Synthesis of Functionalized Aryloxy 1,3-Butadienes and Their Transformation to Diaryl Ethers via Diels–Alder Cycloaddition Reactions

Richard K. Olsen,* Xianqi Feng, Magnus Campbell, Rui-lian Shao, and Shivanand K. Math

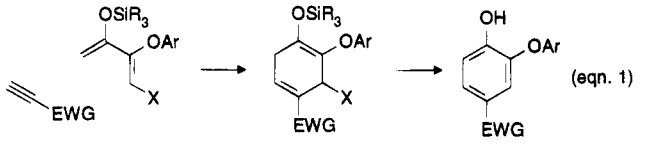
Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300

Received May 10, 1995[⊗]

The Diels–Alder reaction involving cycloaddition of aryloxy-substituted 1,3-butadienes with appropriate acetylenic electrophiles, followed by aromatization of the newly formed cyclohexadiene ring, has been used for the synthesis of diaryl ethers. The functionalized aryloxy 1,3-butadienes employed in this study were prepared by either of two methods: (1) methylenation of aryl esters via the Tebbe or related reagents, and (2) from 1-(aryloxy)-2-propanone by a sequence of formylation or alkylthio methylenation, and subsequent enolsilylation. A tetrasubstituted butadiene containing two phenoxy groups at the 1 and 3 positions also was prepared by the latter method. The cycloaddition reactions of 2,3-dioxy-substituted dienes occurred in high yield, but, as expected, with no regioselectivity to furnish nearly equal mixtures of regioisomeric cycloadducts. In contrast, application of 1,2,3-trihetero-substituted dienes resulted in regiospecific cycloaddition reactions. Transformation of the cyclohexadiene cycloadducts to an aromatic ring was accomplished by dehydrogenation with DDQ or by elimination during the cycloaddition process of a molecule of an alkyl mercaptan. A chiral acetylenic ketone derived from D- or L-serine underwent condensation, without racemization, with aryloxy dienes to provide diaryl ethers related to the isodityrosine antibiotics.

The Diels–Alder reaction is a well-documented, powerful cycloaddition process.[1] In the classical case, the cycloaddition occurs between an electron-rich 1,3-diene and an electrophilic dienophile, usually an alkene or alkyne, to form a cyclohexene or cyclohexadiene ring. The stereochemistry and regiochemistry of the reaction can often be predicted and controlled, these factors, in general, being determined by the nature of substituents appended to the diene or dienophile.

We envisioned the use of aryloxy-substituted 1,3-butadienes as components in a Diels–Alder approach for the synthesis of diaryl ethers. Cyclocondensation of an aryloxy diene and an alkyne-derived dienophile, followed by elimination or oxidation to convert the new six-membered ring to an aromatic ring, would result in formation of a diaryl ether **1** (eq 1).



1

Diaryl ethers are most often prepared by methods related to the classical Ullmann reaction[2] and involve coupling between two aromatic compounds. We are aware of only two preliminary reports[3] of the preparation of diaryl ethers by a Diels–Alder reaction using aryloxy-substituted dienes. Previous communications[4] from our laboratory have established the viability of the Diels–Alder approach to diaryl ethers and specifically to derivatives related to the bis-amino acid-derived diaryl ether isodityrosine (**2**). The cyclic peptide antibiotics K-13 (**3**),[5] and related cyclic peptides[6] OF4949III,[5] piperazinomycin,[7] the bouvardins,[8] and RAI through RAVII[8] all contain an isodityrosine unit. Previous syntheses of isodityrosine[9] and the above isodityrosine peptide antibiotics[10–13] have involved formation of the diaryl ether bond from intact phenolic precursors by use of the Ullmann reaction[9,10] or modified forms of this reaction, as also methods that utilize thallium trinitrate,[11] arene metal (Mn, Fe, or Ru) carbonyls,[12] or aryl iodonium complexes.[13] The complex glycopeptides of the vancomycin and ristocetin

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1995.

(1) Wasserman, H. *Diels–Alder Reaction*; American Elsevier: New York, 1964. Sauer, J.; Sustman, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(2) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.

(3) Carter, S. D.; Thetford, D.; Voyle, M. *J. Chem. Soc., Perkin Trans.* **1990**, 1231. Moreau, P.; Guillaumet, G.; Coudert, G. *Tetrahedron* **1994**, *50*, 3407.

(4) (a) Olsen, R. K.; Feng, X. *Tetrahedron Lett.* **1991**, *32*, 5721. (b) Feng, X.; Olsen, R. K. *J. Org. Chem.* **1992**, *57*, 5811.

(5) Yasuzawa, T.; Shirahata, K. Sano, H. *J. Antibiot.* **1987**, *40*, 455.

(6) Sano, S.; Ikai, K.; Katayama K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685.

(7) Kaneda, M.; Tamai, S.; Nakamura, S.; Hirata, T.; Kushi, Y.; Suga, T. *J. Antibiot.* **1982**, *35*, 1137.

(8) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedjp[f. R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Driek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. Itokawa, H.; Takeya, D.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424.

(9) (a) Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 2053. (b) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211.

(10) Evans, D. A.; Ellman, J. A. J. *Am. Chem. Soc.* **1989**, *111*, 1063. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498. Schmidt, U.; Weller, D. Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227. Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 5061. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000. Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427. Boger, D. L.; Yohannes, D.; Zhou, J.; Patane, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 3420. Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1992**, *33*, 4799.

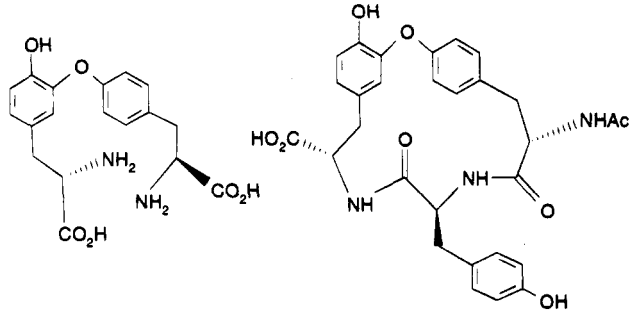
(11) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379. Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957.

(12) Pearson, A. J.; Park, J. G.; Yang, S. H.; Chuang, Y.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 1363. Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092.

(13) Crimmins, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017, 2021.

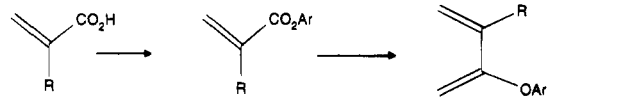
0022-3263/95/1960-6025$09.00/0

families contain a triaryl ether structure composed of two β-hydroxytyrosine units attached at the 3- and 5-positions of a central 4-hydroxyphenylglycine unit.[14a] Preliminary studies toward the synthesis of these antibiotics have involved use of the Ullmann reaction[14b] and arene metal coupling[14c] with nucleophiles for formation of the diaryl ether bonds.



2 3

Preparation of Aryloxy 1,3-Dienes. Two routes have proven practical for the synthesis of aryloxy dienes employed in these studies. These include (1) ester carbonyl methylenation by reaction of α,β-unsaturated aryl esters with the Tebbe reagent[15] or the reagent Cp_2TiMe_2,[16] and (2) enolsilylation[17] of α-(aryloxy)-β-hetero-substituted enones. Dienes **9-11** and the tyrosinol diene **13** were obtained via the first route. Thus, the known acrylic acids **4** and **5**[18] were transformed to their corresponding phenyl esters **6**, **7**, and **8**, respectively, by reaction with the appropriate phenol, a carbodiimide, and 4-(dimethylamino)pyridine.[19] Initially, the modified methylenation reagent[16] Cp_2TiMe_2 was studied for conversion of the aryl esters to diene. Reaction of esters **6** or **7** with this reagent gave dienes **9** and **10** in low yields (31 and 32%, respectively), while the Tebbe reagent[15] gave diene **10** from **7** in 41%. However, use of the Tebbe reagent effected conversion of ester **8** to diene **11** in a

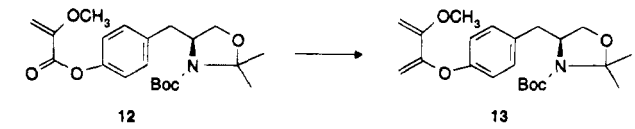


4 R = Me
5 R = OMe

6 R = Me, Ar = C_6H_5
7 R = OMe, Ar = C_6H_5
8 R = Me, Ar = p-$MeOC_6H_4$

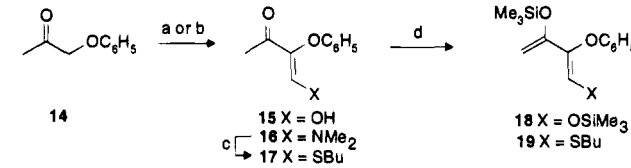
9 R = Me, Ar = C6H5
10 R = OMe, Ar = C_6H_5
11 R = Me, Ar = p-$MeOC_6H_4$

yield of 65%; the more functionalized ester **12** gave diene **13** in a similar yield (64%).[4b] The above dienes lack substituents that would be expected to provide control of regiochemistry in subsequent Diels–Alder reactions, as was indeed the case;[4] however, their cycloaddition reactions were of interest in order to ascertain the utility of a Diels–Alder approach for the synthesis of diaryl ethers.



12 13

A second approach to aryloxy dienes was dictated by the need to prepare dienes containing appropriate regiocontrol elements. The trisubstituted dienes **18**, **19**, and **23** were prepared by the enolsilylation of β-hetero-substituted-α-aryloxy enones **17** and **22**. The additional hetero substituent at the 1-position should control regiochemistry of the Diels–Alder reaction as is well known for related 1,3-dioxy-substituted dienes.[17,20] Formylation[21] of 2-phenoxyacetone (**14**) by reaction with ethyl formate and ethoxide ion was followed by enolsilylation to give trioxygenated diene **18**, though in low overall yield.



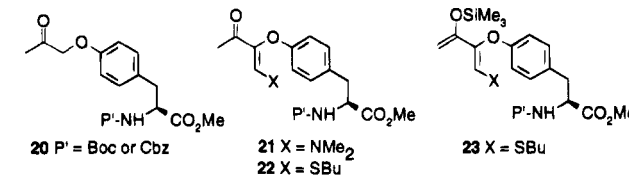
14

15 X = OH
c → 16 X = NMe_2
17 X = SBu

18 X = $OSiMe_3$
19 X = SBu

a. EtOCHO, EtO⁻ b. $CH(OMe)_2NMe_2$ c. BuSH, TsOH d. Me_3SiOTf, Et_3N

The preparation of the trisubstituted dienes **19** and **23** containing a sulfur substituent was accomplished as follows. Ketones **20** were readily prepared from either Boc- or Cbz-L-tyrosine methyl esters by alkylation with chloroacetone upon treatment with K_2CO_3 in acetone. Reaction of ketones **14** or **20** with the dimethyl acetal of dimethylformamide[22] furnished the β-dimethylamino enones **16** and **21**, which upon acid-catalyzed exchange[23] with 1-butanethiol gave enones **17** and **22**, respectively. The major product isolated from these reactions has been assigned the *Z* stereochemistry, as documented for previous cases.[24] NMR data on the crude mixtures from the above two reactions have shown, however, the formation of minor amounts of the corresponding *E* isomer as also a regioisomer formed by methylenation at the other α position of the ketone.



20 P' = Boc or Cbz

21 X = NMe_2
22 X = SBu

23 X = SBu

Enolsilylation[17] of enones **17** or **22**, using trimethylsilyl triflate and triethylamine, yielded the trisubstituted dienes **19** and **23**, which were used directly as obtained in subsequent Diels–Alder reactions. Studies have established dienes **19** and **23** to be ideal substrates for use in the Diels–Alder reaction as the β-alkylthio substituent completely controls the regiochemistry of the

(14) (a) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364. (b) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912. (c) Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425.

(15) Tebbe, F. N.; Parshall, B. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. Pine, S. H.; Zahler, R.; Evans, D. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(16) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(17) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(18) Ogala, N.; Nozakura, S.; Murashashi, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2987.

(19) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(20) Danishefsky, S.; Yan, C.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968.

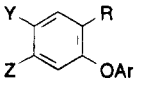
(21) Arnd, M.; Maurer, F. Ger. Offen. DE 3,441,369; *Chem. Abst.* **1986**, *105*, P114616x.

(22) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

(23) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459.

(24) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224.

Table 1. Diaryl Ether Products formed via Diels–Alder Reactions



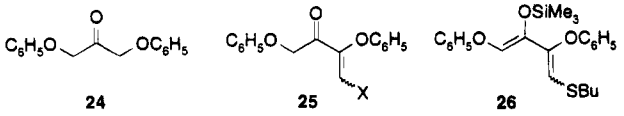
entry	diene	dienophile	product	R	Ar	Y	Z	yield, %
1	**9**	$HC{\equiv}CCO_2Me$	**30a**	Me	C_6H_5	H	CO_2Me	71[a,b]
			30b	Me	C_6H_5	CO_2Me	H	
2	**10**	$HC{\equiv}CCO_2Me$	**31a**	OMe	C_6H_5	H	CO_2Me	79[a,b]
			31b	OMe	C_6H_5	CO_2Me	H	
3	**9**	$MeO_2C{\equiv}CCO_2Me$	**32**	Me	C_6H_5	CO_2Me	CO_2Me	86
4	**11**	$MeO_2C{\equiv}CCO_2Me$	**33**	Me	*p*-MeOPh	CO_2Me	CO_2Me	92
5	**18**	$HC{\equiv}CCO_2Me$	**34**	OH	C_6H_5	H	CO_2Me	40
6	**18**	**29**	**35**	OH	C_6H_5	H	*c*	48
7	**19**	$HC{\equiv}CCO_2Me$	**34**	OH	C_6H_5	H	CO_2Me	64
8	**19**	**29**	**35**	OH	C_6H_5	H	*c*	74

[a] Overall yield obtained, following the Diels–Alder reaction and oxidation with DDQ. [b] Obtained as ≈1:1 mixture of regioisomers. [c] *Z* is the (4*R*)-(3-benzyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)carbonyl group.

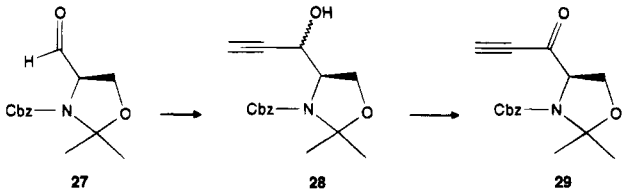
cycloaddition,[25] following which the butylthio group then undergoes elimination to generate the aryl ring. Of importance also is that diene **23** can be prepared with the carboxyl group of the tyrosine moiety existing at the oxidation level of the methyl ester rather than in a reduced form as necessitated in diene **13**, a diene prepared via the Tebbe reagent, which reagent would react with any additional ester group that may be present.

The synthesis of a suitable triaryl ether unit as is found in the glycopeptide vancomycin[14a] envisions a cycloaddition reaction utilizing a 1,3-bis(aryloxy) 1,3-butadiene. The tetrasubstituted diene **26** containing aryloxy groups at the 1,3-positions has been prepared by an approach similar to that described above.

1,3-Diphenoxy-2-propanone (**24**) was prepared by the regioselective ring-opening of glycidyl phenyl ether with phenol catalyzed by cesium fluoride[26] and followed by Moffatt oxidation.[27] Reaction of **24** with *tert*-butoxybis-(dimethylamino)methane (Bredereck's reagent)[28] yielded the aminomethylene derivative **25** (X = NMe_2), which was converted into the β-(*n*-butylthio) enone **25** (X = SBu). Enolsilylation of **25** by reaction with trimethylsilyl triflate[29] completed the synthesis of the 1,3-bis(aryloxy) diene **26**.



Preparation of Acetylenic Ketone 29, a Useful Dienophile. The known[30] oxazolidine aldehyde **27**, when treated with ethynylmagnesium chloride[31] in THF, was converted in 88% yield to a diastereomeric mixture of the acetylenic alcohol **28**. Oxidation of **28** with Jones reagent[32] provided acetylenic ketone **29** in 83% yield. Ynone **29** has proven to be a useful dienophile in the preparation of diaryl ethers related to isodityrosine in that it undergoes cycloaddition in good to excellent yields, is a chiral molecule containing a reduced form of an α-amino acid unit, and does not appear to suffer racemization in the Diels–Alder process.[4]

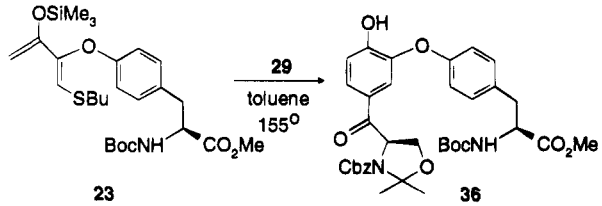


Preparation of Diaryl Ethers from 2-Phenoxy Dienes. Diels–Alder reactions were performed involving cycloaddition between functionalized acetylenes as dienophiles and 1,3-dienes substituted at the 2-position with phenoxy or p-methoxyphenoxy groups. The results of these reactions are listed in Table 1. The reactions were carried out at reflux in toluene for 18–20 h. The 1,4-cyclohexadiene cycloadducts, where isolated (entries 1–4), were oxidized in excellent yields with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[33] at reflux in benzene to form the aromatic ring. For entries 1 and 2, an approximate equal mixture of regioisomers were formed in the cycloaddition reaction; these regioisomers were not separated, but were oxidized to a mixture of regioisomeric diaryl ethers **30a,b** and **31a,b**. As can be seen, high overall yields of diaryl ethers **30-33** were obtained (entries 1–4) from reactions involving the 2,3-disubstituted dienes **9**, **10**, and **11**. In the case of the trisubstituted dienes **18** and **19** (entries 5–7), only moderate to good chemical yields, but high regioselectivity, were obtained; attempts to maximize these yields were not made. The butylthio trisubstituted diene **19** gave higher yields than diene **18** with the two dienophiles that were studied.

Regiocontrolled Synthesis of Isodityrosine Derivatives from Trisubstituted Diene 23. The trisubstituted diene **23** underwent a Diels–Alder reaction with dienophile **29** in a sealed tube at 155 °C in toluene to yield diaryl ether **36** as a single cycloadduct in 77% yield. Under similar reaction conditions, diene **23** underwent cycloaddition with the enantiomeric form of dienophile **29**, prepared from L-serine, to give the diastereomer of

(25) Trost, B. M.; Vladuchichk, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554.
(26) Nambu, Y.; Endo, T. *Tetrahedron Lett.* **1990**, *31*, 1723.
(27) Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y. *J. Org. Chem.* **1987**, *52*, 5621.
(28) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573.
(29) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.
(30) Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
(31) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772.
(32) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. Fieser, L. F.; Fieser, M. *Reagents in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1967; p 142.
(33) For an example of the aromatization of nitro-substituted cyclohexadienes using DDQ, see Ono, N.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1988**, *53*, 251.

36 in 91% yield. Initially, the crude cycloadduct, after removal of solvent, was treated to mild acid hydrolysis, following Danishefsky's procedure,[20] in the expectation of effecting removal of the trimethylsilyl group and causing elimination of the *n*-butylmercaptan. Subsequent studies showed the hydrolysis step not to be needed as the product obtained by direct flash chromatography of the crude Diels–Alder product was the aromatized diaryl ether.



23 36

The regiochemistry of **36** was assigned on the basis of previous studies in our laboratory, in which cycloadducts obtained by the reaction with similar dienes were converted to known isodityrosine[4b] or tyrosine[4a] derivatives. Likewise, in all cases seen so far in which both regioisomers have been obtained, the desired isomer having the same regiochemistry corresponding to **36** has shown a distinctive pattern, a doublet of doublets, for the H_5 aromatic proton ortho to the ketone at the low field end of the aromatic region of the ^1H NMR spectrum. In the other regioisomer, this pattern is not seen and is likely obscured by overlapping peaks.

In summary, the synthesis of tri- and tetrasubstitued 1,3-dienes having aryloxy groups substituted at one or two positions on the diene have been developed. The trisubstituted 2-aryloxy dienes have been shown to undergo thermal cycloaddition reactions with dieneophiles to give, following elimination to an aromatic ring, diaryl ethers. This method has been used to effect the synthesis of diaryl ethers related to the isodityrosine unit found in the isodityrosine peptide antibiotics.

Experimental Section

^1H NMR spectra were recorded on spectrometers at 300 or 400 MHz using $CDCl_3$ as solvent and TMS as the internal standard. ^{13}C spectra were recorded at 100.0, 74.55, or 68.0 MHz. Silica gel TLC plates (1 × 3 in.) were viewed under UV light (254 nm) or developed in an iodine chamber, or immersed in a *p*-anisaldehyde solution or phosphomolybdic acid solution, followed by development of spots on a hot plate. Elemental analyses were performed by M-H-W Laboratories, P. O. Box 15149, Phoenix, AZ 85018. For flash column chromatography, silica gel (Kieselgel 60, 230–400 mesh) was used. FT-IR spectra were recorded on NaCl plates. Melting points are uncorrected. Solvents were purified, when necessary, according to standard procedures.

Synthesis of 2-Substituted Acrylic Acid Aryl Esters 6–8 and 12. A typical procedure was as follows: A solution of *N*-Boc-*N*,*O*-isopropylidene-L-tyrosinol (1.10 g, 3.60 mmol), 2-methoxyacrylic acid (**5**)[18] (0.40 g, 3.90 mmol), DCC (0.82 g, 3.0 mmol), and DMAP (0.49 g, 3.0 mmol) in 20 mL of THF was heated at reflux for 2–3 h, cooled to rt, and stirred overnight. The solution was passed through a short Celite pad and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane as eluant to furnish 1.15 g (82%) of ester **12** as an oil: $[\alpha]_D$ −31.5° (*c* 1.08, $CHCl_3$); IR (neat) 1757, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9 H, *tert*-butyl), 1.47 and 1.66 (two s, Me groups), 2.68 (t, 1 H), 3.16 (dd, 1H), 3.74 (s, 3 H, OMe), 3.79 (m, 2 H, CH_2O), 3.96 and 4.08 (two m, 0.5 H each, α H), 4.80 (s, 1 H, vinyl), 5.56 (s, 1 H, vinyl), 7.16 and 7.24 (two m, 4 H, aryl); ^{13}C NMR (75.44 MHz, $CDCl_3$) (doubling of several peaks was observed due to the presence of rotamers about the urethane bond) δ 23.82 (d), 27.16 (d), 28.47 (d), 33.49 (d), 55.84 (s), 59.03 (s), 65.91 (d), 79.91 (d), 93.75 (d), 94.97 (d), 121.49 (d), 130.34 (d), 136.29 (d), 149.07 (s), 151.55 (s), 152.08 (s), 161.51 (s). Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.42; H, 7.48; N, 3.58. Found: C, 64.50; H, 7.57; N, 3.52.

Phenyl Methacrylate (6). The product was obtained as an oil: IR (neat) 1741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 1 H), 5.76 (s, 1H), 6.39 (s, 1 H), 7.10–7.39 (m, 4 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 18.14, 121.40, 125.49, 126.93, 129.17, 135.69, 150.76, 165.54.

Phenyl 2-Methoxyacrylate (7). The product was obtained as an oil: IR (neat) 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 4.81 (s, 1 H), 5.58 (s, 1 H), 7.13–7.40 (m, 5 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 55.74; 94.91; 121.35, 125.92, 129.35, 150.30, 151.46, 161.42.

***p*-Methoxyphenyl Methacrylate (8).** Product was obtained as an oil: IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3 H), 3.80 (s, 3 H), 5.73 (s, 1 H), 6.33 (s, 1 H), 6.88–7.05 (m, 4 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 18.26, 55.36; 114.29, 122.23, 126.86, 135.84, 144.30, 157.10, 166.04.

Synthesis of Aryloxy Dienes 9–11 and 13. Method A: Use of Tebbe's Reagent. A typical procedure was as follows. To a solution of aryl ester **12** (2.50 g, 6.40 mmol) in 18 mL of toluene and 6 mL of THF was added 5 drops of pyridine and the solution was cooled to −20 to −30 °C. Tebbe's reagent (18 mL of a 0.5 M solution in toluene) was added under nitrogen over 10 min and the mixture was stirred at −20 °C for 40 min and at rt for 2–3 h. The mixture was diluted with 300 mL of petroleum ether (bp 30–60 °C) and passed under medium pressure through a short column of silica gel to remove colored impurities followed by elution with 20% ethyl acetate in hexane. The combined solutions were concentrated in vacuo, and the residue was again subjected to MPLC on silica using 10% ethyl acetate:hexane to provide 1.60 g of product **13** (64% yield). Elution with 25% ethyl acetate:hexane resulted in recovery of 0.50 g of unreacted ester **12**.

Dienes **9-11** and **13**, because they were judged to be somewhat unstable, were characterized only by ^1H NMR and were normally used directly following their preparation. Diene **13** could be stored at −15 °C for a period of time before use.

Method B: Use of Cp_2TiMe_2. A typical procedure was as follows: A solution of ester **12** (0.40 g, 1.0 mmol) and Cp_2TiMe_2 (3.0 mmol) in 8 mL of THF was heated at reflux for 20 h in the dark. The mixture was cooled to rt, partitioned with petroleum ether (bp 30–60 °C), filtered through a short column of silica gel, and concentrated in vacuo. The residue was purified directly by flash chromatography on basic alumina with elution with 5–30% ether in petroleum ether (bp 30–60 °C) to provide 105 mg (26% yield) of diene **13** as an oil.

2-Methyl-3-phenoxy-1,3-butadiene (9). The product was obtained as an oil in 31% yield (method B): ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (d, 3 H), 4.46 (s, 1 H), 4.78 (s, 1 H), 5.10 (s, 1 H), 5.55 (s, 1 H), 7.04–7.37 (m, 5 H).

2-Methoxy-3-phenoxy-1,3-butadiene (10). The product was obtained as an oil in 41% yield by use of method A or in 32% yield by method B: ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3 H), 4.16 (s, 1 H), 4.38 (d, 1 H), 4.66 (d, 1 H), 5.05 (d, 1 H), 6.95–7.24 (m, 5 H).

2-Methyl-3-(*p*-methoxyphenoxy)-1,3-butadiene (11). The product was obtained as an oil in 65% yield by method A: ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 3.82 (s, 3 H), 4.23 (d, 1 H), 4.61 (d, 1 H), 5.10 (d, 1 H), 5.63 (d, 1 H), 6.76–7.29 (m, 4 H).

(4S)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4-[[4-(3-methoxy-1,3-butadien-2-oxy)phenyl]methyl]oxazolidine (13). Diene **13** was obtained as an oil: $[\alpha]_D$ −26° (*c* = 0.72, $CHCl_3$); IR (neat) 2938, 1698, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9 H, *tert*-butyl), 1.46, 1.50, 1.63 (three s, 6 H, Me groups), 2.66 (t, 1 H, benzylic), 3.13 (dd, 1 H, benzylic), 3.67 (s, 3 H, OMe), 3.77 (m, 2 H, CH_2O), 3.95, 4.08 (two m, 0.5 H each, α H), 4.24 (s, 1 H, vinyl), 4.44 (d, 1 H, *J* = 9 Hz, vinyl), 4.74 (s, 1 H, vinyl), 5.11 (d, 1 H, *J* = 9 Hz, vinyl), 6.97 (m, 2 H, aryl), 7.18 (m, 2 H, aryl); ^{13}C NMR (75.44 MHz, $CDCl_3$) (doubling of several peaks observed due to rotamers about the urethane bond) δ 23.32 (d), 27.10 (d), 28.45 (d), 38.29

(d), 55.07 (s), 59.10 (s), 65.88 (d), 79.81 (d), 83.81 (s), 93.73 (d), 94.33 (d), 118.82 (s), 130.40 (d), 133.26 (s), 151.83 (d), 154.70 (d), 155.10 (d), 155.55 (s).

1-Formyl-1-phenoxy-2-propanone (15). Sodium metal (0.28 g, 12 mmol) was added in portions to 8 mL of absolute ethanol. The resulting solution was cooled to 0 °C, and 1-phenoxy-2-propanone (**14**) (1.50 g, 10.0 mmol) and ethyl formate (0.89 g, 12 mmol) were added. The reaction mixture was stirred at rt overnight, poured into 25 mL of 0.5 N HCl, and extracted with ethyl ether (2 × 50 mL). The organic extracts were washed with 1 N HCl and brine and dried over $MgSO_4$. Ketone **15** was obtained by MPLC on silica gel using 30% ethyl acetate in hexane to give 1.10 g (62% yield) of oily product, with 10% of unreacted propanone **14** also being isolated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3 H), 6.93–7.32 (m, 6 H), 7.99 (s, 1 H).

1,3-Bis[(Trimethylsilyl)oxy]-2-phenoxy-1,3-butadiene (18). A solution of formyl ketone **15** (0.42 g, 2.35 mmol) and triethylamine (1.8 mL, 12.8 mmol) in ethyl ether (15 mL) was cooled to −20 °C under nitrogen. Trimethylsilyl triflate (1.0 mL, 5.2 mmol) was added over a few minutes via syringe. The reaction mixture was stirred for 30 min at −20 °C and at rt for 2 h and then diluted with hexane. The hexane layer was passed through a short pad of Na_2SO_4 and the solvent was evaporated in vacuo. The crude diene was used immediately in the subsequent cycloaddition reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 0.26 (s, 9 H), 4.18 (d, J = 0.9 Hz, 1 H), 4.46 (d, J = 0.9 Hz, 1 H), 6.72 (s, 1 H), 6.96 (m, 3 H), 7.23 (m, 2 H).

4-(Dimethylamino)-3-phenoxy-3-buten-2-one (16). A stirred mixture of phenoxyacetone (**14**)(3.0 g, 20 mmol) and *N,N*-dimethylformamide dimethyl acetal (4.76 g, 40 mmol) was refluxed under nitrogen overnight. The volatiles were removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel by elution with 40–60% EtOAc in hexane to afford product as an orange brown solid, 2.1 g (50%): R_f = 0.26 (50% EtOAc in hexane); mp 92–94 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (br s, 3 H), 3.00 (s, 6 H), 6.90 (m, 3 H), 7.30 (m, 3 H); ^{13}C NMR (ppm) 159.91, 130.60, 122.44, 115.66, 25.64. IR ($CHCl_3$, cm^{-1}) 3019, 2977, 2937, 2896, 2815, 1885, 1667, 1575, 1307, 1216, 1047, 757, 669. Two different samples of this compound were submitted for combustion analysis; however, in each case satisfactory data were not obtained.

4-(Butylthio)-3-phenoxy-3-buten-2-one (17). A stirred mixture of **16** (1.4 g, 6.83 mmol), *p*-toluenesulfonic acid monohydrate (0.67 g, 3.52 mmol), and 1-butanethiol (2.00 g, 22.4 mmol) in benzene (37 mL) was heated at reflux under nitrogen for 24 h. The solvent was removed in vacuo and the oily residue partitioned between 10% aqueous $NaHCO_3$ (10 mL) and $CHCl_3$ (30 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined $CHCl_3$ layer was washed with saturated NaCl (30 mL), dried over $MgSO_4$, and concentrated in vacuo to give the crude product, which was purified by flash chromatography on silica gel with elution by 10% EtOAc in hexane to afford product as an orange liquid, 1.3 g (76%): R_f = 0.68 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 3H), 6.90 (m, 3H), 2.80 (t, 2H, J = 7.5 Hz), 2.15 (s, 3H), 1.66 (m, 2H), 1.42 (m, 2H), 0.92 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 192.36, 156.03, 144.94, 133.15, 129.85, 122.52, 114.98, 34.03, 32.55, 25.84, 21.60, 13.62. IR (neat, cm^{-1}) 3090, 3053, 3036, 3011, 2960, 2931, 2873, 2861, 1674, 1598, 1466, 1235, 1057. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81. Found: C, 66.92; H, 7.06; S, 12.67.

1-(Butylthio)-2-phenoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (19). To a stirred solution of enone **17** (0.30 g, 1.2 mmol) in diethyl ether (1.0 mL) under nitrogen at 0 °C was added dropwise triethylamine (0.51 g, 5.0 mmol), and the resulting mixture was stirred at 0 °C for 40 min. Trimethylsilyl trifluoromethanesulfonate (0.46 g, 2.1 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 4 h. Hexane (15 mL) was added, the mixture swirled, and the top layer decanted. Two more 15 mL-portions of hexane were added to the reaction mixture and swirled, and the top layer was decanted each time. The combined hexane layer was dried ($MgSO_4$) and passed through a short column of $MgSO_4$. The eluant was concentrated to give butadiene **19** as a yellow oil, 0.30 g (78%), which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 2 H), 6.90 (m, 3H), 6.30 (s, 1H), 4.40 (s, 1H), 4.19 (s, 1H), 2.60 (t, 2H, J = 7.5 Hz), 1.60 (m, 2H), 1.40 (m, 2H), 0.90 (t, 3H, J = 7.5 Hz), 0.2 (s, 9H); IR (neat, cm^{-1}) 3064, 3041, 2958, 2931, 2873, 1680, 1599, 1591, 1491, 1466, 1053, 753, 691.

***N*-(*tert*-Butyloxycarbonyl)-*O*-(2-oxopropyl)-L-tyrosine Methyl Ester (20, P = Boc).** A solution of *N*-Boc-L-tyrosine methyl ester (3.8 g, 12.9 mmol), chloroacetone (1.55 g, 16.7 mmol), and K_2CO_3 (3.2 g, 23.3 mmol) in 61 mL of acetone was heated at reflux overnight. The mixture was filtered and the filtrate concentrated in vacuo to give the crude product, which was purified by flash chromatography on silica gel with elution by 20% ethyl acetate in hexane to afford **20** as a pale yellow liquid, 4.1 g (91%): R_f = 0.41 (20% EtOAc in hexane); $[\alpha]^{25}_D$ +41.89° (*c* 1.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 2H), 6.80 (m, 2H), 5.00 (d, 1H), 4.50 (s superimposed on a m, 3H), 3.70 (s, 3H), 3.00 (m, 2H), 2.30 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 206.00, 172.00, 157.07, 155.00, 130.78, 129.46, 114.85, 80.0, 73.33, 54.73, 52.46, 37.74, 28.54, 26.87; IR (neat, cm^{-1}) 3369, 2933, 1718, 1613, 1587, 1515, 1438, 1392, 1367, 1252, 1170, 1113, 1060, 1019, 861, 828, 802, 783, 760. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.36; H, 7.13; N, 3.76.

***N*-(*tert*-Butyloxycarbonyl)-*O*-[1-(dimethylamino)-3-oxo-1-buten-2-yl]-L-tyrosine Methyl Ester (21).** A mixture of aryloxy ketone **20** (3.3 g, 9.4 mmol) and *N,N*-dimethylformamide dimethyl acetal (2.33 g, 19.5 mmol) was heated at reflux under nitrogen overnight. The volatiles were removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with elution by 40–60% EtOAc in hexane to afford **21** as a brown liquid, 2.0 g (53%): R_f = 0.29 (70% EtOAc in hexane); $[\alpha]^{25}_D$ +11.25° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0 (d, 2H), 6.8 (d, 2H), 5.0 (d, 1H, J = 7.8 Hz), 4.6 (d, 1H, J = 7.8 Hz), 3.70 (s, 3H), 3.00 (brd s, 8H), 2.00 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 172.31, 158.00, 156.00, 130.57, 114.85, 54.44, 52.11, 38.00, 28.18, 24.00; IR (neat, cm^{-1}) 3306, 2976, 2929,2816, 1891, 1745, 1714, 1669, 1575, 1304, 1020, 760, 662. Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.80; H, 7.59; N, 6.76.

***N*-(*tert*-Butyloxycarbonyl)-*O*-[1-(butylthio)-3-oxo-1-buten-2-yl]-L-tyrosine Methyl Ester (22).** Enone **21** (1.4 g, 3.5 mmol), *p*-toluenesulfonic acid monohydrate (0.35 g, 1.84 mmol), and 1-butanethiol (1.1 g, 12.1 mmol) in benzene (19 mL) were heated at reflux under nitrogen for 24 h. The solvent was removed in vacuo and the oily residue partitioned between 10% aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (15 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined $CHCl_3$ layer was washed with one portion of saturated NaCl (15 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude product, which was purified by flash chromatography on silica gel with elution by 20% ethyl acetate in hexane to afford product **22** as a pale yellow solid, 1.1 g (69%): R_f = 0.14 (20% EtOAc in hexane); $[\alpha]^{26}_D$ +16.40° (*c* 1.00, $CHCl_3$); mp 73–75 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.10 (m, 2H), 6.90 (m, 2H), 5.00 (d, 1H, J = 7.9 Hz), 4.51 (d, 1H, J = 7.9 Hz), 3.70 (s, 3H), 3.00 (m, 2H), 2.80 (t, 2H, J = 7.5 Hz), 2.30 (s, 3H), 1.65 (m, 2H), 1.42 (s, 9H), 1.32–1.50 (m, 2 H), 0.9 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 192.10, 172.28, 154.99, 144.84, 132.95, 130.58, 129.95, 114.96, 80.00, 54.39, 52.14, 37.53, 33.91, 32.38, 28.22, 25.70, 21.45, 13.46; IR ($CHCl_3$, cm^{-1}) 3441, 3023, 2977, 2934, 2896, 1742, 1709, 1677, 1609, 1560, 1505, 1478, 1046, 929, 739, 628. Anal. Calcd for $C_{23}H_{33}NO_6S$: C, 61.17; H, 7.37; N, 3.10; S, 7.10. Found: C, 61.22; H, 7.23; N, 2.98; S, 7.33.

***N*-(*tert*-Butyloxycarbonyl)-*O*-[1-(butylthio)-3-[(trimethylsilyl)oxy]-1,3-butadien-2-yl]-L-tyrosine Methyl Ester (23).** To a stirred solution of **22** (0.85 g, 1.88 mmol) in diethyl ether (1.5 mL) under nitrogen at 0 °C was added dropwise triethylamine (0.80 g, 1.1 mL, 7.84 mmol), and the resulting mixture was stirred at 0 °C for 40 min. Trimethylsilyl trifluoromethanesulfonate (0.72 g, 3.3 mmol) was added drop-

wise, and the reaction mixture was stirred at 0 °C for 4 h. Hexane (24 mL) was added, the mixture swirled, and the top layer decanted. Two more 24 mL-portions of hexane were added to the reaction mixture and swirled, and the top layer was decanted each time. The combined hexane layer was dried over $MgSO_4$ for approximately 30 min and then passed through a short column of $MgSO_4$. The eluant was concentrated to give the butadiene **23** as a yellow oil, 0.96 g (98%), which was used in the next step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H), 7.00 (d, 2H), 6.47 (s, 1H), 4.50 (s, 1H), 4.30 (s, 1H), 3.82 (s superimposed on m, 4H), 3.40 (m, 2H), 2.80 (t, 2H, J = 7.2 Hz), 1.70 (m, 2H), 1.55 (s, 9H), 1.45 (m, 2H), 1.00 (t, 3H, J = 6.9 Hz, 0.35 (s, 9H); IR (neat, cm^{-1}) 3443, 3372, 2959, 2874, 1747, 1718, 1611, 1576, 1087, 1057, 1014, 758, 691.

4-(Dimethylamino)-1,3-diphenoxy-3-buten-2-one (25, X = NMe_2). A mixture of 1,3−diphenoxy-2-propanone (**24**) (2.42 g, 10 mmol) and *tert*-butoxybis(dimethylamino)methane (2.32 g, 13 mmol) was heated a 55 °C under nitrogen with stirring for 20 h. The crude product was purified by flash chromatography on silica gel by elution with 50% EtOAc in hexane to afford enamino ketone **25** as a pale yellow solid, 2.25 g (75%): mp 103−104 °C (EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 6H), 4.72 (s, 2H), 6.80−7.31 (m, 10H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.98, 158.72, 158.15, 139.36, 129.77, 129.11, 123.91, 121.91, 120.76, 114.93, 114.54, 69.23. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.80; H, 6.29; N, 4.73.

4-(Butylthio)-1,3-diphenoxy-3-buten-2-one (25, X = SBu). A stirred mixture of the enamino ketone **25** (3.57 g, 12 mmol), *p*-toluenesulphonic acid monohydrate (1.90 g, 10 mmol), and 1-buthanethiol (3.24 g, 36 mmol) in benzene (60 mL) was heated at reflux under nitrogen for 5 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel with elution by 10% EtOAc in hexane to afford product as a pale yellow solid, 3.32 g (81%), mp 56−58 °C (EtOAc/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.4 Hz), 1.41 (m, 2H), 1.66 (m, 2H), 2.82 (t, 2H, J = 7.4 Hz), 4.81 (s, 2H), 6.79−7.33 (m, 10H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.27, 157.83, 155. 62, 143.04, 134.84, 129.77, 129.35, 122.71, 121.41, 114.84, 114.67, 70.35, 34.07, 32.28, 21.33, 13.35. Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.15; H, 6.48; S, 9.36. Found: C, 70.36; H, 6.35; S, 9.51.

4-(Butylthio)-1,3-diphenoxy-2-[(trimethylsilyl)oxy]-1,3-butadiene (26). To a stirred solution of enone **25** (X = SBu) (0.85 g, 2.5 mmol) in dry ether (2.0 mL) under nitrogen at 0 °C was added triethylamine (1.01 g, 10 mmol), and the resulting mixture was stirred at 0 °C for 40 min. Trimethylsilyl trifluoromethanesulfonate (1.1 g, 5.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. Hexane (30 mL) was added, the mixture swirled, and the top layer decanted. Two more 30 mL-portions of hexane were added to the reaction mixture and swirled and the top layer decanted each time. The combined hexane layer was dried ($MgSO_4$) and passed through a short column of $MgSO_4$. The eluent was concentrated to give butadiene **26** as a pale yellow oil 0.91 g, (88%), which was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.27 (t, 9H, J = 2.4 Hz), 0.90 (t, 3H, J = 7.4 Hz), 1.40 (m, 2H), 1.61 (m, 2H), 2.69 (t, J = 7.4 Hz), 6.18 (s, 1H), 6.40 (s, 1H), 6.81−7.28 (m, 10 H); ^{13}C NMR (100 MHz) δ 157.04, 156.51, 143.44, 133.94, 129.53, 129.50, 126.83, 122.47, 121.93, 115.68, 115.12, 113.39, 33.62, 32.32, 21.51, 13.53, 0.45.

Benzyl (*R*)-4-(1-Hydroxy-2-propynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (28). To a stirred solution of *N*-(benzyloxycarbonyl)-*N*,*O*-isopropylidene-D-serinal (**27**) (1.80 g, 6.84 mmol) in 65 mL of dry THF was added dropwise ethynylmagnesium chloride (20 mL of 0.5 M in THF). The mixture was stirred for 2 h at rt, and the reaction was quenched by the addition of 1.0 mL of water. Diethyl ether (100 mL) was added, and the organic phase was washed with 1 N HCl (65 mL) and brine (65 mL) and dried over $MgSO_4$. This product may be used as obtained or purified by flash chromatography on silica gel with elution by 25% ethyl acetate in hexane to provide a mixture of diastereomeric alcohols **28** (1.75 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$, chemical shifts sensitive to ratio of diastereomers) δ 1.50−1.70 (series of s, 6 H, methyl groups), 2.47 (s, 1 H, alkynyl H), 3.90−4.35 (m, 3 H), 4.65 (m, 1 H), 5.20 (m, 2 H, benzyl), 7.37 (br s, 5 H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.63; N, 4.84. Found: C, 66.34; H, 6.54; N, 4.83.

Benzyl (*R*)-4-(1-Oxo-2-propynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (29). Alcohol **28** (0.40 g, 1.40 mmol) in 5 mL of diethyl ether was treated at rt with 4.0 mL of Jones reagent added over a few min. The mixture was stirred for 15 min and diluted with 100 mL of diethyl ether, and the ether phase was washed with water and brine and dried over $MgSO_4$. The product was purified by flash chromatography on silica gel with elution by 25% ethyl acetate in hexane to yield alkyne **29** as an oil (0.33 g, 83%): $[\alpha]_D$ +53° (*c* 1.26, $CHCl_3$); IR (neat) 3350, 2093, 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers about urethane bond) δ 1.57 and 1.73 (major rotamer), 1.50 and 1.65 (minor rotamer)(4 s, 6 H, methyls), 3.30 (s, 1 H, alkyne H), 4.20 (major) and 4.18 (minor)-(2 br s, 2 H, OCH_2), 4.52 (major) and 4.64 (minor)(t and dd, 1 H, α H), 5.11 (major) and 5.20 (minor)(s and AB q, 2 H, benzyl H), 7.25−7.37 (m, 5 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ (major rotamer) 23.70, 25.03, 65.49, 66.01, 66.89, 79.15, 82.74, 95.71, 127.84, 127.97, 128.30, 135.78, 151.60, 184.59; (minor rotamer) 25.61, 26.02, 64.92, 66.82, 67.54, 82.26, 95.02, 128.10, 128.41, 128.50, 152.77, 183.91. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.98; N, 4.88. Found: C, 66.75; H, 5.98; N, 4.80.

Diels−Alder Cycloaddition Reactions and Oxidation with DDQ for Preparation of Diphenyl Ethers 30−33. A typical procedure is as follows: A solution of diene (0.3 mmol) and acetylenic ester (3 equiv) in 0.5 mL of toluene containing a trace of hydroquinone, in a sealed tube under nitrogen, was heated at reflux for 20 h or until TLC analysis indicated the reaction was complete. The reaction mixture was subject to flash chromatography on silica gel using the appropriate ratio of ethyl acetate in hexane as eluant to furnish the cyclohexadiene cycloadduct, which was characterized by ^{1}H NMR spectral data before oxidation in the next step to the diphenyl ether.

The cycloadduct (0.25 mmol) was heated at reflux with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.50 mmol) in 3 mL of benzene for 2 h. The reaction mixture was subjected to flash chromatography on silica gel to provide a nearly quantitative yield of the resulting diphenyl ethers **30−33** (Table 1).

Diphenyl Ethers 30a and 30b. The products were obtained as an oil and as an approximate 1:1 mixture of regioisomers: IR (neat) 1723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (2 s, 3 H), 3.87 (2 s, 3 H), 6.69−7.95 (m, 8 H). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.35; H, 5.85. Found: C, 74.49; H, 5.90.

Diphenyl Ethers 31a and 31b. The final products were obtained as an oil and as an approximate 1:1 mixture of regioisomers: IR (neat) 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85−3.95 (4 s, 6 H), 6.90−7.90 (m, 8 H). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.47. Found: C, 70.02; H, 5.54.

Dimethyl 5-Methyl-4-phenoxyphthalate (32). Product obtained as an oil: IR (neat) 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 6.97−7.68 (m, 7 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 16.02, 52.32, 52.42, 117.14, 118.81, 123.91, 125.48, 129.89, 131.79, 131.86, 142.42, 155.75, 157.48, 167.21, 167.63. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.98; H, 5.38. Found: C, 67.80; H, 5.41.

Dimethyl 5-Methyl-4-(4-methoxyphenoxy)phthalate (33). Product obtained as an oil: IR (neat) 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 3.82 (s, 6 H), 3.88 (s, 3 H), 6.89−6.94 (m, 6 H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 15.85, 52.08, 52.24, 55.20, 114.83, 114.92, 120.74, 124.15, 130.46, 131.96, 132.07, 148.43, 156.21, 158.76, 166.91, 167.77. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.50. Found: C, 65.61; H, 5.42.

Methyl 4-Hydroxy-3-phenoxybenzoate (34). A. Preparation from Diene 18. A solution of trisubstituted diene **18** (96 mg, 0.30 mmol) and methyl propiolate (50 mg, 0.60 mmol) in 0.25 mL of toluene containing a trace of hydroquinone was heated at reflux in a sealed tube for 15 h. The solvent was removed in vacuo and the residue was treated for 1 h with a mixture of 4 mL of THF and 1 mL of 0.5 N HCl. Diethyl ether

(150 mL) was added, and the ether layer was washed with brine and dried over Na_2SO_4. Diaryl ether **34** was obtained (29 mg, 40% yield) as an oil by flash chromatography on silica gel using 25% ethyl acetate in hexane as eluant: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.05 (br s, 1 H), 7.05–7.85 (m, 8 H). A sample of **34** was treated with 3 equiv each of methyl iodide and K_2CO_3 in DMF to furnish **31a** as established by TLC comparison and superimposable ^{1}H NMR spectra.

B. Preparation from Diene 19. A stirred mixture of diene **19** (0.19 g, 0.59 mmol), methyl propiolate (0.095 g, 1.1 mmol), and toluene (1.5 mL) in a sealed tube was heated at 120 °C (oil bath) for 48 h. Workup of the reaction mixture as described above gave 90 mg (64%) of product after flash chromatography on silica gel with elution by 10% EtOAc in hexane: R_f = 0.27 (10% EtOAc in hexane); mp 120–121 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.00 (m, 8H), 6.18 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 166.39, 156.13, 151.67, 143.46, 130.00, 126.72, 124.08, 122.72, 119.80, 118.26, 115.82, 51.98; IR ($CHCl_3$, cm^{-1}) 3616, 3534, 3356, 3073, 3020, 2954, 2904, 2846, 1713, 1591, 1491, 1045, 1024, 772, 692. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 69.00; H, 5.10.

***N*-(Benzyloxycarbonyl)-*N*,*O*-isopropylidene-β-oxo-3-phenoxy-(*S*)-tyrosinol (35).** A stirred mixture of diene **19** (0.31 g, 0.96 mmol), acetylenic ketone **29** (0.46 g, 1.61 mmol), and toluene (1.0 mL) in a sealed tube was heated at 150 °C (oil bath) for 72 h. After cooling the reaction mixture to rt, the solvent was removed in vacuo to give the crude product as an oil, which was purified on silica gel flash chromatography with elution by 35% ethyl acetate in hexane to afford **35** as a brown liquid, 0.32 g (74%): R_f = 0.49 (35% EtOAc in hexane); $[\alpha]^{25}_D$ +37.9° (*c* 1.00, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$, 1.65:1 ratio of rotamers) δ 7.60–7.00 (m, 13H), 6.40 (s, 1H), 5.30 (dd, 1H, minor rotamer, J = 7.56, 3.24 Hz), 5.20 (dd, 1H, major rotamer, J = 7.56, 3.24 Hz), 5.10 (AB q, 2H, minor rotamer), 4.90 (AB q, 2H, major rotamer), 4.21 (t, 1H, J = 7.8 Hz), 3.9 (m, 1H), 1.70, 1.55 (2s, 6H, major rotamer), 1.60, 1.50 (2s, 6H, minor rotamer); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 193.00, 192.00, 156.00, 152.75, 152.00, 144.27, 135.51, 129.85, 128.38, 128.07, 127.91, 127.81, 127.61, 127.34, 125.36, 118.29, 118.19, 116.18, 95.44, 94.42, 67.53, 66.59, 66.31, 61.12, 60.85, 30.00, 25.56, 25.23, 24.45, 24.24; IR ($CHCl_3$, cm^{-1}) 3533, 3470, 3024, 2978, 2895, 1709, 1590, 1515, 1491, 1477, 1370, 11346, 1047, 850, 739. Anal. Calcd for $C_{26}H_{25}NO_6$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.67; H, 5.81; N, 3.38.

(4*R*)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-[3-[4-[(2*S*)-2-[(*tert*-butyloxycarbonyl)amino]-2-(methoxycarbonyl)-ethyl]phenoxy]-4-hydroxybenzoyl]oxazolidine (36). A stirred mixture of the butadiene **23** (1.70 g, 3.25 mmol), alkyne **29** (1.74 g, 6.07 mmol), and toluene (9.2 mL) in a sealed tube was heated at 155 °C (oil bath) for 72 h. After cooling the reaction mixture to rt, the solvent was removed in vacuo to give an oil, which was purified by flash chromatography on silica gel, using 20–50% EtOAc in hexane as eluant, to afford **36** as a light brown foam, 1.61 g (77%): R_f = 0.59, 50% EtOAc in hexanes; $[\alpha]^{25}_D$ +37.04° (*c* 1.00, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 1.8 and 8.5, 1H), 7.47–6.90 (m, 11H), 6.25 (s, 1H), 5.40 (dd, 1H, J = 7.14 Hz, 3.5 Hz, minor rotamer), 5.30 (dd, 1H, J = 7.14 Hz, 3.5 Hz, major rotamer), 5.2 (AB q, 2H, minor rotamer), 5.0 (AB q, 2H, major rotamer), 4.60 (d, 1H, J = 6.42 Hz), 4.30 (t, 1H, J = 8.6 Hz), 3.95 (m, 1H), 3.70 (s, 3H), 3.10 (m, 2H), 1.75, 1.60 (2s, 6H, major rotamer), 1.70, 1.53 (2s, 6H, minor rotamer), 1.40 (s, 9H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 194.16, 173.20, 156.13, 156.03, 153.61, 145.31, 137.17, 137.04, 131.90, 129.55, 129.24, 129.14, 128.96, 128.77, 128.51, 126.51, 119.69, 119.49, 117.21, 96.59, 95.96, 81.12, 78.54, 68.58, 67.71, 67.48, 67.04, 66.85, 62.89, 62.02, 55.46, 53.29, 38.60, 29.27, 26.73, 26.42, 25.64, 25.40, 16.20; IR ($CHCl_3$, cm^{-1}) 3613, 3520, 3436, 3351, 3068, 3020, 2983, 2955, 2883, 1741, 1708, 1602, 1598, 1052, 1029, 1018, 760, 699. Anal. Calcd for $C_{35}H_{40}N_2O_{10}$: C, 64.80; H, 6.22; N, 4.32. Found: C, 64.71; H, 6.18; N, 4.17.

Acknowledgment. This work was supported by a grant from the National Institutes of Health, Grant GM47360.

JO9508715