of 1 M acetic acid. Workup gave 2.56 g of **6** as a yellow solid [FTIR (KBr pellet) 1559 (NO_2) and 1355 cm^{-1} (NO_2)].

Polymer-Supported 3-(3-Butenyl)-3a,4-dihydro-6-[*p*-benzyl(oxy)]-4-phenyl-3*H*,6*H*-furo[3,4-*c*]isoxazole 7. To a solution of 5.00 g of **4** in 20 mL of benzene was added 66.1 mg (0.65 mmol) of triethylamine followed by 1.59 g (13.4 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 4 days and then quenched with 5 mL of water and stirred overnight. Workup afforded 4.96 g of **7**.

Polymer-Supported 3-(3-Butenyl)-3a,4-dihydro-6-[*p*-benzyl(oxy)]-4-methyl-3*H*,6*H*-furo[3,4-*c*]isoxazole 8. To a mixture of 3.25 g of **5** in 10 mL of benzene was added 79.3 mg (0.78 mmol) of triethylamine followed by 1.620 g (13.6 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 2 days. Workup afforded 3.04 g of **8**.

Polymer-Supported 3-(3-Butenyl)-3a,4-dihydro-6-[*p*-benzyl(oxy)]-3*H*,6*H*-furo[3,4-*c*]isoxazole 9. To a mixture of 2.56 g of **6** in 10 mL of benzene was added 118.3 mg (1.17 mmol) of triethylamine followed by 1.427 g (11.98 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 3 days and then quenched with 2 mL of water and stirred overnight. Workup afforded 2.57 g of **9** [FTIR (KBr) 1248, 1173, 1024 cm^{-1}].

(±)-(2*R,5*R**,1′*S**,2′*R**)- and (±)-(2*R**,5*S**,1′*S**,2′*R**)-2-(1-Cyano-2-hydroxy-2-phenethyl)-5-(iodomethyl)tetrahydrofuran (10a and 10b).** To a cooled (−78 °C) solution of 4.75 g of **7** in 20 mL of CH_2Cl_2 was added 6 mL of 1 M ICl in CH_2Cl_2. The reaction was stirred for 3 h, the cold bath was removed and replaced with a room temperature water bath, the reaction was quenched with a mixture of 6 mL of 1 M $Na_2S_2O_3$(aq) and 6 mL of $NaHCO_3$(aq), and the mixture was stirred vigorously until the polymer support lightened in color. The polymer support was then filtered and washed with (4 × 25 mL) CH_2Cl_2 followed by 10 mL of water. The filtrate was collected, the organic layer removed, and the aqueous layer extracted with (6 × 30 mL) CH_2Cl_2. The combined organics were washed with brine and dried (Na_2SO_4), and the solvent removed in vacuo. The crude material was purified by flash chromatography using 25% EtOAc/*n*-hexane to give 108 mg of **10a/10b**. The *cis/trans* ratio was 2.2:1 (**10a:10b**) as determined from ^{1}H NMR integration of the crude product. The diastereomers were separated by HPLC (*n*-hexane/CH_2Cl_2/2-

propanol (88/10/2)) [**10a**: R_f = 0.23 (25/75 EtOAc/*n*-hexane; t_R = 9 min; mp 82.8–83.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.96–2.04 (m, 2H), 2.06–2.18 (m, 2H), 2.95 (dd, 1H, *J* = 3.0, 4.5 Hz), 3.27 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.34 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.50 (s, 1H), 4.08–4.13 (m, 1H), 4.17–4.23 (m, 1H), 5.07 (d, 1H, *J* = 5.0 Hz), 7.34–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.0, 29.9, 30.6, 47.3, 73.5, 79.1, 80.4, 117.3, 126.1, 128.6, 128.7, 140.0; FTIR (neat) 3466, 2246, 1058 cm^{-1}. Anal. Calcd: C, 47.08; H, 4.52; N, 3.92. Found: C, 47.13; H, 4.49; N, 3.90. **10b** R_f = 0.23 (25/75 EtOAc/*n*-hexane; t_R = 8 min; mp 97.1–97.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.68–1.77 (m, 1H), 2.09–2.16 (m, 1H), 2.18–2.23 (m, 1H), 2.29–2.34 (m, 1H), 2.90 (dd, 1H, *J* = 2.5, 5.0 Hz), 3.28 (d, 2H, *J* = 5.5 Hz), 3.50 (s, 1H), 4.18–4.23 (m, 1H), 4.26–4.32 (m, 1H), 5.08 (d, 1H, *J* = 5.0 Hz), 7.33–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.8, 31.2, 32.0, 47.2, 73.8, 78.7, 79.6, 117.3, 126.2, 128.6, 128.7, 140.0; FTIR (neat) 3466, 2246, 1058 cm^{-1}. Anal. Calcd: C, 47.08; H, 4.52; N, 3.92. Found: C, 47.12; H, 4.49; N, 3.83]. The resulting polymer of this reaction was washed, filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane, and then dried under vacuum overnight [FTIR (KBr) 2725 (CHO) and 1698 cm^{-1} (HC=O)].

Iodine Monobromide Cyclization. *Via* a procedure analogous to that employed in the synthesis of **10a** and **10b** by iodine monochloride cyclization, 2 mL of 1 M IBr in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 1.06 g of **7** in 5 mL of CH_2Cl_2 and stirred for 2.5 h. Workup and purification as described gave 27.1 mg of **10a** and **10b** in a *cis*:*trans* ratio of 4.0:1 (**10a:10b**). The resulting polymer of this reaction was washed and filtered with 3 × 20 mL each of hot water, DME, ether, chloroform and dichloromethane and then dried under vacuum overnight [FTIR (KBr) 1698 cm^{-1} (HC=O)].

Iodine Monobromide in Toluene. *Via* a procedure analogous to that employed in the synthesis of tetrahydrofurans **10a and 10b** by iodine monochloride cyclization, 4 mL of 1 M IBr in CH_2Cl_2 was added to a cooled (−80 °C) mixture of 2.04 g of **7** in 8 mL of toluene and stirred for 19 h. Workup and purification as described gave 47.7 mg of tetrahydrofurans **10a** and **10b** in a *cis*/*trans* ratio of 2.3:1 (**10a:10b**). The resulting polymer of this reaction was washed and filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane and then dried under vacuum overnight [FTIR (KBr) 1698 cm^{-1} (HC=O)].

***N*-Iodosuccinimide Cyclization.** *Via* a procedure analogous to that employed in the synthesis of tetrahydrofurans **10a** and **10b** by iodine monochloride cyclization, 421 mg of *N*-iodosuccinimide in 5 mL of CH_2Cl_2 was added to a cooled (−78 °C) mixture of 0.91 g of **7** in 5 mL of CH_2Cl_2 and stirred for 9 h. The cold bath was allowed to slowly raise to 10 °C. Workup and purification as described gave 13.7 mg of tetrahydrofurans **10a** and **10b** in a *cis*:*trans* ratio of 2.6:1 (**10a:10b**). The resulting polymer of this reaction was washed and filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane and then dried under vacuum overnight [FTIR (KBr) 1698 cm^{-1} (HC=O)].

(±)-(2*R,5*R**,1′*R**,2′*S**)-, (±)-(2*R**,5*S**,1′*R**,2′*S**)-, (±)-(2*R**,5*R**,1′*R**,2′*R**)-, and (±)-(2*R**,5*S**,1′*R**,2′*R**)-2-(1-Cyano-2-hydroxypropyl)-5-(iodomethyl)tetrahydrofuran (11a, 11b, 11c and 11d).** *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 3.2 mL of 1 M ICl in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 3.03 g of **8** in 15 mL of CH_2Cl_2 and stirred for 1.5 h. Workup and purification as described gave 46.8 mg of **11a/11b/11c/11d**. The ratio of diastereomers was determined by capillary GLC of the crude reaction mixture (150–200 °C, rate 5 °C/min, t init = 5 min) to be 48:38:10:4 (**11a:11b:11c:11d**). The diastereomers were separated by HPLC with 2-propanol/*n*-hexane (7.5/92.5) [high-resolution mass spec (CI, isobutane) *m*/*z* 296.0155; (M + H)$^+$, calcd for $C_9H_{15}INO_2$ 296.0149. **11a:** GLC t_R = 15.01 min; HPLC t_R = 16.0 min; R_f = 0.16 (40% ethyl ether/*n*-pentane); ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3H, *J* = 6.5 Hz), 1.93–2.06 (m, 2H), 2.07–2.21 (m, 2H), 2.74 (t, 1H, *J* = 3.0 Hz), 3.25 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.28 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.33 (d, 1H, *J* = 3.0 Hz), 4.10–4.21 (m, 2H), 4.22–4.29 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0, 21.6, 30.1, 30.5, 45.6, 67.7, 79.9, 80.3, 117.1; FTIR (neat) 3460, 2245, 1054 cm^{-1}. **11b**: GLC t_R 14.89 min; HPLC t_R = 14.5 min; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3H, *J* = 6.3 Hz), 1.66–1.80 (m, 1H), 2.01–2.16 (m, 1H), 2.24–2.37 (m, 2H), 2.67 (dd, 1H, *J* = 2.6, 2.8 Hz), 3.26 (d, 2H, *J* = 5.5 Hz), 4.15 (dq, 1H, *J* = 2.6, 6.3 Hz), 4.25 (ddt, 1H, *J* = 5.6, 8.4, 8.4 Hz), 4.36 (ddd, 1H, *J* = 2.8, 6.1, 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 9.7, 21.5, 31.4, 31.9, 45.5, 67.9, 79.5; FTIR (neat) 3460, 2245, 1056 cm^{-1}. **11c:** GLC t_R = 13.48 min; HPLC t_R = 13.0 min; R_f = 0.19 (40% ethyl ether/*n*-pentane); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, *J* = 6.5 Hz), 1.96–2.02 (m, 2H), 2.12–2.19 (m, 2H), 2.43 (d, 1H, *J* = 6.0 Hz), 2.73 (dd, 1H, *J* = 3.0, 7.5 Hz), 3.23 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.29 (dd, 1H, *J* = 6.0, 10.0 Hz), 4.12–4.24 (m, 2H), 4.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.4, 21.9, 29.6, 30.9, 45.5, 66.5, 76.3, 79.9, 118.2; FTIR (neat) 3460, 2245, 1064 cm^{-1}. **11d:** GLC t_R = 13.55 min; HPLC t_R = 11.5 min; R_f = 0.23 (40% ethyl ether/*n*-pentane); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, *J* = 6.5 Hz), 1.72–1.80 (m, 1H), 1.98–2.13 (m, 1H), 2.15–2.38 (m, 2H), 2.45 (d, 1H, *J* = 6.0 Hz), 2.67 (dd, 1H, *J* = 3.0, 7.5 Hz), 3.27 (d, 2H, *J* = 5.5 Hz), 4.14–4.24 (m, 2H), 4.46 (ddd, 1H, *J* = 3.0, 6.0, 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 10.4, 21.9, 30.9, 32.3, 45.4, 66.6, 75.8, 79.1; FTIR (neat) 3460, 2245, 1060 cm^{-1}]. The resulting polymer of this reaction was washed and filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane and then dried under vacuum overnight [FTIR (KBr) 1698 cm^{-1} (HC=O)].

Iodine Monobromide Cyclization. *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 5.0 mL of 1 M Br in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 5.22 g of **8** in 20 mL of CH_2Cl_2 and stirred for 2 h. Workup and purification as described gave 63.7 mg of **11a/11b/11c/11d** in a ratio of 62:18:11:9 (**11a:11b:11c:11d**).

(±)-(2*R,5*R**,1′*S**)- and (±)-(2*R**,5*S**,1′*S**)-2-(1-Cyano-2-hydroxyethyl)-5-(iodomethyl)tetrahydrofuran (12a and 12b). Iodine Monobromide Cyclization.** *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 3 mL of 1 M IBr in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 2.57 g of **9** in 10 mL of CH_2Cl_2 and stirred for 1.5 h. Workup and purification as described gave 21.0 mg of **12a/12b** in a *cis*/*trans* ratio of 3.88:1 (**12a:12b**). The diastereomers were separated by HPLC (*n*-hexane/CH_2Cl_2/2-propanol (86/10/4)) [**12a**: R_f = 0.20 (30/70 EtOAc/*n*-hexane); t_R = 15 min; ^{1}H NMR ($CDCl_3$) δ 1.95–2.03 (m, 2H), 2.13–2.18 (m, 2H), 2.93 (dt, 1H, *J* = 3.5, 5.5 Hz), 3.24 (dd, 1H, *J* = 7.0, 10.0 Hz), 3.29 (dd, 1H, *J* = 5.5, 10.0 Hz), 3.92–3.97 (m, 2H), 4.13 (m, 1H), 4.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.4, 29.6, 30.8, 40.2, 61.5, 77.8, 79.9, 118.1; FTIR (neat) 3460, 2246, 1058 cm^{-1}. **12b:** R_f = 0.20 (30/70 EtOAc/*n*-hexane); t_R = 13 min; ^{1}H NMR ($CDCl_3$) δ 1.75 (ddt, 1H, *J* = 8.5, 10.5, 13.0 Hz), 2.04 (ddt, 1H, *J* = 8.5, 10.0, 13.0 Hz), 2.22–2.38 (m, 2H), 2.85 (ddd, 1H, *J* = 3.0, 5.5, 6.0 Hz), 3.24 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.28 (dd, 1H, *J* = 5.0, 10.0 Hz), 3.92 (dd, 1H, *J* = 6.0, 11.0 Hz), 3.98 (dd, 1H, *J* = 5.5, 11.0 Hz), 4.21 (ddt, 1H, *J* = 5.0, 6.0, 8.0 Hz), 4.34 (ddd, 1H, *J* = 3.0, 6.0, 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 9.9, 31.0, 32.2, 40.2, 61.7, 77.6, 79.3, 118.2; FTIR (neat) 3460, 2246, 1058 cm^{-1}; high-resolution mass spec (CI, isobutane) *m*/*z* 281.9981 [(M + H)$^+$, calcd for $C_8H_{13}INO_2$ 281.9993]. The resulting polymer of this reaction was washed and filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane and then dried under vacuum overnight [FTIR (KBr) 1698 cm^{-1} (HC=O)].

Polymer-Supported β-Nitrostyrene 13. To a solution of 10.12 g of polymer-supported aldehyde in 25 mL of nitromethane was added 2.123 g (27.54 mmol) of ammonium acetate followed by 25 mL of glacial acetic acid. The reaction mixture was refluxed for 3.5 h. Workup yielded 9.61 g of **13** as a yellow solid [FTIR (KBr pellet) 1633 (C=CNO_2) and 1343 cm^{-1} (C=CNO_2)].

Polymer-Supported 1-[(1-Phenyl-2,6-heptadienyl)oxy]-2-nitroethylbenzene 14. Potassium hydride (0.574 g, 35% in mineral oil, 5.01 mmol) was suspended in 10 mL of THF. To this mixture was added 763.6 mg (4.06 mmol) of 1-phenyl-2,6-heptadien-1-ol in 10 mL of THF, and the resulting alkoxide was stirred for 0.5 h and then added by cannula into a cooled (−42 °C) mixture of 2.04 g of **13** in 10 mL of THF. After 3.5 h, the cold bath was removed and replaced with an ice bath. The reaction was quenched with 100 mL of 1 M acetic acid

and upon workup gave 2.00 g of **14** [FTIR (KBr pellet) 1559 (NO_2) and 1376 cm^{-1} (NO_2)]. The 1-phenyl-2,6-heptadien-1-ol was recovered from the organic filtrate and distilled by Kugelrohr distillation to give 476 mg (2.53 mmol).

Polymer-Supported 3-(3-Butenyl)-3a,4-dihydro-6-[*p*-phenyl]-4-phenyl-3*H*,6*H*-furo[3,4-*c*]isoxazole 16. To a mixture of 2.00 g of **14** in 10 mL of benzene was added 38.7 mg (0.38 mmol) of triethylamine followed by 0.783 g (6.57 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 29 h and then quenched with 2 mL of H_2O and stirred overnight. Workup afforded 1.98 g of **16**.

Iodine Monobromide Cyclization of 16. *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 2.5 mL of 1 M IBr in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 1.98 g of **16** in 9 mL of CH_2Cl_2 and stirred for 2 h. Workup and purification as described gave 18.3 mg of **10a/10b**. The ratio of diastereomers was determined to be 3.4:1 (**10a:10b**) *cis*:*trans* by ^1H NMR integration of the crude reaction mixture.

Polymer-Supported 1-[(1-Methyl-2,6-heptadienyl)oxy]-2-nitroethylbenzene 15. Potassium hydride (0.855 g, 35% in mineral oil, 7.46 mmol) was washed with (4 × 20 mL) hexane, dried under a stream of argon, and resuspended in 10 mL of THF. To this mixture was added 809.0 mg (6.41 mmol) of 1-methyl-2,6-heptadien-1-ol in 10 mL of THF, and the resulting alkoxide was stirred for 1.5 h and then added by cannula into a cooled (−41 °C) mixture of 3.02 g of **13** in 20 mL of THF. After 5.5 h, the cold bath was removed and replaced with an ice bath. The reaction was quenched with 50 mL of 1 M acetic acid and upon workup gave 3.07 g of **15** [FTIR (KBr pellet) 1559 (NO_2) and 1376 cm^{-1} (NO_2)]. The dienol was recovered from the organic filtrate and Kugelrohr distilled to give 517 mg (4.10 mmol).

Polymer-Supported 3-(3-Butenyl)-3a,4-dihydro-6-(*p*-phenyl)-4-methyl-3*H*,6*H*-furo[3,4-*c*]isoxazole 17. To a mixture of 3.07 g of **15** in 10 mL of benzene was added 87.3 mg (0.86 mmol) of triethylamine followed by 1.521 g (12.8 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 24 h and then quenched with 3 mL of H_2O and stirred overnight. Workup afforded 2.97 g of **17**.

Iodine Monochloride Cyclization of 17. *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 2 mL of 1 M ICl in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 1.44 g of **17** in 10 mL of CH_2Cl_2 and stirred for 2 h. Workup and purification as described gave 29.6 mg of **11a/11b/11c/11d**. The ratio of diastereomers was determined by capillary GLC of the crude reaction mixture (150−200 °C, rate 5 °C/min, *t* (init) = 5 min) to be 54:32:8:6 (**11a:11b:11c:11d**).

Iodine Monobromide Cyclization of 17. *Via* a procedure analogous to that employed in the synthesis of **10a/10b** by iodine monochloride cyclization, 2 mL of 1 M IBr in CH_2Cl_2 was added to a cooled (−78 °C) mixture of 1.53 g of **17** in 10 mL of CH_2Cl_2 and stirred for 2 h. Workup and purification as described gave 16.6 mg of **11a/11b/11c/11d**. The ratio of diastereomers was determined by capillary GLC of the crude reaction mixture (150−200 °C, rate 5 °C/min, *t* (init) = 5 min) to be 65:15:11:9 (**11a:11b:11c:11d**).

Polymer-Supported 1-[(2,7-Octadienyl)oxy]-2-nitroethyl-*p*-benzyl(oxy)benzene 18. Potassium hydride (35% in mineral oil, 687 mg, 5.99 mmol) was suspended in 10 mL of THF. To this mixture was added 594 mg (4.71 mmol) of 2,7-octadien-1-ol in 5 mL of THF, and the resulting alkoxide solution was stirred for 1 h and then added by cannula into a cooled (−41 °C) mixture of 2.36 g of **3** in 15 mL of THF. After 21 h, the reaction had reached 15 °C and the reaction was quenched with 50 mL of 1 M HCl and upon workup gave 2.45 g of **18** [FTIR (neat) 1555, 1380 cm^{-1}].

Polymer-Supported (±)-(3α,3aα,6α)- and (±)-(3α,3aα,6β)-3-(4-Pentenyl)-3a,4-dihydro-6-[*p*-benzyl(oxy)phenyl]-3*H*,6*H*-furo[3,4-c]isoxazole (19). To a mixture of 2.45 g of **18** in 10 mL of benzene was added 25 drops of triethylamine followed by 724 g (6.08 mmol) of phenyl isocyanate. The reaction mixture was stirred at room temperature for 72 h. Workup afforded 2.47 g of **19**.

Polymer-Supported *p*-Benzyl(oxy)benzylamine (21). To a mixture of 115 mg (3.03 mmol) of lithium aluminum hydride in 15 mL of ether was added 187 mg of **3**. The reaction was refluxed for 2 days and then quenched with 10 mL of sodium potassium tartrate (20%, aq). Workup provided 148 mg of **21** as a white solid [FTIR (KBr pellet) 3432 (NH_2 str) and 1620 cm^{-1} (NH_2 wag)].

(±)-(2*R,5*S**,1′*S**,2′*R**)-2-(1-Cyano-2-hydroxy-2-phenethyl)-5-methyltetrahydrofuran (22).** To a solution of 44.2 mg (0.124 mmol) of **10a** and 3.0 mg (0.018 mmol) of AIBN in 2 mL of benzene was added 112.3 mg (0.386 mmol) of tributyltin hydride. The reaction was refluxed for 3.5 h and the benzene removed under a stream of argon and replaced with 2 mL of ether. Then 2.0 mL of KF (aq) was added and the mixture stirred for 1 h. The organic layer was removed and the aqueous layer extracted with (6 × 2 mL) ether. The combined organics were washed with brine and dried (MgSO4), and the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 25% ethyl acetate/hexane and then recrystallized from ethyl acetate and hexane to give 22.3 mg (78% yield) of **22** [R_f = 0.23 (25/75 EtOAc/*n*-hexane; mp 89.2−89.5 °C; ^1H NMR ($CDCl_3$) δ 1.35 (d, 3H, *J* = 6.0 Hz), 1.68−1.78 (m, 1H), 1.90−2.14 (m, 3H), 2.93 (dd, 1H, *J* = 3.1, 3.7 Hz), 4.05−4.16 (m, 2H), 5.05 (d, 1H, *J* = 3.7 Hz), 7.34−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.6, 30.1, 31.8, 47.2, 73.6, 76.4, 78.4, 117.0, 125.7, 128.1, 128.3, 140.0; FTIR (neat) cm^{-1}. Anal. Calcd: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.57; H, 7.34; N, 5.96.].

(±)-(2*R,5*R**,1′*S**,2′*R**)-2-(1-Cyano-2-hydroxy-2-phenethyl)-5-methyltetrahydrofuran (23).** To a solution of 22.0 mg (0.062 mmol) of **10b** and 2.2 mg (0.013 mmol) of AIBN in 2 mL of benzene was added 61.9 mg (0.213 mmol) of tributyltin hydride. The reaction was refluxed for 4 h and the benzene removed under a stream of argon and replaced with 2 mL of ether. Then 2 mL of KF (aq) was added and the mixture stirred for 1 h. The organic layer was removed and the aqueous layer extracted with (6 × 2 mL) ether. The combined organics were washed with brine and dried (MgSO4), and the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 25% ethyl acetate/hexane and then recrystallized from ethyl acetate and hexane to give 8.5 mg (60% yield) of **23** [R_f = 0.27 (25/75 EtOAc/*n*-hexane; mp 78.9−80.0 °C; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, *J* = 6.0 Hz), 1.46−1.59 (m, 1H), 1.97−2.11 (m, 1H), 2.15−2.24 (m, 2H), 2.88 (dd, 1H, *J* = 2.4, 3.0 Hz), 4.25−4.30 (m, 1H), 4.36−4.46 (m, 1H), 5.07 (d, 1H, *J* = 3.0 Hz), 7.31−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 31.4, 33.3, 47.3, 74.1, 77.5, 78.4, 117.4, 125.9, 128.4, 128.6, 140.2; FTIR (neat) 2925, 2244 (CN), 1455 (CH_3), 1091 (C−O) cm^{-1}].

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