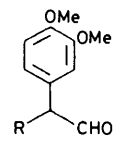
Applications of Substituted Arylacetaldehydes in the Total Synthesis of Mesembrane Alkaloids. Part 2.[1] An Alternative Synthesis of (±)-Sceletium Alkaloid A_4

By **Craig P. Forbes** * and **George L. Wenteler**, Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

The substituted arylacetaldehydes (±)-2-(3,4-dimethoxyphenyl)pent-4-enal (1c) is shown to serve as a precursor in the total synthesis of the mesembrane alkaloid (±)-sceletium alkaloid A_4.

SUBSTITUTED arylacetaldehydes of the type (1) have been shown to be useful precursors in the total synthesis of *seco*-mesembrane alkaloids.[1,2] It has also been shown that a judicious choice of substituents in the *seco*-precursor can lead to alkaloids of the mesembrane series. For example (±)-joubertinamine (2) was converted into (±)-mesembranone (3) by oxidative ring closure.[3] The latter principle has been demonstrated during a projected synthesis of the *seco*-mesembrane alkaloid tortuosamine [2,4] (4) and has resulted in an alternative synthesis of Sceletium alkaloid A_4 (5).[5] The key step in this synthetic pathway involves the formation of the 1-methyl-2,3,3a,4,5-9b-hexahydro-1*H*-pyrrolo-[3,2-*c*]quinoline ring system of (5) from the amino-substituted diprotected 1,5-dioxo-system (6). This

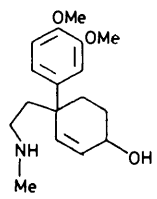


(1)

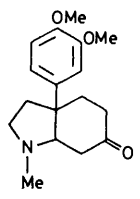
a; R = H

b; R = $CH_2CH_2NMe_2$

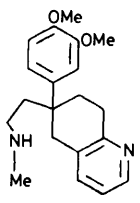
c; R = $CH_2CH{=}CH_2$



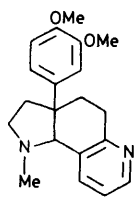
(2)



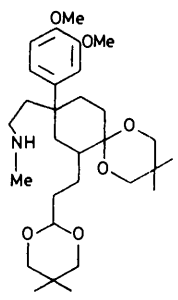
(3)



(4)



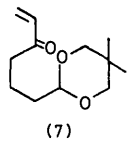
(5)



(6)

transformation involves two dehydrative ring closures followed by dehydrogenation of the resulting dihydropyridine [6] (Scheme).

Robinson annulation of (±)-2-(3,4-dimethoxyphenyl)-pent-4-enal (1c) (prepared by the mono-allylation of 3,4-dimethoxyphenylethanenitrile in tetrahydrofuran–hexamethylphosphoramide at −78 °C, followed by reduction with di-isobutylaluminium hydride in dry toluene) with 6-(5,5-dimethyl-1,3-dioxan-2-yl)hex-1-en-3-one (7) [5,7] in refluxing aqueous ethanolic KOH gave



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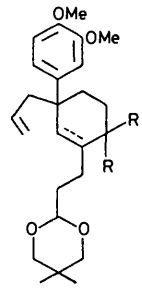
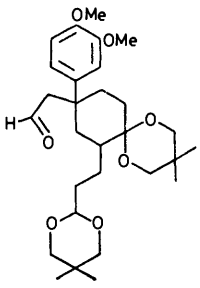


(8)

a; R,R = O, αβ-unsaturation

b; R,R = O, αβ-saturation

c; R,R = $OCH_2CMe_2CH_2O$, αβ-saturation



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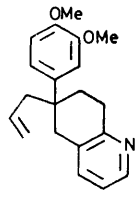
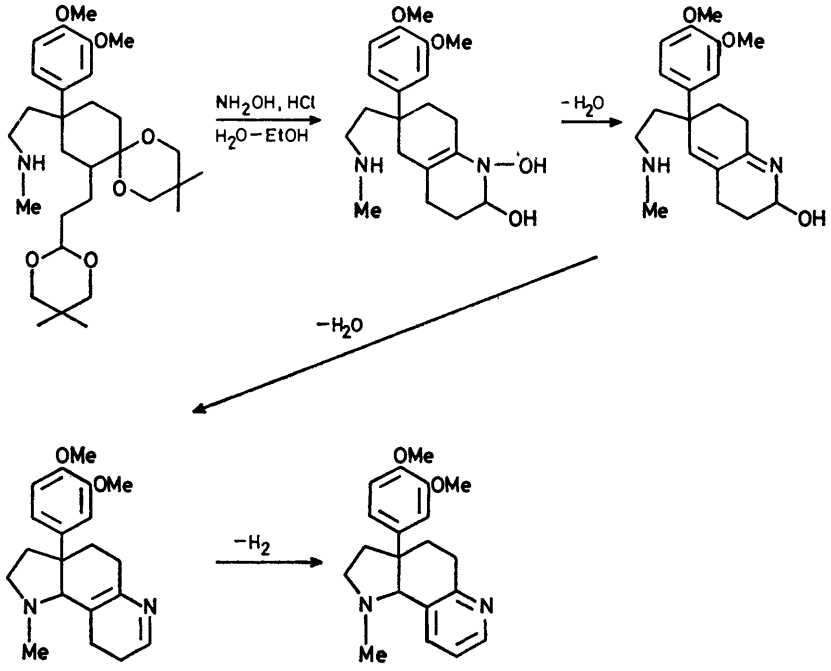


(10)

the monoprotected 1,5-dioxo-compound (8a) in 35% overall yield. Lithium–liquid ammonia reduction of (8a) followed by quenching of the reaction with a large excess of anhydrous sodium benzoate before work-up produced the saturated ketone (8b) in 90% yield. Protection of the oxo-function of (8b) by acetal formation with 2,2-dimethylpropane-1,3-diol to give the bis-acetal (8c) followed by cleavage of the allyl side-chain with osmium tetraoxide and sodium metaperiodate in ether–water [8] gave the aldehyde (9) which was readily converted into the amine (6) by reductive amination with methylamine hydrochloride and sodium cyanoborohydride in dry methanol in 35% overall yield.[9,†] Treat-

† The alternative route in our original projected total synthesis of (±)-tortuosamine involving initial formation of the pyridine ring and subsequent elaboration of the allyl side-chain was unsuccessful. Construction of the pyridine ring by treatment of (8b) with an excess of hydroxylamine hydrochloride in refluxing aqueous ethanol to produce the allyl-substituted pyridine (10) proceeds smoothly in 45% yield.[5,10] However, oxidative cleavage of the allyl side-chain, required for construction of the amino-alkyl substituent, failed. Both ozone (MeOH, Me_2S, −78 °C) and osmium tetraoxide–sodium metaperiodate in ether–water produced complex mixtures containing little or none of the desired aldehyde. [The failure to produce the desired compound by ozonolysis is not entirely unexpected (see ref. 11).]



SCHEME

ment of (6) with a ten-fold excess of hydroxylamine hydrochloride in refluxing 88% aqueous ethanol [5,10] for 36 h produced (±)-Sceletium alkaloid A_4 in 54% yield.* The overall yield of (±)-Sceletium alkaloid A_4 based on (±)-α-allyl-3,4-dimethoxyphenylethanal (1a) was 6%.

EXPERIMENTAL

I.r. spectra were obtained on a Unicam SP 200 or Beckman 4250 spectrophotometer; ^{1}H n.m.r. spectra were determined with a Varian HA 100 spectrometer with tetramethylsilane as internal reference. Mass spectra and accurate mass measurements were made on a Du Pont 21.492 B mass spectrometer. Melting points were obtained on a Kofler micro hot stage. Solvents were dried and purified by standard procedures.

(±)-α-*Allyl*-3,4-*dimethoxyphenylethanenitrile*.— Di-isopropylamine (13.7 g, 136 mmol) was added dropwise to butyl-lithium (7.6 g, 119 mmol) in hexane (60 ml) at 0 °C under dry nitrogen. The resulting mixture of lithium di-isopropylamide was cooled to −78 °C, diluted with tetrahydrofuran (THF) (100 ml), and treated dropwise with hexamethylphosphoramide (20 g, 123 mmol) in THF (60 ml) and then with 3,4-dimethoxyphenylethanenitrile (20 g, 113 mmol) in THF (60 ml) over 30 min. The mixture was stirred for 1 h at −78 °C and the resulting anion solution was treated with 1-bromoprop-2-ene (14.4 g, 119 mmol) in THF (20 ml) dropwise during 30 min. The mixture was stirred for 30 min, allowed to warm to room temperature, quenched with 5% aqueous HCl (200 ml), and extracted with chloroform (4 × 50 ml). The organic phase was washed with 5% aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and concentrated to an oil (30.1 g). Chromatography over silica gel (900 g) and elution with hexane–ether (4 : 1 v/v) produced starting material (5.3 g, 27%); αα-diallyl-3,4-dimethoxyphenylethanenitrile (200 mg), $\nu_{max.}$ (neat) 3 070, 2 940, 2 850, 2 270, 1 640, 1 525, 1 475, 1 450, 1 260, 1 035, 1 150, 930, and 770 cm^{-1}, δ(CCl_4) 2.61 (d, 4 H, *J* 7 Hz, 2 CH_2CH=CH_2), 3.77 and 3.78 (2 s, 6 H, 2 OCH_3), 4.98—6.00 (2 overlapping ABM systems, 2 CH=CH_2), and 6.82 (m, 3 H, aromatic), M^+ (70 eV) 257 (9%); and (±)-α-*allyl*-3,4-*dimethoxyphenylethanenitrile* (12.1 g, 49%), m.p. 58—60 °C (from ether–hexane), $\nu_{max.}$ (CCl_4) 3 080, 3 000, 2 940, 2 830, 2 270, 1 645, 1 535, 1 480, 1 455, 1 432, 1 280, 1 162, 1 150, 1 040, and 938 cm^{-1}, δ(CCl_4) 2.52 (t, 2 H, *J* 7 Hz, CH_2CH=CH_2), 3.65 (t, 1 H, 7 Hz, ArC*H*), 3.75 and 3.78 (2 s, 6 H, 2 OCH_3), 4.97—6.05 (3 H, ABM, CH=CH_2), and 6.74 (s, 3 H, aromatic), M^+ (70 eV) 217 (20%) (Found: C, 71.9; H, 6.8; N, 6.45%. $C_{13}H_{15}O_2N$ requires C, 71.86; H, 6.96; N, 6.44%).

(±)-2-(3,4-*Dimethoxyphenyl*)*penten*-4-*al* (1c).—(±)-α-Allyl-3,4-dimethoxyphenylethanenitrile (3.04 g, 14 mmol) was dissolved in dry toluene (50 ml) and cooled to 10 °C under dry nitrogen. The solution was treated dropwise with di-isobutylaluminium hydride (11 ml; 1.43M-solution in toluene; 1.1 mol equiv.) during 10 min. The resulting mixture was stirred for 1 h, treated with 5% aqueous H_2SO_4 (200 ml), and stirred for a further 2 h. The mixture was extracted with ether (3 × 70 ml) and the organic phase was washed with saturated brine (1 × 100 ml), dried ($MgSO_4$), and concentrated to produce the homogeneous (±)-*aldehyde* (1c) (2.56 g, 85%), $\nu_{max.}$ (neat) 2 580, 2 565, 1 712, 1 520, 1 465, 1 255, 1 135, and 1 025 cm^{-1}, δ(CCl_4) 2.18—2.93 (m, 2 H, CH_2), 3.52 (t with fine splitting by the aldehydic proton, 1 H, *J* 7.0 and 1.6 Hz, *H*C–CHO), 3.76 (s, 6 H, 2 OCH_3), 4.80—5.90 (ABM, 3 H, CH=CH_2), 6.55—6.85 (m, 3 H, aromatic), and 9.52 (d, 1 H, *J* 1.6 Hz, CHO). A small sample gave a *semicarbazone*, m.p. 113—116 °C (from light petroleum–acetone) (Found: C, 60.6; H, 6.7; N, 15.2%. $C_{14}N_{19}N_3O_3$ requires C, 60.63; H, 6.90; N, 15.15%).

* This transformation proved to be sensitive to the amount of water present and would not, for example, proceed in 96% aqueous ethanol, conditions which have previously been successfully used for construction of the pyridine ring.[5,10]

(±)-4-*Allyl*-4-(3,4-*dimethoxyphenyl*)-2-[2-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*ethyl*]*cyclohex*-2-*en*-1-*one* (8a).—A mixture of the aldehyde (1c) (682 mg, 3.1 mmol) and the vinyl ketone (7) (659 mg, 3.1 mmol) in 96% aqueous ethanol (60 ml) was added dropwise to a refluxing solution of KOH (400 mg, 7.1 mmol) in 96% aqueous ethanol (60 ml) during 10 min under nitrogen. The mixture was refluxed for a further 5 min and ethanol and water were removed azeotropically with benzene under reduced pressure. The residue, chromatographed over alumina, (50 g) and eluted with increasing volumes of ether in hexane gave the homogenous *annulation product* (8a) (1.13 g, 85%), $\nu_{max.}$ (neat) 3 005, 2 900, 2 800, 1 670, 1 580, 1 250, 1 130, 1 030, and 790 cm^{-1}; $\delta(CCl_4)$ 0.70 (s, 3 H, CH_3), 1.05—2.85 (m, 13 H, including a CH_3 singlet at δ 1.17), 3.18—3.73 (m, 4 H, $-CH_2CMe_2CH_2-$), 3.80 (s, 6 H, 2 OCH_3), 4.36 (t, 1 H, acetal proton), 4.90—5.85 (m, 4 H, ABM with overlapping singlet, $CH=CH_2$ and CH=CR−CO), and 6.55—6.95 (m, 3 H, aromatic) (Found: C, 71.9; H, 8.4%; M^+, 414.241 4. $C_{25}H_{34}O_5$ requires C, 72.44; H, 8.27%; *M*, 414.240 6).

(±)-*Birch-reduction Product* (8b).—The annulation product (8a) (870 mg, 2.1 mmol) in dry THF (25 ml) was added dropwise to liquid ammonia (380 ml; freshly distilled from sodium) containing lithium (145 mg, 21 mmol, 10 mol equiv.). The mixture was stirred for 3 h and treated with dry sodium benzoate (4 g). The resulting bright yellow solution was stirred for 5 min and treated with ammonium chloride (1 g). The colourless solution so formed was evaporated under a stream of nitrogen and the residue was partitioned between ether (100 ml) and water (50 ml). The layers were separated and the aqueous phase was re-extracted with ether (25 ml). The combined organic phase was dried ($MgSO_4$) and concentrated to produce the *oxo-acetal* (8b) (790 mg, 90%), $\nu_{max.}$ (neat) 2 940, 1 708, 1 588, 1 523, 1 479, 1 260, 1 138, 1 112, 1 025, and 920 cm^{-1}, $\delta(CCl_4)$ * 0.68 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.05—2.85 (m, 13 H), 3.20—3.72 (distorted AB q, 4 H, $-OCH_2CMe_2-CH_2O-$), 3.72—3.89 (2 d, 6 H, 2 OCH_3), 4.30 (distorted t, 1 H, acetal), 4.72—5.68 (two overlapping ABM systems, 3 H, $CH=CH_2$), and 6.65—7.00 (m, 3 H, aromatic) (Found: C, 71.95; H, 8.65%; M^+, 416.256 4. $C_{25}H_{36}O_5$ requires C, 72.09; H, 8.71%; *M*, 416.256 3).

(±)-4-*Allyl*-4-(3,4-*dimethoxyphenyl*)-2-[2-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*ethyl*]*cyclohexan*-1-*one* 2,2-*Dimethyltrimethylene Acetal* (8c).—The oxo-acetal (8b) (700 mg, 1.68 mmol) was dissolved in dry toluene (250 ml), treated with 2,2-dimethylpropane-1,3-diol (182 mg, 1.75 mmol) and toluene-*p*-sulphonic acid (33 mg, 0.175 mmol, 0.1 mol equiv.), and refluxed for 18 h. Further catalyst (0.1 mol equiv.) was added after 5 h. The condensed solvent was continuously passed through a thimble containing powdered calcium hydride. The solution was cooled, washed with 5% aqueous sodium hydrogencarbonate (50 ml), dried ($MgSO_4$), and concentrated to produce the crude bis-acetal (8c) (830 mg, 98%). Chromatography over neutral grade III alumina with ether gave the pure bis-acetal (700 mg, 82%) as an oil; $\nu_{max.}$ (neat) 2 930, 1 585, 1 520, 1 468, 1 250, 1 018, and 1 021 cm^{-1}; $\delta(CCl_4)$ * 0.69 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.00—2.70 (m, 13 H), 3.10—3.70 (m, 8 H, 2 $-OCH_2CMe_2CH_2O-$), 3.79 and 3.81 (2 s, 6 H, 2 OCH_3), 4.20—4.37 (m, 1 H, acetal), 4.65—5.58 (distorted ABM system, 3 H, $CH=CH_2$), and 6.73 (s, 3 H, aromatic) (Found: C, 71.25; H, 9.65%; M^+, 502.333 7. $C_{30}H_{46}O_6$ requires C, 71.68; H, 9.22%; *M*, 502.329 2).

(±)-4-(3,4-*Dimethoxyphenyl*)-2-[2-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*ethyl*]-4-*formylmethylcyclohexan*-1-*one* 2,2-*Dimethyltrimethylene Acetal* (9).—The bis-acetal (8c) (150 mg, 0.29 mmol) was partitioned between ether (25 ml) and water (25 ml) and treated with osmium tetraoxide (20 mg, 0.08 mmol, 0.27 mol equiv.). The mixture was vigorously stirred for 10 min and treated with sodium metaperiodate (3.2 g, 15 mmol, 51 mol equiv.) in portions during 20 min. The mixture was stirred for 18 h, the ether layer was separated, and the aqueous phase was re-extracted with ether (2 × 15 ml). The combined ether phases were dried ($MgSO_4$) and concentrated to give the crude aldehyde (9) (176 mg). Chromatography over neutral grade III alumina with pentane–ethyl acetate (1 : 1) v/v produced the homogeneous *aldehyde* (127 mg, 84%); $\nu_{max.}$ ($CHCl_3$) 2 940, 1 712, 1 590, 1 523, 1 470, 1 256, 1 120, and 1 025; $\delta(CCl_4)$ * 0.68 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.00—2.80 (m, 13 H), 3.15—3.70 (m, 8 H, $-OCH_2CMe_2CH_2O-$), 3.79 and 3.81 (2 s, 6 H, 2 OCH_3), 4.20—4.40 (m, 1 H, acetal), 6.65—6.98 (m, 3 H, aromatic), and 9.25—9.37 (m, 1 H, aldehyde) (Found: C, 68.75; H, 8.7%; M^+, 504.309 2. $C_{29}H_{44}O_7$ requires C, 69.02; H, 8.79%; *M*, 504.308 5).

(±)-4-(3,4-*Dimethoxyphenyl*)-2-[2-(5,5-*dimethyl*-1,3-*dioxan*-2-*yl*)*ethyl*]-4-(2-*methylaminoethyl*)*cyclohexan*-1-*one* 2,2-*Dimethyltrimethylene Acetal* (6).—The aldehyde (9) (150 mg, 0.29 mmol) and dry methylamine hydrochloride (182 mg, 2.69 mmol, 9.2 mol equiv.) were dissolved in anhydrous methanol (25 ml) and treated with sodium cyanoborohydride (23 mg, 0.36 mmol 1.24 mol equiv.). The mixture was stirred at room temperature for 1 h, treated with sodium carbonate (280 mg), and refluxed for 30 min. The mixture was cooled, filtered, and concentrated. The residue was chromatographed over neutral grade III alumina and eluted with increasing proportions of chloroform in ether to give the homogeneous *amine* (6) (77 mg, 51%), $\nu_{max.}$ ($CHCl_3$) 3 080, 3 020, 1 590, 1 515, 1 465, 1 235, 1 090, and 995 cm^{-1}; $\delta(CCl_4)$ * 0.67 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.00—2.75 (m, 18 H, including an NCH_3 singlet at δ 2.20), 3.04—3.70 (m, 8 H, $-OCH_2CMe_2CH_2O-$), 3.77 and 3.78 (2 s, 6 H, 2 OCH_3), 4.20—4.40 (m, 1 H, acetal), and 6.65—6.85 (m, 3 H, aromatic) (Found: C, 69.2; H, 9.4; N, 2.7%; M^+, 519.351 2. $C_{30}H_{49}NO_6$ requires C, 69.33; H, 9.50; N, 2.69%; *M*, 519.355 7).

(±)-*Sceletium Alkaloid* A_4 (5).—The amine (6) (60 mg, 0.11 mmol) was dissolved in 88% aqueous ethanol (25 ml), treated with hydroxylamine hydrochloride (80 mg, 1.1 mmol, 10 mol equiv.), and refluxed for 36 h. The mixture was basified with KOH (400 mg) in ethanol (4 ml). Ethanol and water were removed azeotropically under reduced pressure with benzene. The residue was filtered through neutral grade III alumina with ether to yield crude (±)-Sceletium alkaloid A_4 (5) (20 mg, 54%) as an oil which crystallised from ether. Recrystallisation from ethyl acetate produced prisms, m.p. 153—156 °C (lit.,[12] 153.5—154.5 °C), undepressed on admixture with an authentic specimen, identical (i.r., ^1H n.m.r., t.l.c., mass spectrum) with an authentic specimen (Found: *m/e* 325.189 9. $C_{20}H_{26}N_2O_2$ requires *M* + 1, 325.191 5).

(±)-6-*Allyl*-6-(3,4-*dimethoxyphenyl*)-5,6,7,8-*tetrahydroquinoline* (10).—The oxo-acetal (8b) (500 mg, 1.2 mmol) was dissolved in 96% aqueous ethanol (150 ml), treated with hydroxylamine hydrochloride (417 mg; 6.0 mmol, 5 mol

* The ^1H n.m.r. spectrum of this compound consisted of two overlapping spectra due to the presence of a pair of diastereoisomeric racemates.

equiv.) and the mixture was refluxed under nitrogen for 22 h. The solution was cooled, basified with 0.4M-KOH (12 ml), and azeotroped to dryness under vacuum with benzene. The residue, chromatographed over neutral grade III alumina and eluted with 1 : 1 v/v benzene–ethyl acetate, produced the *allyl-substituted pyridine* (10) (167 mg, 45%), $\nu_{max.}$ (neat) 2 930, 1 590, 1 525, 1 455, 1 250, 1 145, and 1 030 cm^{-1}, $\delta(CCl_4)$ 1.15—3.30 (m, 8 H, 4 CH_2), 3.68 (s, 6 H, 2 OCH_3), 4.70—5.75 (ABM, 3 H, $CH{=}CH_2$), 6.55—6.73 (m, 3 H, aromatic), 6.91 (dd, 1 H, J 4.4 and 4.8 Hz, H_M of AMX), 7.30 (d with fine splitting, 1 H, J 8 Hz, H_A of AMX), and 8.20 (d with fine splitting, 1 H, J 4.2 Hz, H_X of AMX) (Found: C, 77.6; H, 7.4; N, 4.4%; M^+, 309.172 6. $C_{20}H_{23}NO_2$ requires C, 77.63; H, 7.49; N, 4.53%; M, 309.172 9).

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REFERENCES

[1] Part 1, C. P. Forbes, W. J. Schoeman, H. F. Strauss, E. M. M. Venter, G. L. Wenteler, and A. Wiechers, *J.C.S. Perkin I*, 1980, 906.

[2] P. W. Jeffs, T. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, 1974, **39**, 2703.

[3] K. Psotta and A. Wiechers, *Tetrahedron*, 1979, **35**, 255 and references cited therein.

[4] F. O. Snyckers, F. Strelow, and A. Wiechers, *Chem. Comm.*, 1971, 1467.

[5] C. P. Forbes, G. L. Wenteler, and A. Wiechers, *Tetrahedron*, 1978, **34**, 487 and references cited therein.

[6] U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.

[7] C. P. Forbes, G. L. Wenteler, and A. Wiechers, *J.C.S. Perkin I*, 1977, 2353.

[8] R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.

[9] R. F. Borch, M. D. Bernstein, and D. H. Durst, *J. Amer. Chem. Soc.*, 1971, **93**, 2897.

[10] R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, 1975, **40**, 3495.

[11] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, 1963, **19**, 247.

[12] P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Comm.*, 1971, 1466.