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2-(2-NITROETHYL)-1,3-DIOXOLANE AS REAGENT FOR 3-OXOPROPYL ANION SYNTHON : A NEW ROUTE TO JASMONOID AND PROSTAGLANDIN INTERMEDIATES

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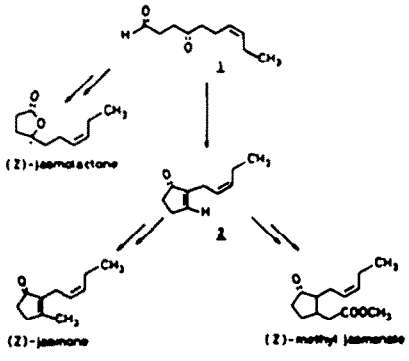
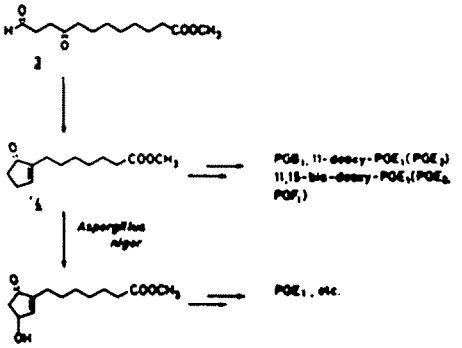
Abstract: 2-(2-Nitroethyl)-1,3-dioxolane is a versatile reagent for 3-oxopropyl anion synthon. New methodology, based on nitroaldol condensation, oxidation and direct or indirect denitration sequence is developed for the conversion of 2-(2-nitroethyl)-1,3 dioxolane into (Z)-1,4-dioxodec-7-ene, (Z)-2-(2-pentenyl)-2-cyclopenten-1-one , methyl 9,12-dioxododecanoate and methyl 7-(5-oxocyclopentenyl)heptanoate, which are popular intermediates for syntheses of (Z)-jasmonoids and prostaglandins.

We have reported a new general synthesis of 1,4-diketones which we have utilized, *inter alia*, in an efficient preparation of (Z)-jasmone and dihydrojasmone[1]. During our work we were attracted by the relevant importance of (Z)-1,4-dioxodec-7-ene (1) as common intermediate in syntheses of olfactively interesting constituents of essential oil of jasmine flowers[2] as (Z)-γ-jasmolactone[3], (Z)-jasmone[4-6] and methyl (Z)-jasmonate[3,7-9] *via* (Z)-2-(2-pentenyl)-2-cyclopenten-1-one (2) as outlined in Scheme 1. On the other hand it is well known that methyl 9,12-dioxododecanoate (3) can be considered the parent compound[10-15] of methyl 7-(5-oxocyclopentenyl)heptanoate (4), a popular intermediate for prostaglandine syntheses[16,17] (Scheme 2).

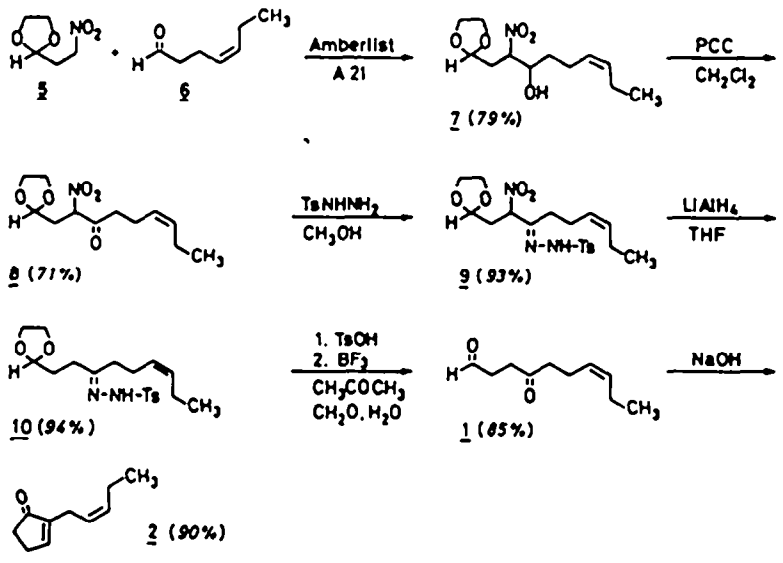


SCHEME 1

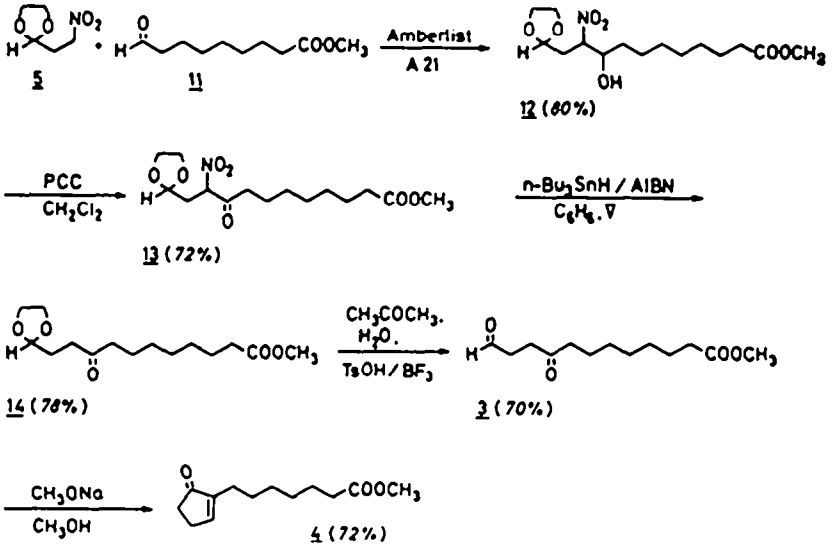


SCHEME 2

In connection with our interest in the construction of carbocyclic structures of natural products by means of nitroalkane derivatives as functionalized alkyl anions synthons, we wish to report a novel approach to synthetize compounds 1 and 2 (Scheme 3) and compounds 3 and 4 (Scheme 4). In both cases we used 2-(2-nitroethyl) 1,3-dioxolane (5) as reagent for 3-oxopropyl anion synthon.



SCHEME 3



SCHEME 4

The protected nitroaldehyde 5 was easily prepared in respectable yield from commercial 2-(2-bromoethyl)-1,3-dioxolane by reaction with sodium nitrite in dimethyl formamide or with nitrite anion bonded to a macroporous quaternary ammonium Amberlite resin (Amberlite IRA 900) according to a method reported by Gelbard and Colonna.[18,19]

The starting point for our synthesis of target compound 1 was the nitroaldol condensation (Henry reaction) on Amberlist A-21[20] surface without solvent between the protected nitroaldehyde 5 and the readily available (Z)-4-heptenal (6). The resulting nitroalcohol 7 was oxidized with pyridinium chlorochromate (PCC) in dichloromethane at room temperature[21]. Reaction of nitroketone 8 with p-toluenesulfonylhydrazine in methanol furnished the corresponding p-toluenesulfonylhydrazone 9 as crystalline derivative. Denitration of compound 9 by treatment with lithium aluminium hydride in tetrahydrofuran (THF) [22,23] and consecutive acid regeneration of carbonyl groups afforded the desired (Z)-1,4-dioxodec-7-ene (1) in 42% overall yield. Cyclodehydratation of compound 1 was carried out in a two phase system of 1% sodium hydroxide-ether during three days at room temperature and furnished cyclopentenone 2 in 90% yield.[24] In the infrared spectrum the absorption at 970 cm^{-1} characteristic of the (E)-isomer was almost negligible.[25,26]

In the case of the target molecule 3 we undertook the synthesis by reacting the protected nitroaldehyde 5 with methyl 9-oxononanoate (11).The latter is a readily available building block derived from cheap natural product as aleuritic acid by oxidative cleavage.[14] The nitroaldol condensation performed again on Amberlist A-21 without solvent gave 12 in good yield. Treatment of the latter with PCC in dichloromethane furnished the α-nitroketone 13, whose direct denitration with tri-n-butyltin hydride[27] and azobisisobutironitrile (AIBN) in refluxing benzene afforded the protected aldehydo keto ester 14. Subsequent deprotection of compound 14 was carried out in acetone-water with catalytic amounts of p-toluensulfonic acid and boron trifluoride etherate complex and furnished the free aldehydo keto ester 3 in 32% overall yield. Finally exposure of the latter to methanolic sodium methoxide afforded methyl 7-(5-oxocyclopentenyl)heptanoate (4) in 72% yield.

Compounds 1,2,3 and 4 were shown to be identical with authentic specimens independently prepared, by spectroscpy (IR, ^{1}H NMR) and chromatography (TLC,GLC).

Until the outset of our investigations, we were interested in the possibility that functionalized nitroalkanes might serve as convenient and efficient tools for C-C bond forming reactions. We hope that the realization of this goal carring out nitroaldol condensation, oxidation and direct or indirect denitration sequence may open up a new entry into syntheses of structurally complex substances.

EXPERIMENTAL

Proton NMR spectra were recorded at 90MHz on a Varian EM 390 instrument. ^{1}H NMR shifts are given in parts per milion from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. Mycroanalyses were performed by using C,H,N Analyzer Model 185 from Hewlett-Packard Co. Vapor-phase chromatographic analyses were performed on a Carlo Erba Fractovap 4160 HRGC instrument using capillary column of fused silica (0.40-45nm x 25 mt) with Carbowax 20 M. 2-(2-Bromoethyl)-1,3-dioxolane, (Z)-4-heptenal (6), p-toluenesulfonylhydrazine,tri-n-butyltin hydride, azobisisobutironitrile (AIBN), lithium aluminium hydride, Amberlite IRA 900, Amberlist A-21, pyridinium chlorochromate (PCC) are commercial materials. However, 2-(2-bromoethyl)-1,3-dioxolane can also be prepared by the method of Büchi and Wuest[28] and (Z)-4-heptenal (6) can be prepared according the procedure of Stetter and Kuhlmann[29] or by the method of A.I. Meyers and coworkers.[30] Tetrahydrofuran (THF) was obtained anhydrous by distillation over lithium aluminium hydride under argon. Benzene was dried by refluxing over sodium and stored over A4 molecular sieves.

2-(2-Nitroethyl)-1,3-dioxolane (5). 2-(2-Bromoethyl)-1,3-dioxolane (18.7 g, 10.35×10^{-2} mol) is added dropwise to a stirred solution of $NaNO_2$ (12.4 g, 180 mmol) in 200 ml of dimethyl formamide. The solution was stirred for seven hours at room temperature, then poused into 300 ml of cold water and extracted three times with ether (3x70ml). The combined extracted solution are dried, passed through a bed of Florisil and evaporated to afford 8.36 g (55%) of 5: bp 58/0.1 mm_{Hg}; IR(neat) 1550(NO_2) cm^{-1}; ^1H NMR δ 5.15-4.95 (m,1H); 4.52 (t,2H,J=6.75Hz); 4.20-3.70 (m,4H); 2.60-2.25 (m,2H). Anal. Calcd for $C_5H_9NO_4$: C,40.80; H,6.16; N,9.51. Found: C,41.00; H,6.20; N,9.10.

(Z)-1-(1,3-Dioxolan-2-yl)-2-nitronon-6-en-3-ol (7). A 100 ml, two necked flask was equipped with mechanical stirrer, charged with compound 5 (3.94g, 26 mmol); (Z)-4-heptenal (6) (3.0g, 26mmol) was added and the mixture was stirred during 5 min. Amberlist A-21 (8.0g) was added and stirring continued for 4 hours. After standing for 18 h the Amberlist was washed with dichloromethane (3x30 ml). The filterd extract is evaporated at reduced pressure to give crude nitroalkanol 7. The product was purified by short column chromatography (SiO_2 0.063-0.200) with ethyl acetate-n-hexane (25:75) as eluent, and 5.13g (79%) of 7 was obtained as an oil: IR(neat): 3435(OH), 1550(NO_2) cm^{-1}. ^1H NMR δ 5.65-5.15 (m,2H); 5.10-4.90 (m,1H); 4.85-4.55 (m,1H); 4.20-3.70 (m,5H); 2.80-1.30 (m,8H); 0.98 (t,3H,J=7.5Hz). Anal. Calcd for $C_{12}H_{21}NO_5$: C,55.58; H,8.16; N, 5.40. Found: C,55.71; H,8.06; N,5.28.

(Z)-1-(1,3-Dioxolan-2-yl)-2-nitronon-6-en-3-one (8). In a 100 ml two neck round-bottom flask equipped with a mechanical stirrer, pyridinium chlorochromate (2.75g, 12.8 mmol) was sospended in anhydrous dichloromethane (50 ml) in the presence of molecular sieves (5g). The nitro-alcohol 8 (2.2g, 8.5mmol) was added all at once. The mixture was stirred at room temperature for 24 hr and then another portion of PCC (1.37, 6.4mmol) was added. The mixture was stirred at room temperature for additional 12 hr. The mixture was diluted with ether (60 ml) and the supernatant liquid was decanted from the rest. The organic solution was passed through a short pad of Florisil to give a clear solution. Elimination of the solvent afforded 1.55g (71%) of 8 as an oil. IR(neat) 1730(CO), 1550(NO_2) cm^{-1}. ^1H NMR δ 5.63-5.15 (m,3H); 5.10-4.95 (m,1H); 4.10-3.75 (m,4H); 2.90-1.95 (m,8H); 0.92 (t,3H,J=7.5Hz). Anal Calcd for $C_{12}H_{19}NO_5$: C,56.02; H,7.44; N,5.44. Found: C,55.88; H,7.53; N,5.55.

(Z)-1-(1,3-Dioxolan-2-yl)-2-nitronon-6-en-3-one p-toluenesulfonylhydrazone (9). A solution of p-toluenesulfonylhydrazine (0.63g, 3.4mmol) in methanol (5ml) was added to a solution of compound 8 (0.83g, 3.2mmol) in methanol (5ml) and the mixture was allowed to stand at room temperature for 12 hr. Water was added and the solution extracted with ether (3x30ml). The ethereal solution was dried and evaporated to afford the crude p-toluenesulfonylhydrazone which crystallize from cyclohexane-dichloromethane: 1.25g (93%) of product 9 was obtained: mp 94-95°C. IR(KBr) 3210(NH), 1545(NO_2), 1340, 1165(SO_2) cm^{-1}. ^1H NMR δ 7.57 (AA'BB' pattern, 4H, J=8.0Hz); 5.55-5.05 (m,3H); 4.95-4.80 (m,1H); 4.05-3.68 (m,4H); 2.70-1.70 (m+s,11H); 0.9 (t,3H,J=7.5Hz). Anal. Calcd for $C_{19}H_{27}N_3O_6S$: C,53.64; H,6.40; N,9.88; S,7.52. Found: C,53.75; H,6.42; N,9.93; S,7.40.

(Z)-1-(1,3-Dioxolan-2-yl)-non-6-en-3-one p-toluenesulfonylhydrazone (10). Dry tetrahydrofuran (15ml) was placed in a dried nitrogen flushed 100 ml flask fitted with a septum inlet and a magnetic stirring bar. Lithium aluminium hydride (0.133g, 3.5mmol) was added and the mixture cooled to 0°C. p-Toluenesulfonylhydrazone 9 (0.5g, 1.17mmol) was dissolved in dry tetrahydrofuran (10ml) and added dropwise. The mixture was stirred for 20 min at 0°C, treated carefully with cold water, acidified with 2N H_2SO_4 and extracted carefully with ether (2x50ml). The ether layer was dried ($MgSO_4$), passed through a bed of Florisil (10g) and the solvent was removed at reduced pressure. Pure product 10 was obtained (0.42g, 94%) as an oil. IR(neat): 3230(NH); 1340, 1165(SO_2). ^1H NMR δ 7.57 (AA'BB' pattern, 4H, J=8.0Hz); 5.48-5.05 (m,2H); 4.90-4.58 (m,1H); 4.15-3.65 (m, 4H); 2.42 (s,3H); 2.38-1.62 (m,10H); 0.95 (t,3H,J=7.5Hz). Anal. Calcd for $C_{19}H_{28}N_2O_4S$: C, 59.98; H,7.42; N,7.36; S,8.41. Found: C,60.10; H,7.33; N,7.25; S,8.98.

(Z)-1,4-dioxodec-7-ene (1). Compound 10 (0.70g, 1.84mmol) was dissolved in acetone (25 ml) and water (2.5ml). p-Toluenesulfonic acid (0.4g, 2.3mmol) and paraformaldehyde (0.56g, 1.84mmol) were added and the mixture was stirred at room temperature for 4hr and then boron trifluoride etherate was added (0.25ml). The mixture was stirred at room temperature (15hr) and then evaporated at reduced pressure, diluted with ether (50ml) and the organic layer dried (Na_2SO_4). Solvent was removed at reduced pressure and the crude product was purified by chromatography over a silica gel column (SiO_2 0.0063-0.200) with ethylacetate-n-hexane (20/80) as eluent; 0.26g (85%) of 1 was obtained: bp 94/ 0.8mm_{Hg}. IR(neat) 1715, 1730 (CO) cm^{-1}. ^1H NMR δ 9.82 (s,1H); 5.60-5.10 (m,2H); 2.72 (s,4H); 2.65-1.80 (m,6H); 0.97 (t,3H,J=7.5Hz). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H,9.59. Found: C,71.50; H,9.70.

-(Z)-2-(2-Pentenyl)-2-cyclopenten-1-one (2). Compound 2 was obtained treating 1 (0.4g,2.3mmol) with 1% NaOH (10ml) and ether (15ml) with stirring during 3 days according the procedure of Stork[24]. 0.29g (90%) bp 76/0.1mm$_{Hg}$. IR (neat) 1720(CO); 1630(C=C) cm^{-1}. ^{1}H NMR δ7.40-7.20(m,1H); 5.70-5.15(m,2H); 3.02-1.80; 0.98(t,3H,J=7.5Hz). Anal Calcd for $C_{10}H_{14}O$: C,79.95; H,9.39. Found: C,8.01; H,9.30.

Methyl 11-(1-3-Dioxolan-2-yl)-10-nitro-9-hydroxyundecanoate (12).A 100 ml two necked flask was equipped with mechanical stirrer, charged with compound 5(1.58g,10.7 mmol). Methyl 9-oxononanoate (11)[14] (2.0g,10.7mmol) was added and the mixture stirred during 5 min. Aberlist A-21 (3.3g) was added and stirring continued for 4 hr. After standing for 13 h, the Amberlist was washed with dichloromethane (3x20 ml). The filtered extract is evaporated at reduced pressure to give crude nitroalcohol 12. This product was purified by short column chromatografphy (SiO_2 0.0063-0.200) with ethylacetate-n-hexane (25:75) as eluent, and 2.86g of 12 was obtained as an oil: IR(neat)3470(OH),1725(CO),1550(NO_2)cm^{-1}. ^{1}H NMR δ 5.15-4.93(m,1H);4.90-4.53(m, 1H); 4.20-3.70(m,5H); 3.68(s,3H); 2.90-2.00(m,5H); 1.85-1.00(m,12H). Anal. Calcd for $C_{15}H_{27}NO_7$: C,54.04; H,8.16; N,4.20. Found: C,54.20; H,8.25; N,4.31.

Methyl 11-(1,3-Dioxolan-2-yl-10-nitro-9-oxoundecanoate (13).In a 100 ml two necked flask equipped with a mechanical stirrer, pyridinium chlorochromate (2.6g,12mmol) was suspended in anhydrous dichloromethane (30 ml) in the presence of molecular sieves (3.0g, A4). Nitroalcohol 12(2.65g,7.95mmol) was added all at once. The mixture was stirred at room temperature for 24 hr and then another portion of PCC (1.3 g,6.0mmol) was added. The mixture was diluted with ether (50 ml) and the supernatant liquid was decanted from the rest. The organic solution was passed through a short pad of Florisil to give a clear solution. Elimination of the solvent afforded 1.85 g(70%) of 13: mp 53°C.IR(KBr) 1730(CO),1555(NO_2) cm^{-1}. ^{1}H NMR δ 5.52-5.25(m,1H); 5.10-4.90(m,1H); 4.10-3.77(m,4H); 3.65(s,3H); 2.85-2.15(m,4H); 1.90-1.10(m,12H). Anal.Calcd for $C_{15}H_{25}NO_7$: C,54.37; H,7.61; N,4.23. Found: C,54.50; H,7.55; N,4.31.

Methyl 11-(1,3-Dioxolan-2-yl)-9-oxoundecanoate(14).Compound 13 (0.75g,2.26mmol)and AIBN (0.15g,0.91 mmol)were dissolved in dry benzene (15 ml). Tri n-butyltin hydride (1.15g,4.0mmol) was added under nitrogen.The solution was refluxed for 5 hr ,then evaporated and passed through a short column chromatography ($SiO_2$0.063-0.200) with ethyl acetate -n-hexane (25:75) as eluent.The pure product 14 was obtained (0.5g,78% yield) as an oil. IR(neat) 1710,1733(C=O)cm^{-1}. ^{1}H NMR δ 5.00-4.85(m,1H); 4.10-3.75 (m,4H); 3.65(s,3H); 2.75-1.10(m,18H).Anal.Calcd for $C_{15}H_{26}O_5$: C, 62.91; H,9.15.Found C,63.01; H,9.07.

Methyl 9,12-Dioxododecanoate (3).Compound 14 was dissolved in acetone (20ml) and water (2ml), distilled boron trifluoride etherate (0.3ml) and p-toluenesulfonic acid (66mg,0.35mmol) were added and the mixture was stirred at room temperature until all aldehyde was formed (TLC monitoring).The solution was evaporated at reduced pressure diluted with ether (50ml) and the organic layer washed with Na_2CO_3solution, water and dried (Na_2SO_4). Solvent was removed at reduced pressure to afford 0.24g (71%)of pure 3. as an oil. IR(neat): 1730,1715(C=O)cm^{-1}. ^{1}H NMR δ 9.82(s,1H); 3.65(s,3H); 2.72 (s,4H); 2.48(t,2H,J=7.5Hz); 2.31(t,2H,J=7.5Hz); 2.82-1.05(m,10H). Anal.Calcd for $C_{13}H_{22}O_4$: C, 64.44; H,9.15. Found: C,64.52; H,9.06.

7-(5-Oxocyclopentenyl)heptanoate (4).Compound 4 was obtained from 3 (0.2g,0.82mmol) working under the same conditions using sodium methoxide in methanol as reported[15]; 72% yield; bp 115/0.1mm$_{Hg}$. IR(neat) 1705,1725(C=O); 1630(C=C) cm^{-1}. ^{1}H NMR δ7.40-7.25 (m,1H); 3.67(s,3H); 2.70-1.10(m,16H). Anal.Calcd for $C_{13}H_{20}O_3$: C,69.61; H,8.99. Found C,69.71; H,9.03.

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REFERENCES.

1.- G.Rosini,R.Ballini, P.Sorrenti, Tetrahedron,39,4127(1983).
2.- E.P.Demole,Cap X Fragrance of Jasmine in "Fragrance Chemistry.The Science of Sense of Smell", Ed.Ernst T.Theimer,Academic Press,New York, 1982,pp349-396.
3.- P.Dubs,R.Stussi,Helv.Chim.Acta , 61,990(1978).
4.- G.Buchi, B.Egger,J.Org.Chem.,36,2021(1971).
5.- P.A.Grieco,J.Org.Chem.,37,2363(1972).
6.- K.Oshima,H.Yamamoto,H.Nozaki,J.Am.Chem.Soc.,95,4446(1973).
7.- A.I.Meyers,N.Nazarenko,J.Org.Chem.,38,176(1973).
8.- I.Matsuda,S.Murata,Y.Izumi,J.Org.Chem.,45,237(1980).
9.- T.Sato,T.Kawara,K.Sakata,T.Fujisawa,Bull.Chem.Soc.Jpn.,54,505(1981).
10.- Zhiyu Liu,Weipeng Han, Hua Hsueh Husueh Pao,39,358(1981). C.A.95,486(1981).
11.- Y.Naoshima,S.Mizubuchi,S.Wakabayashi,Agric.Biol.Chem.,43,1765 (1979).
12.- V.R.Mamdapur, C.S.Subramaniam,P.J.Thpmas,M.S.Chadha, Indian J.Chem.Sec.B, 269 (1979).
13.- U.Valcavi,P.Farina,SInnocenti,V.Marotta,Synthesis,124(1983).
14.- J.M.Reuter,R.G.Salomon,J.Org.Chem.43,4247(1978) and references cited therein.
15.- E.Wenkert,B.L.Buckwalter,A.A.Craveiro,E.L.Sanchez,S.S.Sathe,J.Am.Chem.Soc.,100 1267(1978).
16.- "New Synthetic Routes to Prostaglandins and Tromboxanes" Ed.S.M.Roberts and F. Scheinmann Academic Press,London,1982.
17.- J.S.Bindra,R.Bindra "Prostaglandin Synthesis" Academic Press, New York, 1977.

18.- G.Gelbard,S.Colonna,Synthesis,113(1972).
19.- R.L.Crumbie,J.S.Nimitz,H.S.Mosher,J.Org.Chem.,47,4040(1982).
20.- Amberlist A-21 was more effective than alumina : G.Rosini,R.Ballini,P.Sorrenti Synthesis,1014)1983).
21.- G.Rosini,R.Ballini,Synthesis,543(1983).
22.- G.Rosini,R.Ballini,V.Zanotti,Synthesis,137(1983).
23.- G.Rosini,R.Ballini,Synthesis,228(1983).
24.- G.Stork,A.A.Ozorio,A.Y.W.Leong,Tetrahedron Lett.,5175(1978).
25.- L.Crombie,S.H.Harper,J.Chem.Soc.,869(1952).
26.- In a mixture of isomers, the vinylic carbons of (Z)-disobstituted alkenes ca be distinguished from the corresponding carbons of (E)-alkenes: D.E.Dorman,M.Jautelat,J.D.Roberts,J.Org.Chem.,36,2757(1971).
27.- N.Ono,I.Hamamoto,H.Miyiake,A.Kaji,Chem.Lett.,1079(1982).
28.- G.Buchi, H.Wuest,J.Org.Chem.,31,977(1966).
29.- H.Stettert, H.Kuhlmann,Synthesis, 379(1975).
30.- A.I.Meyers,A.Nabeya,H.W.Adickes,I.R.Politzer,G.R.Malone,A.C.Kovelesky,R.L.Nolen R.C.Portnoy, J.Org.Chem.,38,36(1973).