Diels-Alder Reactivity of Pyrano[3,4-*b*]indol-3-ones, Stable Analogues of Indole-2,3-quinodimethanes[1]

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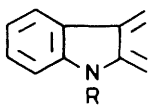
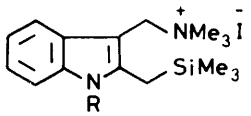
The pyrano[3,4-*b*]indol-3-ones (**13a,b**), stable synthetic analogues of indole-2,3-quinodimethanes, undergo Diels–Alder reactions with acetylenes to give, with concomitant loss of carbon dioxide, carbazoles. Thus, reaction with dimethyl acetylenedicarboxylate and dibenzoylacetylene gives the carbazole diesters (**15a,c**) and dibenzoylcarbazoles (**15b,d**) respectively. The dibenzoylcarbazoles (**15b,d**) react with hydrazine to give pyridazo[4,5-*b*]carbazoles (**16**). The pyranoindolones (**13**) also react with benzyne to give the benzo[*b*]carbazoles (**18**).

Indole-2,3-quinodimethanes (**1**) have been the subject of considerable synthetic interest in the last few years. Simple indole-2,3-quinodimethanes (**1**; R = Me and Bu^{t}OCO) and (**1**; R = COPh) have been generated by treatment of trimethylsilylmethyl gramine derivatives (**2**) with fluoride ion,[2] or by reaction of the 2,3-bis(bromomethyl)indole (**3**) with sodium iodide[3] respectively. In the presence of dienophiles, such as *N*-phenylmaleimide, the indole-2,3-quinodimethanes (**1**) can be intercepted in Diels–Alder reactions in varying yield. Intramolecular Diels–Alder reactions of indole-2,3-quinodimethane substrates such as (**4**) and (**5**) have also been investigated, and this strategy has formed the basis of some elegant synthetic work by Magnus and co-workers leading to indole alkaloids.[4]



(**1**)



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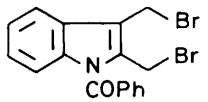

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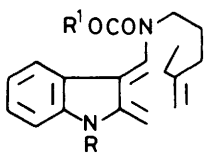

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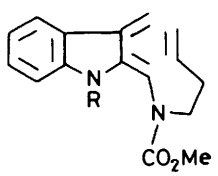
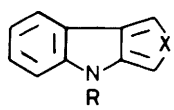


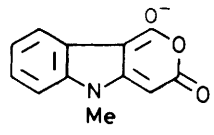
(**5**)

More recently, attention has turned to cyclic systems as stable synthetic analogues of (**1**), and the pyrrolo[3,4-*b*]indoles (**6**)[5] and (**7**),[6] and the thieno- (**8**),[7] selenolo- (**9**),[7] and furo-[3,4-*b*]-indoles (**10**)[8] have been prepared, and their intermolecular Diels–Alder reactions investigated. The anionic 2,3-quinodimethane-like intermediate (**11**) has also been generated by treatment of the corresponding anhydride with strong base,[9] and in common with all the other approaches mentioned, requires the indole nitrogen to be protected.

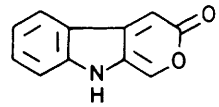
However, there is another approach to indole-2,3-quinodimethanes which is simple to carry out, does not require protection of the indole nitrogen, and is based on the



(**6**) X = NCH_2Ph, R = Ph
(**7**) X = NH or NCO_2Me, R = SO_2Ar
(**8**) X = S, R = COPh
(**9**) X = Se, R = COPh
(**10**) X = O, R = SO_2Ph



(**11**)



(**12**)

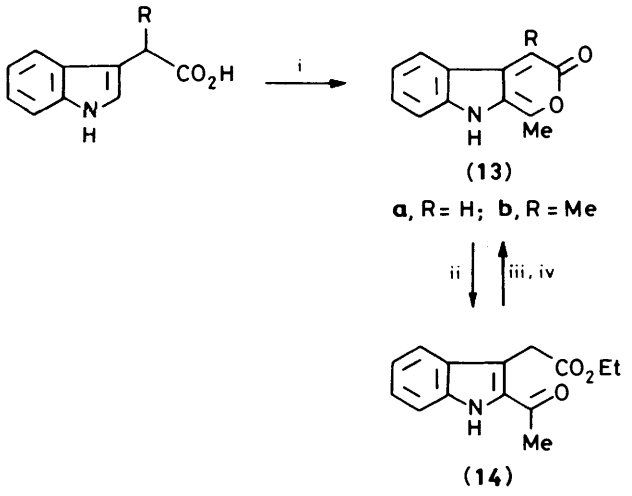
pyrano[3,4-*b*]indol-3-one ring system (**12**). The preparation and Diels–Alder reactions of these compounds were first reported by Plieninger and co-workers over 20 years ago,[10] but they have not been used in synthesis since. The results reported in full herein extend Plieninger's original work, and demonstrate that pyrano[3,4-*b*]indol-3-ones are useful synthetic analogues of indole-2,3-quinodimethanes. After the preliminary account[1] of this work appeared, other workers also reported Diels–Alder reactions of pyranoindolones.[11]

Results and Discussion

The pyranoindolone (**13a**) was prepared from commercially available indol-3-ylacetic acid by treatment of an acetic anhydride solution with freshly distilled boron trifluoride–diethyl ether exactly as described by Plieninger and co-workers,[10] although attempted recrystallisation from boiling ethanol resulted in ring-opening to give the ethyl ester (**14**). However, this ester could be reconverted into (**13a**) by alkaline hydrolysis followed by cyclodehydration in acetic anhydride[10] (Scheme 1). The dimethyl analogue (**13b**) was similarly prepared from 2-indol-3-ylpropionic acid, obtained by reaction of indole with lactic acid.[12] Both pyranoindolones (**13**) are high melting, orange crystalline compounds.

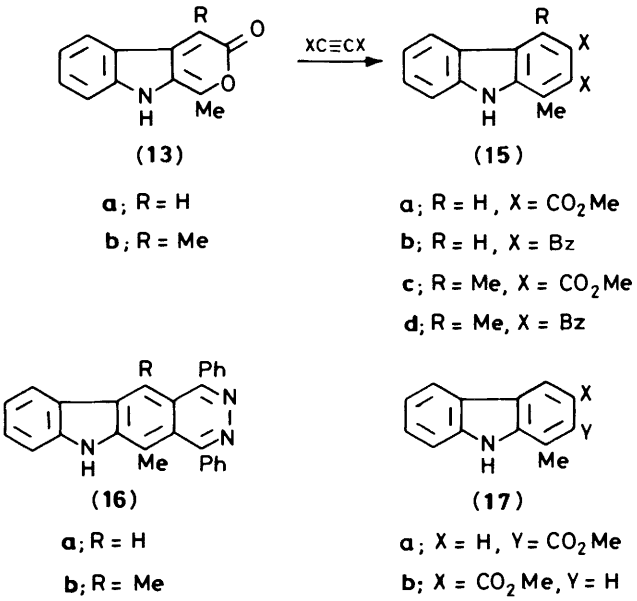
Although the Diels–Alder reactions of the pyranoindolone (**13a**) with olefinic dienophiles are already adequately described,[10] only one addition to an acetylenic dienophile was reported and this involved heating the pyrone (**13a**) in a large excess of dimethyl acetylenedicarboxylate (DMAD) without solvent. Therefore the preparation of carbazoles from pyranoindolones (**13**) and acetylenes was investigated in more detail.

The pyranoindolone (**13a**) reacted only slowly with DMAD in boiling toluene. After 7 h at reflux, thin layer chromatography indicated that although some of the required product was being formed, the reaction mixture consisted mainly of starting



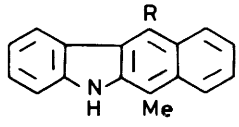
Scheme 1. *Reagents*: i, $(MeCO)_2O$–BF_3–Et_2O; ii, EtOH–heat; iii, NaOH–EtOH–H_2O; iv, $(MeCO)_2O$–heat

material. This slow reaction is ascribed to the poor solubility of the pyrone (**13a**) in toluene, even at reflux. No reaction at all occurred in refluxing tetrahydrofuran (THF) in which the pyrone is freely soluble, but in boiling bromobenzene the Diels–Alder reaction occurred readily to give, with concomitant loss of carbon dioxide, the carbazole (**15a**) in 81% yield. Reaction of the pyrone (**13a**) with dibenzoylacetylene (DBA) gave the carbazole (**15b**) (76%). Similarly, the dimethylpyranoindolone (**13b**) reacted with DMAD and DBA to give the carbazoles (**15c**) (67%) and (**15d**) (52%), respectively. The carbazole (**15d**) could not be obtained analytically pure, the analysis figures being consistent with the presence of 1 equiv. of water despite prolonged drying. Both carbazoles (**15b**) and (**15d**) reacted rapidly with hydrazine hydrate to give the yellow pyridazo-[4,5-*b*]carbazoles (**16a**) and (**16b**).



When the unsymmetrical acetylene, methyl propiolate, was used as the dienophile, Diels–Alder reaction with the pyrone (**13a**) gave a mixture of the carbazoles (**17a**) and (**17b**) in approximately equal amounts. This observed lack of regioselectivity with an acetylenic dienophile contrasts sharply with the very recent results of Narasimhan and Gokhale.[11] These workers report that the pyranoindolone (**13a**) reacts with olefinic dienophiles such as 2-chloroacrylonitrile in THF to give, in the presence of 2,4,6-trimethylpyridine, 3-cyano-1-methylcarbazole (82—85%) in a highly regioselective Diels–Alder reaction, although in neat 2,4,6-trimethylpyridine the reaction was unselective.

The pyranoindolones (**13**) are also suitable diene substrates for the highly reactive dienophile benzyne. Addition of benzenediazonium-2-carboxylate (**CAUTION!**) to a boiling 1,2-dichloroethane solution of the pyrone (**13a**) gave 6-methyl-5*H*-benzo[*b*]carbazole (**18a**) (44%). The same benzocarbazole (**18a**) was also obtained, although in lower yield, when the commercially available 2-(3,3-dimethyltriazen-1-yl)benzoic acid[13] was used as the benzyne precursor. The data obtained for compound (**18a**) (see the Experimental section) contrast with those previously reported[14] in that there are differences in melting point and the chemical shift of the methyl group in the ^1H n.m.r. spectrum. The structure of the present compound (**18a**) was supported by the nuclear Overhauser effect, in which pre-irradiation of the NH caused the expected strong enhancement of the methyl signal. The pyranoindolone (**13b**) reacted similarly with benzyne to give 6,11-dimethyl-5*H*-benzo[*b*]carbazole (**18b**) in yields of 31—38% depending on the benzyne precursor. Although the yields in the Diels–Alder reaction with benzyne are only moderate, the present method constitutes the shortest route to benzo[*b*]carbazoles, being just three steps from indole.



(**18**)

a; R = H

b; R = Me

In summary, pyrano[3,4-*b*]indol-3-ones, first described in 1964, are useful indole-2,3-quinodimethane equivalents which merit further attention.

Experimental

For general points see ref. 15.

1-*Methylpyrano*[3,4-b]*indol*-3-*one* (**13a**).—Prepared exactly as described in the literature[10] with the omission of the ethanol recrystallisation step, and had m.p. 260—262 °C (decomp.) [lit.,[10] m.p. 260 °C (decomp.)], $\nu_{max.}$(Nujol) 3 160br, 1 695, 1 605, and 1 565 cm^{-1}; δ [250 MHz; $(CD_3)_2SO$] 2.54 (3 H, s), 6.40 (1 H, s), 7.00 (1 H, ~t, *J* 8 Hz), 7.20 (1 H, d, *J* 8 Hz), 7.47 (1 H, ~t, *J* 8 Hz), 7.84 (1 H, d, *J* 8 Hz), and 10.26 (1 H, br); *m/z* 199 (M^+), 185, 171, 143, and 40 (base).

1,4-*Dimethylpyrano*[3,4-b]*indol*-3-*one* (**13b**).—Freshly distilled boron trifluoride–diethyl ether (1 ml) was added dropwise over 45 min to a stirred solution of 2-indol-3-ylpropionic acid[12] (1.00 g) in acetic anhydride (2.5 ml) at 0 °C. The mixture was stirred at 0 °C for a further 30 min, diluted with ether (10 ml), and the orange solid was filtered off. The solid was washed with ether (25 ml), aqueous sodium hydrogen carbonate (50 ml), and water (50 ml), and dried *in vacuo* for 15 h to give the *title compound* (**13b**) as a bright orange powder (0.49 g, 43%), m.p.

240—243 °C (decomp.), $\nu_{max.}$(Nujol) 3 150br, 1 690, 1 610, and 1 570 cm^{-1}; δ [250 MHz; $(CD_3)_2SO$] 2.36 (3 H, s), 2.48 (3 H, s), 7.04 (1 H, ~t, *J* 7 Hz), 7.21 (1 H, d, *J* 7 Hz), 7.50 (1 H, ~t, *J* 7 Hz), 7.97 (1 H, d, *J* 7 Hz), and 10.35 (1 H, br); *m/z* 213 (M^+), 211 (base), 183, 154, and 115.

Reaction of the Pyranoindolone (**13a**) *with DMAD.*—A mixture of the pyranoindolone (**13a**) (111 mg, 0.56 mmol) and DMAD (124 mg, 0.87 mmol) in bromobenzene (25 ml) was heated under reflux under nitrogen for 3 h. The solvent was evaporated to leave a solid which was recrystallised from chloroform–light petroleum to give dimethyl 1-methyl-9*H*-carbazole-2,3-dicarboxylate (**15a**) (135 mg, 81%), m.p. 184—185 °C (lit.,[10] m.p. 187 °C), $\nu_{max.}$(Nujol) 3 320, 1 725, and 1 695 cm^{-1}; δ (250 MHz; $CDCl_3$) 2.47 (3 H, s), 3.93 (3 H, s), 4.00 (3 H, s), 7.29 (1 H, m), 7.46 (2 H, m), 8.06 (1 H, d, *J* 6 Hz), 8.51 (1 H, br), and 8.56 (1 H, s); *m/z* 297 (M^+, base), 266, 207, and 179.

Reaction of the Pyranoindolone (**13a**) *with DBA.*—A mixture of the pyranoindolone (**13a**) (74 mg, 0.37 mmol) and DBA (86 mg, 0.37 mmol) in bromobenzene (20 ml) was heated under reflux under nitrogen for 5 h. The solvent was evaporated, and the residue chromatographed to give a solid which was recrystallised from toluene–hexane to give 2,3-*dibenzoyl*-1-*methyl*-9H-*carbazole* (**15b**) (109 mg, 76%) as pale yellow crystals, m.p. 221—222 °C (Found: C, 83.3; H, 4.9; N, 3.6. $C_{27}H_{19}NO_2$ requires C, 83.3; H, 4.9; N, 3.6%); $\nu_{max.}$(Nujol) 3 360br, 1 660, and 1 645 cm^{-1}; $\lambda_{max.}$(EtOH) 239sh (log ε 4.52), 246 (4.56), and 284 nm (4.48); δ (250 MHz; $CDCl_3$) 2.40 (3 H, s), 7.2—7.6 (9 H, m), 7.7—7.9 (4 H, m), 8.02 (1 H, d, *J* 7 Hz), 8.24 (1 H, s), and 8.73 (1 H, br); *m/z* 389 (M^+), 312, 284, 254, and 105.

Reactions of the Pyranoindolone (**13b**) *with DMAD.*—A mixture of the pyranoindolone (**13b**) (71 mg, 0.34 mmol) and DMAD (107 mg, 0.75 mmol) in bromobenzene (15 ml) was heated under reflux under nitrogen for 1.5 h. The solvent was evaporated, and the residue chromatographed to give a yellow solid which was recrystallised from chloroform–hexane to give *dimethyl* 1,4-*dimethyl*-9H-*carbazole*-2,3-*dicarboxylate* (**15c**) (70 mg, 67%) as pale yellow crystals, m.p. 151—153 °C (Found: C, 69.4; H, 5.5; N, 4.6. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%); $\nu_{max.}$(Nujol) 3 380 and 1 712 cm^{-1}; δ (250 MHz; $CDCl_3$) 2.56 (3 H, s), 2.86 (3 H, s), 3.91 (6 H, s), 7.27 (1 H, m), 7.46 (2 H, m), 8.17 (1 H, m), and 8.38 (1 H, br); *m/z* 311 (M^+, base), 280, 264, and 221.

Reaction of the Pyranoindolone (**13b**) *with DBA.*—A mixture of the pyranoindolone (**13b**) (72 mg, 0.34 mmol) and DBA (77 mg, 0.33 mmol) in bromobenzene (15 ml) was heated under reflux under nitrogen for 1 h. The solvent was evaporated and the residue chromatographed to give a yellow solid which was recrystallised from chloroform–hexane to give 2,3-*dibenzoyl*-1,4-*dimethyl*-9H-*carbazole* (**15d**) (69 mg, 52%) as pale yellow fluffy crystals, m.p. 224—225 °C (Found: C, 79.6; H, 5.2; N, 3.3. $C_{28}H_{21}NO_2 \cdot H_2O$ requires C, 79.8; H, 5.5; N, 3.3%); $\nu_{max.}$(Nujol) 3 350, 1 660, 1 650, and 1 595 cm^{-1}; $\lambda_{max.}$(EtOH) 244sh (log ε 4.63), 253 (4.66), and 290 nm (4.23); δ (250 MHz; $CDCl_3$) 2.34 (3 H, s), 2.67 (3 H, s), 7.36 (5 H, m), 7.50 (5 H, m), 7.73 (3 H, m), 8.21 (1 H, d, *J* 8.5 Hz), and 8.34 (1 H, br); *m/z* 403 (M^+), 402, 326, 283, 254, 105, and 77 (base).

Reaction of the Dibenzoylcarbazole (**15b**) *with Hydrazine.*—A mixture of the dibenzoylcarbazole (**15b**) (71 mg) and hydrazine hydrate (6 drops) in ethanol (4 ml) was heated on a steam-bath for 0.5 h. On cooling, bright yellow crystals of 5-*methyl*-1,4-*diphenyl*-6H-*pyridazo*[4,5-b]*carbazole* (**16a**) (53 mg, 80%) separated, m.p. >305 °C (Found: C, 84.2; H, 5.0; N, 10.9. $C_{27}H_{19}N_3$ requires C, 84.1; H, 5.0; N, 10.9%); $\nu_{max.}$(Nujol) 3 240br and 1 608 cm^{-1}; *m/z* 385 (M^+) and 384 (base).

Reaction of the Dibenzoylcarbazole (**15d**) *with Hydrazine.*—A mixture of the dibenzoylcarbazole (**15d**) (14 mg) and hydrazine hydrate (5 drops) in ethanol (3 ml) was heated on a steam-bath for 0.5 h. Concentration of the solution gave a yellow solid which was recrystallised from aqueous ethanol to give 5,11-*dimethyl*-1,4-*diphenyl*-6H-*pyridazo*[4,5-b]*carbazole* (**16b**) (6 mg, 43%), m.p. >300 °C (Found: C, 84.1; H, 5.35; N, 10.4. $C_{28}H_{21}N_3$ requires C, 84.2; H, 5.3; N, 10.5%); $\nu_{max.}$(Nujol) 3 340, 1 618 and 1 600 cm^{-1}; *m/z* 400, 399 (M^+, base), 398, 384, and 354.

Reaction of the Pyranoindolone (**13a**) *with Methyl Propiolate.*—A mixture of the pyranoindolone (**13a**) (151 mg, 0.76 mmol) and methyl propiolate (226 mg, 2.7 mmol) in bromobenzene (25 ml) was heated under reflux under nitrogen for 3 h. Further methyl propiolate (153 mg) was added and the refluxing continued for a further 2 h. The solvent was evaporated and the residue was chromatographed to give a 1:1 mixture of methyl 1-methyl-9*H*-carbazole-2-carboxylate (**17a**) and methyl 1-methyl-9*H*-carbazole-3-carboxylate (**17b**) as a pale yellow solid (152 mg, 84%); δ (250 MHz; $CDCl_3$) 2.58 (s), 2.84 (s), 3.95 (s), 3.97 (s), 7.27 (m), 7.46 (m), 7.82 (d, *J* 8.2 Hz), 7.93 (d, *J* 8.2 Hz), 8.10 (m), 8.24 (br), and 8.67 (s).

Reaction of the Pyranoindolone (**13a**) *with Benzyne.*—(*a*) *From benzenediazonium-2-carboxylate.* A 1,2-dichloroethane slurry of benzenediazonium-2-carboxylate[16] (**CAUTION!**) [from anthranilic acid (548 mg, 4 mmol)] was added in 5 portions over 20 min to a stirred refluxing solution of the pyranoindolone (**13a**) (288 mg, 1.45 mmol) in 1,2-dichloroethane (30 ml). The mixture was refluxed for a further 30 min, allowed to cool, and evaporated to dryness. The residue was chromatographed to give 6-*methyl*-5H-*benzo*[b]*carbazole* (**18a**) (148 mg, 44%), m.p. 158.5—160 °C (lit.,[14] 210—211 °C) (Found: C, 88.1; H, 5.6; N, 6.1. $C_{17}H_{13}N$ requires C, 88.3; H, 5.7; N, 6.1%); $\nu_{max.}$(Nujol) 3 420 and 1 615 cm^{-1}; $\lambda_{max.}$(EtOH) 233 (log ε 4.46), 266sh (4.71), 272 (4.47), 284sh (4.60), 298 (4.51), 322 (3.91), 337 (3.91), 383 (3.62), and 403 nm (3.66); δ (250 MHz; $CDCl_3$) 2.79 (3 H, s), 7.23 (1 H, m), 7.45 (4 H, m), 7.79 (1 H, br), 8.09 (3 H, m), and 8.41 (1 H, s); *m/z* 231 (M^+, base) and 230.

(*b*) *From* 2-(3,3-*dimethyltriazen*-1-*yl*)*benzoic acid.* A stirred mixture of the pyranoindolone (**13a**) (71 mg, 0.36 mmol) and 2-(3,3-dimethyltriazen-1-yl)benzoic acid (140 mg, 0.73 mmol) in bromobenzene (15 ml) was heated under reflux under nitrogen for 2 h. The solvent was evaporated and the residue chromatographed to give 6-methyl-5*H*-benzo[*b*]carbazole (**18a**) (20 mg, 24%).

Reaction of the Pyranoindolone (**13b**) *with Benzyne.*—(*a*) *From* 2-(3,3-*dimethyltriazen*-1-*yl*)*benzoic acid.* A stirred mixture of the pyranoindolone (**13b**) (70 mg, 0.33 mol) and 2-(3,3-dimethyltriazen-1-yl)benzoic acid (125 mg, 0.65 mmol) in bromobenzene (15 ml) was heated under reflux under nitrogen for 2 h. The solvent was evaporated and the residue chromatographed to give 6,11-dimethyl-5*H*-benzo[*b*]carbazole (**18b**) (25 mg, 31%), m.p. 206.5—210 °C (lit.,[14] 209—211 °C; lit.,[17] 211—212 °C) $\nu_{max.}$(Nujol) 3 420, 1 622, and 1 610 cm^{-1}; $\lambda_{max.}$(EtOH) 231 (log ε 4.34), 269 (4.69), 279sh (4.62) 298 (4.49), 322 (3.77), 337 (3.59), 383 (3.56), and 404 nm (3.62); δ (250 MHz; $CDCl_3$) 2.80 (3 H, s), 3.22 (3 H, s), 7.26 (1 H, m), 7.4—7.6 (4 H, m), 7.83 (1 H, br), 8.14 (1 H, d), and 8.35 (2 H, m); *m/z* 245 (M^+, base), 230, 165, 122, and 115.

(*b*) *From benzenediazonium-2-carboxylate.* A 1,2-dichloroethane slurry of benzenediazonium-2-carboxylate (**CAUTION!**) [from anthranilic acid (548 mg, 4 mmol)] was added in 4

portions over 10 min to a stirred refluxing solution of the pyranoindolone (**13b**) (80 mg, 0.37 mmol) in 1,2-dichloroethane (20 ml). The mixture was refluxed for a further 30 min, cooled, evaporated, and the residue chromatographed to give 6,11-dimethyl-5*H*-benzo[*b*]carbazole (**18b**) (35.5 mg, 38%).

References

1 Preliminary communication, C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 1984, 925.
2 E. R. Marinelli, *Tetrahedron Lett.*, 1982, **23**, 2745.
3 B. Saroja and P. C. Srinivasan, *Tetrahedron Lett.*, 1984, **25**, 5429.
4 P. Magnus, P. M. Cairns, and C. S. Kim, *Tetrahedron Lett.*, 1985, **26**, 1963; P. D. Magnus and N. L. Sear, *Tetrahedron*, 1984, **40**, 2795; P. Magnus, T. Gallagher, P. Brown, and P. Pappalardo, *Acc. Chem. Res.*, 1984, **17**, 35, and references therein.
5 W. M. Welch, *J. Org. Chem.*, 1976, **41**, 2031.
6 C.-K. Sha, K.-S. Chuang, and J.-J. Young, *J. Chem. Soc., Chem. Commun.*, 1984, 1552.
7 A. Shafiee and S. Sattari, *J. Heterocycl. Chem.*, 1982, **19**, 227.
8 M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, 1983, **24**, 5435; G. W. Gribble and M. G. Saulnier, *J. Chem. Soc., Chem. Commun.*, 1984, 168.
9 Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, 1984, **25**, 309.
10 H. Plieninger, W. Müller, and K. Weinerth, *Chem. Ber.*, 1964, **97**, 667.
11 N. S. Narasimhan and S. M. Gokhale, *J. Chem. Soc., Chem. Commun.*, 1985, 86.
12 H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, 1963, **28**, 1246.
13 J. Nakayama, O. Simamura, and M. Yoshida, *J. Chem. Soc., Chem. Commun.*, 1970, 1222.
14 S. Kano, E. Sugino, S. Shibuya, and S. Hibino, *J. Org. Chem.*, 1981, **46**, 2979.
15 C. J. Moody and J. G. Ward, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2895.
16 F. M. Logullo, A. H. Seitz, and L. Friedman, *Organic Synth.*, Coll. Vol 5, p. 54.
17 D. A. Taylor, M. M. Baradarani, S. J. Martinez, and J. A. Joule, *J. Chem. Res.*, 1979, (*S*), 387; (*M*) 4801.

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