Total synthesis of *cis*-clerodane diterpenoids: (−)-agelasine A and (+)-(3*R*,4*S*,5*R*,8*S*,9*R*,10*S*)-3,4-epoxyclerod-13-en-15,16-olide

Edward Piers,* M. Livain Breau, Yongxin Han, Guy L. Plourde and Wen-Lung Yeh
Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

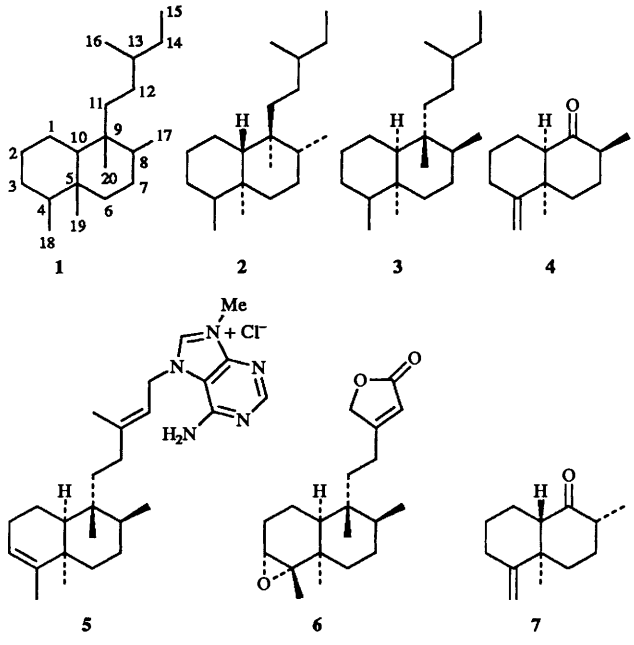
The preparation of the enantiomerically homogeneous bicyclic iodide **26** and its use as a key intermediate for the total syntheses of the *cis*-clerodane diterpenoids (−)-agelasine A **5** and (+)-(3*R*,4*S*,5*R*,8*S*,9*R*,10*S*)-3,4-epoxyclerod-13-en-15,16-olide **6** are described.

Members of the very large family of clerodane diterpenoids, which share the general carbon skeleton **1**, have been isolated from a wide range of terrestrial[1] and marine[2] organisms. Collectively, the relatively small number of clerodanes that have been tested exhibit a variety of biological activities, including antiviral, antibiotic, antitumour and insect antifeedant properties.[1,2] However, it appears that most of the clerodanes that have been isolated and structurally characterised have not yet been screened for biological activity.[1]

Structurally, the clerodanes may be divided into two subgroups, depending on whether the substituted bicyclo-[4.4.0]decane framework is *trans*- or *cis*-fused.[1] Most of the *trans*-clerodanes exhibit the relative configuration shown in formula **2**, while a majority of the *cis*-clerodanes display configurations at carbons 8, 9, 10 that are epimeric with those of **2** (see general formula **3**).[1,2]

The development of a general approach to the synthesis of both *trans*- and *cis*-clerodanes constitutes a current research program in our laboratories. Recent reports[3,4] have described, *inter alia*, the synthesis of the enantiomerically homogeneous *cis*-fused ketone **4** and the use of this substance as an effective intermediate for the total synthesis of two members of the *trans*-clerodane group of natural products. We now disclose that **4** can also serve as an efficacious synthetic precursor to *cis*-clerodanes. Explicitly, we describe the first total synthesis of (−)-agelasine A, a structurally novel natural product of mixed biogenesis† that possesses the absolute configuration portrayed in **5**, exhibits antimicrobial activity and strongly inhibits the activity of the enzyme Na,K-ATPase.[5,6] We also report the synthesis of the *cis*-clerodane (+)-**6**, which, apparently, is a diastereoisomer of a natural product isolated from *Ageratina saltillensis* (B. L. Robo) King and Robinson.[7]

Conversion of the ketone **4** into the bicyclic intermediate **26**‡ is summarised in Scheme 1. Since base-promoted equilibration of **4** provides nearly exclusively the diastereoisomeric ketone **7**,[3] it was necessary to effect a one-carbon homologation of **4** under conditions that would not cause epimerisation of one or both of the stereogenic centres adjacent to the carbonyl group. Fortunately, the reagent [$Me_3Si(Cl)CH$]Li **8**[8] served admirably in this regard. Reaction of **4** with **8** in tetrahydrofuran (THF) containing *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) produced, in 94% yield, the epoxide **9** as a 1:1 mixture of epimers.§ Although these diastereoisomers could be partially separated by radial chromatography on silica gel and were individually characterised, it was convenient to employ the mixture for the next conversion. Thus, sequential treatment of **9** with BF_3·Et_2O, MeOH and dilute hydrochloric acid provided the aldehydes **10** and **11** in isolated yields of 14 and 70%, respectively. Conversion of a mixture (ratio ~1:10)¶ of the latter substances into the corresponding oximes **12** and **13**, followed by dehydration[9] of these derivatives, afforded the epimeric nitriles **14** (minor) and **15** (major) in a combined yield of 93%. These diastereoisomers (mp 84–85 and 46–47 °C, respectively) could be separated by chromatography and were fully characterised.‖



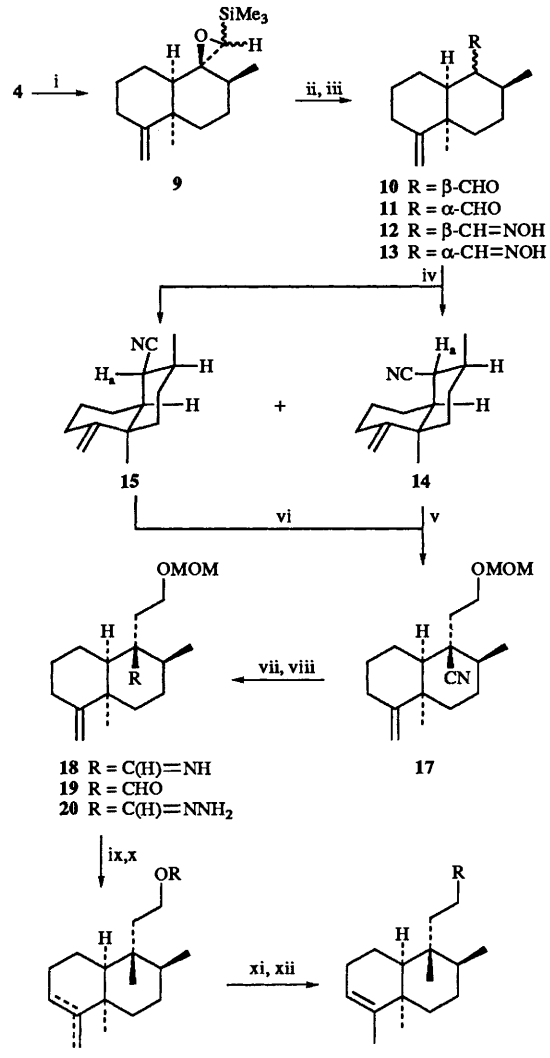
† Agelasine A, along with a number of other structurally interesting natural products, has been isolated from the Okinawan marine sponge *Agelas nakamurai* Hoshino.[5,6]

‡ All compounds reported herein exhibited spectra consistent with structural assignments and new compounds gave satisfactory elemental analyses.

§ For steric reasons, reagent **8** would be expected to approach the carbonyl group of **4** from the α (convex) face. Consequently, it is reasonable to conclude that the isomers of **9** are epimeric at the Me_3Si-bearing carbon.

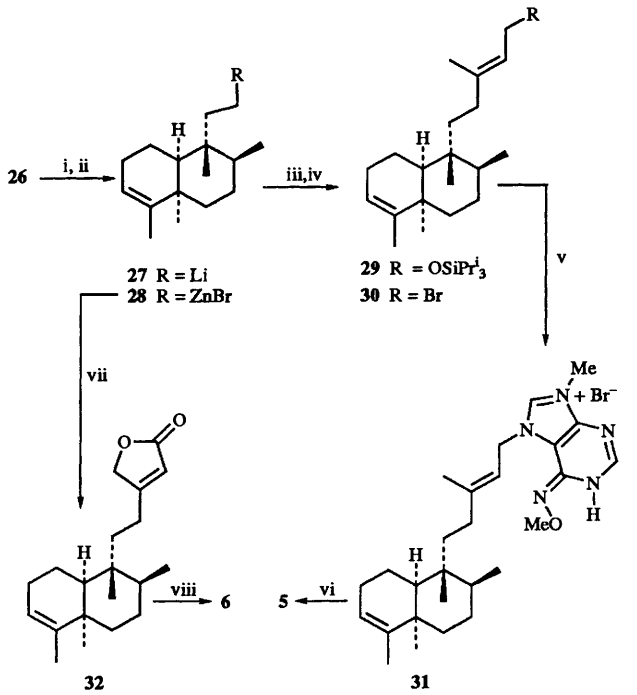
¶ The ratio of **10**:**11**, obtained from **9**, varied somewhat from experiment to experiment.

‖ The configurations of **14** and **15** at the cyano-bearing carbons were confirmed by ^1H NMR spectroscopy. In the spectra of these materials, the protons H_a give rise to signals at δ 2.61 (br dd, *J* 2, 2 Hz) and 2.23 (dd, *J* 12, 12 Hz), respectively.



Scheme 1 *Reagents and reaction conditions:* i, $[Me_3Si(Cl)CH]Li$ **8**, THF, TMEDA, −60 to −40 °C, 15 min, then warmed to 0 °C; NH_4Cl, H_2O (94%); ii, BF_3·Et_2O, CH_2Cl_2, −78 °C, 5 min, warmed to −20 °C, 10 min, recooled to −78 °C; MeOH, −78 °C to room temperature; 1 mol dm^{-3} hydrochloric acid, room temp., 15 min (84%); iii, H_2NOH·HCl, pyridine, *N*,*N*-dimethylformamide, 70 °C, 2 h (98%); iv, $SOCl_2$, 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2, room temp., 30 min (95%); v, LDA, THF, HMPA, 0 °C, 30 min; $ICH_2CH_2OCH_2OMe$ **16**, 0 °C, 30 min, room temp., 3.5 h (79%); vi, KDA, THF, −78 °C, 1 h, −50 °C, 2 h; **16**, −50 °C to room temp. (93%); vii, (**17**→**18**), Bu^i_2AlH, DME, 60 °C, 12 h; degassed water and then degassed 1 mol dm^{-3} hydrochloric acid to pH 4; viii, (**18**→**20**), H_2NNH_2 (excess), DEG, 120–140 °C, 4.5 h; ix, (**20**→**21**–**24**), KOH, DEG, 220–230 °C, 12 h, with distillation of excess of H_2NNH_2 (61% from **17**); x, (**21**, **22**→**23**, **24**), PPTS, Me_3COH, reflux, 4 h (84%); xi, (**23**, **24**→**25**), *p*-TsOH, $CHCl_3$, room temp., 10 h (91%); xii, (**25**→**26**), Ph_3P, I_2, imidazole, CH_2Cl_2, room temp., 7 h (97%)

Sequential treatment of the nitrile **14** with lithium diisopropylamide (LDA) and 1-iodo-2-(methoxymethoxy)ethane **16** in THF containing hexamethylphosphoramide (HMPA) provided **17**** in 79% yield. In contrast, a similar protocol



Scheme 2 *Reagents and reaction conditions:* i, (**26**→**27**), Bu^tLi, Et_2O, −78 °C to room temp.; ii, (**27**→**28**), $ZnBr_2$, THF–Et_2O, −78 °C to room temp.; iii, **33** [$Pd_2(dba)_3$], Ph_3As, THF–Et_2O, room temp., 36 h (73%); iv, (**29**→**30**), Ph_3PBr_2, CH_2Cl_2, room temp., 15 min; v, **34**, Bu_4NI, DMA, 60 °C, 3 h (47% from **29**); vi, Zn, HOAc, MeOH, H_2O, 60 °C, 14 h; NaCl, H_2O (88%); vii, **35**, as in iii, 27 h (51%); viii, MCPBA, CH_2Cl_2, 0 °C, 2 h (83%)

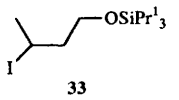
involving **15** as substrate resulted primarily in recovered starting material and produced **17** in only minor amounts. Further experimentation showed that removal of the sterically hindered proton H_a in **15** by LDA in THF–HMPA is a very sluggish process. Fortunately, use of the base prepared from Bu^tOK, Pr^i_2NH and BuLi [*i.e.* Pr^i_2NK (KDA)][10] gave much better results and provided the desired product **17** cleanly and efficiently (93%).

Conversion of the nitrile function in **17** into a methyl group was initiated by reduction with Bu^i_2AlH in 1,2-dimethoxyethane (DME). Although the resultant imine **18** could be hydrolysed ($MeCO_2H$, THF, water) to the corresponding aldehyde **19**, this conversion was slow and inefficient. Furthermore, Huang–Minlon reduction of **19** produced the required product **21** in poor yield. Happily, much improved results were obtained *via* a reaction sequence that by-passed the aldehyde **19**. Thus, reaction of the imine **18** with hydrazine in diethylene glycol (DEG), followed by direct treatment of the resultant hydrazone **20** with KOH at elevated temperatures, gave a mixture of products consisting of the isomeric MOM ethers **21** and **22** (ratio ~2:1, 50% yield), accompanied by the corresponding alcohols **23** and **24** (ratio ~2:1, 11%). Sequential treatment of this mixture with pyridinium toluene-*p*-sulfonate (PPTS) in *tert*-butyl alcohol (hydrolysis of the MOM ether function)[11] and anhydrous toluene-*p*-sulfonic acid (*p*-TsOH) in chloroform (isomerisation of the double bond) provided the olefinic alcohol **25**†† (mp 91–92 °C) in 76% overall yield. Conversion of **25** into the iodide **26** was straightforward.

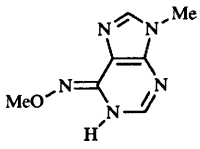
The syntheses of (−)-agelasine A **5** and the *cis*-clerodane **6**

** Alkylation of the anion derived from **14** (or **15**) would be expected to be highly stereoselective, with the alkylating agent approaching the anion from the sterically less encumbered α face.

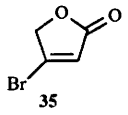
†† The racemic modification of this alcohol has been prepared previously[12,13] *via* a route very different from that employed in our work.



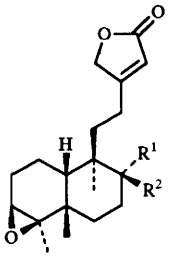
33



34



35



36 R^1 = Me, R^2 = H
37 R^1 = H, R^2 = Me

are outlined in Scheme 2. Subjection of **26** to lithium–iodine exchange,[14,15] followed by addition of a solution of $ZnBr_2$ in THF to the resultant lithio species **27**, gave the organozinc reagent **28**. Cross coupling of **28** with the vinyl iodide **33**,[4] catalysed by tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] in the presence of triphenylarsine,[16] provided the diene **29** (73% yield). Upon treatment with triphenylphosphine dibromide in CH_2Cl_2[17] **29** was converted directly into the allylic bromide **30**. Since the latter intermediate was found to be quite unstable, it was treated immediately after preparation with the adenine derivative **34**[18] in *N*,*N*-dimethylacetamide (DMA) in the presence of tetrabutylammonium iodide. Although the required product **31** (mp 158–160 °C, 47% yield) derived from this reaction was accompanied by an appreciable quantity (44%) of the substance resulting from alkylation of **34** at the methoxy-bearing nitrogen, these two materials could readily be separated by chromatography (silica gel).

Completion of the synthesis of (−)-agelasine A **5** required reductive removal of the methoxy group from **31**. In a paper describing a total synthesis of (−)-agelasine B, a *trans*-clerodane derivative, it was reported that a reduction of this type can be effected by use of zinc in aqueous acetic acid at 60 °C.[19] Since, in our work on (−)-agelasine B we were unable to achieve this reported result, an electrochemically based method was developed.[4] We now report that reductive conversion of **31** into (−)-**5** is conveniently and efficiently accomplished under carefully defined conditions involving treatment of the former substance with zinc (10 equiv.) in *aqueous methanol containing a small amount* (5 *equiv.*) *of glacial acetic acid.* Subsequent anion exchange and chromatographic purification provided synthetic (−)-agelasine A **5**, mp 169–171 °C, $[\alpha]_D^{26}$ (MeOH) −29.2.‡‡

Palladium(0)-catalysed cross coupling of the organozinc species **28** with the unsaturated bromo lactone **35**[20] provided the butenolide **32**. Treatment of **32** with *m*-chloroperbenzoic acid (MCPBA) resulted in the chemo- and stereo-selective§§ epoxidation of the cyclohexene double bond and afforded the *cis*-clerodane (+)-**6** {colourless oil, $[\alpha]_D^{24}$ (MeOH) +11.1} in 42% yield from **26**. The report by Fang *et al.*[7] describes, *inter alia*, the isolation and structural elucidation of a clerodane natural product whose constitution and relative stereochemistry was represented[7] by formula **36**. However, careful perusal of the ORTEP drawing[7] derived from an X-ray crystallographic study indicated that this substance possesses the structure (relative configuration) shown in **37**. Indeed, comparison of the spectral data of our synthetic (+)-**6** with those reported for the natural product isolated by Fang *et al.*[7] showed clearly that these compounds are not identical. To our knowledge, (+)-(3*R*,4*S*,5*R*,8*S*,9*R*,10*S*)-3,4-epoxyclerod-13-en-15,16-olide **6** (or its enantiomer) has not yet been isolated from natural sources.

In summary, we have developed a general synthetic approach to *cis*-clerodane diterpenoids and have described the first total syntheses of (−)-agelasine A **5** and the *cis*-clerodane (+)-**6**. Obviously, the key synthetic intermediate **26** could serve as an effective precursor to other *cis*-clerodanes as well.

Experimental

Conversion of the ketone 4 into the aldehydes 10 and 11

To a cold (−60 °C) stirred solution of $[Me_3Si(Cl)CH]Li$[8] (3 mmol) in dry THF (10 cm³, argon atmosphere) was added dropwise a solution of the ketone **4** (408 mg, 2.12 mmol) in dry THF (5 cm³). The mixture was stirred at −60 to −40 °C for 15 min and then was allowed to warm to 0 °C. Saturated aqueous NH_4Cl (10 cm³) was added to the mixture which was then extracted with Et_2O (3 × 20 cm³). The combined extracts were washed (brine), dried ($MgSO_4$), and concentrated. Radial chromatography [4 mm silica gel plate, light petroleum–Et_2O (99:1)] of the remaining material gave pure samples of the two epimers of **9** (50 mg, 8%, mp 71.5–72 °C; 154 mg, 26%, mp 74–75 °C) and these substances were individually characterised. Also obtained was a mixture of the two isomers (355 mg, 60%).

To a cold (−78 °C) stirred solution of **9** (843 mg, 3.03 mmol, ~1:1 mixture of epimers) in dry CH_2Cl_2 (20 cm³, argon atmosphere) was added dropwise BF_3·Et_2O (0.39 cm³, 3.18 mmol). The mixture was stirred at −78 °C for 5 min, warmed to −20 °C for 10 min and then was recooled to −78 °C. MeOH (0.8 cm³) was added to the mixture which was then allowed to warm to room temperature. After this, hydrochloric acid (1 mol dm⁻³; 10 cm³) was added to the mixture which was then stirred vigorously for 15 min. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 10 cm³) and the combined extracts were washed with saturated aqueous Na_2CO_3 (15 cm³), dried ($MgSO_4$) and concentrated. Radial chromatography [2 mm silica gel plate, light petroleum–Et_2O (98:2)] of the residue gave, in order of elution, the epimeric aldehydes **11** (440 mg, 70%, colourless oil) and **10** (85 mg, 14%, colourless oil).

Compound **11**: $[\alpha]_D^{26}$ +20.1¶¶ (*c* 1.25, MeOH); δ_H(400 MHz, $CDCl_3$) 9.33 (1 H, d, *J* 6), 4.82 (1 H, br s), 4.65 (1 H, br s), 2.37–2.27 (1 H, m), 2.16–2.02 (3 H, m), 1.94–1.85 (1 H, m), 1.73–1.22 (8 H, m), 1.15 (3 H, s) and 0.82 (3 H, d, *J* 6.5); δ_C(50.3 MHz, $CDCl_3$) 206.1, 149.9, 109.0, 56.6, 42.6, 38.8, 36.9, 33.0, 32.5, 29.8, 29.7, 24.7, 21.1 and 20.3; ν_{max}(neat)/cm⁻¹ 1724 and 1638 (Found: C, 81.25; H, 10.7. $C_{14}H_{22}O$ requires C, 81.49; H, 10.75%).

Compound **10**: $[\alpha]_D^{23}$ +24.1 (*c* 3.81, MeOH); δ_H(400 MHz, $CDCl_3$) 10.07 (1 H, d, *J* 5), 4.84 (1 H, br s), 4.78 (1 H, br s), 2.44–2.18 (4 H, m), 2.05–1.92 (2 H, m), 1.86 (1 H, dd, *J* 9, 5), 1.75–1.30 (6 H, m), 1.20 (3 H, s) and 0.93 (3 H, d, *J* 7); δ_C(50.3 MHz, $CDCl_3$) 203.9, 153.7, 107.3, 59.1, 46.7, 39.0, 35.2, 33.9, 32.4, 28.7, 27.6, 26.4, 24.0 and 19.5; ν_{max}(neat)/cm⁻¹ 1709 and 1636 (Found: C, 81.2; H, 10.7. $C_{14}H_{22}O$ requires C, 81.49; H, 10.75%).

Acknowledgements

We thank NSERC of Canada for a Postdoctoral Fellowship (to M. L. B.) and Merck Frosst Canada Inc. and NSERC of Canada for financial support.

‡‡ The ^1H and ^{13}C NMR spectral data of this material agreed very well with the data recorded in the literature for the natural product.[5,6]

§§ The peroxy acid would be expected to approach the double bond from the sterically more open convex face of the bicyclic system.

¶¶ [α] Values quoted as 10^{-1} deg cm² g⁻¹ and *J* values as Hz.

References

1 A. T. Merritt and S. V. Ley, *Nat. Prod. Rep.*, 1992, **9**, 243.
2 D. J. Faulkner, *Nat. Prod. Rep.*, 1984, **1**, 251; 1984, **1**, 551; 1986, **3**, 1; 1987, **4**, 539; 1988, **5**, 613; 1990, **7**, 269; 1991, **8**, 97; 1992, **9**, 323; 1993, **10**, 497; 1994, **11**, 355.
3 E. Piers and J. Roberge, *Tetrahedron Lett.*, 1991, **32**, 5219.
4 E. Piers and J. Roberge, *Tetrahedron Lett.*, 1992, **33**, 6923.
5 H. Nakamura, H. Wu, Y. Ohizumi and Y. Hirata, *Tetrahedron Lett.*, 1984, **25**, 2989.
6 H. Wu, H. Nakamura, J. Kobayashi, M. Kobayashi, Y. Ohizumi and Y. Hirata, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2495.
7 N. Fang, S. Yu, T. J. Mabry, K. A. Abboud and S. H. Simonsen, *Phytochemistry*, 1988, **27**, 3187.
8 C. Burford, F. Cooke, G. Roy and P. Magnus, *Tetrahedron*, 1983, **39**, 867.
9 A. Arrieta and C. Palomo, *Synthesis*, 1983, 472.
10 S. Raucher and G. A. Koolpe, *J. Org. Chem.*, 1978, **43**, 3794.
11 H. Monti, G. Léandri, M. Klos-Ringuet and C. Corriol, *Synth. Commun.*, 1983, **13**, 1021.
12 T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Monden and H. Iio, *J. Chem. Soc., Chem. Commun.*, 1983, 1516.
13 T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Monden and H. Iio, *Tetrahedron*, 1988, **44**, 6607.
14 W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, 1990, **55**, 5404.
15 E. Negishi, D. R. Swanson and C. J. Rousset, *J. Org. Chem.*, 1990, **55**, 5406.
16 V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585.
17 J. M. Aizpurua, F. P. Cossio and C. Palomo, *J. Org. Chem.*, 1986, **51**, 4941.
18 T. Fujii, T. Saito, T. Sakuma, M. Minami and I. Inoue, *Heterocycles*, 1981, **16**, 215.
19 H. Iio, K. Asao and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, 1985, 774.
20 G. Jas, *Synthesis*, 1991, 965.

Paper 4/07668K
Received 15*th December* 1994
Accepted 27*th February* 1995