NEW DIELS-ALDER REACTIONS WITH VINYLINDOLES: A REGIO- AND STEREOCONTROLLED ACCESS TO ANNELLATED INDOLES AND DERIVATIVES

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Abstract —— New structural aspects of vinylindoles for predicting the outcome of Diels-Alder reactions are presented for the first time. Novel, mostly regio- and stereoselective cycloaddition reactions with 3- and 2-vinylindoles are described briefly and, in some cases, new applications for the syntheses of alkaloids are discussed.

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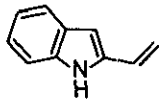
1. Introduction

Selectively functionalized 2- and 3-vinylindoles **1** and **2** represent 4π-components and are thus synthetically attractive building blocks for the regio- and stereocontrolled construction of annellated indoles as well as of indole and carbazole alkaloids[1-4]. These compounds are also of pharmacological interest as model substances and the [4+2]-cycloaddition has now established itself as a preparatively valuable concept for their syntheses. Cycloaddition reactions with vinylheterocycles generally make possible a flexible access to polycyclic heterocycles having substitution patterns that cannot be obtained so simply and elegantly by other routes.



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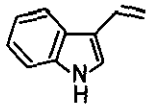

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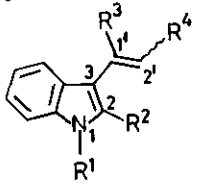
The results of cycloadditions with vinylindoles published up to 1983 have already been summarized in a review[3]. However, further interesting synthetic results which also contain new structural aspects have been published in the last few years so that a summary of the newer Diels-Alder reactions with vinylindoles is worthwhile. General methods for the synthesis of vinylindoles as heterocyclic, donor-activated 1,3-dienes are given in Refs.[1,2]

2. Structural Characteristics of Vinylindoles for Predicting the Results of Cycloaddition Reactions

^{1}H- and ^{13}C-nmr spectroscopic studies on selected 3-vinylindoles are in accord with the fundamental π-electron density of a 1-aminobutadiene structural unit incorporated in a heterocyclic framework[5]. The steric and/or electronic effects on the charge distribution are, for example, reflected sensitively in the ^{13}C-nmr chemical shifts listed in Table 1. With the exception of the methoxy derivatives, the 2'-carbon atoms of the vinyl groups all exhibit high π-charge densities. According to the polarity concept, this center thus controls the orientation of the cycloaddition partner when unsymmetrical dienophiles are employed. The N-donor capacity more than compensates for the acceptor character of a 2'-alkoxycarbonyl

Table 1. ^{13}C-nmr Chemical Shifts of the 1-Aminobutadiene Moieties of Selected 3-Vinylindoles (in DMSO-d_6)[5].



R^1	R^2	R^3	R^4	C-2	C-3	C-1'	C-2'
SO_2Ph	H	H	H	127.35	124.84	127.35	115.65
E/SO_2Ph	H	H	CO_2Et	129.87	117.74	135.28	118.00
Z/SO_2Ph	H	H	OMe	123.00	117.20	93.39	149.43
E/SO_2Ph	H	H	OMe	120.52	118.89	94.85	149.90
E/SO_2Ph	Me	H	OMe	131.37	116.41	95.06	150.88
SO_2Ph	H	H	H	127.35	124.84	127.35	115.65
Me	H	Ph	H	127.64	114.74	142.97	110.97
SO_2Ph	H	Ph	H	125.22	123.25	140.18	116.19
SO_2Ph	Me	p-MeOPh	H	136.50	112.91	139.27	115.51
H	H	3-indolyl	H	124.87	116.91	136.54	108.00

function, as can be seen from the experimental results with indolylacrylates as push-pull butadiene systems (see below and also Table 1).

An N-benzenesulfonyl group inductively weakens the enophile reactivity of the 3-vinylindoles. However, Diels-Alder reactions with N-acceptor substituted 3-vinylindoles and reactive dienophiles, sometimes under Lewis acid catalysis, can still be realized well experimentally.

A recognized model for the analysis of reactivity, regio- and stereochemistry (e.g. endo/exo-stereoselectivity) of Diels-Alder reactions is the FMO concept[6,7]. For this purpose, He(I) PE spectra of some 3-vinylindoles have been recorded and the frontier orbital topologies have been determined by SCF-MO calculations in order to obtain a reliable analysis of the $HOMO_{diene}$ energies of vinylindoles[5]. Thus, 1'-donor substituted 3-vinylindoles all exhibit a first vertical ionization potential of about + 7 eV which is attributed to the π-HOMO energy[5]. It can be safely assumed that [4+2]-cycloadditions with electron-rich vinylindoles in principle proceed under $HOMO_{diene}$-$LUMO_{dienophile}$ control. However, it should also be possible to realize $LUMO_{diene}$ controlled cycloadditions and this has been proved recently by experiment (see below).

Selected SCF-MO calculations to represent the frontier orbital topologies have been performed on the parent compound 3-vinylindole and on 1,1'-bisindolylethene (Fig. 1)[5]. From the HOMO of the d^4 system, the regiochemistry and also a favored secondary frontier orbital interaction (endo-preference) can be deduced without difficulty for reactions with the corresponding dienophiles. In fact, an endo-preference (Figs. 2 and 3) has been found experimentally under Lewis acid catalysis and, in particular, when cyclic dienophiles are used with both 3- and 2-vinyl-

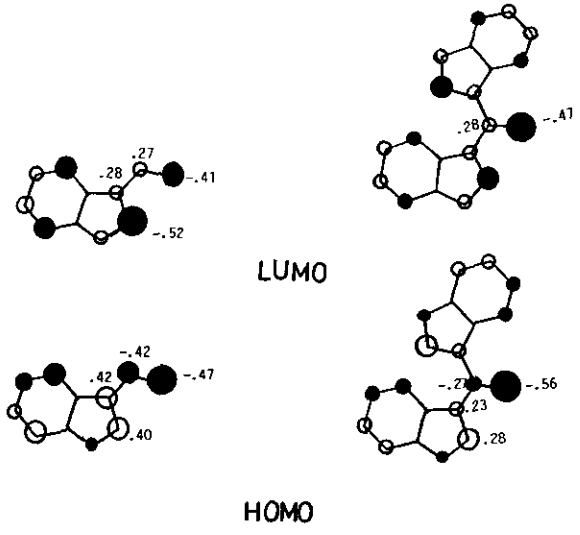


Fig. 1. Topologies of the Frontier Orbitals of 3-Vinylindole and 1,1'-Bisindolylethene (SCF Method, PPP-Process)[5].

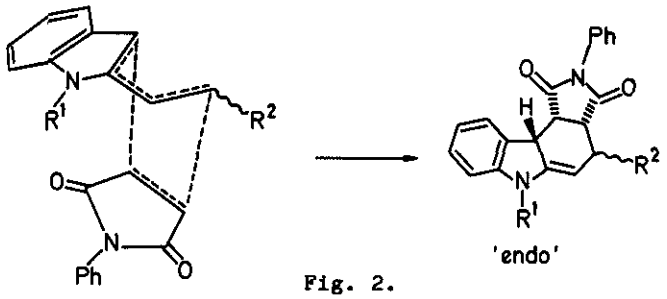


Fig. 2.

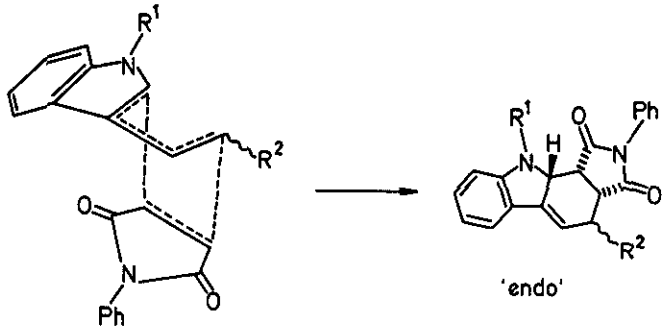


Fig. 3.

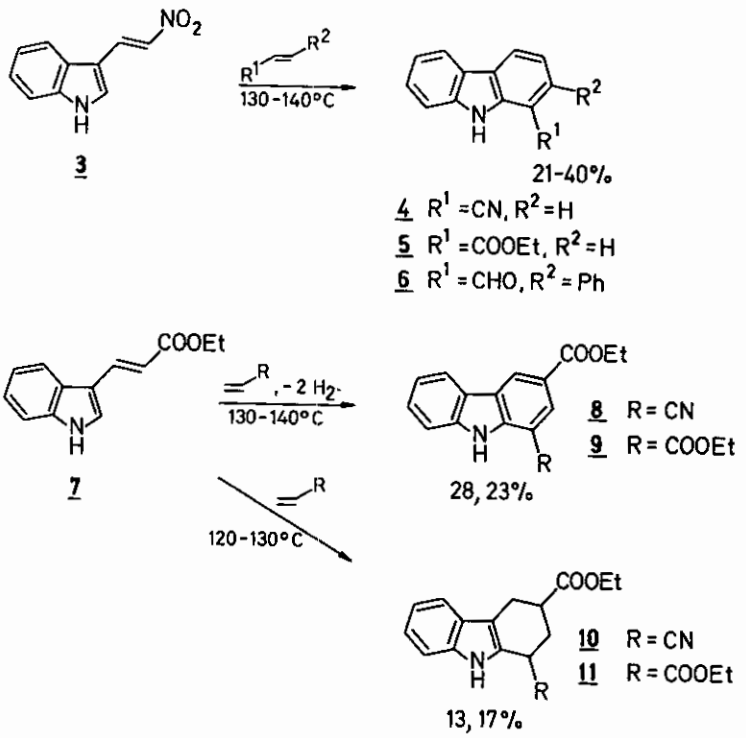
Figs. 2 and 3. endo-Transition States for 2'-Substituted 2- and 3-Vinylindoles with N-Phenylmaleimide.

indoles. In principle, analogous predictions can be made for the reactivity in the 2-vinylindole series but the available experimental data are not sufficient to allow generalizations.

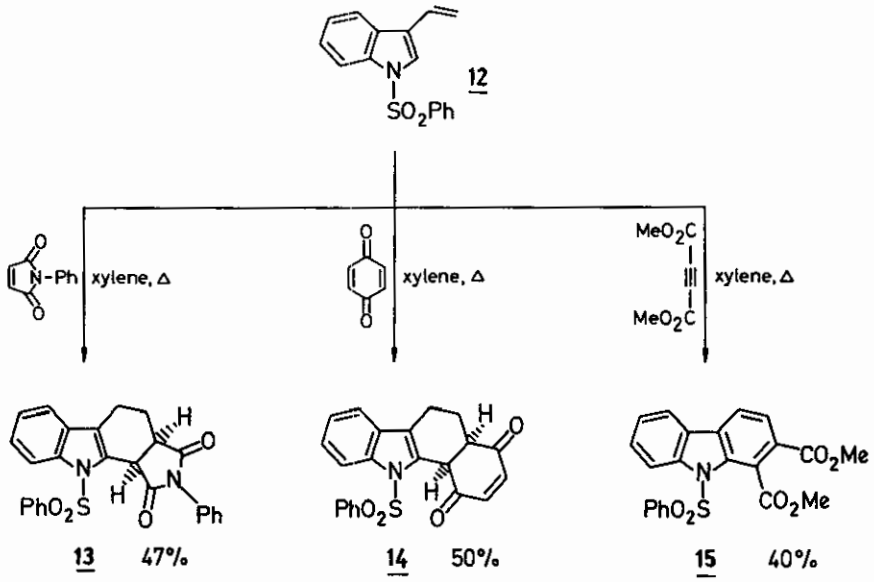
3. Reactions with 3-Vinylindoles

In spite of the 2'-acceptor function in 3-vinylindoles, Diels-Alder reactions with less reactive dienophiles such as, for example, acrylonitrile, ethyl acrylate, and cinnamaldehyde can be achieved without difficulty by working at 130-140 °C in a sealed tube[8]. Thus, for example, 3-(ß-nitrovinyl)-indole (3) and acrylonitrile, ethyl acrylate, and cinnamaldehyde undergo direct regiospecific reactions to give the 14π-carbazoles **4-6** via [4+2]-cycloaddition, HNO_2 elimination, and thermally induced dehydrogenation[8].

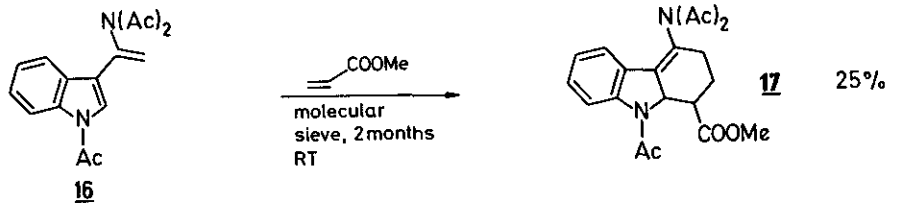
On the other hand, 3-(ß-ethoxycarbonylvinyl)-indole (7) reacts with acrylonitrile and ethyl acrylate to give the carbazoles **8** and **9** as well as the tetrahydrocarbazoles **10** and **11** in a temperature controlled reaction. The 'ortho'-cycloadducts formed in this series may be attributed to the high donor capacity of the indole nitrogen atom.

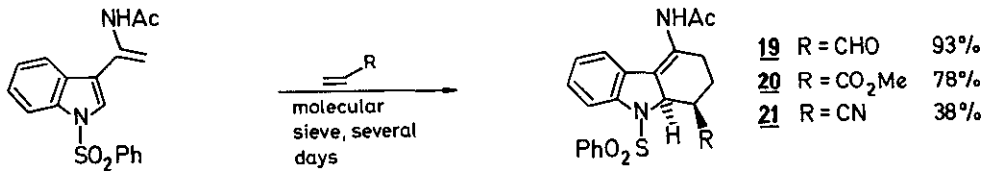


As a consequence of a new and elegant access to 1-benzenesulfonyl-3-vinylindole (**12**), its cycloadditions with N-phenylmaleimide, dimethyl acetylenedicarboxylate, and p-benzoquinone have been studied[9]. Heating under reflux in xylene with **12** results in the formation of the new [a]annellated or functionalized carbazole derivatives **13-15**; in each case indolization has occurred via thermally induced [1,3-H]-shifts.



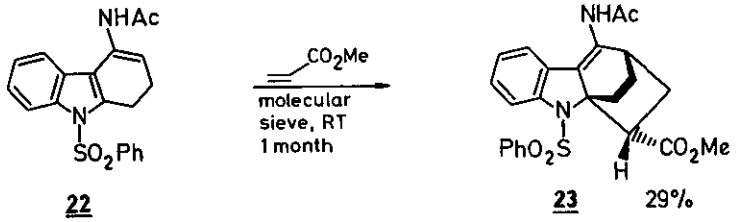
Also, the now easily accessible 3-indolylenimides and -enamides can undergo cycloaddition as 3-vinylindole building blocks with acrolein and acrylic acid derivatives to furnish new 4-(acetylamino)-1,2,3,9a-tetrahydrocarbazoles without difficulty[10]. Thus, for example, the enimide **16** reacts with neat methyl acrylate as both dienophile and solvent under molecular sieve catalysis (extremely mild conditions) to yield the tetrahydrocarbazole **17**.





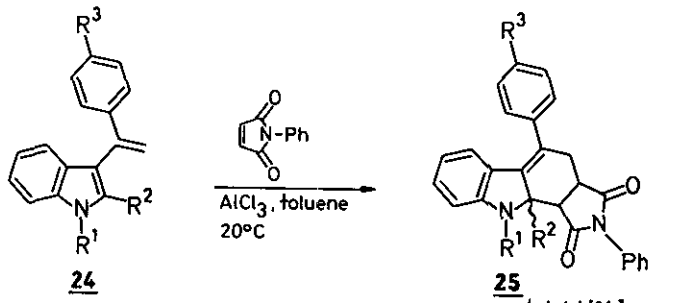
The enamide **18** reacts with acrolein, methyl acrylate, and acrylonitrile to give the cycloadducts **19-21** following the same regiochemistry.

Also, the tricyclic enamide **22** with its very reactive planar s-cis-fixed 3-vinylindole structure can undergo cycloaddition in this manner. The Diels-Alder reaction with methyl acrylate results directly in the bridged tetracycle **23**[10], a skeleton which is also present in Pleiocarpine-type alkaloids. From the stereochemistries of the cycloadducts **17**, **19**, **20**, **21**, and **23**, a concerted cycloaddition via an endo-transition state may be deduced.



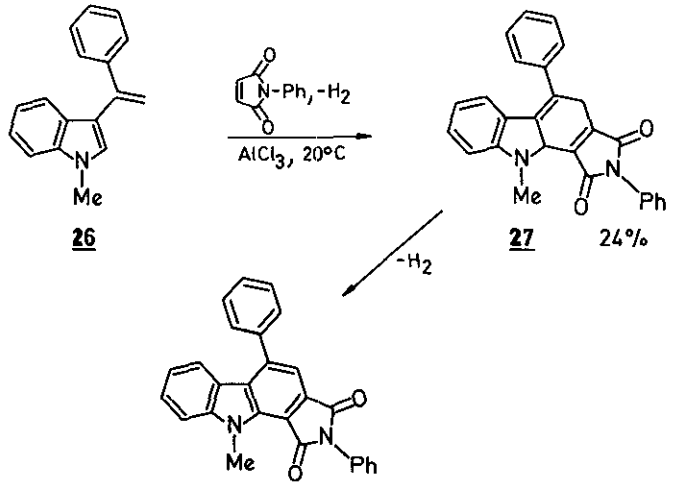
1'-Phenyl substituted 3-vinylindoles **24** react under $AlCl_3$ catalysis with pronounced endo-preference to give the new [a]annellated carbazole derivatives **25**[11]. The endo/exo-product distribution in dependence on both time and temperature has been monitored by quantitative tlc-remission measurements[11].

On the other hand, the 3-vinylindole **26** reacts to form the cycloadducts **27** and **28**, which represent the products of a dehydrogenative Diels-Alder reaction[11].



24 25

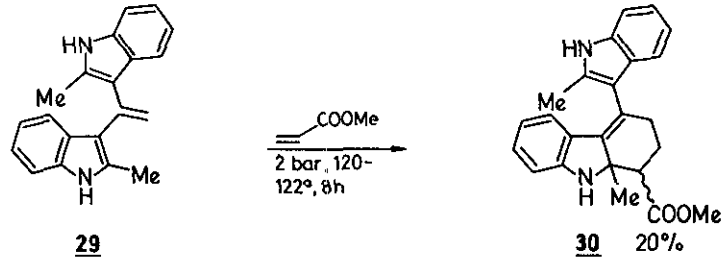
R^1	R^2	R^3	yield [%] endo	exo
SO_2Ph	Me	OMe	12	-
SO_2Ph	H	H	11	-
Me	Me	H	43	11
SO_2Ph	Me	H	4	-



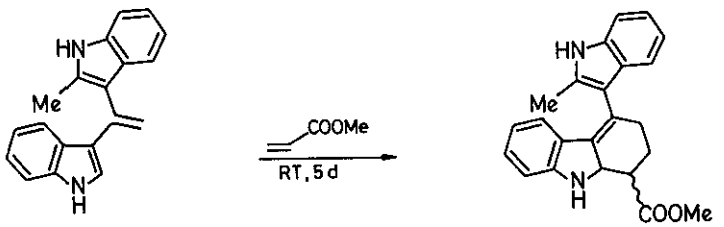
26 27 24%

28 14%

A comprehensive initial study on Diels-Alder reactions of cross-conjugated 3-vinylindoles having triene structural elements is given in Ref.[12] Whereas, for example, the bisindolylethene **29** reacted with methyl acrylate to give the cis/trans-tetrahydrocarbazoles **30**, the unsymmetrical bisindolylethene **31** reacted with regio- and positional selectivity to give the carbazole derivative **32**. In the latter case, steric effects most certainly control the positional chemistry[11].

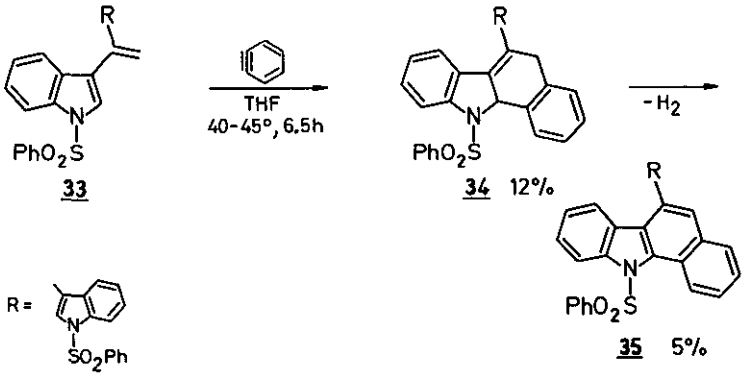


29 30 20%



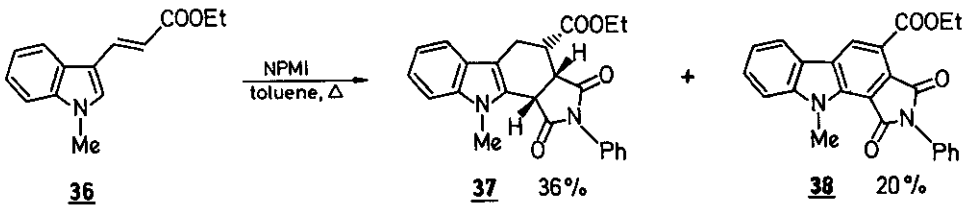
31 32 25%

The highly reactive, in situ generated benzyne only undergoes successful cycloaddition with N-acceptor substituted bisindolylethene, as illustrated by the sequence 33 ⟶ 34 ⟶ 35[12].

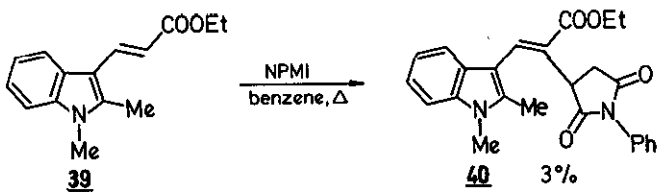


33 34 12% 35 5%

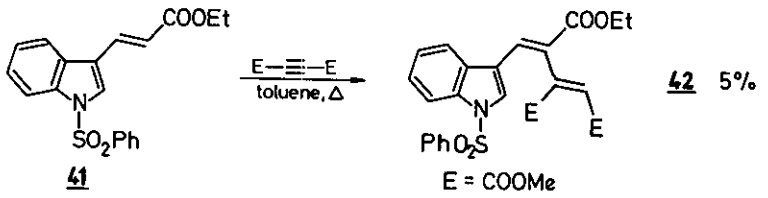
Steric and electronic affects also control the results of further new reactions of 2'-substituted 3-vinylindoles with carbon- and heterodienophiles. Thus, for example, the (E)-ethyl indolylacrylate 36 reacts directly with N-phenylmaleimide (NPMI) to furnish the carbazole derivatives 37 (d.e. > 95%) and 38[13]. The reaction of 39, in contrast, stops at the Michael adduct 40 stage since the ring closure is apparently prevented by steric factors. Analogously, the ethyl indolylacrylate 41 with lowered $HOMO_{diene}$ energy reacts with dimethyl acetylenedicarboxylate to give the Michael adduct 42 only[13].



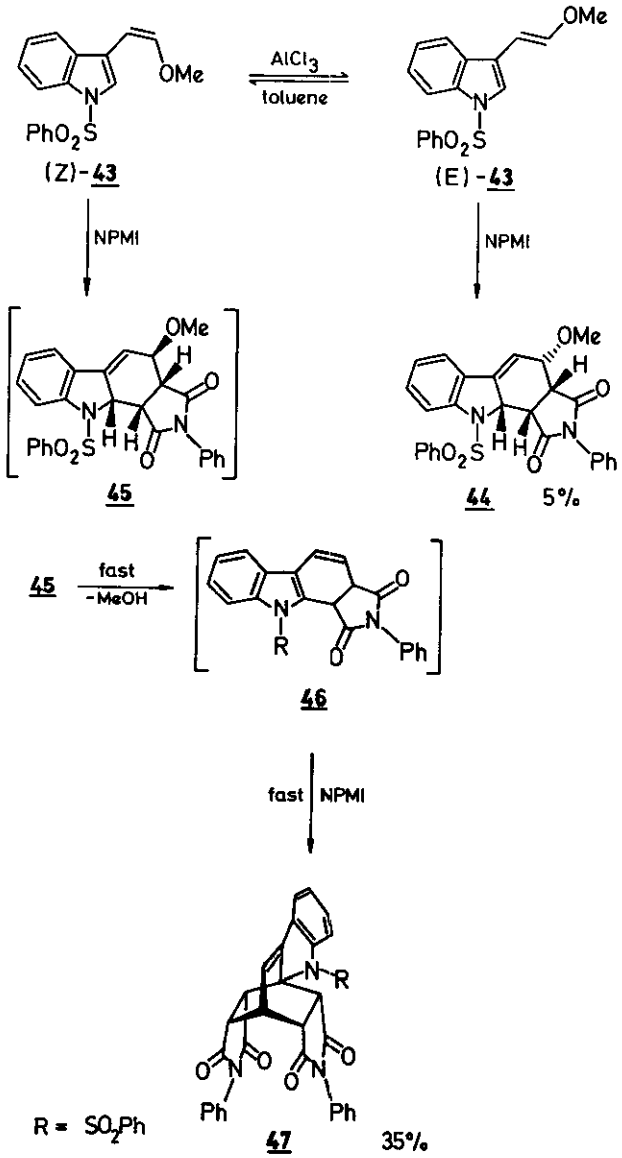
36 37 36% 38 20%



39 40 3%

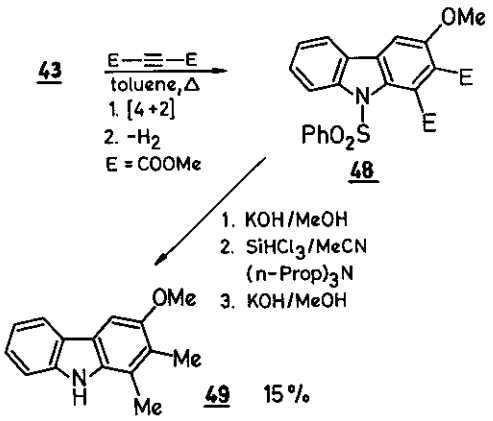


An interesting product distribution was observed in the Diels-Alder reactions of 2'-methoxy substituted 3-vinylindoles (enol ethers of 3-indolylacetaldehyde)[13]. Thus, for example, (E/Z)-43 reacted with NPMI under $AlCl_3$ catalysis to give initially the endo-cycloadduct 44. The epimer 45 derived directly from the Z-isomer could not be detected, apparently as a result of its instability. Its existence,

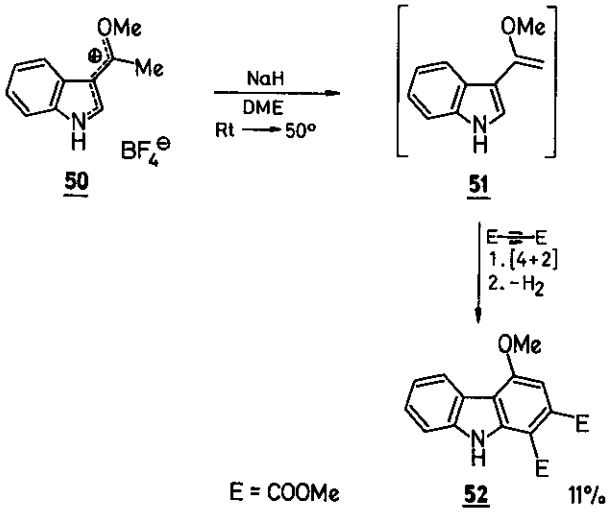


however, was confirmed by its rapid subsequent reaction to yield the double Diels-Alder product **47** (d.e. > 95%). The reactive s-cis-fixed 3-vinylindole **46** must be assumed as an intermediate in this sequence. Since it can be demonstrated that **47** cannot be formed from **44**, the reaction route to **47** via **45** is thus verified experimentally[13]. In principle, four isomers (two with C_s and an enantiomeric pair with C_1 symmetry) are feasible in the cycloaddition of **46** and NPMI. The configuration of the C_s-symmetrical double cycloadduct **47** was unambiguously elucidated from the ^{1}H-NOESY spectra[13].

Compound **43** was used initially for the synthesis of 4-demethoxycarbazomycin (**49**)[14]. [4+2]-Cycloaddition of **43** with dimethyl acetylenedicarboxylate and dehydrogenation of the initially formed cycloadduct gave **48**. Hydrolysis of **48** to give the isolable, free dicarboxylic acid and reduction of the two carboxyl groups led finally to **49**.

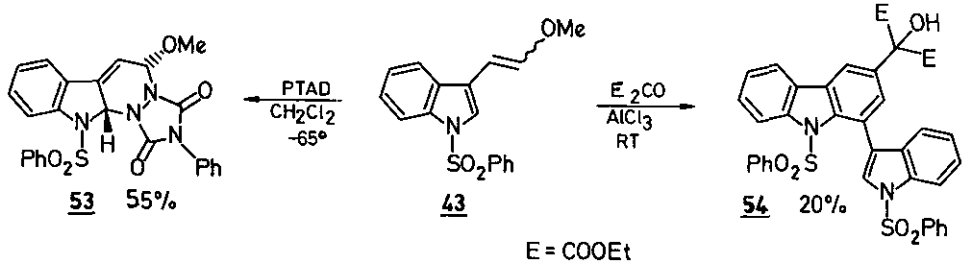


In the course of the study of this methodology, the regioisomeric 3-demethoxycarbazomycin was also prepared for the first time by an 'in situ' 3-vinylindole



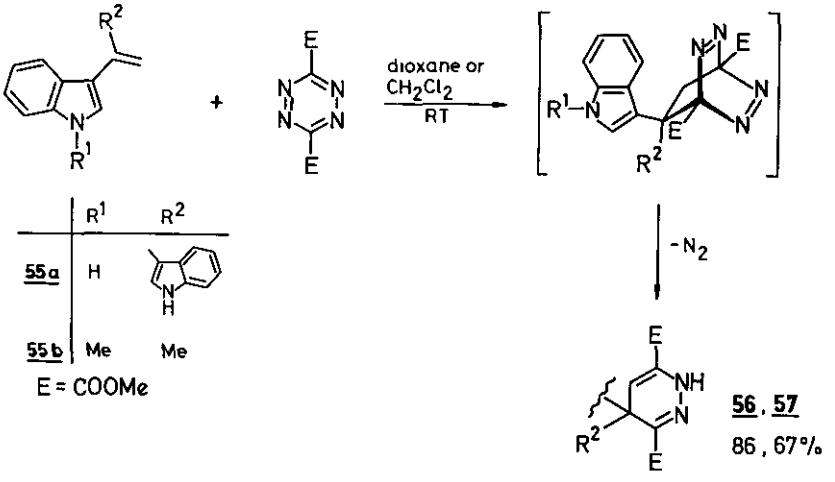
process[15]. The thermally stable indolyl(methoxy)methylcarbenium tetrafluoroborate (50) was deprotonated *in situ* to the reactive (N-unprotected!) 3-vinylindole **51**. A [4+2]-trapping reaction of **51** with dimethyl acetylenedicarboxylate and subsequent dehydrogenation step gave the carbazole **52**, which was reduced to 3-demethoxycarbazomycin (28% yield) by known methods[15].

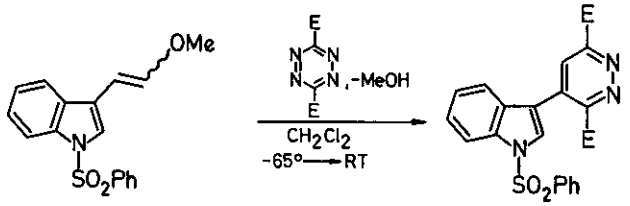
Compound **43** also undergoes varying reactions with heterodienophiles. Thus, for example, the highly reactive N-phenyltriazolinedione (PTAD) reacts smoothly in a stereospecific [4+2]-cycloaddition to give the tetracyclic [b]annellated indole **53**[16]. In contrast, the CO-polarized diethyl mesoxalate reacts with **43** in the sense of an electrophilic addition at the d^4 vinyl function. Subsequent elimination of methanol and dimerization leads to the new carbazole derivative **54**[16].



In the last few years, new structural aspects of the cycloaddition (conformation, relative configuration) have been determined by high resolution ^{1}H-nmr spectroscopy and X-ray structural analysis[10,17]. Thus, for example, the cyclohexene rings in the pyrrolo[a]annellated tetrahydrocarbazoles of type **25** and **44** generally take up a slightly twisted boat conformation both in solution and in the crystal state[17].

According to predictions from the FMO concept, Diels-Alder reactions with inverse electron demand should also be realizable with electron-rich 3-vinylindoles[6,7]. Indeed, the new substituted 1,2-diazines **56** and **57** and, after elimina-





43 58 45%

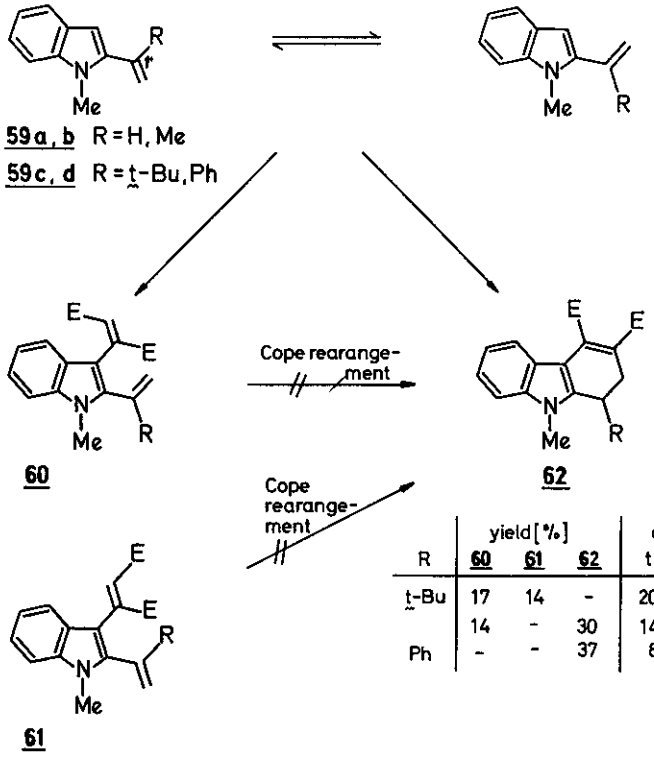
E = COOMe

tion of methanol, 58, were prepared for the first time from the 3-vinylindoles 55a,b as well as 43 and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate as the 4π-system[18].

4. Reactions with 2-Vinylindoles

The synthetic potential of 2-vinylindoles as 4π-components for Diels-Alder reactions has not been probed so extensively since accesses to this interesting structural class are still associated with a relative high synthetic effort[2].

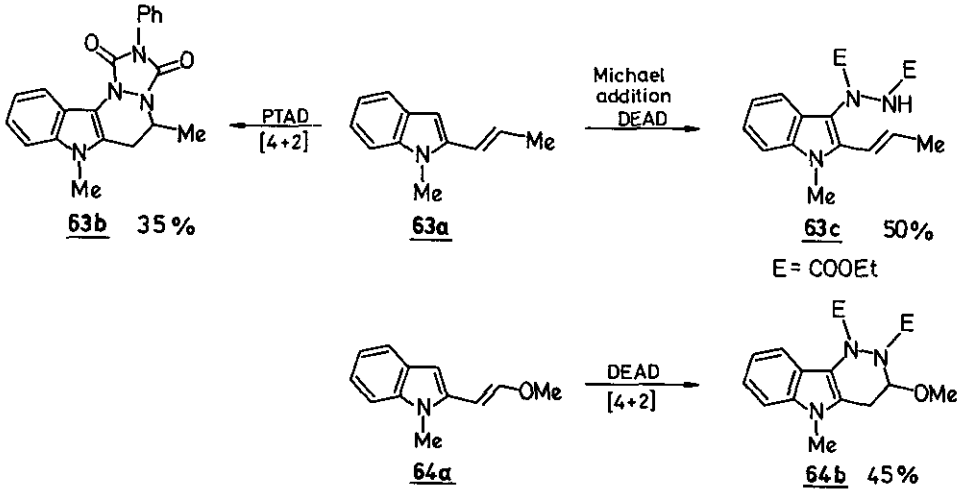
In a recent report the reactivity of 1'-substituted 2-vinylindoles in comparison to vinylpyrroles with dimethyl acetylenedicarboxylate as dienophile was systematically investigated[19]. It was found that the overall reaction rates of 1'-



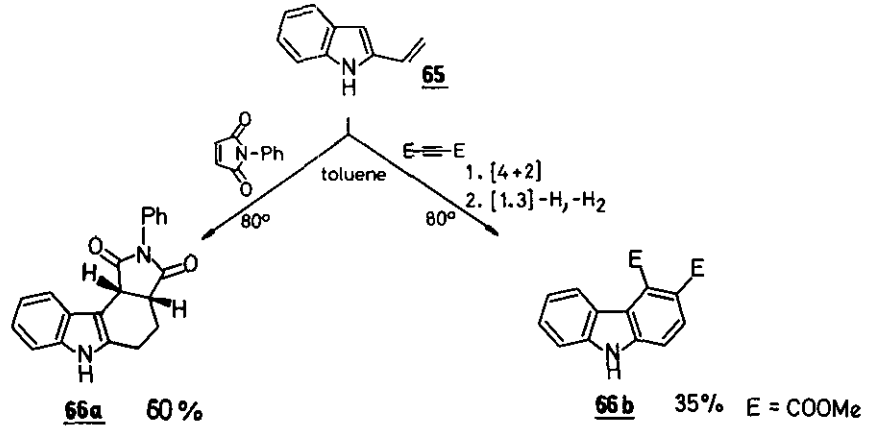
R	yield [%] 60	61	62	conditions t	T
t-Bu	17	14	-	20d,	20°
	14	-	30	14d,	62°
Ph	-	-	37	8d,	62°

substituted 1-(1-methyl-2-indolyl)-ethenes with dimethyl acetylenedicarboxylate are about 100 to 1000 times lower than the overall rates of reaction with the corresponding 2-vinylpyrroles[19]. In somes cases, steric hindrance between the N-methyl group on the indole ring and the 1'-substituent on the ethene moiety renders the assumption of a coplanar cisoid conformation more difficult and thus a competing Michael addition can take place in addition to the cycloaddition. Whereas, for example, **59a,b** polymerize too rapidly, with **59c,d** (R = t-Bu, Ph) the cycloadditon can be realized under defined conditions. In the case of **59c**, Michael addition competes with the cycloaddition[19].

New investigations on the reactions of 2'-substituted 2-vinylindoles with azodienophiles have shown that reaction of **63a** with 4-phenyl-1,2,4-triazoline-3,4-dione (PTAD) gives rise to the cycloadduct **63b** whereas that with diethyl azodicarboxylate (DEAD) leads to the Michael adduct **63c**[20]. In contrast, the electron-rich indolyl enol ether **64a** reacts to give the cycloadduct **64b** exclusively[20].

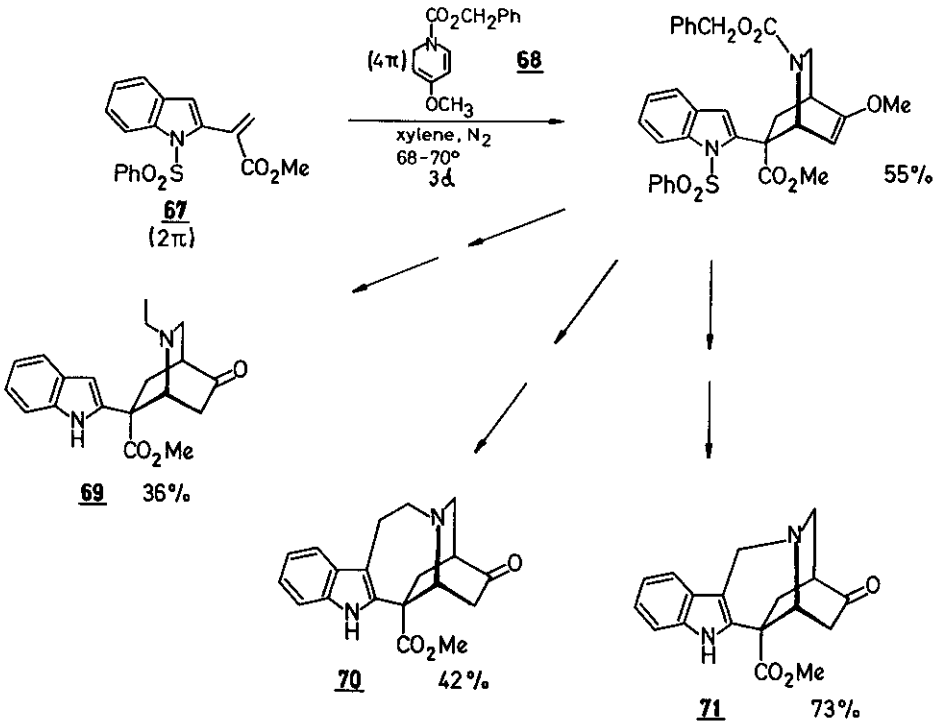


After an intramolecular Wittig reaction[21], the parent 2-vinylindole (**65**) was obtained for the first time[22]. [4+2]-Cycloadditions of the stable, crystalline

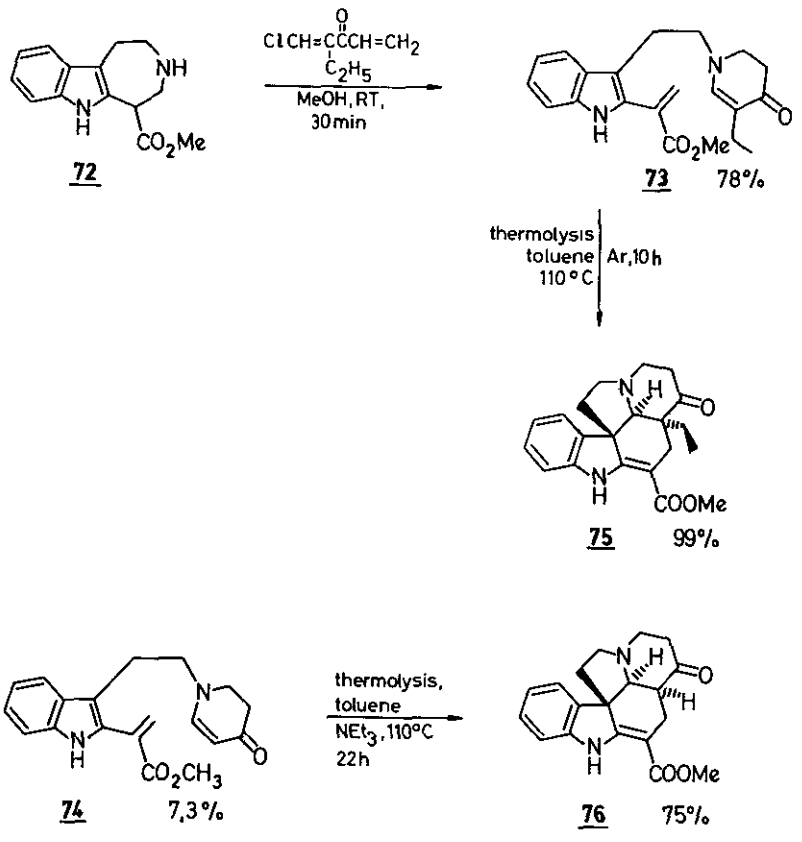


compound **65** with carbon dienophiles gave rise to the expected carbazole derivatives **66a** and **66b**[22].

In an earlier publication[2], we pointed out the great significance of the methyl 2-(2-indolyl)-acrylate **67** as a 2-vinylindole building block for the regio- and stereocontrolled synthesis of Iboga and Aspidosperma alkaloids; this has recently been reconfirmed by reports on further variations. Thus, the Diels-Alder reaction of methyl N-benzenesulfonylindole-2-(2-propenoate) (**67**) (as 2π-component) and 1-(benzyloxycarbonyl)-4-methoxy-1,2-dihydropyridine (**68**) (as 4π-component) was recently exploited as the key step in the syntheses of 20-deethyl-15-oxo-analogs of Iboga alkaloids such as, for example, the oxocoronaridine derivatives **69**, **70**, and **71**[23].



In the course of studies on biomimetic syntheses of Aspidosperma alkaloids, intramolecular Diels-Alder reactions of secodine derivatives were reinvestigated. The syntheses of isolated 15-oxo-$\Delta^{20(21)}$-secodine (**73**) and deethyl-15-oxo-$\Delta^{20(21)}$-secodine (**74**) from methyl 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5-carboxylate (**72**) by spiroquaternization or, alternatively, by a bridged azepine pathway were described[24]. Thermolyses of these secodine derivatives gave 15-oxovincadifformine (**75**) and deethyl-15-oxovincadifformine (**76**). Subsequent transformations led to tabersonine and deethylvincadifformine, respectively. In the key steps, the 2-vinylindole structural units in **73** and **74** served as 4π-components[24]. A further variant is reported in Ref.[25].



REFERENCES

1. E. Akgün and U. Pindur, J. Heterocyclic Chem., 1985, 22, 585; L. Pfeuffer and U. Pindur, Monatsh. Chem., 1987, **118**, 1031; U. Pindur and R. Adam, J. Heterocyclic Chem., in press.
2. E. Akgün and U. Pindur, Chimia, 1985, **39**, 264.
3. U. Pindur and L. Pfeuffer, Chem.-Ztg., 1986, **110**, 95.
4. R.A. Jones, 'Comprehensive Heterocyclic Chemistry,' Vol. 4, ed. by C.W. Bird and G.W.H. Cheeseman, Pergamon Press, Oxford, 1984, pp. 279 ff.
5. U. Pindur and L. Pfeuffer, Helv. Chim. Acta, in press.
6. J. Sauer and R. Sustmann, Angew. Chem. 1980, **92**, 733; Angew. Chem. Int. Ed. Engl., 1980, **19**, 779.
7. I. Fleming, 'Frontier Orbitals and Organic Reactions,' Verlag Chemie, Weinheim, 1979.
8. R.S. Kusurkar and U.G. Patil, Indian J. Chem., 1986, **25B**, 1038.
9. B. Saroja and P.C. Srinivasan, Synthesis, 1986, 748.
10. P.H. Götz, J.W. Bats, and H. Fritz, Liebigs Ann. Chem., 1986, 2065.

11. L. Pfeuffer and U. Pindur, Chimia, 1987, **41**, 126.
12. L. Pfeuffer and U. Pindur, Chimia, 1986, **40**, 124.
13. L. Pfeuffer and U. Pindur, Helv. Chim. Acta, 1987, **70**, 1419.
14. U. Pindur and L. Pfeuffer, Heterocycles, 1987, **26**, 325.
15. U Pindur and L. Pfeuffer, Tetrahedron Lett., 1987, **28**, 3079.
16. L. Pfeuffer and U. Pindur, Monatsh. Chem., 1987, **118**, 1073.
17. L. Pfeuffer, U. Pindur, H.-J. Sattler, W. Massa, and G. Frenzen, Liebigs Ann. Chem., in press.
18. U. Pindur and L. Pfeuffer, Chimia, 1987, **41**, 125.
19. R.A. Jones, P.M. Fresneda, T.A. Saliente, and J.S. Arques, Tetrahedron, 1984, **40**, 4837.
20. M.H. Kim and U. Pindur, unpublished results.
21. M. Le Corre, A. Hercouet, Y. Le Stanc, and H. Le Baron, Tetrahedron, 1985, **41**, 5313.
22. M. Eitel, and U. Pindur, Tetrahedron Lett., in press.
23. R.J. Sundberg, M. Amat, and A.M. Fernando, J. Org. Chem. 1987, **52**, 3151.
24. M.E. Kuehne, W.G. Bornmann, W.G. Earley, and I. Marko, J. Org. Chem., 1986, **51**, 2913.
25. M.E. Kuehne, D.E. Podhorez, T. Mulamba, and W.G. Bornmann, J. Org. Chem., 1987, **52**, 347.

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