Tetrahedron Vol. 45, No. 3, pp. 767 to 774, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
© 1989 Pergamon Press plc

MONOTERPENOIDS — VII[a]

A SIMPLE SYNTHESIS OF (-)-CIS-CARONALDEHYDIC ACID HEMIACETAL FROM (+)-CAR-3-ENE[b]

Deepa Bakshi, Verinder K. Mahindroo, R. Soman[c] and Sukh Dev*
Malti-Chem Research Centre, Nandesari, Vadodara, India

(*Received in UK* 9 *November* 1988)

Abstract - (+)-Car-3-ene has been converted by a simple route into (-)-cis-caronaldehydic acid hemiacetal, an important intermediate in the commercial production of certain synthetic pyrethroids.

(-)-cis-Caronaldehydic acid hemiacetal (1) is an important intermediate in the commercial production of deltamethrin (5), a highly potent synthetic pyrethroid insecticide[1]. Besides, compound 1 and its equivalents (such as 2, 3), both in the optically active and racemic forms, constitute economic intermediates for the synthesis of a variety of other cis-pyrethroids[2], of which special mention may be made of alphamethrin (±6)[3] and RU 38702 (7)[1c]. Thus, it is not surprising that synthesis of 1 and its equivalents have attracted considerable attention[1b,4]. Current manufacture of 1, it appears, is based on ozonolytic degradation of optically active trans-chrysanthemic acids, obtained by resolution of synthetic racemic acid[1a,b]. To us, (+)-car-3-ene appeared a potentially valuable starting material, and in continuation of our earlier work[5] aimed at sophisticated utilization of (+)-car-3-ene (4), we now report[6] on a simple economic synthesis of 1 from 4.

There have been earlier[8] and concurrent[9] attempts aimed at an economic transformation of (+)-car-3-ene (4) into 1. However, these methods leave much to be desired. Our process is shown in Fig. 1.

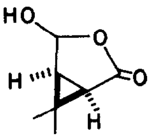
The key reaction in this process is an economic conversion of carene into the C_9 keto-acid 12. This compound was first reported as a minor component of a complex product obtained from permanganate oxidation of car-3-ene.[10] However, this method has no preparative value. A preparative method involving four steps (ozonolysis,

---

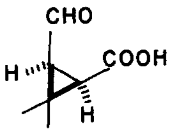
[a] Part VI: Tetrahedron, in print.

[b] MRC Communication No. 64.

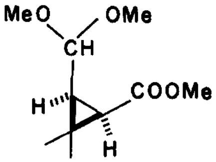
[c] Present address: Sudershan Chemicals Industries, Pune 411 001



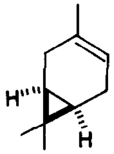
1



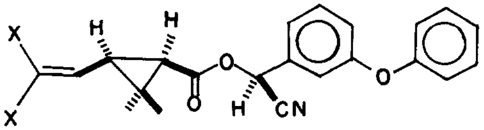
2



3

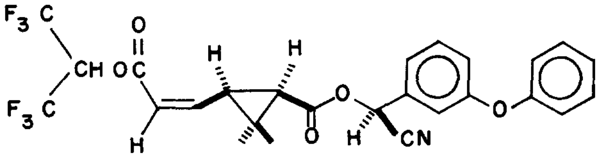


4



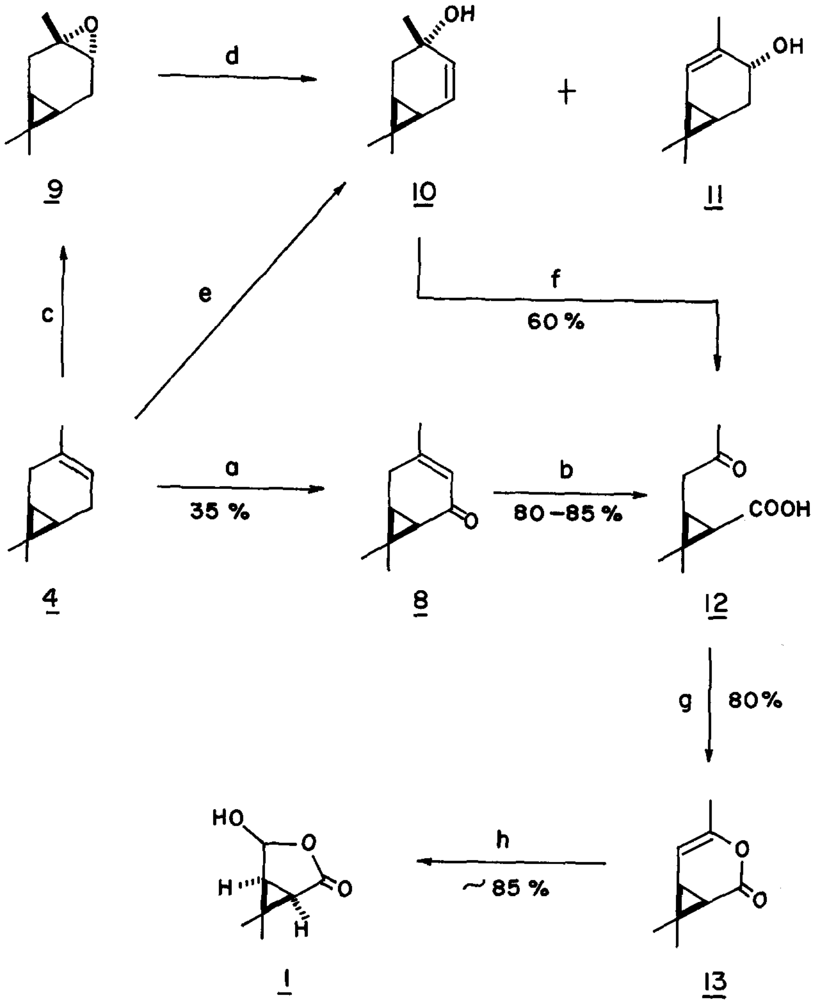
5: X = Br

6: X = Cl



7

enol acetylation, ozonolysis, and oxidation) from carene has been described by a Japanese group.[11] An effort to adopt a simplified version of this sequence did not prove promising. Attention was then directed to car-3-en-5-one (8), readily available (in a low, but acceptable yield) by simple transition metal-catalyzed air oxidation of car-3-ene,[7a,12] as a possible substrate for further oxidation to 12. Ozonolysis of this enone was investigated under a variety of conditions (e.g. see Table 1) and finally conditions were standardized (ozonolysis in EtOAc, work-up with limited amount of Na_2SO_3) to get the desired keto-acid 12 in yields of 90-95% from carenone (8).



Reagents. a : O_2, Co^{++}

b : O_3; Na_2SO_3

c : AcOOH/or pinane hydroperoxide

d : $KOBu^t$, pyr.

e : O_2, hν, Rose Bengal

f : O_3; H_2O_2 aq

g : Ac_2O, H^+

h : O_3; Me_2S

Fig. 1. Synthesis of (−)-cis-caronaldehydic acid hemiacetal from (+)-car-3-ene

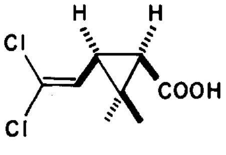
Table 1. Ozonolysis of car-3-en-5-one: work-up with different reagents[a]

No.	Reagent used for work-up	Yield of keto acid 12 (%)
1	Dimethyl sulphide[13]	98%
2	Triphenylphosphine[14]	69%
3	Pyridine[14]	96%
4	Thiourea[15]	92%
5	$NaHSO_3$[14]	89%
6	Na_2SO_3[14]	87%

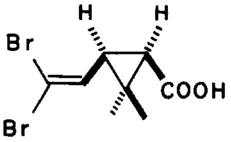
[a] 3.785 g of enone in 40 ml EtOAc ozonized at 0-5° and the product treated with different reagents.

Another convenient route to 12 was also worked out. In the conversion of (+)-car-3-ene to (+)-car-2-en-4α-ol (11), an intermediate in the preparation of (+)-carvone[5c], (-)-car-4-en-3α-ol (10) is a byproduct[5c,16]. Oxidative degradation of 10 to 12 was explored in an effort to utilize this byproduct. A number of cases of cleavage of C-2, C-3 bond during ozonolysis of 1-en-3-ols (e.g. linalool, manool, etc.) have been recorded.[17] Such a cleavage in the case of car-4-en-3-ol (10) should result in the production of the desired keto acid 12. After much exploratory studies (solvent and temp for ozonation, reagent for work-up) conditions (vide Experimental) could be established for ozonolytic degradation of 10 to 12 in yields of ~60%. It may be noted that the product of ozonolysis was a mixture of 12 and the corresponding aldehyde (CHO in place of COOH) and the mixture, without separation, was further oxidized with air to effect conversion of the aldehyde to the acid.

Exposure of keto acid 12 to Ac_2O in presence of a macroreticular sulphonic acid resin[18] readily furnished enol lactone 13. Ozonolysis of 13 under specific conditions furnished 1 along with cis-caronaldehydic acid 2. Conditions were also established for the direct isolation (after ozonolysis of 13) of methyl (1R)-cis-caronaldehydic ester dimethyl acetal (3), a stable product preeminently suited for further elaboration to pyrethroid acids. cis-Caronaldehydic acid hemiacetal and its equivalents have been converted into pyrethroid acids, such as cis-permethric acid (14) and cis-deltamethric acid (15) by a number of methods.[2a,19,20]



14



15

EXPERIMENTAL

M.ps and b.ps are uncorrected. Optical rotations were measured on a Schmidt + Haensch electronic polarimeter model Polatronic 1.

Following instruments were used for spectral/analytical data: Perkin-Elmer model 402UV spectrophotometer; Perkin-Elmer Infrared Spectrophotometer, model 267; Perkin-Elmer model R32 (90 MHz) NMR spectrometer; Hewlett-Packard 5700A gas chromatogram (column: Al, 180 cm x 3 cm or 360 cm x 3 mm; support: Chromosorb 60-80; H_2 as carrier gas).

Welsbach (USA) ozonator model T-408 was used for generating ozonized oxygen.

(-)-Car-3-en-5-one (8)

This was prepared by air-oxidation of car-3-ene, in presence of 3% cobalt stearate,at ∿40°, as reported earlier.[7a,12] A 100% pure (GLC, TLC) sample, obtained by column chromatography (SiO_2gel/II; elution with 5% EtOAc in C_6H_6) had: b.p. 80-85°(bath)/0.6 mm, n_D^{30} 1.5061, $\{\alpha\}_D^{26^\circ}$ -184° ($CHCl_3$, c 1.9%). {Lit.$\{\alpha\}_D^{20^\circ}$-271°($CHCl_3$)}. For ozonolysis ∿80% pure (GLC: 10% DEGS,360 cm x 4 mm Al column, 150°) carenone 8 was employed; this material had: b.p. 83-85°/0.5 mm, n_D^{25} 1.5055-1.5060, $d_4^{25^\circ}$ 0.9840-0.9850.

(-)-cis-3-(2'-Oxopropyl)-2,2-dimethylcyclopropane-1-carboxylate (12)

(a) Ozonolysis of car-3-en-5-one (8). A soln of car-3-en-5-one (50g, 0.33 mole) in EtOAc (450 ml) was cooled to 0-2°, and a stream of ozonized oxygen (∿2% O_3 w/w; 2l/min) was passed at this temp till O_3 was no longer consumed (KI aq-boric acid test) and there was no unchanged enone (TLC: ∿4.5 hr, ∿16g O_3). At this point, N_2 was bubbled through the reaction mixture to expel any unreacted O_3, and the soln added slowly (∿40 min) to cold Na_2SO_3 aq (20.0 g in 160 ml water; 0-2°) with vigorous stirring at 0-5°. The EtOAc layer was separated, the aq part saturated with NaCl and extracted with EtOAc (30 ml x 3). The combined EtOAc extract was washed with water (30 ml x 3), brine (30ml x 1) and dried (Na_2SO_4), and freed of solvent to get crude 12, which was distilled, b.p. 110-112°/ 0.5 mm, $n_D^{25^\circ}$ 1.4665, $\{\alpha\}_D^{25^\circ}$ -44.1° ($CHCl_3$, c 9%), yield 40.5g (purity 95%; a small sample was esterified with CH_2N_2 and the product analyzed by GLC: 5% Carbowax 20M, column 180 cm x 3 m, 170°). This yield amounts to 85% (100% 12) based on carenone of 100% purity.

Methyl ester, b.p. 110-112°/25 mm, $n_D^{26^\circ}$ 1.4544, IR (neat): 1720, 1325, 1175, 1140, 1090, 940 and 860 cm^{-1}. ^1H-NMR (CCl_4): C-Me (3H, s, 1.12 ppm; 3H, s, 1.22 ppm), COMe (3H, s, 2.08 ppm), $COCH_2$ (2H, d, 2.78 ppm, J = 6Hz), OMe (3H, s, 3.59 ppm) (Li .[11]:$\{\alpha\}_D^{14^\circ}$ -23.7°, $CHCl_3$; IR. Lit.[22] for the antipode: $\{\alpha\}_D^{20^\circ}$ + 38.2°, $CHCl_3$; IR; ^1H-NMR).

(b) Ozonolysis of car-4-en-3-ol (10). A soln of (+)-car-4-en-3-ol (10)[5c] (3.068g, 0.02 mole) in EtOAc (100 ml) was ozonized exactly as above. After completion of ozonation and removal of excess O_3 (by N_2), H_2O_2 aq (35%, 3 ml) was added to the ozonide soln and the mixture stirred, at room temp (∿30°), for 12 hr. The reaction mixture was next washed with water, dried (Na_2SO_4) and the product freed of solvent. The residue (3.55 g) was taken up in EtOAc (10 ml) and the soln vigorously stirred under an atmosphere of O_2 for 5 hr at room temp. Dimethyl sulphide (0.5ml) was then added to destroy any peroxides, the product after the usual work-up esterified with CH_2N_2 and distilled to get methyl ester of 12 as a colorless liquid (2.11 g), b.p. 110-113°/25 mm, (GLC purity 80%).

Enol-lactone 13

Distilled keto acid 12 (36.5g, 0.214 mole) and Ac_2O (32.8g, 0.323 mole) were stirred at room temp. (∿30°) in the presence of Amberlyst-15 (5g, Rohm & Haas Co.), with exclusion of moisture and O_2, till the conversion was complete (∿3 hr; TLC, SiO_2-$CaSO_4$, hexane: EtOAc,2:1). After completion of this reaction, the resin was filtered, washed with some Ac_2O and the product freed of Ac_2O-AcOH (under reduced pressure at ∿80°) to get a material, which was distilled to furnish pure 13 (GLC purity, 98%), b.p. 68-70°/1.0 mm, m.p. 44.5-45.0°, $[\alpha]_D$-108.8° ($CHCl_3$, *c* 8%) (Lit.[8a]: m.p. 44-44.5°; $[\alpha]_D^{25°}$ -85.6°, $CHCl_3$). UV (EtOH): λ_{max} 214 (ε1780), 245 nm (ε1143). IR (neat): 1745, 1725, 1702, 1385, 1340, 1315, 1225, 1180, 1115, 1050, 1007, 998, 975, 962, 905, 855, 825, 810, 770,685, and 650 cm^{-1}, ^{1}H-NMR (CCl_4); C-Me (3H, s, 1.04 ppm; 3H, s, 1.30 ppm; 3H, s, 1.89 ppm), cyclopropane H (2H, m, 1.65 ppm), C=CH (1H, dx allylic coupling, 4.97 ppm, J = 4Hz). Mass: m/z 152 (M^+, 30%), 137 (9%), 124(8%), 109(100%), 95(5%), 91(5%), 81(26%),79(9%), 53(12%), 43(26%).

(-)-cis-Caronaldehydic acid hemiacetal (1)

The above enol-lactone (25.05g, 0.165 mole) in MeOH (150 ml) was ozonized at 0-5° till no more ozone was consumed (2.5 hr, total O_3 passed 8.6 g). The 'ozonide' soln was then added to a soln of Me_2S (12.2g, 0.20 mole) in MeOH (15 ml) at 5° under stirring at such a rate (∿10 min) so as to keep the temp of the reaction mixture below 20°. After completion of addition, stirring was continued at 20-30° till peroxide test (KI-AcOH) was negative (∿1 hr). MeOH was distilled off, and to this residue an aq soln of oxalic acid (0.5%, 540 ml) added and the mix stirred at room temp for 3 hr. The product was taken up in EtOAc (200 ml x 3), washed with water (30 ml x 3), dried (Na_2SO_4) and freed of solvent. The crude product was dissolved in minimum amount of hot acetone (∿20 ml) and cooled. The crystalline hemiacetal (1) that separated was collected by filtration, 13.51g (57.8%), m.p. 114-115°. A small amount was recrystallized from acetone to get colourless plates/prisms, m.p. 117-118°, $[\alpha]_D$-102° (EtOH, *c* 2%). (Lit. [8b, 23]: m.p. 116-117.5°[8b]; $[\alpha]_D^{28°}$ - 101.5°, EtOH[8b]). IR (Nujol): 3310, 3082, 1720(broad), 1358, 1322, 1215, 1190, 1130, 1120, 1090, 1050, 990, 945, 905, 890, 852, 792, 780, 670 and 630 cm^{-1}. ^{1}H-NMR ($CDCl_3$)[24]: essentially three singlets at 1.23, 1.32 and 2.1 ppm (each approx. 3H); (C_6H_6) C-Me (3H, s, 0.57;

3H, s, 0.90 ppm), 2 cyclopropyl H and CHOH (1H, d, 1.65 ppm, J = 7Hz; 1H, q, 1.65 ppm, J_1= 7Hz, J_2 = 14Hz; 1H, d, 2.1 ppm, J = 7Hz). Mass: m/z 127(8%), 113(31%), 97(58%), 96(92%), 83(65%), 81 (55%), 69(49%), 67(100%), 55(51%), 53(70%).

The filtrate from the above crystallization is rich in the hydroxy lactone (1) and the corresponding aldehyde acid (2), and was converted into the methyl ester of aldehydic acid 2. The filtrate was freed of solvent and the residue (7.67g) taken up in MeOH (80 ml) containing some p-toluene sulfonic acid (p-TSA; 2.0g) and the soln refluxed for 5 hr. Sodium acetate (2.0 g) was, then, added to the cooled reaction mixture and MeOH distilled off. The residue was taken up in light petroleum (50 ml), washed with water, dried and freed of solvent. The residue was mixed with 0.5% aq oxalic acid (40 ml), the mixture stirred at room temp for 2 hr and worked up to furnish the methyl ester of aldehydic acid, which was distilled, b.p. 60-65°/1 mm ($n_D^{25^\circ}$ 1.4597), yield 6.55 g (total yield of 1 + Me ester of 2, 83% on enol-lactone). IR (neat): 1732, 1705, 1335, 1228, 1210, 1140, 1127, 1097, 880, 840 and 790 cm^{-1}. ^1H-NMR (CCl_4): C-Me (3H, singlets at 1.27, 1.52 ppm), cyclopropyl H (2H, m, 1.6-2.1 ppm), OMe (3H, s, 3.67 ppm), CHO (1H, d, 9.60 ppm, J = 6Hz).

(-)-cis-Caronaldehydic acid hemiacetal dimethylacetal (3)

Enol-lactone 13 (22.8g, 0.15 mole) was ozonized and worked up with Me_2S (11.3g, 0.182 mole) exactly as described above. To the final methanolic soln, p-TSA (2.0g) was added and the soln refluxed for 5 hr. This was worked up to furnish the required 3 as a mobile liquid (27.68g, 91.4%; GLC purity 95%), b.p. 88-90°/1 mm, $n_D^{25^\circ}$ 1·4420. IR (neat): 1730, 1190, 1142, 1095, 1055, 960, 930 and 840 cm^{-1}. ^1H-NMR (CCl_4): C-Me (3H singlets at 1.17, 1.25 ppm), cyclopropyl H (2H, m,1.20-1.60 ppm), OMe (3H, singlets at 3.24, 3.27, 3.62 ppm), CHOMe (1H, d, 4.75 ppm,J = 7.5Hz).

REFERENCES AND NOTES

[1] (a) Deltamethrin monograph, Roussel Uclaf, Romainville (1982); (b) J. Tessier, Chem. and Ind. 199 (1984); (c) J.R. Tessier in Recent Advances in the Chemistry of Insect Control (Editor: N.F. Janes), p. 26, The Royal Society of Chemistry, London (1985).

[2] (a) D. Arlt, M. Jautelat and R. Lantzsch, Angew. Chem. Int. Ed. 20, 703 (1981); (b) K. Naumann in Chemie der Pflanzenschutz-und Schadlingsbekampfungsmittel : Chemie der synthetischen Pyrethroid-Insektizide (Editor: R. Wegler), vol. 7, pp. 217, Springer-Verlag, Berlin (1981).

[3] The Agrochemicals Handbook, Sheet A649/Jun 86, Royal Society of Chemistry,Nottingham (1986).

[4] (a) H.G. Schmidt in Recent Advances in the Chemistry of Insect Control (Editor: N.F Janes), p. 178, The Royal Society of Chemistry, London (1985); (b) M. Schneider, N. Engel and H. Boensmann, Angew. Chem. Int. Ed. 23, 64 (1984).

[5] (a) R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974); (b) V.P. Rajan, S.N. Bannore, H.N. Subbarao and Sukh Dev, Tetrahedron 40, 983 (1984); (c) M.H. Shastri, D.G. Patil, V.D.Patil and Sukh Dev, Tetrahedron 41, 3083 (1985); (d) Sukh Dev, Current Science 52, 1125 (1983); (e) Sukh Dev, Proceedings of 11th IUPAC International Symposium on Chemistry of Natural Products, Vol. 4 (Part 1), p. 433, Bulgarian Academy of Sciences, Golden Sands (1978); (f) Sukh Dev, Proceedings of International Symposium on Medicinal and Aromatic Plants (Editors: R.S. Thakur, A. Husain, O.P. Vermani and R. Tewari), p. 77, Central Institute of Medicinal and Aromatic Plants, Lucknow (1983); (g) Sukh Dev, 31st International Congress of Pure and Applied Chemistry, Section 4, p. 63, Bulgarian Academy of Sciences, Sofia (1987).

6 This method has been reported earlier in several lectures[5d,f,g], and has been covered in patents.[7]

7 (a) A.N. Misra, V.K. Yadav, R. Soman and Sukh Dev, Indian Patent 155122 (1982); (b) M.R. Sarma, R. Soman and Sukh Dev, Indian Patent 155123 (1982); (c) D. Gupta, R. Soman and Sukh Dev, Indian Patent 155124 (1982); (d) D. Gupta, R. Soman and Sukh Dev, Indian Patent 155125 (1982); (e) D. Gupta, A.N. Misra, R. Soman and Sukh Dev, Indian Patent 155126 (1982); (f) D. Gupta R. Soman and Sukh Dev, Indian Patent 155130 (1983); (g) D. Gupta, R. Soman and Sukh Dev, Indian Patent 155131 (1983).

8 (a) S.A. Roman, U.S. Patent 4,132,717 (1979); (b) S.A. Roman, U.S. Patent 4,156,692 (1979)

9 A.K. Mandal, D.P. Borude, R. Armugasamy, N.R. Soni, D.G. Jawalkar, S.W. Mahajan, K.R. Ratnam and A.D. Goghare, Tetrahedron 42, 5715 (1986).

10 J. Simonsen and L.N. Owen, The Terpenes, Vol. II, p. 61, The University Press, Cambridge (1957).

11 M. Matsui, H. Yoshioka, Y. Yamada, H. Sokamoto and T. Kitahara, Agr. Biol. Chem. 29, 784 (1965); 31, 33 (1967).

12 (a) C.S. Sharma, Ph.D. Thesis, Poona University (1974); (b) D.A. Baines and W. Cocker, J. Chem. Soc. Perkin I 2232 (1975).

13 (a) J.J. Pappas, W.P. Keaveney, E. Gancher and M. Berger, Tetrahedron Lett. 4273 (1966); (b) P L. Stotter and J.B. Eppner, Tetrahedron Lett. 2417 (1973).

14 P.S. Bailey, Ozonation in Organic Chemistry, Vol. I, p. 131, Academic Press, New York (1978).

15 D. Gupta, R. Soman and Sukh Dev, Tetrahedron 38, 3018 (1982).

16 K. Gollnick, S. Schroeter, G. Ohloff, G. Schade and G.O. Schenck, Liebig's Ann. 687, 14 (1965).

17 (a) P. Vlad and M. Soucek, Collec. Czech. Chem. Commun. 27, 1726 (1962); (b) J.R. Hosking, Ber. Dtsch. Chem. Ges. 69, 780 (1936); (c) J.A. Barltrop D. Giles, J.R. Hanson and N.A.J. Rogers, J. Chem. Soc. 2534 (1962); (d) P.K. Grant and H.T.L. Liau, Aust. J. Chem. 31, 1791 (1978); (e) R.L. Cargill and B.W. Wright, J. Org. Chem. 40, 120 (1975).

18 S.A. Patwardhan and Sukh Dev, Synthesis 348 (1974).

19 M. Elliott, N.F. Janes and D.A. Pulman, J. Chem. Soc. Perkin I, 2470 (1974).

20 (a) W.G. Salmond, Tetrahedron Lett. 1239 (1977); (b) W.G. Taylor, Synthesis 554 (1980).

21 W.D.P. Burns, M.S. Carson, W. Cocker and P.V.R. Shannon, J. Chem. Soc. (C) 3033 (1968).

22 W. Cocker, H.S.J. Lauder and P.V.R. Shannon, J. Chem. Soc. Perkin I 332 (1975)

23 Roussel Uclaf, British Patent 1283225 (1972).

24 ^{1}H-NMR spectrum of caronaldehydic acid hemiacetal (1) in $CDCl_3$ is deceptive. However, in benzene, various protons appear in the required multiplicity. Still, there are interesting features in ^{1}H-NMR spectra of 1 in these two solvents, and these will be discussed elsewhere.