close-lying electronic states, originating either from Jahn-Teller distortion or by solvent-induced lifting of the 3-fold orbital degeneracy of the mononegative anion. In this model, $\tau_c \sim \exp(\Delta E/kT)$ denotes the average time of the radical in its ground state, ΔE denoting the energy difference of the electronic singlet to the remaining doublet. The resulting $J(\omega) \sim \tau_c/(1 + \omega^2\tau_c^2)$ leads to $T_2^{-1} = T_1^{-1} \sim \exp(\Delta E/kT)$ in the limit $\omega_0^2\tau_c^2 \ll 1$. The anticipated thermally-activated contribution to T_2 can be used for a determination of ΔE, after subtracting the high-temperature width of 700 kHz, as is shown in Figure 2. It is tempting to correlate this value of $\Delta E = 450$ cm^{-1} with a value, deduced from the g-factor shift relative to the free electron value.[3] Following the arguments of Kato et al., we obtain $\Delta E' = 210$ cm^{-1}. Considering the various assumptions used in ref 3, this factor-of-two agreement is very satisfactory.

Various questions still remain unanswered. Firstly, in agreement with all other EPR results, no ^{13}C satellites have been observed. However, using a simple Karplus-Fraenkel estimate, $a(C^{13}) \simeq (-10) \times 2.8/60$ MHz = -460 kHz is obtained, just at the resolution limit of our experiment. Secondly, the postulated charge separation also leads to the formation of a cation radical, which was also not visible. A possible explanation might be the generation of a radical adduct with unresolved hfs, therefore not detectable with a $\pi/2$ excitation. Search with an echo sequence, however, was also unsuccessful, excluding radicals with $T_2 \geq 500$ ns.

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Polymer-Supported Synthesis of 2,5-Disubstituted Tetrahydrofurans

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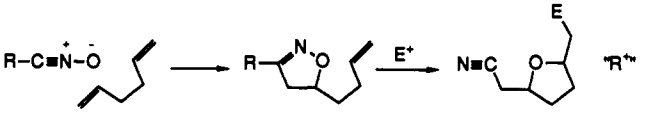
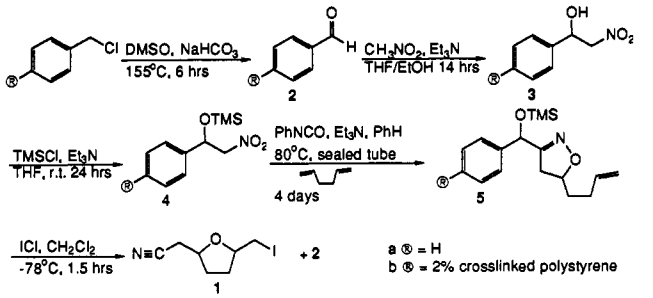
Polymer-supported synthesis is an important tool for the development of new synthetic strategies in organic chemistry,[2] and the literature associated with polymer-supported reagents and catalysts is extensive.[3] Merrifield's pioneering work in the area of polymer-supported polypeptide synthesis[4] delineated many of the benefits of a polymer-supported synthetic strategy, with the most obvious being ease of workup and ease of product isolation. In addition, side product formation is often minimized when the reactive species is covalently attached to a polymer support.[5] Intrigued by these potential advantages, we set out to explore the application of polymer-supported reactions in multistep synthetic organic chemistry and describe herein a polymer-supported strategy which improves upon an α,ω-diene → cyclic ether protocol recently reported from our laboratories.[6] Thus, the targeted process involves the five-step synthesis of 2,5-disubstituted tetrahydrofurans via a tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence.

Scheme I



Scheme II



2,5-Disubstituted tetrahydrofurans are important structural elements in many polyether antibiotics[7] and, as a compound class, have proven to be synthetically challenging molecules.[8] In earlier work, we demonstrated that the tandem process outlined in Scheme I provides useful entry to such compounds. Unfortunately, the protocol as originally developed suffers one major drawback when carried out under normal homogeneous conditions.[9] That is, it utilizes an α,ω-diene substrate in the 1,3-dipolar cycloaddition step and thus requires selective monoaddition of the nitrile oxide to this dipolarophile. However, in solution a second nitrile oxide is free to react with the remaining terminal alkene, leading to the undesired product of bis 1,3-dipolar cycloaddition. As previously reported, this bis addition can be suppressed by using the diene in a 10-fold excess. Clearly as the α,ω-diene becomes more complex and/or expensive, this solution to the bis-addition problem becomes less and less attractive.

As an approach to solving this problem, we considered potentially beneficial the partial isolation that might be achieved by covalent attachment of the nitrile oxide moiety to an insoluble polymer matrix. The terminal alkene remaining after isoxazole formation would be less accessible to another polymer-bound nitrile oxide, which would then have a higher probability of reacting with remaining diene. The latter could then be used in smaller excess. An additional benefit of the polymer-supported method is that the iodocyclization reaction was envisioned to liberate exclusively the target cyclic ether. This transformation also would simultaneously regenerate a functionalized polymer, which could be recycled through this synthetic scheme.

The planned synthesis thus had two polymer prerequisites: (1) straightforward generation of a polymer-bound nitrile oxide precursor and (2) incorporation of cation-stabilizing functionality (in the polymer-bound R group) to facilitate the electrophilic cyclization reaction. We felt it most convenient to meet these requirements in the context of the functionality accessible from Merrifield's polystyrene resin.[10] The approach outlined in Scheme II appeared to be especially attractive since the final cyclization step would regenerate the initial polymer-bound aldehyde for potential recycling. The chemistry presented in Scheme II was first investigated using conventional solution-phase methods (i.e., encircled R = H) and employing a 10-fold excess of α,ω-diene in the critical cycloaddition step. We thus obtained the final product, 2-(cyanomethyl)-5-(iodomethyl)tetrahydrofuran (**1**), as

(1) Sloan Foundation Fellow (1987-1991) and NIH RCDA recipient (1989-1994; EC00182).
(2) (a) Xu, Z.-H.; McArthur, C. R.; Leznoff, C. C. *Can. J. Chem.* **1983**, *61*, 1405. (b) Fréchet, J. M. J. *Tetrahedron* **1981**, *37*, 663. (c) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327. (d) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135.
(3) (a) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 971. (b) Blanton, J. R.; Salley, J. M. *J. Org. Chem.* **1991**, *56*, 490.
(4) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
(5) Schore, N. E.; Najdi, S. D. *J. Am. Chem. Soc.* **1990**, *112*, 441.
(6) Kurth, M. J.; Rodriguez, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7577.
(7) O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205.
(8) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(9) Kurth, M. J.; Rodriguez, M. J.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 283.
(10) Dupas, G.; Decormeille, A.; Bourguignon, J.; Queguiner, G. *Tetrahedron* **1989**, *45*, 2579.

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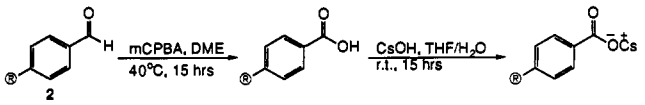
Scheme III



a 1:1.92 mixture of diastereomers in an 18% overall yield[11] from benzaldehyde. Attention was next turned to the polymer-supported version of this reaction protocol.

Commercially available 2%-cross-linked Merrifield polymer was oxidized to aldehyde[12] **2b** and condensed with nitromethane to form polymer-bound 2-nitro-1-phenylethan-1-ol **3b**. The hydroxyl moiety was protected as the trimethylsilyl ether **4b** in order to avoid dehydration to the corresponding β-nitrostyrene. Subsequent phenyl isocyanate mediated dehydration[13] of the nitroalkane moiety presumably generated the polymer-bound nitrile oxide, which then underwent 1,3-dipolar cycloaddition with 1,5-hexadiene (2–3-fold excess) to give the polymer-bound isoxazole **5b**. After each step in this sequence, polymer characterization was accomplished by comparing the IR spectrum[14] of the functionalized polymer with that of the solution-phase analog. Finally, electrophilic cyclization of the isoxazole with iodine monochloride at −78 °C gave **1** and regenerated the polymer-bound aldehyde. Using 3 equiv of 1,5-hexadiene, the overall yield was 0.26 mmol of **1**/g of polymer. The overall yield using 2 equiv of 1,5-hexadiene was 0.19 mmol of **1**/g of polymer. When the polymer-bound aldehyde was recycled through this reaction scheme, **1** was obtained to the extent of 0.07–0.11 mmol/g of polymer. In parallel with the solution-phase chemistry, the cis:trans ratio for **1** was 1:2.1.

A determination of the degree of functionalization of the polymer at the aldehyde stage was carried out in order both to accurately estimate the number of equivalents of α,ω-diene used and to assess the overall chemical yield of **1**.

Oxidation of the aldehyde **2** to a carboxylic acid (*m*-CPBA) followed by neutralization with cesium hydroxide and gravimetric analysis showed the degree of functionalization to be 0.65 ± 0.04 mequiv of aldehyde/g of polymer[15] (Scheme III). With this value as a basis, the overall yield of the 2-(cyanomethyl)-5-(iodomethyl)tetrahydrofuran from the polymer-bound aldehyde **2b** was calculated to be 40% using 3 equiv of 1,5-hexadiene and 29% using 2 equiv of 1,5-hexadiene. These yields were considerably higher than those of the solution-phase synthesis. When recovered polymer-bound aldehyde was recycled through the sequence, the overall yield of **1** was 11–17%.

We have shown that polymer-supported, multistep synthetic sequences can deliver small molecule targets. The diversity of reactions, solvents, and conditions presented in this five-step sequence demonstrates the versatility of the polymer-supported methodology. Reaction conditions are only slightly, if at all, different from those used in conventional synthesis, and it is also significant that the desired cyclic ether is formed exclusively; no other products are cleaved from the polymer support. In addition, the polymer support is sufficiently robust to be recovered and recycled through the reaction sequence.

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Supplementary Material Available: Detailed descriptions of synthesis and characterization of both solution-phase and polymer-supported reactions, including relevant FTIR, NMR, and elemental analysis data (3 pages). Ordering information is given on any current masthead page.

(11) Typical yield for a single run through the complete sequence. Using individually optimized yields for each step, an idealized overall yield of 29% is calculated.

(12) Ayres, J. T.; Mann, C. K. *J. Polym. Sci., Polym. Lett. Ed.* **1965**, *3*, 505.

(13) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474.

(14) Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492. The IR stretches are in agreement with those cited in this paper for similar compounds.

(15) These data are in agreement with IR and quantification results cited in ref 14.

Biosynthesis of Azoxy Compounds. Investigations of Valanimycin Biosynthesis†

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The antibiotic valanimycin (**1**) is a naturally occurring azoxy compound produced by *Streptomyces viridifaciens* MG456-hF10. In addition to antibacterial activity, valanimycin exhibits potent antitumor activity against L1210 and P388 mouse leukemia cells.[1] As a naturally occurring azoxy compound, valanimycin is a member of a growing class of natural products which now includes the cycad toxins macrozamin and cycasin,[2-5] the carcinogen elaiomycin (**2**),[6-10] the antifungal agents LL-BH872α[11-13] and maniwamycins A and B,[14] and the nematocidal compounds jietacins A and B.[15]

Investigations of elaiomycin biosynthesis previously carried out in our laboratory revealed that the β-nitrogen atom and C-5–C-12 of **2** are derived from *n*-octylamine.[16] Additional investigations showed that the α-nitrogen atom and C-2–C-4 of **2** are derived from L-serine, while C-1 is derived from C-2 of acetate.[17] Further studies of elaiomycin were precluded due to insurmountable microbiological difficulties. We have therefore begun to examine the biosynthesis of valanimycin in a continuing effort to understand the biosynthesis of azoxy compounds and the mechanism of N–N bond formation. We would now like to summarize the results of our initial studies.

† This paper is dedicated to the memory of Edward Leete (1928–1992), a pioneer in the field of biosynthetic investigations.

(1) Yamato, M.; Iinuma, H.; Naganawa, H.; Yamagishi, Y.; Hamada, M.; Masuda, T.; Umezawa, H. *J. Antibiot.* **1986**, *39*, 184.

(2) Lythgoe, B.; Riggs, N. V. *J. Chem. Soc.* **1949**, 2716.

(3) Langley, B. W.; Lythgoe, B.; Riggs, N. V. *Chem. Ind. (London)* **1951**, 75.

(4) Riggs, N. V. *Chem. Ind. (London)* **1956**, 926.

(5) Korsch, B.; Riggs, N. V. *Tetrahedron Lett.* **1964**, 523.

(6) Haskell, T. H.; Ryder, A.; Bartz, Q. R. *Antibiot. Chemother.* **1954**, *4*, 141.

(7) Stevens, C. L.; Gillis, B. T.; French, J. C.; Haskell, T. H. *J. Am. Chem. Soc.* **1956**, *78*, 3229.

(8) Stevens, C. L.; Gillis, B. T.; French, J. C.; Haskell, T. H. *J. Am. Chem. Soc.* **1958**, *80*, 6088.

(9) Stevens, C. L.; Gillis, B. T.; Haskell, T. H. *J. Am. Chem. Soc.* **1959**, *81*, 1435.

(10) Taylor, K. G.; Riehl, T. *J. Am. Chem. Soc.* **1972**, *94*, 250.

(11) McGahren, W. J.; Kunstmann, M. P. *J. Am. Chem. Soc.* **1969**, *91*, 2808.

(12) McGahren, W. J.; Kunstmann, M. P. *J. Am. Chem. Soc.* **1970**, *92*, 1587.

(13) McGahren, W. J.; Kunstmann, M. P. *J. Org. Chem.* **1972**, *37*, 902.

(14) Takahashi, Y.; Nakayama, M.; Watanabe, I.; Deushi, T.; Ishiwata, H.; Shiratsuchi, M.; Otani, G. *J. Antibiot.* **1989**, *42*, 1541.

(15) Imamura, N.; Kuga, H.; Otoguro, K.; Tanaka, H.; Omura, S. *J. Antibiot.* **1989**, *42*, 156.

(16) Parry, R. J.; Rao, H. S. P.; Mueller, J. *J. Am. Chem. Soc.* **1982**, *104*, 339.

(17) Parry, R. J.; Mueller, J. *J. Am. Chem. Soc.* **1984**, *106*, 5764.

0002-7863/92/1514-10062$03.00/0