Tetrahedron Vol. 39, No 13, pp. 2227 to 2230, 1983
Printed in Great Britain.

0040–4020/83 $3.00 + .00
Pergamon Press Ltd.

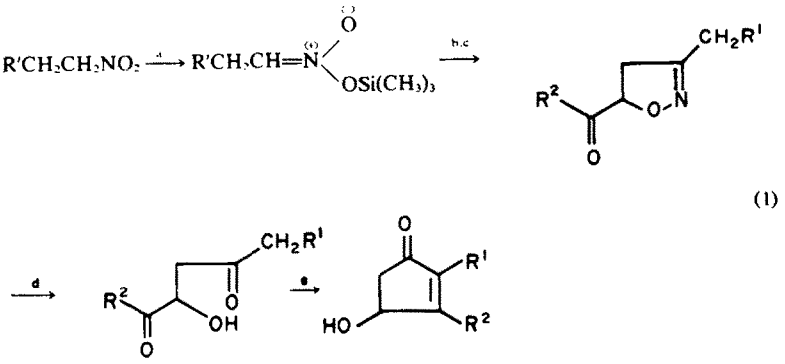
SILYL NITRONATES IN ORGANIC SYNTHESIS. SYNTHESIS OF PROSTAGLANDIN INTERMEDIATES

NALIN B. DAS and KURT B. G. TORSSELL*
Department of Organic Chemistry, Chemical Institute, University of Aarhus, 8000 Aarhus C, Denmark

(*Received in the UK 25 June* 1982)

Abstract—The target molecule **1b** has been prepared by a new methodology *via* silyl nitronates and 2-isoxazolines. Since **1a** was converted earlier into PGE_1 our approach constitutes a novel entrance to prostaglandins.

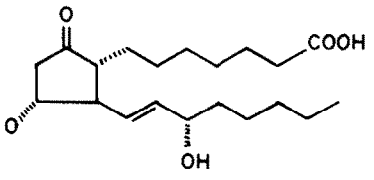
The versatility of silyl nitronates and the derived 2-isoxazolines as precursors for a number of classes of compounds was demonstrated in a preceding, exploratory paper.[1] 4-Hydroxy-2-pentenones can be prepared in good yields in few steps from primary nitro compounds and vinyl ketones.



(1)

a. Et_3N, $ClSi(CH_3)_3$, b. $R^2COCH=CH_2$, c. *p*-TsOH, d. Ti^{3+}, e. OH^-.

The cyclopentene moiety is contained in several important naturally occurring compounds such as steroids, rethrolones, prostanoids etc. and simple routes to this 5-ring system are therefore always in demand.[2,3] Of special interest is the fact that the cyclization of the hydroxydiones from (1) directly gives cyclopentenones suitably functionalized for further elaboration into prostanoids, e.g. PGE_1



PGE_1

Furthermore, the synthesis shown in eqn (1) is convergent and of general applicability, because our choice of side chains, i.e. our choice of nitro and vinyl derivatives (R^1 and R^2) is quite optional.

This work describes a novel entrance to prostaglandins, a group of hormones, which have been and still are the object of numerous synthetic studies.[4]

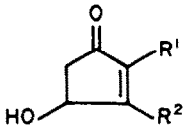
It was decided to synthesize an intermediate which can be converted in few steps to the naturally occurring prostaglandins. Therefore, the prostanoid **1a** synthesized by Miyano *et al.*[5,6] was chosen as our primary goal. Hence, we needed as starting material an ω-nitrocarboxylic ester to form the upper chain (R^1) and a suitable substituted vinyl ketone for the lower chain (R^2). ω-Nitrocarboxylic acids are available by several methods and the nitration of cyclic ketones was chosen by chance as a convenient route.[7] Here another concession was made purely from economic reasons. Cyclononanone gives the required 9-nitrononanoate, but it is a rather costly chemical. Therefore we carried out all our exploratory work with the considerably less expensive cyclooctanone, which was converted to 8-nitrooctanoate. If the synthesis worked out satisfactorily with the lower homologue, it will certainly work in the 9-nitrononanoate series. As we shall see later, it was not necessary to prepare or use this compound, since our work gradually led to more convenient procedures, better suited for large scale preparations.

It was established in our exploratory study[1] that the general strategy as shown in (1) worked well for 8-nitrooctanoate and methyl vinyl ketone, giving the O-methylated prostanoid **2**. However, two problems remained to be solved.

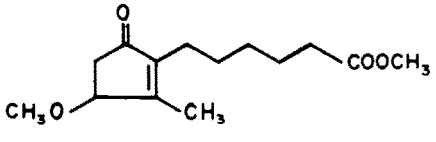
Firstly, we wish to obtain the hydroxylated derivative **1c** directly from **3a** by the base catalyzed cyclization. Persevering experimentation led eventually

to a useful procedure. By performing the cyclization of **3a** in two phase aqueous sodium hydroxide **1c** is formed in a reasonably good yield. The ester **3a** is slowly hydrolyzed and enters the aqueous phase in a low concentration as a carboxylate, which seems to favour the cyclization.

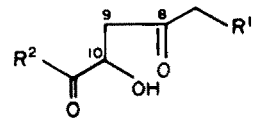
The second problem concerned the choice of R^2. It should not contain enolizable protons leading to an undesired condensation with the other carbonyl group. From this point of view the easily available acetoxymethyl vinyl ketone[1,8] is not the best choice. It gave **4a** with the silyl nitronate of nitropropane, but **4a** on reduction with Ti^{3+} showed extensive elimination of the acetoxy group with formation of a methyl group in aqueous methanol.[1] This undesired side reaction could be considerably repressed by carrying out the reduction in aqueous acetic acid. However, subsequent base catalyzed cyclization of **3b** did not give the desired products **1d** or **1e.** This approach was therefore abandoned and we turned our interest temporarily twoards **1f,** a lower homologue of another intermediate in Miyano's synthesis, which conceivably could be prepared from **4b** according to eqn 1. Preparation of **4b** and other 2-isoxazolines with an α,β-unsaturated side chain requires the cross conjugated 1,4-dien-3-ones as dipolarophiles, a class of compounds notorious for their instability. The preparative methods of this class of compounds are also limited. The simplest route to these dienones is acylation of vinyl silanes with α,β-unsaturated acid chlorides[9] and our results are accounted for in an accompanying paper.[10] **4b** and **4c** were prepared from vinyl 2-phenylethenyl ketone and methyl 8-nitrooctanoate and nitropropane, respectively. The subsequent reduction of **4b** and **4c** with Ti^{3+} in methanol gave a disappointingly small yield of the desired compounds **3c** and **3d.** According to the ^1H NMR spectra the main products are the saturated derivatives **3e** and **3f,** respectively. Some cleavage of the C^5–O bond had also occurred. It has been noted earlier that the double bond of α,β-unsaturated ketones is reduced by titanous ions.[11]



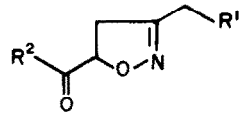
1a $R^1 = (CH_2)_4COOH$, $R^2 = CHO$
1b $R^1 = (CH_2)_5COOH$, $R^2 = CHO$
1c $R^1 = (CH_2)_5COOH$, $R^2 = CH_3$
1d $R^1 = CH_3$, $R^2 = CH_2OAc$
1e $R^1 = CH_3$, $R^2 = CH_2OH$
1f $R^1 = (CH_2)_5COOH$, $R^2 = CH{=}CHC_6H_5$
1g $R^1 = (CH_2)_5COOH$, $R^2 = CH{=}C(CH_3)_2$
1h $R^1 = CH_3$, $R^2 = CH{=}C(CH_3)_2$
1i $R^1 = CH_3$, $R^2 = CHO$



2



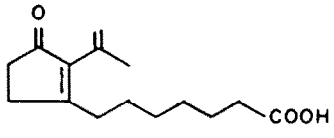
3a $R^1 = (CH_2)_4COOCH_3$, $R^2 = CH_3$
3b $R^1 = CH_3$, $R^2 = CH_2OAc$
3c $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH{=}CHC_6H_5$
3d $R^1 = CH_3$, $R^2 = CH{=}CHC_6H_5$
3e $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH_2CH_2C_6H_5$
3f $R^1 = CH_3$, $R^2 = CH_2CH_2C_6H_5$
3g $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH{=}C(CH_3)_2$
3h $R^1 = CH_3$, $R^2 = CH{=}C(CH_3)_2$



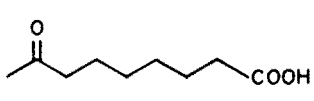
4a $R^1 = CH_3$, $R^2 = CH_2OAc$
4b $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH{=}CHC_6H_5$
4c $R^1 = CH_3$, $R^2 = CH{=}CHC_6H_5$
4d $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH{=}C(CH_3)_2$
4e $R^1 = CH_3$, $R^2 = CH{=}C(CH_3)_2$
4f $R^1 = (CH_2)_5COOCH_3$, $R^2 = CH{=}C(CH_3)_2$

It was reasoned that an increased electron density in the olefinic bond combined with steric hindrance should hamper this reduction. Condensation of methyl 8-nitrooctanoate and nitropropane with 2-methylpropenyl vinyl ketone gave **4d** and **4e**, respectively, and in fact, subsequent reduction with Ti^{3+} in aqueous acetic acid gave **3g** and **3h** in good yields, which by base catalyzed cyclization gave **1g** and **1h,** respectively. The aqueous acetic acid medium seems to increase the selectivity of the titanous ion reduction.

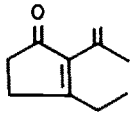
In addition to the desired cyclization product **1g,** **3g** gave small amounts of **5** and **6**, which could be separated by TLC. The formation of **5** can be explained by the supposition that **3g** was contaminated by some C^{10} dehydroxy derivative and that the C^8-carbonyl condenses with C^{12} with concomitant shift of the double bond to $C^{13,14}$.



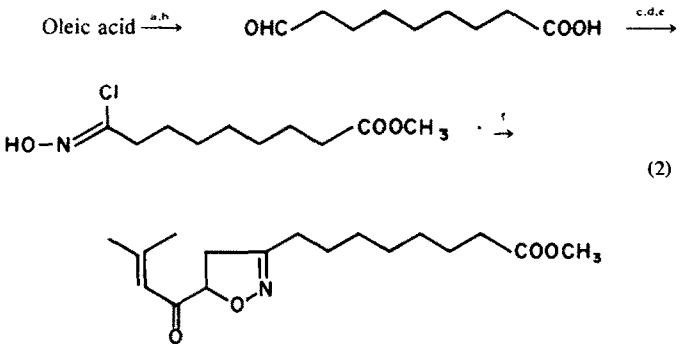
5



6



7



4f

a. H_2O_2, H^+, b. $Pb(OAc)_4$, c. CH_3OH, H^+, d. NH_2OH, e. Cl_2, f. NEt_3, 2-methylpropenyl vinyl ketone.

The formation of **6** is explained by a retro aldol condensation at C.[9,10] The structural proof of **5** rests on MS, ^1H and ^{13}C NMR spectroscopic evidence. Base catalyzed cyclization of **3h** gave similarly rise to minor amounts of **7**. Cleavage of the side chain of **1g** and **1h** with sodium periodate and osmium tetroxide gave the aldehydes **1b** and **1i**. The spectral characteristics of **1b** were practically identical to those of the higher homologue **1a**.[5]

In conjunction with related work on the utilization of 2-isoxazolines in organic synthesis, an alternative route to **4f** was worked out.[12] Oleic acid can be hydroxylated and cleaved to 9-oxy-nonanoic acid in large scale operations according to standard procedures (eqn 2). Subsequent oximation and chlorination gives the chloro oxime, from which the nitrile oxide can be generated by addition of base and added to the olefin *in situ*.[13]

Having access to **4f**, the higher homologue of **4d**, we consider that we have arrived at a formal synthesis of PGE_1.

EXPERIMENTAL

2-(5-Carboxypentyl)-3-formyl- 4 -hydroxy-2-cyclopentenone, **1b**. **1g** (100 mg, 0.37 mmole), sodium periodate (200 mg) and osmium tetroxide (0.5 mg) dissolved in water (2 ml), dioxane (2 ml) and methanol (1 ml) were stirred under nitrogen for 8 h at 25°. Aqueous solium chloride (2 ml) was added, the precipitate filtered, and the solution extracted with ether. Evaporation of the solvent and purification of the product by TLC (ether, 20% petrol ether) gave **1b** (70 mg, 78%) contaminated by a small amount of the starting material, **1g**. ^1H NMR ($CDCl_3$): δ 1.0–3.0 (11H, m), 2.85 (1H, dd, J = 19 and 6 Hz), 5.21 (1H, br.d., J = 6 Hz), 10.40 (1H, s). UV (MeOH): λ_{max} 233. MS: M^+ 240, 222, 204, 176, 55.

1i was synthesized analogously by oxidative cleavage of **1h** (100 mg), 12 h, in water (2 ml) and methanol (3 ml). The crude product was purified by TLC (silica, ether, 40% petrol ether) to yield **1i** (65 mg, 77%) contaminated by some **1h**. ^1H NMR ($CDCl_3$): δ 2.13 (3H, s), 2.4 (1H, dd, J = 18.8 and 2.6 Hz), 2.9 (1H, dd, J = 18.8 and 5.8 Hz), 5.20 (1H, br.d, J = 5 Hz), 10.41 (1H, s).

2-(5-Carboxypentyl)-3-methyl-4-hydroxy-2-cyclopentenone, **1c**. **3a** (240 mg, 0.93 mmole) was stirred under nitrogen for 3 h with aqueous sodium hydroxide (5 ml, 10%). Aqueous sodium chloride (5 ml) was added and by extraction with ether some starting material (30 mg) was recovered. Acidification with diluted hydrochloric acid and extraction with ether gave crude **1c** (170 mg). Chromatography on a TLC plate (silica, $CHCl_3$, 30% EtOAc) yielded pure **1c** (80 mg, 38%). ^1H NMR ($CDCl_3$): δ 1.0–1.9 (6H, m), 2.07 (3H, s), 2.0–2.5 (5H, m), 2.72 (1H, dd, J = 18.6 Hz), 4.69 (1H, br.d, J = 5 Hz), 5.9 (2H, br.s.). MS M^+ 226.

2-(5-Carboxypentyl)-3-(2-metylpropenyl) - 4 - hydroxy-2-cyclopentenone, **1g**. **3g** (520 mg, 1.74 mmole) was stirred for 5 h under N_2 at 25° with aqueous sodium hydroxyde (10%, 15 ml). Acidification, ether extraction and purification of the crude product by TLC ($CHCl_3$, 10% CH_3 OH) gave **1g** (190 mg, 41%) as an oil. ^1H NMR ($CDCl_3$): δ 1.0–3.0 (12H, m), 1.90 (3H, s), 1.97 (3H, s), 5.02 (1H, br.s), 6.00 (1H, br.s). MS (M^+) 266. **5**, liquid, and **6**, m.p. 38° (lit[14] 40.5°) could be isolated from the TLC plate as a somewhat faster moving fraction. ^1H NMR ($CDCl_3$) **5**: δ 1.0–2.0 (8H, m), 1.86 (3H, s), 2.0–2.7 (8H, m), 4.66 (1H, br.s), 5.10 (1H, br.s). ^{13}C NMR ($CDCl_3$): δ 22.21 (CH_3), 24.46 (CH_2), 27.37 (CH_2), 28.65 (CH_2), 29.12 (2 × CH_3), 31.38 (CH_2), 34.04 (CH_2), 34.43 (CH_2), 116.28 ($H_2C=$), 137.31 (C=), 142.94 (C=), 174.76 (C=), 179.0 (C=O), 208.63 (C=O). MS (M^+) 250. ^1H NMR ($CDCl_3$) **6**: 1.1–1.9 (8H), 2.10 (3H, s), 2.1–2.6 (4H, m).

1h was obtained as a liquid from **3h** according to the same method in 43% yield, purified by preparative TLC (silica, $CHCl_3$, 3% CH_3OH), 10% NaOH, 2.5 h, N_2, 25°. ^1H NMR ($CDCl_3$): δ 1.69 (3H, s), 1.83 (3H, s), 1.97 (3H, s), 2.3 (1H, dd, J = 18 and 2 Hz), 2.8 (1H, dd, J = 18 and 5 Hz), 4.93 (1H, br.d, J = 5 Hz), 5.98 (1H, s). MS (M^+) 166. A fast moving fraction contained **7**. ^1H NMR ($CDCl_3$): δ 1.08 (3H, t, J = 7 Hz), 1.91 (3H, br.s), 2.50 (2H, q, J = 7 Hz), 2.69 (4H, s), 4.78 (1H, br.s), 5.17 (1H, br.s).

The preparation of the compounds **3a** and **4a** is described in Ref. 1 and **4f** in Ref. 12.

General procedure for reduction of 2-isoxazolines

The 2-isoxazolines (10 mmole) were dissolved in acetic acid (50 ml) and an aqueous Ti^{3+} solution (2–2.5 equivalents, 50 ml, pH adjusted to *ca* 2–2.5) was added. The mixture was stirred under nitrogen for *ca* 1–10 days (decolouration). Water was added and the solution was extracted in a continuous extractor with methylene chloride. Evaporation yielded the β-hydroxyketone which in most cases was sufficiently pure for further transformations.

1-Acetoxy-3-hydroxy-2,5-heptandione, **3b**. From **4a**,[1] 7.5 h, 2 equiv. Ti^{3+}, yield 72% (TLC, silica, $CHCl_3$, 1% CH_3OH), liquid. ^1H NMR ($CDCl_3$): δ 1.04 (3H, t, J = 7.0 Hz), 2.13 (3H, s), 2.49 (2H, q, J = 7.0 Hz), 2.92 (2H, d, J = 5.2 Hz), 4.15 (1H, br.s), 4.51 (1H, t, J = 5.2 Hz), 5.01 (2H, s).

Methyl 8,11-dioxo-10-hydroxy-13-methyl-12-tetradecenoate, **3g**. From **4d**, 2d, 2.4 equiv. Ti^{3+}, yield 61% (TLC, silica, $CHCl_3$, 15% EtOAc), Liquid. ^1H NMR ($CDCl_3$): δ 1.1–1.8 (8H, m), 1.95 (3H, s), 2.20 (3H, s), 2.1–2.6 (4H, m), 2.73 (1H, d, J = 4.5 Hz), 2.75 (1H, d, J = 6.5 Hz), 3.63 (3H, s), 4.45 (1H, dd, J = 4.5 and 6.5 Hz), 6.15 (1H, br.s). MS (M^+) 298.

5-Hydroxy-8-methyl-7-nonen-3,6-dione, **3h**. From **4e**, 2d,

2.4 equiv. Ti^{3+}, yield 70% (TLC, silica, $CHCl_3$, 15% EtOAc), liquid. ^1H NMR ($CDCl_3$): δ 1.05 (3H, t, J = 7.2 Hz), 1.96 (3H, s), 2.20 (3H, s), 2.50 (2H, q, J = 7.2 Hz), 2.73 (1H, d, J = 6.8 Hz), 2.75 (1H, d, J = 4.2 Hz), 3.9 (1H, br.s), 4.46 (1H, dd, J = 6.8 and 4.2 Hz), 6.14 (1H, br.s).

General procedure for the preparation of the 2-*isoxazolines*, **4b, c, d, e**. A mixture of the nitro compound (10 mmole, triethylamine (15 mmole), the vinyl ketone (15 mmole, and trimethyl chlorosilane (15 mmole) were refluxed in benzene:acetonitrile (2:1, 20 ml) for 1 h. The mixture was cooled, filtered, and again refluxed with toluene-*p* sulfonic acid (0.5 g) for 1 h. Methylene chloride (15 ml) was added, the solution washed with water and aqueous sodium bicarbonate, dried over sodium sulfate, evaporated and the remaining 2-isoxazoline purified by distillation or chromatography. The yield is 60–90%.

4b. From vinyl 2-phenylethenyl ketone[10] and methyl 8-nitro-octanoate,[1] yield 58%, liquid, purified by chromatography (silica, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.1–1.8 (8H, m), 2.0–2.5 (4H, m), 3.17 (1H, d, J = 10.1 Hz), 3.23 (1H, d, J = 7.0), 3.61 (3H, s), 5.08 (1H, dd, J = 10.1 and 7.0 Hz), 7.16 (1H, d, J = 16.2 Hz), 7.0–7.7 (5H, m), 7.69 (1H, d, J = 16.2 Hz).

4c. From vinyl 2-phenylethenyl ketone[10] and nitropropane, yield 55%, liquid, purified by TLC (silica, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.18 (3H, t, J = 7.5 Hz), 2.42 (2H, q, J = 7.5 Hz), 3.25 (1H, d, J = 10.8 Hz), 3.28 (1H, d, J = 7.2 Hz), 5.17 (1H, dd, J = 10.8 and 7.2 Hz), 7.22 (1H, d, J = 16 Hz), 7.2–7.8 (5H, m), 7.80 (1H, d, J = 16 Hz).

4d. From vinyl 2-methyl-1-propenyl ketone[10] and methyl 8-nitro-octanoate,[1] yield 93%, liquid, purified by TLC (silica, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.1–1.8 (8H, m), 1.97 (3H, s), 2.19 (3H, s), 2.1–2.5 (4H, m), 3.12 (1H, d, J = 10.2 Hz), 3.14 (1H, d, J = 7.5 Hz), 3.65 (3H, s), 4.84 (1H, dd, J = 10.2 and 7.5 Hz), 6.44 (1H, br.s). MS (M^+) 295.

4e. From vinyl 2-methyl-1-propenyl ketone[10] and nitropropane, bp 84–88°/0.1 mmHg, yield 88%, liquid. ^1H NMR ($CDCl_3$): δ 1.16 (3H, t, J = 7.5 Hz), 1.96 (3H, s), 2.19 (3H, s), 2.38 (2H, q, J = 7.5 Hz), 3.15 (1H, d, 10.0 Hz), 3.17 (1H, d, 7.5 Hz), 4.83 (1H, dd, J = 10.0 and 7.5 Hz), 6.43 (1H, br.s).

Acknowledgement—We wish to thank DANIDA for a fellowship to N.B.D.

REFERENCES

[1]S. H. Andersen, N. B. Das, R. D. Jørgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma and K. B. G. Torssell, *Acta Chem. Scand.* **B36**, 1 (1982).
[2]R. A. Ellison, *Synthesis* 397 (1973).
[3]T. L. Ho, *Synth. Commun.* **4**, 265 (1974).
[4]J. S. Bindra and R. Bindra, *Prostaglandin Syntheses*, Academic Press, New York (1977).
[5]M. Miyano, C. R. Dorn and R. A. Mueller, *J. Org. Chem.* **37**, 1810 (1972).
[6]M. Miyano and M. A. Stealey, *Ibid.* **40**, 1748 (1975).
[7]H. Feuer and P. M. Pivawer, *Ibid.* **31**, 3152 (1966).
[8]G. F. Hennion and F. D. Kupiechi, *Ibid.* **18**, 1601 (1953).
[9]J.-P. Pillot, J. Dunogues and R. Calas, *Bull. Soc. Chim. France* 2143 (1975).
[10]G. Kjeldsen, J. S. Knudsen, L. S. Petersen and K. B. G. Torssell, *Tetrahedron* **39**, 2237 (1983).
[11]L. C. Blaszczak and J. E. McMurry, *J. Org. Chem.* **39**, 258 (1974).
[12]S. R. Mukerji, K. K. Sharma and K. B. G. Torssell, *Tetrahedron* **39**, 2231 (1983).
[13]Ch. Grundmann and P. Grünanger, *The Nitrile Oxides*. Springer-Verlag, Berlin (1971).
[14]M. Asano and H. Takahashi, *J. Pharm. Soc. Japan* **68**, 188 (1948).