Stereoselective 1,3-Dipolar Cycloadditions of Photochemically Generated Azomethine Ylides to Oppolzer's Chiral Acryloyl Sultam. An Asymmetric Approach to Quinocarcin

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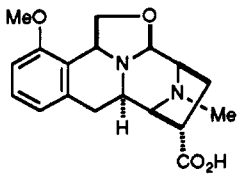
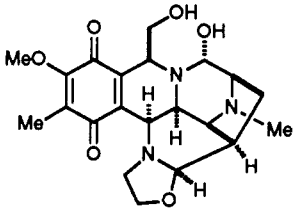
Summary: Photochemically generated azomethine ylides undergo highly stereoselective 1,3-dipolar cycloadditions (ds >25:1) to chiral acryloyl sultams to give the substituted 3,8-diazabicyclo[3.2.1]octane moiety of quinocarcin.

We recently reported that azomethine ylides such as **4** undergo smooth 1,3-dipolar cycloadditions with methyl acrylate to give mixtures of cycloadducts **6–9** (X = OMe) possessing the diazabicyclo[3.2.1]octane moiety common to both quinocarcin (**1**) and naphthyridinomycin (**2**).[1-4]



quinocarcin (**1**)



naphthyridinomycin (**2**)

While the exo selectivity associated with these intermolecular cycloadditions was good (**6** + **7**):(**8** + **9**) ≅ 5:1, the lack of any appreciable diastereoselectivity with the chiral azomethine ylides **4b** and **4c** was disappointing (**6**:**7** ≅ 1:1 in both cases). Since the benzylic stereocenter was apparently unable to exert any control (1,4-asymmetric induction) over addition to the prochiral faces of azomethine ylide **4**, the possibility of using a chiral acrylate or acrylamide to control the diastereofacial selectivity of this process was considered.[5,6]

There were at least two problems associated with this plan at the time of its conception: (1) chiral acrylates/acrylamides that exhibited high facial selectivity during cycloadditions *in the absence of Lewis acids* were generally unknown and (2) the behavior of such auxiliaries under the photochemical conditions used to generate **4** could not be predicted with certainty. Thus, we were encouraged by a Letter from Curran's laboratory[7] that documented good facial selectivity during 1,3-dipolar cycloadditions between Oppolzer's chiral acryloyl sultam **5**[8] and various nitrile oxides. *We now report that sultam* **5** *also provides excellent diastereofacial control for 1,3-dipolar cycloaddition reactions of photochemically generated azomethine ylides such as* **4**, *setting the stage for a concise enantioselective synthesis of quinocarcin and related substances.*[9,10]

Table I. Auxiliary-Controlled Intermolecular Cycloadditions[a]

entry	aziridine	chiral acrylamide	cycloadduct, X = (–)- or (+)-sultam	% yield[b]
1	**3a**	(–)-**5**	**6a**	39 (42)
			8a	16 (17)
2	**3b**	(–)-**5**	**6b**	61 (69)[c]
3	**3c**	(–)-**5**	**6c**	58 (65)
4	**3c**	(+)-**5**	**7c**	55 (64)
5	**3d**	(–)-**5**	**6d**	45 (55)
6	**3d**	(+)-**5**	**7d**	46 (56)

[a] General procedure: To a 0.1 M solution of the aziridine **3** in dry spectrophotometric grade 1,4-dioxane was added 0.2 equiv of *N*-acryloyl sultam **5**. This solution was purged with N_2 gas for 2 min and then photolyzed at 2537 Å (Rayonet photochemical reactor) for 30 min with TLC monitoring. The procedure was repeated until a total of 1.2 equiv of *N*-acryloyl sultam had been added. At this point, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel eluting with EtOAc–hexanes. [b] Yield based on recovered **3** in parentheses. [c] Since racemic **3b** was used, this product consisted of a 1:1 mixture of diastereomers epimeric at the benzylic stereocenter.

Photolysis of the previously reported model aziridines **3a-d** at 2537 Å in the presence of the chiral acryloyl sultams (–)- and (+)-**5** led to the results collected in Table I.[11] A number of trends are apparent from this data. First, the dipolarophile face selectivity associated with

(1) Garner, P.; Sunitha, K.; Shanthilal, P. *Tetrahedron Lett.* **1988**, *29*, 3525.

(2) For a related approach to the 3,8-diazabicyclo[3.2.1]octane portion of quinocarcin based on 1,3-dipolar cycloaddition to an achiral 2-oxidopyrazinium species, see: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187.

(3) Quinocarcin: Tomita, F.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463. Takahashi, K.; Tomita, F. *Ibid.* **1983**, *36*, 468; Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1705.

(4) Naphthyridinomycin: Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A.; Singh, K.; Vezina, C. *J. Antibiot.* **1975**, *28*, 497. Sygusch, J.; Brisse, F.; Hanessian, S.; Kluepfel, D. *Tetrahedron Lett.* **1974**, 4021; Errata: *Ibid.* **1975**, 170. Cyanocyclin: Zmijewski, M. J., Jr.; Goebel, M. *J. Antibiot.* **1982**, *35*, 524. Hayashi, T.; Noto, T.; Nawata, Y.; Okazaki, H.; Sawada, M.; Ando, K. *Ibid.* **1982**, *35*, 771. SF-1739 HP/naphthocyanidine: Itoh, J.; Omoto, S.; Kodama, Y.; Hisamatsu, T.; Niida, T.; Ogawa, Y. *Ibid.* **1982**, *35*, 642.

(5) For general surveys of the application of chiral auxiliaries to asymmetric cycloadditions, see: Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, Chapter 7; Oppolzer, W. *Angew, Chem., Int. Ed. Engl.* **1984**, *23*, 876.

(6) An intramolecular variant of this strategy can be used to access the 6-endo-substituted diazabicyclo[3.2.1]octane system as required for naphthyridinomycin: Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041.

(7) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555. (See also: Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Ibid.* **1988**, *29*, 3559). More recently, a novel chiral acrylimide derived from Kemp's triacid was shown to impart even higher levels of asymmetric induction to nitrile oxide cycloadditions: Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238.

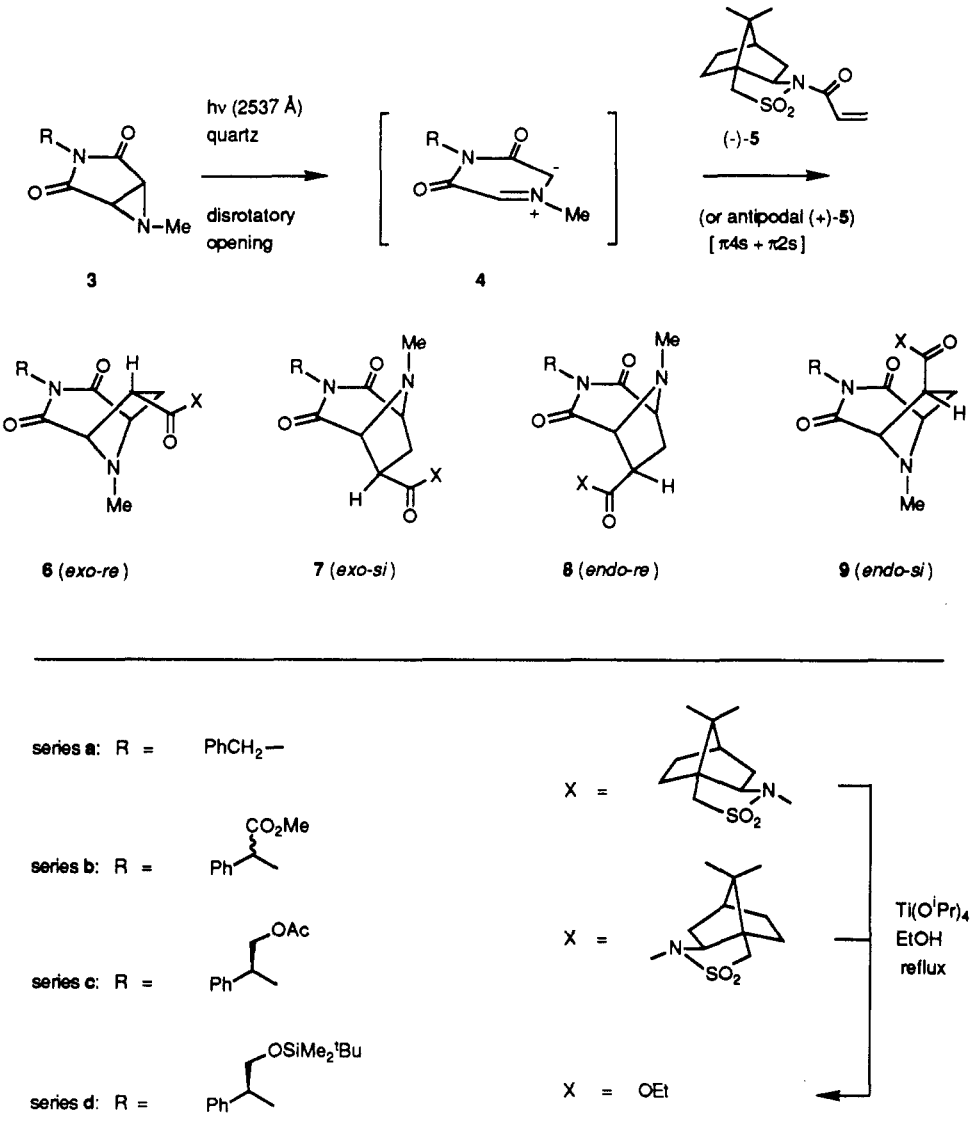
(8) Preparation of **5**: Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. For a comprehensive review of camphor-derived chiral auxiliaries, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (The original article contains printer errors; a corrected version was reprinted in the Errata section of *Tetrahedron* **1987**, *43*, Issue 18).

(9) Total synthesis of (±)-quinocarcinol: Danishefsky, S.; Harrison, P. J.; Webb, R. R., II; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421. Total synthesis of (±)-quinocarcin: Fukuyama, T.; Nunes, J. J. *Ibid.* **1988**, *110*, 5196. Related synthetic work: Williams, R. M.; Ehrlich, P. P.; Zhai, W., Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615. Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. Enantiospecific approaches: Saito, S.; Matsuda, F.; Terashima, S. *Ibid.* **1988**, *29*, 6301. Saito, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Terashima, S. *Ibid.* **1989**, *30*, 7423. Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Ibid.* **1990**, *31*, 2105.

(10) Total synthesis of (±)-cyanocyclin A: Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478. Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *Ibid.* **1987**, *109*, 1587. Related synthetic work: Parker, K. A.; O'Fee, R. *Ibid.* **1983**, *105*, 654. Parker, K. A.; Cohen, I. D.; Babine, R. E. *Tetrahedron Lett.* **1984**, *25*, 3543. Danishefsky, S.; O'Neill, B. T.; Springer, J. P. *Ibid.* **1984**, *25*, 4203. Danishefsky, S.; O'Neill, B. T.; Taniyama, E.; Vaughan, K. *Ibid.* **1984**, *25*, 4199. Evans, D. A.; Biller, S. A. *Ibid.* **1985**, *26*, 1911; **1985**, *26*, 1907. Fukuyama, T.; Frank, R. K.; Laird, A. A. *Ibid.* **1985**, *26*, 2955. Fukuyama, T.; Laird, A. A. *Ibid.* **1986**, *27*, 6173.

(11) Compounds **3a-d** were prepared from the corresponding benzylamines as described in refs 1 and 6. Satisfactory IR, ^1H and ^{13}C NMR, and HRMS data have been obtained for all substances shown.

Scheme I



these cycloadditions was uniformly excellent (ds >25:1) as judged by ^{1}H NMR analysis of the (unresolved) cycloadduct mixtures and in one case comparison with an independantly prepared diastereomeric standard (vide infra). It is assumed that the model for asymmetric induction proposed by Curran for nitrile oxide cycloaddition holds here as well: that is *re* attack of (−)-**5** and *si* attack of (+)-**5**. In contrast to analogous reactions involving acrylate ester dipolarophiles,[1,12] we found it necessary to perform this bimolecular cycloaddition so as to keep the concentration of dipolarophile at a minimum owing to the inherent photochemical sensitivity/instability of **5**.[13] Another dipolarophile-related difference showed up as a decrease in exo selectivity with the benzylamine-derived substrate **3a** (entry 1). This result was of some concern to us since the endo isomer actually possessed the "wrong" diastereomeric configuration (compare **6** and **8**), thus subverting our goal of complete stereocontrol. However, once we turned to the sterically more demanding chiral aziridines **3b–d** (as required by target structure 1), the exo mode of cycloaddition was exclusive (entries 2–6).

The usual reductive or basic conditions could not be used for removal of the sultam auxiliary because of the instability of the cyclic imide functional group towards these reaction conditions. Fortunately, we found that the cycloadducts could be converted to their corresponding ethyl esters in good yield and the sultam efficiently recovered by means of titanium(IV)-mediated alcoholysis:[14] Exposure of adducts **6a,b,d** and **7d** to 5–8 equiv of Ti(O^{i}Pr)$_4$ in refluxing ethanol led to the isolation of the corresponding ethyl esters in 61–75% yield along with 70–90% of the reusable sultam.[15] This novel application of Seebach's transesterification methodology should prove useful for removal and recovery of this chiral auxiliary in

(12) The three chiral acrylates derived from menthol, ethyl lactate, and 10-(dicyclohexylsulfonylamido)isoborneol underwent clean cycloaddition but, as expected (cf. Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14), showed no facial selectivity whatsoever in the absence of a Lewis acid. Attempts to incorporate Lewis acids into this photochemically initiated reaction have thus far been unsuccessful.

(13) Independant UV studies indicated that **5** absorbs about 10 times as much light at 254 nm as does either methyl acrylate or the aziridine **3a**. Furthermore, a control experiment showed that bulk photolysis of **5** for a period of 1 h *in the absence of aziridine* resulted in its complete decomposition.

(14) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138. Evans has used this methodology to convert analogous carboximides into their corresponding benzyl esters: Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123.

(15) Titanium(IV)-mediated alcoholysis of the adducts **6c** and **7c** was accompanied by the expected acetolysis but the resulting alcohol apparently promoted nonregioselective opening of the imide functionality as well.

other contexts as well. Note that once the chiral auxiliaries are removed the ester (X = OEt) derived from exo *si* adduct **7d** corresponds to the minor diastereomer of reaction **3d** + (−)-**5** and visa versa. This relationship permitted us to set the diastereofacial selectivity of these cycloadditions at >25:1 by simply evaluting the level of cross-contamination of these two esters via ^{1}H NMR spectroscopy.

These results suggest that an efficient and enantioselective entry to the quinocarcin family of DNA-reactive alkaloids based on auxiliary controlled 1,3-dipolar cycloaddition is viable. Further work along these lines including confirmation of the proposed model for asymmetric induction is currently underway and will be reported on in due course.

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Synthesis of Oxepins via the Cope Rearrangement of *cis*-2,3-Divinyl Epoxides

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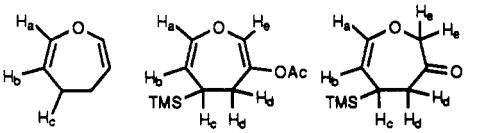
Summary: The Cope rearrangement of *cis*-2,3-divinyl epoxides, which may be readily prepared from enynols, provides a flexible and efficient route to the oxepin ring system.

The presence of the oxepin nucleus in a number of natural products of biological interest[1] has spurred the development of synthetic strategies for preparing this ring system.[2] One potentially attractive approach is the Cope rearrangement of divinyl epoxides, which leads to 4,5-dihydrooxepins through four-carbon ring expansion of the epoxide. The few reported examples of such rearrangements,[3] although supporting the viability of this approach, are mostly limited to a handful of symmetrically substituted substrates. To be truly useful, a general and efficient route to unsymmetrically substituted *cis*-2,3-divinyl epoxides, in particular those that are functionalized to allow for the further elaboration of the oxepin ring following the Cope rearrangement, is needed. We report herein a five-step synthesis of the 4,5-dihydrooxepins **3a–e** from readily available enynols **1a–e**[4] in which the key step is the [3,3] sigmatropic rearrangement of the *cis*-2,3-divinyl epoxides **2a–e**.

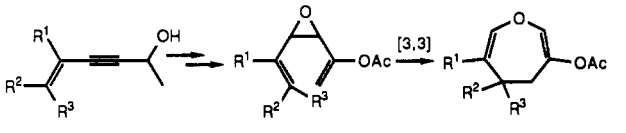
Table I. Assignment of ^{1}H NMR Data[a]



6 **3a** **7**

	6[b]	3a	7[c]
H_a	6.13 (d, 7.4)	6.17 (dd, 7.6, <1)	6.44 (dd, 6.6, 2.7)
H_b	4.82 (m)	4.85 (t, 7.6)	4.78 (ddd, 6.5, 3.5, 1)
H_c	2.30 (m)	1.79 (dtd, 7.6, 4.7, 0.7)	1.71 (dtd, 12.2, 3.6, 2.7)
H_d		2.84 (ddd, 16.4, 4.7, 1.8)	3.21 (t, 12.1)
		2.35 (dd, 16.4, 4.7)	2.52 (ddd, 12.2, 3.6, 1)
H_e		6.39 (d, 1.8)	4.36 (d, 17.6)
			4.32 (d, 17.6)

[a] ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$. Chemical shifts are in ppm downfield from TMS calculated by using a shift of 7.26 ppm for $CHCl_3$ as an internal reference. All resonances are for one proton. Following the chemical shifts are the multiplicity and coupling constant(s) in hertz. [b] Reference 15. [c] Reference 16.



1a-e **2a-e** **3a-e**

a: R^1 = H, R^2 = TMS, R^3 = H. **b**: R^1 = Me, R^2 = R^3 = H. **c**: R^1 = R^2 = $-(CH_2)_4-$, R^3 = H. **d**: R^1 = H, R^2 = C_5H_{11}, R^3 = H. **e**: R^1 = R^2 = H, R^3 = C_5H_{11}.

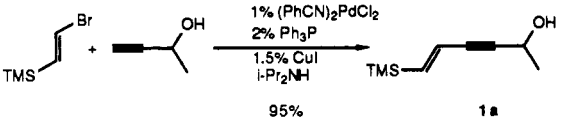
The sequence that was used to transform the enynols into oxepins is illustrated for enynol **1a** in Scheme I. Since

(1) For examples among marine natural products, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251–84, 551–90; **1986**, *3*, 1–33; **1988**, *5*, 613–63.

(2) Via the cyclization of epoxy alcohols: (a) Chen, R.; Rowand, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6609–11. (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611–2. (c) Kocienski, P.; Love, C.; Whitby, R. *Tetrahedron Lett.* **1988**, *29*, 2867–70. (d) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335–40. Via the cyclization of dithiono esters: (e) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800–2. (f) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1362–4. Via the reduction of mixed ketal derivatives: (g) Nicolaou, K. C.; Duggan, M. E.; Hwang, K.-C. *J. Am. Chem. Soc.* **1986**, *108*, 2468–9. (h) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504–6. (i) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136–7. (j) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153–61. Via the cyclization of an oxonium ion with a carbon nucleophile: (k) Cockerill, G. S.; Kocienski, P.; Threadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093–100. (l) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911–3. (m) Molander, G. A.; Andrews, S. W. *J. Org. Chem.* **1989**, *54*, 3114–20. (n) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695–707.

(3) (a) Braun, R. A. *J. Org. Chem.* **1963**, *28*, 1383–4. (b) Stogryn, E. L.; Gianni, M. H.; Passannante, A. J. *J. Org. Chem.* **1964**, *29*, 1275–6. (c) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385–401. (d) Pommelet, J. C.; Manisse, N.; Chuche, J. *Tetrahedron* **1972**, *28*, 3929–41. (e) Balci, M.; Sütbeyaz, Y. *Tetrahedron Lett.* **1983**, *24*, 4135–8. (f) Sütbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312–7.

(4) For this study, 5-methyl-5-hexen-3-yn-2-ol (**1b**) was purchased from Farchan Laboratories. Enynol **1c** was prepared by the addition of the lithium acetylide of 1-ethynylcyclohexene (Aldrich Chemical Co.) to acetaldehyde. The remaining enynols, as illustrated for **1a**, were obtained in excellent yield via the Sonogashira reaction.[5]



95% **1a**

(5) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–70.