Search for New Membrane-active Substances: Synthesis of Tropan-3-ols with Alkyl, Alkenyl and Alkenynyl Groups at the Bridgehead†

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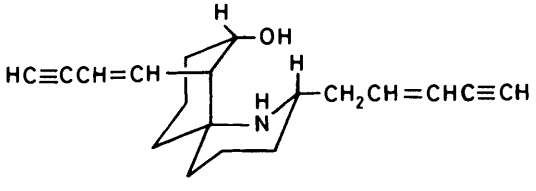
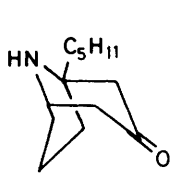
The synthesis of tropan-3-ols with alkyl, alkenyl, and alkynyl groups at the bridgehead is described. The new compounds have been considered as new membrane-active substances that would serve as model compounds for histrionicotoxin (**1**). Application of the Noyori route to 2-substituted pyrroles was unsuccessful. In order to avoid difficulties in obtaining individual long-chain 4-keto aldehydes for the Robinson condensation of each new model compound a key tropane intermediate (**8**) was prepared instead. The first attempts to extend the chains of the mesyl ester of the diol (**8b**) and iodomethyltropanol (**9b**) by Grignard type coupling failed. Therefore we embarked on a Wittig reaction of the tropane-1-carbaldehyde (**11**) synthesized in high yield from the diol (**8**). Indeed, both pent-1-enyl- and pentyltropanols, (**12**) and (**13**) were obtained. Coupling with an acetylenic phosphorane led to the pent-1-enynyltropanol (**14**). A further new key compound, namely 3β-acetoxytropan-1-ylacetaldehyde (**15**) was also synthesized as a precursor to conjugated tropanyl enynes which would more closely resemble the natural product (**1**).

Histrionicotoxin (**1**) has been used as a probe in binding studies at the acetylcholine receptor and its ionic channel.[1] The natural product has not been synthesized but perhydrohistrionicotoxin is available by synthesis[2] and in view of its physiological activity, comparable to compound (**1**), most recent bioassays were performed with the saturated species. Another structural variation of (**1**) suggested by Witkop[3] was based on the steric resemblance or rather on similar interprosthetic distances of granatanol {azabicyclo[3.3.1]nonan-3-ol} with the 1-azaspiro-[5.5]undecane skeleton of (**1**). Indeed, adaline, an alkaloid, 1-pentylnorgranatan-3-one (**2**) and dihydroadaline were active, both of which are available by synthesis.[4] A further suggestion[5] for exploring structure–activity relationships involved the preparation of 1-alkyl- and 1,5-dialkyl-nortropanols (**3**). The simplest representative of this group, 1-methyltropan-3-one was obtained from levulinaldehyde by the Robinson route by Blount and Robinson[6] in good yield. Unfortunately, generalization of the method to higher homologues seemed to be difficult, owing to the problems in synthesizing the key intermediates and to the diminished reactivity of long-chain 4-keto aldehydes. Therefore a more intricate study seemed desirable.



(**1**)



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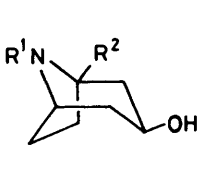
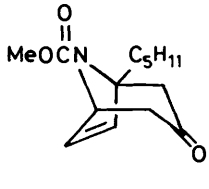


(**3**) a; R^1 = Me; R^2 = n-C_5H_{11}
b; R^1 = H; R^2 = n-C_5H_{11}



(**4**)

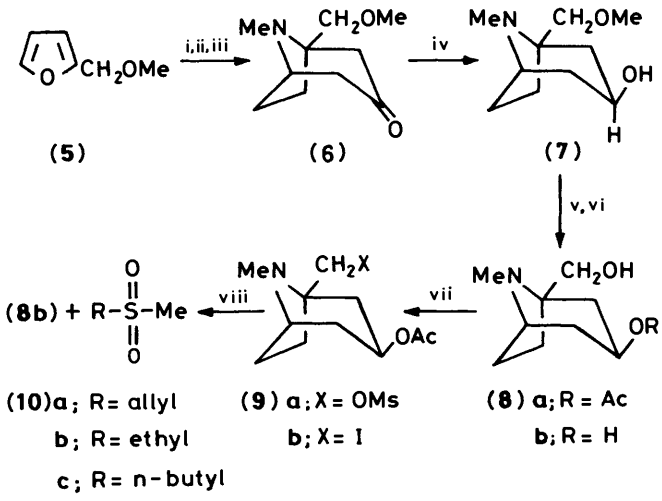
Results and Discussion

The method of Noyori *et al.*[7] *i.e.* the coupling of *N*-methoxycarbonylpyrrole with tetrabromoacetone in the presence of nonacarbonyldi-iron to trop-6-en-3-one was appealing in view of the easy access of 2-alkyl- and 2,5-dialkyl-*N*-methoxycarbonylpyrroles, provided their reactivity would prove to be adequate. Although, *N*-methoxycarbonyl-2-pentylpyrrole reacted under the Noyori conditions,[8] isolation and purification of *N*-methoxycarbonyl-1-pentyltrop-6-en-3-one (**4**) was difficult.[9] Since these problems proved insurmountable in larger batches, the experiments were discontinued.

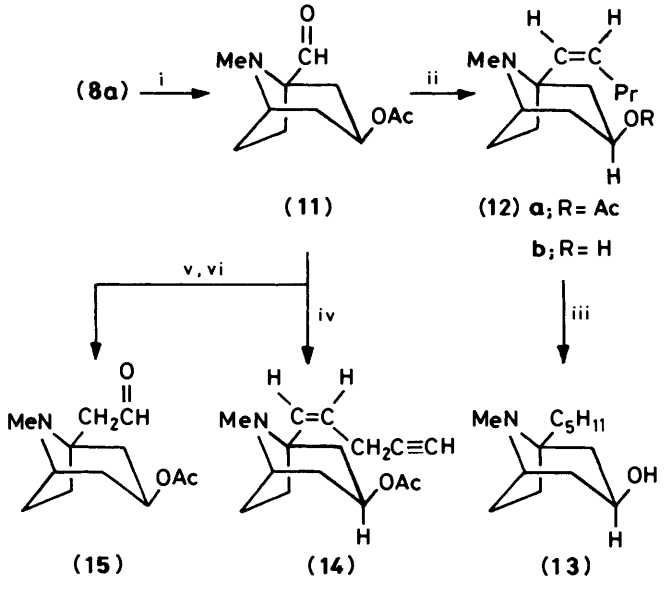
After several failures with other methods, we returned to the Robinson route. This time, however, the synthesis was aimed at a key tropane intermediate with a substituent in position 1 which, in turn, could be converted into different alkyl, or alkenyl groups. Thus the cumbersome preparation of different keto aldehydes could be avoided.

(±)-1-Methoxymethyltropan-3-one (**6**) obtained by Kebrle and Karrer[10] from methyl furfuryl ether (**5**) was selected for this role (see Scheme 1). The yields of the Clauson-Kaas[11] methoxylation of compound (**5**), and in the Robinson condensation[12] were improved. Furthermore, the hydrogenation of the dihydrofuran to the tetrahydrofuran was successfully achieved under atmospheric pressure instead of high pressure.[10] The overall yield was thus 55—60%. Reduction of the ketone (**6**) with sodium and ethanol in boiling toluene[13] gave a 90% yield of (±)-1-methoxymethyltropan-3β-ol (**7**) indicating a high degree of thermodynamic stereocontrol. All derivatives prepared from compound (**6**) were racemates. The β-configuration of the hydroxy group was established by ^{1}H n.m.r. spectroscopy. First-order analysis of the multiplet of δ 4.1 gave $J_{2ax.,3}$ and $J_{2eq.,3}$ as 10.2 and 6.6 Hz, respectively. The hydroxy group was then blocked by acetylation and the methyl ether group was cleaved. A number of ether-splitting reagents, *e.g.* triphenylphosphine dibromide[14] and trimethylsilyl chloride[15] failed to react. However, boron tribromide[16] in chloroform gave, upon work-up, 1-hydroxymethyltropan-3β-yl acetate (**8a**)

† Portions of this work were presented in August 1984 at the 188th National Meeting of the American Chemical Society [see 'Abstracts of Papers,' 188th National Meeting of the American Chemical Society, Philadelphia, PA, 1984]. Taken in part from the Ph.D dissertation of Ramalinga Dharanipragada to West Virginia University, 1985.



Scheme 1. *Reagents:* i, Br_2–MeOH; ii, Ni–H_2; iii, $(CO_2HCH_2)_2CO$–$MeNH_2$·HCl–sodium citrate; iv, Na–EtOH; v, Ac_2O–AcCl–DMPA; vi, BBr_3; vii, $MeSO_2Cl$–2,6-dimethylpyridine; viii, RMgBr–CuI or R_2CuLi



Scheme 2. *Reagents:* i, DMSO–$COCl_2$, −40 °C–*N*-methylpiperidine, room temp.; ii, Ph_3P=CHPr; iii, H_2–Ni; iv, Ph_3P=$CHCH_2C$≡CH; v, Ph_3P=CHOMe; vi, BBr_3

quantitatively. The next step was the conversion of the hydroxy group into a better leaving group to be followed by coupling with a C-nucleophile. This task appears to be simple except that the system was of the neopentyl type. Thus, some difficulties could be foreseen and indeed, thionyl chloride failed to give the chloromethyl derivative. Mesyl chloride however, in the presence of 2,6-dimethylpyridine gave a crystalline methanesulphonyl ester (**9a**). The sulphonate group was not displaced when treated with sodium methoxide in methanol, only transesterification of the 3β-acetate taking place. However, treatment with lithium aluminium hydride caused hydrogenolysis to 1-methyltropan-3β-ol[6] to occur, as expected.

Next, the coupling reaction was attempted using different organomagnesium[17] and cuprate[18] reagents. Unfortunately, allylmagnesium bromide–copper iodide gave allyl methyl sulphone (**10a**), besides 1-hydroxymethyltropan-3β-ol (**8b**) and ethyl- and butyl-magnesium bromides reacted in the same way. Primary toluene-*p*-sulphonates are known to couple smoothly with lithium diorganocuprates.[19] The formation of a dialkyl ether as a by-product was explained by a similar reaction. Earlier, Meyers isolated complex sulphones from the action of butyl toluene-*p*-sulphonate upon a lithium dihydro-oxazine.[20] The analogy is not perfect, for in our case no ditropanyl ether was formed. We tried to overcome the attack of the carbanion on the sulphur of the methanesulphonate by converting the methanesulphonate ester into the 1-iodomethyltropanol, first by sodium iodide. When that reagent failed to work, magnesium iodide was used and thus 1-iodomethyltropan-3β-yl acetate (**9b**) was obtained in high yield without the skeletal rearrangement that might be expected[21] of a neopentyl system. Unfortunately, the iodide (**9b**) then failed to undergo a coupling reaction with a variety of carbon nucleophiles [allyl-, butyl-magnesium bromide in the presence of copper(I) iodide] so this approach was abandoned.

Our next synthetic plan involved oxidation of the dihydroxy monoacetate (**8a**) to the aldehyde (**11**), followed by chain extension using the Wittig reaction (see Scheme 2). The primary alcohol (**8a**) proved to be quite resistant towards chromium(VI) reagents, *e.g.* pyridinium dichromate,[22] or chlorochromate,[23] alone or over crushed molecular sieves,[24] or alumina,[25] Collins reagent[26] *etc.* Manganese dioxide[27] oxidized the *N*-methyl group to a formyl group while leaving the hydroxymethyl function intact. Fortunately, dimethyl sulphoxide in combination with DCC and trifluoroacetic acid gave the 3β-acetoxytropane-1-carbaldehyde (**11**) in 40% yield. The ^1H n.m.r. spectrum showed a singlet at δ 9.5 for the aldehyde proton and the i.r. spectrum (film) showed strong absorption at 1 720 cm^{-1}. The Moffatt oxidation[28] was further refined and yields up to 50% were achieved by using 2,3-dichloropropionic acid instead of trifluoroacetic acid. Finally, an almost quantitative yield of compound (**11**) was attained by using oxalyl chloride[29] combined with dimethyl sulphoxide.

Once the key intermediate 3β-acetoxytropane-1-carbaldehyde (**11**) was obtained we were able to attempt the chain extension by the Wittig reaction. Reaction with butylidenetriphenylphosphorane gave, upon work-up, 1-pent-2-enyltropan-3β-yl acetate (**12a**). The mass spectrum indicated an M^+ ion at 251 as expected for the olefinic product. The i.r. spectrum lacked the *trans*-alkene absorption at 965 cm^{-1} but had a strong peak at 675 cm^{-1} for the out-of-plane vibration of a cis-alkene bond. The ^1H n.m.r. spectrum indicated the presence of a pair of alkene protons at δ 5.2 (sharp d) and δ 5.4 (pair of doublets); the lower field proton shows a coupling constant J 6 Hz, which corroborates the exclusive *cis* stereochemistry at the double bond. This observation is in line with the rule[30] that hindered aldehydes give predominantly *cis*-alkenes in the Wittig reaction. The acetylated alkene (**12a**) underwent methanolysis in the presence of potassium carbonate to give (±)-pent-1-enyltropan-3β-ol (**12b**). Hydrogenation of the latter over Raney nickel under 1 atm led to 1-pentyltropan-3β-ol (**13**). Thus, two out of the projected 1-alkyl- and alkenyl-tropanols have been synthesized.

Application of further, olefinic and acetylenic phosphoranes is expected to widen the series of tropanols (**12**), (**13**) we wish to synthesize. As the next step, the aldehyde (**11**) reacted with but-3-ynylidenetriphenylphosphorane (prepared from 4-bromobut-1-yne[31]) to give 1-pent-1-en-4-ynyl-3β-acetoxytropane (**14**). The mass spectrum showed the M^+ ion at 247 and the i.r. spectrum indicated terminal acetylene (3 300 cm^{-1}) and acetate (1 720 cm^{-1}) functionalities. The ^1H n.m.r. signals at δ 5.5 (J 11 Hz) corresponds to *cis* vinylic protons and that at δ 2.2 indicated the presence of a terminal acetylenic proton.

In order to further expand the series of 1-alkyl, alkenyl, and alkenynyl tropan-3-ols, the homologation of the tropane-1-carbaldehyde to the tropan-1-ylacetaldehyde as a second, new

key compound was undertaken. The aldehyde (**15**) was synthesized in 20% yield from the aldehyde (**11**) by Wittig reaction with methoxymethylenetriphenylphosphorane[32] and subsequent cleavage of the resulting enol ether with boron tribromide. Studies on improving the yields of this reaction and application of this 3β-acetoxytropan-1-ylacetaldehyde for the preparation of a wide range of alk-1-enynyltropanols are in progress.

In addition to the preparation of the tertiary amines (**12**)—(**15**) we are planning to synthesize the 1-substituted nortropanols for biological screening. Such model compounds would be structurally closer to histrionicotoxin than the tertiary amines. Preliminary screening of compounds (**12**) and (**13**) is already in progress.

Experimental

Melting points were determined on a Mel-Temp apparatus and are uncorrected. I.r. spectra were recorded on Beckman IR8 and Beckman IR10 spectrophotometers. ^{1}H N.m.r. spectra were recorded on a Varian EM-360 (60 MHz) spectrometer using $SiMe_4$ as an internal standard. ^{13}C N.m.r. were recorded on a Varian CFT-20 (20 MHz) spectrometer, using tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan 4021 mass spectrometer with an INCOS data system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. T.l.c. was performed on 100-μm-thick precoated silica gel sheets by Eastman. For column chromatography, Merck silica gel 60 (230—400 mesh) was used as the adsorbent.

Furfuryl Methyl Ether (**5**).—Furfuryl alcohol (225 ml, 2.6 mol) and methyl iodide (162 ml, 2.6 mol) were stirred and cooled in an ice–salt bath to −10 °C. To this mixture, finely powdered potassium hydroxide pellets (148 g, 2.6 mol) were added in small portions below 25 °C. When all the potassium hydroxide had been added, the mixture was stirred for a further 6 h at 20 °C after which time, ice-cold water (200 ml) was added and the layers were separated. The product was extracted with ether (900 ml), and the ethereal extracts dried (Na_2SO_4) and evaporated. Distillation of the residual oil at 1 atm (b.p. 130—134 °C) gave furfuryl methyl ether (**5**) (192 g, 66%) as a colourless liquid; $\nu_{max.}$(film) 3 100, 3 000, 1 600, 1 500, 1 450, 1 350, 1 150, 1 000, 950, and 750 cm^{-1}; δ 3.25 (s, 3 H, CH_2OMe), 4.3 (s, 2 H, CH_2OMe), 6.3 (s, 2 H), and 7.4 (s, 1 H).

2,5-*Dimethoxy*-2-*methoxymethyl*-2,5-*dihydrofuran*.—The procedure by Kebrle and Karrer[10] has been modified for larger scale work. In a four-necked 1-l reaction vessel (equipped with a mechanical stirrer, low-temperature thermometer, drying tube filled with Drierite and a dropping funnel) absolute methanol (400 ml), dry benzene (100 ml), anhydrous sodium carbonate (208 g, 1.96 mol) and 2-methoxymethylfuran (100 ml, 0.892 mol) were cooled to −15 °C. To this was added methanolic bromine [prepared by the dropwise addition of bromine (47.4 ml, 0.892 mol) to absolute methanol (47.4 ml, 0.892 mol) below −10 °C.]. during *ca.* 2 h. The mixture was stirred for a further 5 h at −10 °C when anhydrous sodium sulphate (50 g) was added, the cooling bath removed, and the mixture stirred for 0.5 h at room temperature. The salts were filtered off and washed with dry ether and benzene. The filtrate was stirred with anhydrous potassium carbonate (50 g) for 8 h after which it was filtered and the filtrate evaporated; anhydrous ether (1 l) was added to the residue until no more solids precipitated. The mixture was filtered and evaporated to give a brownish oil which was distilled at 0.1 mmHg (b.p. 45—50 °C) to give a diastereoisomeric mixture of (±)-2,5-dimethoxy-2-methoxymethyl-2,5-dihydrofuran as a colourless oil (111.6 g, 72%); $\nu_{max.}$(film) 3 000, 1 640 (C=C), 1 450, 1 350, 850, and 750 cm^{-1}; δ_H 3.2 (s, 2 H), 3.5—3.8 (several singlets, 9 H, OMe), 5.6 (s, 1 H), and 5.9—6.2 (m, 2 H, C=CH).

(±)-2,5-*Dimethoxy*-2-*methoxymethyltetrahydrofuran*.—Distilled 2,5-dimethoxy-2-methoxymethyldihydrofuran (35 g, 0.201 mol) was dissolved in absolute ethanol (100 ml) in a Pyrex hydrogenation bottle. Raney nickel[11b] W-2 (20 g) was added and the compound was hydrogenated at 2 atm until the calculated amount of hydrogen was consumed (within 15 min). The catalyst was filtered off and the solvent evaporated. Distillation of the residual oil (b.p. 45—48 °C at 0.1 mmHg) gave the expected cyclic diacetal of 5-methoxy-4-oxopentanal (32 g, 90%); $\nu_{max.}$(film): 3 000, 1 450, 1 350, 850, and 720 cm^{-1}; δ 1.9—2.0 (m, 4 H), 3.1—3.3 (m, 11 H, OMe, OCH_2), and 5.0 (m, 1 H, acetal H).

(±)-1-*Methoxymethyltropan*-3-*one* (**6**).—2,5-Dimethoxy-2-methoxymethyltetrahydrofuran (100 g, *ca.* 0.568 mol) in 1M-HCl (500 ml) was kept at 80 °C for 20 min. The mixture was rapidly cooled in ice and the keto aldehyde was used immediately in the Robinson condensation.

In a 3-necked 2 l flask equipped with a mechanical stirrer, reflux condenser, and addition funnel, acetonedicarboxylic acid (133 g, 0.91 mol) was added to the solution of the keto aldehyde and the solution adjusted to pH 5 by the careful addition of solid potassium carbonate with cooling. Aqueous sodium citrate (12%; 600 ml) followed by methylammonium chloride (80 g) were then added and the total volume of the solution was adjusted to 1 000 ml with water. The resulting solution was stirred for 40 h at room temperature when the release of carbon dioxide ceased. The final pH was adjusted to 10 with solid potassium carbonate.

The mixture was then heated to 60 °C and cooled. The solution was concentrated to 300 ml and extracted with ether in a continuous liquid-liquid extractor for 24 h. The ethereal extract was dried (Na_2SO_4) and the solvent removed by evaporation. The resulting crude oil was distilled at 0.4 mmHg, b.p. 65—70 °C, to give a light yellowish viscous oil (62 g, 60%), $\nu_{max.}$(film) 3 000, 1 710 (br, C=O), 1 450, 1 410, 1 350, 1 200, 1 150, and 100; δ 1.5—2.9 (m, 11 H), and 3.5 (m, 6 H, CH_2OMe, 1-H). Kebrle and Karrer[10] reported 40% yield when no citrate buffer was used.

For analytical purposes the *picrate* was prepared from the distilled tropanone (**6**) and a saturated alcholic solution of picric acid (5 ml). Washing with absolute methanol and drying gave a product, m.p. 170—171 °C (Found: C, 46.7; H, 4.9; N, 13.5. $C_{16}H_{20}N_4O_9$ requires C, 46.6; H, 4.8; N, 13.5%).

(±)-1-*Methoxymethylpseudotropine* (**7**).—Sodium (23 g, 1 mol) was powdered by refluxing in dry toluene (500 ml). A mixture of 1-methoxymethyltropinone (85 g, 0.4645 mol), absolute ethanol (21 ml, 0.58 mol) and dry toluene (100 ml) was added dropwise at such a rate as to maintain reflux. After 12 h the mixture was cooled, and absolute ethanol (200 ml) was added, followed by water (200 ml). The organic and aqueous layers were separated and the lower layer was extracted with ether (3 × 200 ml). The combined organic layers were washed with saturated aqueous sodium chloride dried (Na_2SO_4) filtered, and the solvents evaporated. The residual brownish oil was distilled at 0.4 mmHg (b.p. 110—112 °C) to give 1-methoxymethyltropan-3β-ol (75 g, 90%); $\nu_{max.}$(film) 3 400, 1 450, 1 250, 1 100, 1 050, and 900 cm^{-1}; δ 1.5—1.8 (m, 8 H), 2.4 (s, 3 H, NMe), 3.3 (m, 6 H), and 4.1 (m, 1 H, $J_{2,3}$ 10.2 and 6.6 Hz 3-H).

Dry hydrogen chloride was bubbled through a solution of compound (**7**) (10 g, 0.054 mol) in absolute ethanol (200 ml), until pH 2—3 was reached. The ethanol was evaporated on a

rotatory evaporator and the resulting solid was dried *in vacuo* for 6 h (11.9 g, 100% m.p. 177—179 °C) (Found: C, 54.2; H, 9.0; Cl, 16.0; N, 6.2; O, 14.6. $C_{10}H_{20}ClNO_2$ requires C, 54.7; H, 9.0; Cl, 16.0; N, 6.3; O, 14.4%).

(±)-3β-*Acetoxy*-1-*methoxymethyltropane Hydrochloride*.—1-Methoxymethylpseudotropine hydrochloride (7 g, 31.8 mol) was dissolved in freshly distilled acetic anhydride (125 ml) and acetyl chloride (50 ml). To this was added 4-dimethylaminopyridine (DMAP) (0.20 g, 2 mmol) and the mixture refluxed overnight. The acetyl chloride and acetic anhydride were removed by evaporation. To the brown oily residue, acetone (20 ml) was added. White crystals (7 g, 85%) were obtained, and washed with cold acetone (5 ml), m.p. 153—156 °C (Found: C, 54.5; H, 8.5; Cl, 13.45; N, 5.25; O, 17.9. $C_{12}H_{22}ClNO_3$ requires C, 54.6; H, 8.3; Cl, 13.4; N, 5.3; O, 18.2%); $\nu_{max.}$ 2 900, 1 720, 1 370, 1 240, and 1 020 cm^{-1}; δ 2.2—2.5 (m, 11 H), 2.9 (s, 3 H, NMe), 3.3 (s, 5 H, OMe, OCH_2), and 4.9—5.2 (m, 1 H, 3β-H).

(±)-3β-*Acetoxy*-1-*hydroxymethyltropane* (**8a**).—In a 3-necked 500-ml flask equipped with a mechanical stirrer, addition funnel with septum, reflux condenser with a nitrogen in/outlet, (±)-3β-acetoxy-1-methoxymethyltropane hydrochloride (5 g, 19 mmol) was dissolved in dry chloroform (200 ml). A 1M-solution of boron tribromide (100 ml, 99 mmol) in methylene chloride were transferred *via* a cannula to the addition funnel by pressure of nitrogen. It was added dropwise from the addition funnel to the reaction mixture at 20 °C. The mixture was stirred for 16 h after which time it was poured onto crushed ice, and the solution adjusted to pH 11 using concentrated ammonium hydroxide solution. The organic and aqueous layers were separated. The aqueous layer was extracted with chloroform (2 × 100 ml), dried (Na_2SO_4), filtered, and the solvent evaporated. The crude primary alcohol (**8a**) (4 g, 99%) was pure enough for subsequent oxidation to the aldehyde (**11**) and was used without any further purification. $\nu_{max.}$ 3 400br (OH), 2 950, 1 720s (OCOMe), 1 450, 1 300, 1 200, 1 020, 900, and 800 cm^{-1}; δ 1.5—1.9 (m, 8 H), 2.1 (s, 3 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H), 3.5 (s, 2 H, CH_2OH), 4.4 (s, 1 H, exchangeable with D_2O), and 5.1 (m, 1 H).

(±)-3β-*Acetoxy*-1-*methylsulphonyloxymethyltropane* (**9a**).—In a 100 ml-flask 3β-acetoxy-1-hydroxymethyltropane (**8**) (4.88 g, 23 mmol) freshly distilled methanesulphonyl chloride (1.9 ml, 25 mmol), and 2,6-dimethylpyridine (2.7 ml) were dissolved in dry chloroform (50 ml). The mixture was stirred at 20 °C for 24 h and then poured onto water. Dilute ammonium hydroxide was added until pH = 10 was reached. The chloroform layer was washed with water and saturated aqueous sodium chloride, dried (Na_2SO_4), and filtered, and the solvent was evaporated. Trituration of the residue with light petroleum and carbon tetrachloride resulted in the precipitation of the sulphonate (**9a**) as a solid (3.5 g, 53%), m.p. 89—91 °C (Found: C, 49.5; H, 7.3; N, 4.8; S, 10.7. $C_{12}H_{21}NO_5S$ requires C, 49.4; H, 7.25; N, 4.8; S, 10.9%); $\nu_{max.}$ 3 000, 1 720, 1 360, and 1 170 cm^{-1}; δ 1.5—2.0 (m, 8 H), 2.3 (s, 3 H, NMe), 3.4 (m, 1 H, 5-H), 4.2 (s, 2 H), 3.1 (s, 3 H, SO_3Me), 2.0 (s, 3 H), and 5.2 (q, 1H).

Conversion of the Acetoxy Methanesulphonate (**9a**) *into* 1-*Methylsulphonyloxymethyltropan*-3β-*ol*.—The sulphonate (**9a**) (0.52 g, 1.8 mmol) and sodium methoxide (0.24 g, 4.5 mol) were dissolved in absolute methanol (100 ml). The mixture was stirred at 20 °C for 6 h, and then refluxed for 1 h. Methanol was evaporated on a rotary evaporator and the residue was poured into ice–water. The mixture was extracted with ether, and the extract dried (Na_2SO_4) and evaporated to give the crude deacetylated product (0.3 g, 76%), δ 1.3—1.8 (m, 8 H), 2.3 (s, 3 H, NMe), 3.1 (s, 3 H, SO_3Me), 3.3 (m, 1 H), and 4.2 (m, 3 H).

Hydrogenolysis of the Sulphonate (**9a**) *to* 1-*Methyltropan*-3β-*ol*.—A solution of the sulphonate (**9a**) (0.5 g, 1.7 mmol) in anhydrous ether (50 ml) was added to lithium aluminium hydride (0.2 g, 5.1 mmol) at 0 °C. The mixture was stirred, then warmed to 20 °C, and finally refluxed for 3 h. The reaction mixture was then poured onto ice–water and dilute hydrochloric acid was added to bring the pH to 3. The aqueous layer was made alkaline (pH = 10) with dilute ammonium hydroxide and extracted with ether. The extract was washed with water, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give an oil (0.29 g, 74%) which was shown by ^1H n.m.r. to be 1-methyltropan-3β-ol, δ 1.1 (s, 3 H, 1-Me), 1.5—2.0 (m, 8 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H, 5-H), and 3.9 (m, 1 H), (3β-H).

Attempts to Couple 3β-*Acetoxy*-1-*mesyloxymethyltropane* (**9a**) *with Grignard Reagents in the Presence of a Copper Catalyst*.—(*a*) The sulphonate (**9a**) (1.89 g, 7.6 mmol) was dissolved in dry tetrahydrofuran (50 ml) and copper(I) iodide (0.72 g). At −30 °C, 1M-allylmagnesium bromide (38 ml, 72 mmol) in tetrahydrofuran was added dropwise and the mixture was stirred at −30 °C for 1 h, and then at 20 °C for a further 16 h. Work-up by the addition of water and extraction with chloroform gave a residue (0.49 g), whose spectral data was consistent with those expected for the allyl methyl sulphone (**10a**), $\nu_{max.}$(film) 1 640 (C=C), 1 350v (SO_2), and 1 120v (SO_2); δ 2.9 (s, 3 H, O_2SMe), 3.8 (d, 2 H, CH_2S), and 5.3—5.8 (m, 3 H, HC=C). The ^1H n.m.r. spectrum was also compared with that of authentic allyl phenyl sulphone.

(*b*) A similar procedure as described under (*a*) was used with ethylmagnesium bromide. Work-up by a similar procedure gave a mixture apparently of ethyl methyl sulphone (**10b**) and 3-methylpentan-3-ol, δ 1.2—1.5 (m), 2.3 (m), 2.8 (s).

(*c*) The same procedure as described under (*b*), except that 1M-Li_2CuCl_4 in dry tetrahydrofuran (0.5 ml) was used as the catalyst, in place of copper(I) iodide, gave ethyl methyl sulphone (**10b**).

Attempts to Couple 3β-*Acetoxy*-1-*mesyloxymethyltropane* (**9a**) *with Carbanions*.—Copper(I) iodide (1.62 g, 8.5 mmol) was suspended in tetrahydrofuran (25 ml) and cooled to −40 °C. To the suspension, 2.46M-butyl-lithium (6.9 ml, 17 mmol) was added dropwise *via* syringe with stirring; this caused the solution to turn deep blue. The sulphonate (**9a**) (0.85 g, 3.4 mmol) in THF (20 ml) was added dropwise. The mixture was maintained at −30 °C for 1 h then at 20 °C for 1 h. Water was added and the aqueous layer extracted with chloroform. Removal of the chloroform from the organic layer gave an oil which proved to be butyl methyl sulphone (**10c**), δ 0.9 (m), 1.3 (m), 2.5 (m). The by-product, presumed to be the diol (**8b**), being easily soluble in water, was not isolated.

Conversion of the Sulphonate (**9a**) *into the Iodide* (**9b**).—Magnesium iodide was prepared as follows. Magnesium (0.62 g, 265 mmol) was suspended in anhydrous ether (25 ml) and iodine (6.75 g, 265 mmol) was added. Meanwhile, the sulphonate (**9a**) (1.5 g, 5.3 mmol) was dissolved in chloroform (25 ml). The magnesium iodide solution was transferred by nitrogen and the mixture refluxed for 24 h. After the solvent had been evaporated the residue was adjusted with dilute ammonium hydroxide solution to pH 10, prior to extraction with chloroform. The extract washed with 5% aqueous sodium hydrogen sulphite and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give an oil (0.8 g, 39%) which proved to be the iodomethyltropane (**9b**) (Found: C, 41.1; H, 5.7; N, 4.5. $C_{11}H_{18}INO_2$ requires C, 40.9; H, 5.6; N, 4.3%); $\nu_{max.}$ 2 900, 1 720, 1 250, and 1 000 cm^{-1}; δ 1.5—1.8 (m, 8 H), 2.0

(s, 3 H, OCOMe), 2.3 (s, 3 H, NMe), 3.2 (s, 2 H), 3.3 (m, 1 H), and 4.9—5.2 (m, 1 H).

Attempted Coupling of Allylmagnesium Bromide with 3β-*Acetoxy*-1-*iodomethyltropane*.—Copper(I) iodide (0.6 g, 3 mmol) was added to a solution of the iodomethyl compound (**9b**) (1 g, 3 mmol), in tetrahydrofuran (25 ml) and HMPA* (25 ml). The mixture was transferred into the reaction flask under nitrogen. At −10 °C, allylmagnesium bromide (15.5 ml, 15 mmol solution in THF) was added *via* a syringe. The mixture was brought to 20 °C and stirred for 72 h and then heated to reflux for 0.5 h. Work-up gave only unchanged (**9b**).

Swern Oxidation of 3β-*Acetoxy*-1-*hydroxymethyltropane* (**8a**) *to* 3β-*Acetoxy*-1-*formyltropane* (**11**).—A solution of oxalyl chloride (3.6 ml, 42 mmol) in dichloromethane (50 ml) was placed in a flask equipped with mechanical stirrer, a low-temperature thermometer, a Claisen-adapter with dropping funnels, one containing dimethyl sulphoxide (6.5 ml, 0.09 mol) diluted with methylene chloride (20 ml) and the other containing 3β-acetoxy-1-hydroxymethyltropane (**8a**) (4 g, 19 mmol) dissolved in dimethyl sulphoxide (20 ml). The flask was cooled to −60 °C and the dimethyl sulphoxide solution was added dropwise under nitrogen to the oxalyl chloride solution. The reaction mixture was then stirred for 30 min at −60 °C. The methylene chloride solution of compound (**8a**) was then added dropwise and the solution stirred for an additional 1 h between −40 °C and −60 °C. Finally, *N*-methylpiperidine (11 ml, 0.095 mol) was added and the solution stirred for a further 15 min; it was then allowed to warm up to 20 °C. Water (30 ml) was added and the pH adjusted to 11 with dilute ammonium hydroxide solution. The organic and aqueous phases were separated and the aqueous layer extracted with methylene chloride (3 × 100 ml). The combined organic layers were washed with water and saturated aqueous NaCl and then dried (Na_2SO_4). Filtration followed by evaporation of the solvent gave the aldehyde (**11**) (3.8 g, 95%) as a light yellow oil, which was column chromatographed on silica gel using chloroform as the eluant (Found: C, 62.4; H, 7.9; N, 7.0. $C_{11}H_{17}NO_3$ requires C, 62.5; H, 8.0; N, 6.7%); $\nu_{max.}$(film) 2 900, 1 750, 1 350, 1 250, 1 070, 900, and 720 cm^{-1}; δ 1.5—1.8 (m, 8 H), 2.0 (s, 3 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H), 5.1—5.4 (m, 1 H, 3β-H), and 9.7 (s, 1 H, C*H*); *m/z* 211.1 (M^+), 196.1, 185.1, 168.1, 152.1, 122.1, 111.1, and 96.1 (base peaks, 82.1, 67.1, and 55.0).

Pfitzner-Moffatt Oxidation of 3β-*Acetoxy*-1-*hydroxymethyltropane*.—The alcohol (**8a**) (0.8 g, 3.7 mmol) was dissolved in ethyl acetate (100 ml) and to this solution was added dimethyl sulphoxide (12 ml), dicyclohexylcarbodi-imide (2.25 g, 11.1 mmol), and trifluoroacetic acid (0.4 ml, 5.5 mmol). The mixture was stirred at 20 °C for 48 h. The ethyl acetate was removed on a rotary evaporator and the dimethyl sulphoxide was removed by vacuum distillation. Water (50 ml) was added to the residue and the aqueous layer was extracted with ether to remove dicyclohexylurea. The aqueous layer was adjusted with dilute ammonium hydroxide to pH 11 and then extracted with chloroform. Removal of the chloroform gave 3β-acetoxy-1-formyltropane (**11**) (0.3 g, 40%).

Wittig Reactions of 3β-*Acetoxy*-1-*formyltropane* (**11**).—(*a*) *With butylidenetriphenylphosphorane*. A 3-necked flask was equipped with a reflux condenser, a septum, additional funnel and nitrogen adapter. Butyltriphenylphosphonium bromide (5.45 g, 8.43 mmol) was dissolved in dry tetrahydrofuran (25 ml) and ultimately 1.6M-butyl-lithium (15.3 mmol) in tetrahydrofuran (8 ml) was added dropwise *via* syringe, during which time a deep red colour developed. The mixture was stirred at 20 °C for 30 min and then refluxed for 45 min. The aldehyde (**11**) (1.8 g, 8.5 mmol) in dry tetrahydrofuran (25 ml) was then added dropwise and the mixture was refluxed for 40 h. Water (10 ml) was added dropwise at 0 °C, followed by 2M-hydrochloric acid (10 ml) and the mixture stirred for 30 min. The solvent was evaporated on a rotary evaporator and the pH was adjusted to 2 with dilute hydrochloric acid. Water was added (100 ml) and the water layer was extracted with benzene (500 ml) followed by ether (500 ml) to remove triphenylphosphine oxide. The aqueous layer was made alkaline (pH 10) with dilute ammonium hydroxide and extracted with ether. The ethereal layer was washed with water and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated under reduced pressure to give a liquid (1.78 g), which was purified on a column of silica gel. Pure 3β-hydroxy-1-pent-1-enyltropane (**12b**) (0.9 g, 50%) was eluted with chloroform–methanol ammonium hydroxide (85:14:1, v/v). The t.l.c. of the product (**12b**) gave one spot of R_F ($CHCl_3$) 0.39 (Found: C, 74.1; H, 10.3, N, 6.6. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.0; N, 6.6%); $\nu_{max.}$(film) 3 200br (OH), 2 900, 1 680m, 1 400, 1 200, and 675 (*cis*-alkene); δ_H 0.9 (t, 3 H, Me), 1.2—2.1 (m, 12 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H), 3.8—4.1 (m, 1 H), 4.3 (br s, 1 H, exchangeable with D_2O), and 5.3 (m, 2 H, C=C); *m/z* 208.9 (M^+), 191.8, 179.8, 163.8, 149.8 (base peak), 135.8, 121.8, 109.8, 95.8, 80.8, 67.8, and 54.8; δ_C($CDCl_3$) 132.98, 131.25, 66.0, 63.69, 60.33, 57.28, 42.58, 36.63, 34.65, 34.08, 33.71, 30.91, 27.55, 23.70, 18.8, and 13.8.

(*b*) *Preparation of* 3β-*Acetoxy*-1-*pent*-1-*enyltropane* (**12a**).—The same procedure as described under (*a*) was used except that only 1.4 equiv. of the phosphonium salt and 1.3 equiv. of butyllithium were used in place of 1 equiv. of the aldehyde. The reaction was carried out at 20 °C for 40 h. The crude product was chromatographed on silica gel [eluant: $CHCl_3$–MeOH–NH_4OH (84:15:1, v/v)] to give the acetate (**12a**) as a light yellow liquid (1.0 g, 50%) (Found: N, 5.6. $C_{15}H_{25}NO_2$ requires N, 5.57%); δ 0.9 (t, 3 H), 1.5—2.0 (m, 15 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H, 5-H), 4.9 (m, 1 H, 3-H), and 5.5 (m, 2 H).

Deacetylation of 3β-*Acetoxy*-1-*pent*-1-*enyltropane*.—The acetate (**12a**) (0.8 g, 3.2 mmol) was dissolved in anhydrous methanol (50 ml) and anhydrous potassium carbonate (4.5 g, 32 mmol) was added to the mixture; it was then stirred at 20 °C for 10 h. The solid was filtered off, the methanol evaporated off, and the pH of the residue was adjusted to 2 with dilute hydrochloric acid. Water (25 ml) was then added and the aqueous layer extracted with ether. The water layer was made alkaline with dilute ammonium hydroxide and extracted with chloroform. The extract was evaporated to give a crude product which was chromatographed on a silica gel column eluant: methanol–ammonium hydroxide (99:1, v/v) to give 0.5 g (75%) 1-pent-1-enyltropan-3β-ol (**12b**) as a light yellow liquid, $\nu_{max.}$(film) 3 200br (OH), 2 900, 1 680m, 1 400, 1 200, and 675 (*cis*-alkene); δ 0.9 (t, 3 H), 1.2—2.1 (m, 12 H), 2.3 (s, 3 H, NMe), 3.3 (m, 1 H), 3.8—4.1 (m, 1 H, 3-H), 4.3 (br s, 1 H, exchangeable by D_2O), and 5.3 (m, 2 H, HC=CH).

(±)-1-*Pentyltropan*-3β-*ol* (**13**).—Pent-1-enyltropan-3β-ol (**12a**) (0.75 g, 36 mmol) was dissolved in absolute methanol (50 ml) and Raney nickel (W-2) (1 g) was added. The mixture was hydrogenated at 2 atm for 3 h. The catalyst was filtered off and the filtrate evaporated to leave (±)-1-pentyltropan-3β-ol (**13**) as a light yellow liquid (0.7 g, 93%), δ 0.9 (t, 3 H, Me), 1.5—2.1 (m, 19 H), 2.5 (s, 3 H, NMe), 3.4—3.6 (m, 2 H), and 6.5 (br s, 1 H, exchangeable by D_2O); *m/z* (20 eV) 211.2 (M^+), 194.2, 182.1, 166.1, 152.1, 138.1, 126.1, 111.1, 96.1 (base peak), 82.0, and 67.0.

The corresponding hydrochloride was prepared by bubbling

* HMPA = Hexamethylphosphoric triamide.

dry HCl through a solution of the amine (**13**) in chloroform (20 ml), until a stoicheiometric amount had been absorbed. Evaporation of the solvent left a foam which turned into a fine white powder, m.p. 139—142 °C (Found: C, 62.2; H, 10.4; N, 5.5. $C_{13}H_{26}ClNO$ requires C, 62.4; H, 10.5; N, 5.6%); δ 0.9 H (t, 3 H, Me), 1.4 (m, 11 H), 2.1—2.3 (m, 8 H), 2.9 (d, 3 H NMe), and 3.9 (br m, 1 H).

But-3-ynyltriphenylphosphonium Bromide.—1-Bromobut-3-yne (9.85 g, 74 mmol) and triphenylphosphine (29.4 g, 110 mmol) were dissolved in dry benzene (100 ml). The mixture was heated to reflux for 24 h when two layers were formed. The top layer was decanted off and the bottom layer was extracted with benzene (100 ml) to remove any unchanged starting material, separated and kept under reduced pressure. A yellow solid was obtained (4.5 g, 15%), m.p. 152—154 °C, δ 2.0 (m, 1 H, C≡CH), 2.8—2.9 (m, 4 H, CH_2CH_2), and 7.9—8.0 (m, 15 H).

Wittig Reaction of But-3-ynylidenetriphenylphosphorane with 3β-Acetoxy-1-formyltropane.—3-Butynyltriphenylphosphonium bromide (4.32 g, 11 mmol) was in dry THF (75 ml) suspended and cooled to 0 °C. 1.6M-n-Butyl-lithium in light petroleum (6.3 ml, 10 mmol) was then added dropwise *via* syringe and the mixture was stirred at 0 °C for 2 h, then warmed to 20 °C and stirred for a further 1 h. A solution of the aldehyde (**11**) (1.8 g, 8.5 mmol) in dry THF (25 ml) was added dropwise at 20 °C and mixture was stirred at this temperature for 24 h and then refluxed for 12 h. Finally, it was cooled to 20 °C and worked-up to give a light yellow liquid (0.7 g, 33%) after elution with $CHCl_3$–MeOH–NH_4OH (85:14:1, v/v) on silica gel. The spectral data are in agreement with the structure of 3β-acetoxy-1-(pent-1-en-4-ynyl)tropane (**14**) (Found: C, 72.7; H, 8.6. $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.5%); $\nu_{max.}$(film) 3 300 (HC≡C), 3 000, 2 250 (C≡C), 1 720 (OCOMe), 1 250, 1 020, 900, and 750 cm^{-1}; δ 1.8—2.0 (m, 11 H), 2.3 (s, 3 H, NMe), 5.5 (m, 2 H, *J* 11 Hz); *m/z* 247 (M^+).

3β-Acetoxytropan-1-ylacetaldehyde (**15**).—In a 3-necked flask equipped with a reflux condenser, addition funnel, septum and a magnetic stirrer, methoxymethyltriphenylphosphonium chloride (5.1 g, 14.7 mmol) was suspended in dry tetrahydrofuran (15 ml). A solution of potassium t-butoxide (1.67 g, 14.7 mmol) in tetrahydrofuran (20 ml), was added dropwise and the mixture was stirred at 20 °C for 1 h during which period a deep red colour developed. The aldehyde (**11**) (1.5, 7 mmol) in tetrahydrofuran (10 ml) was then added dropwise. When the colour of the solution turned light yellow. The mixture was stirred at 20 °C for 72 h after which time water (20 ml) was added and the solvent evaported on a rotary evaporator. Work-up as in the previous experiment gave the mixture of geometric isomers of 3β-acetoxy-1-(2-methoxyvinyl)tropane (1.1 g), δ 1.6—1.8 (m, 8 H), 2.0 (s, 3 H, OCOMe), 2.3 and 2.35 (s, 3 H, NMe), 3.5 and 3.6 (s, 3 H, OMe), 3.3 (m, 1 H), 4.3 and 5.9 (d, 2 H, *cis* HC=CH, *J* 8 Hz), and 4.7 and 6.4 (d, 2 H, *trans J* 15 Hz).

The enol ether (1 g, 4 mmol) was used for hydrolysis without further purification, and was dissolved in methylene chloride (100 ml). To this was added dropwise, a solution of boron tribromide (21 mmol) in methylene chloride (22 ml), at 0 °C. The solution was kept at 20 °C for 24 h with stirring after which time it was poured onto crushed ice and made alkaline (pH 10) with dilute aqueous ammonium hydroxide. Extraction with chloroform and evaporation of the solvent from the organic phase left a residue which after chromatography on silica gel with chloroform gave crude 3β-acetoxytropan-1-ylacetaldehyde (**15**) (0.18 g, 20%) (Found: C, 63.8; H, 8.3. $C_{12}H_{19}NO_3$ requires C, 64.0; H, 8.45%); δ 1.5—1.8 (m, 8 H), 2.0 (s, 3 H, OCOMe), 2.2—2.4 (m, 5 H), 3.3 (m, 1 H, 5-H), 4.9 (m, 1 H, 3-H), and 9.7 (t, 1 H, CHO).

Note added in proof: Since the submission of this manuscript a synthesis of histrionicotoxin has been reported (S. C. Carey, M. Aratani, and Y. Kishi, *Tetrahedron Lett.*, 1985, **26**, 5887).

References

1 J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1971, **68**, 1870.
2 (*a*) M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.*, 1975, **40**, 2009; (*b*) T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *J. Org. Chem.*, 1975, **40**, 2011; (*c*) E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, 1975, **97**, 430; (*d*) E. J. Corey, M. Petrzilka, and Y. Ueda, *Helv. Chim. Acta*, 1977, **60**, 2294; (*e*) D. A. Evans, E. W. Thomas, and R. E. Cherpeck, *J. Am. Chem. Soc.*, 1982, **104**, 3695; (*f*) S. A. Godleski, D. J. Heacock, J. D. Meinhart, and S. V. Wallendael, *J. Org. Chem.*, 1983, **48**, 2101; (*g*) K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque, and E. X. Albuquerque, *Helv. Chim. Acta*, 1982, **65**, 252.
3 W. Burgermeister, W. L. Klein, M. Nirenberg, and B. Witkop, *Mol. Pharmacol.* 1978, **14**, 751.
4 (*a*) E. Gössinger and B. Witkop, *Monatsh Chem.*, 1980, **111**, 803; (*b*) R. K. Hill and L. Renbaum, *Tetrahedron*, 1982, **38**, 1959; (*c*) D. H. G. Medina, D. S. Grierson and H. P. Husson, *Tetrahedron Lett.*, 1983, 2099.
5 B. Witkop, personal communication.
6 B. K. Blount and R. Robinson, *J. Chem. Soc.*, 1933, 1511.
7 R. Noyori, Y. Baba, and Y. Hayakawa, *J. Am. Chem. Soc.*, 1974, **96**, 3336.
8 Zing-Jung In, M. S. Thesis to West Virginia University, Morgantown, WV (1978).
9 J. Case, W. Ecsy, and G. Fodor, MEDI 008, Abstract, 178th ACS National Meeting, Washington, DC, September 9, 1979.
10 J. Kebrle and P. Karrer, *Helv. Chim. Acta*, 1954, **37**, 484.
11 (*a*) N. Clauson-Kaas, *Acta Chem. Scand.*, 1952, **6**, 556; (*b*) R. Mozingo, *Org. Synth.*, Coll. Vol. III, 1955, 181.
12 G. Gal, I. Simonyi, and G. Tokar, *Acta Chim. Acad. Sci. Hung.*, 1955, **6**, 360.
13 (*a*) A Nickon and L. Fieser, *J. Am. Chem. Soc.*, 1952, **74**, 5566; (*b*) R. Willstatter, *Chem. Ber.*, 1896, **29**, 936.
14 A. G. Anderson Jr. and F. J. Freenor, *J. Org. Chem.*, 1972, **37**, 626.
15 (*a*) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 1977, **42**, 3761; (*b*) E. J. Corey and K. Shimoji, *J. Am. Chem. Soc.*, 1983, **105**, 1662.
16 (*a*) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, 1968, **24**, 2289; (*b*) E. J. Corey, N. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, 1969, **91**, 5676; (*c*) A. Brossi, F. Hsu, and K. Rice, *J. Org. Chem.*, 1982, **47**, 5214.
17 G. Fouquet and M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 82.
18 G. Posner, 'Substitution Reactions Using Organocopper Reagents,' *Org. React.*, 1972, **22**, 253.
19 C. R. Johnson, and G. A. Dutra, *J. Am. Chem. Soc.*, 1973, **95**, 7777.
20 A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem Soc.*, 1969, **91**, 763.
21 P. Place, M. Roumestant, and J. Gore, *Bull. Soc. Chim. Fr.*, 1976, 169.
22 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
23 E. J. Corey and J. Suggs, *Tetrahedron Lett.*, 1975, 2647.
24 J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, 1980, 561.
25 Y. S. Cheng, W. L. Liu, and S. Chen, *Synthesis*, 1980, 223.
26 J. C. Collins and W. W. Hess, *Org. Synth.*, 1972, **52**, 5.
27 J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.
28 K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1965, **87**, 5661.
29 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
30 (*a*) E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, 1973, **95**, 5778; (*b*) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, 1967, **89**, 2758.
31 G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 1950, 3650.
32 S. G. Levine, *J. Am. Chem. Soc.*, 1958, **80**, 6150.

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