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Prins Reaction of 2-Oxabicyclo[3.3.0]oct-6-en-3-one and Related Derivatives+

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Abstract: *Reaction of formaldehyde with the title olefinic lactone in acetic acid affords diacetate of 1,3-diol (**2a**) as the main product in 50 - 60% yield via regioselective trans-addition. Less favourable results were obtained with related bicyclic derivatives.*

Introduction

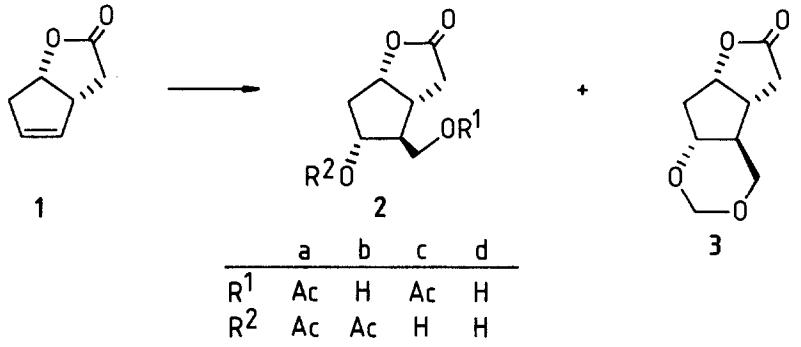
The acid catalyzed addition of formaldehyde to olefins (Prins reaction)[1,2] offers a widely used method to convert olefins into 1,3-diols or 1,3-dioxanes. The synthetic value of this reaction has been considerably enhanced by the pioneering work of Fodor et al.[3] who recognized that the addition of formaldehyde to cyclohexene affords *trans*-2-hydroxymethylcyclohexanol (as the diacetate or cyclic acetal of formaldehyde) without detectable formation of corresponding *cis* products. In spite of numerous studies[4-11] no generally accepted mechanism of the Prins reaction seems to be available at present.

Results and Discussion

With the aim to avoid application of hazardous materials (e. g. thallium and tin compounds) in Corey's brilliant synthesis of prostaglandins[12] we began systematic search for a simplified preparation of a key compound (**2**) to render large scale production of prostaglandins secure and economical as well[13].

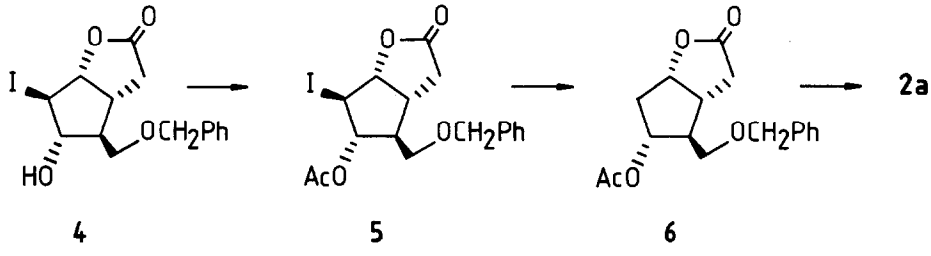
Contrary to our expectations of modest yields, the addition of formaldehyde to the unsaturated bicyclic lactone (**1**) took place smoothly in acetic acid in the presence of sulfuric acid as catalyst at 75 - 80 °C affording **2a** in 60 - 70% yield together with several minor by-products out of which **2b** (3%), **2c** (8%), and **3** (9.5%) could be isolated by chromatography on silica gel. Synthesis of **2a** via Prins reaction represents an enantiospecific route to natural prostaglandins and their analogues[13]. Since the unsaturated lactone (**1**) has been reported to be available[14] in enantiomerically pure form by asymmetric hydroboration of methyl cyclopenta-2,4-dienylacetate this route can be performed without resolution of the starting material.

+Dedicated to Professor G. Fodor on the occasion of his 75th birthday.



Scheme 1.

Unequivocal assignment of structure and stereochemistry of **2a** could be achieved by comparison with an authentic sample prepared from Corey's iodolactone **4**[12].



Scheme 2.

Acetylation of **4** with acetyl chloride in pyridine followed by deiodination with tributyltin hydride in ether and subsequent cleavage of the benzyl ether moiety with boron trifluoride etherate in acetic anhydride furnished **2a**. Deacetylation in methanol afforded **2d** identical to that obtained via the Prins reaction (m. p., mixed m. p., $[\alpha]_D$, ^{13}C NMR, TLC).

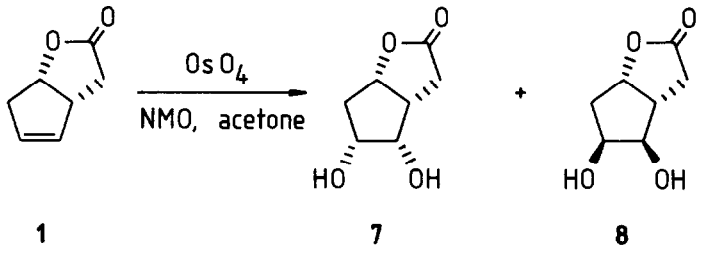
Characterization of the monoacetyl derivatives (**2b,c**) has been implemented, on the one hand, by their conversion into known diacetate (**2a**), on the other hand, both monoacetates (**2b,c**) gave a lactone diol identical to **2d** after deacetylation. The structure and stereochemistry of the secondary monoacetate (**2b**) has been further confirmed by comparison with authentic sample obtained from **6** by hydrogenolysis on Pd-C in ethyl acetate.

Formation of m-dioxane derivative **3** in low yield is not unexpected[1,2] and seems to be consistent with the general experience that cyclic formals are preferentially formed in aqueous solution. The configuration of **3** has been revealed by its acid catalyzed methanolysis to **2d** with concomitant removal of methylal. Inversely, acetalization of **2d** using a large excess of methylal with $POCl_3$ as catalyst gave rise to **3** in high yield.

By virtue of the high crystallity of the lactone diol (**2d**), the Prins reaction provides an exceptionally simple and economical method for the synthesis of **2** containing four of the five asymmetric centres present in natural $PGF_{2\alpha}$. Thus, acidic resin catalysed methanolysis of the crude reaction

mixture followed by precipitation with ether furnishes pure **2d** in 50-65% yield without tedious and expensive chromatography.

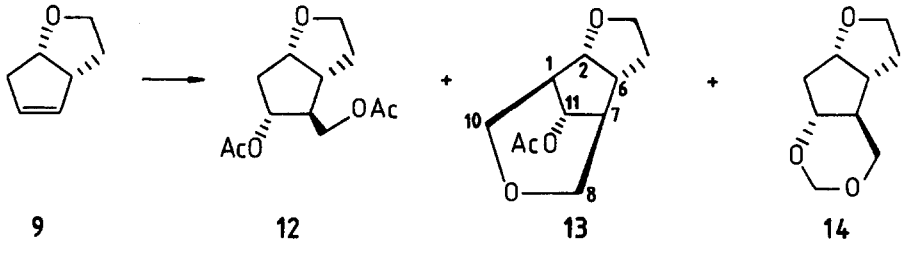
The apparently complete regioselectivity of the addition of formaldehyde to **1** in acetic acid proved to be exceptional in the case of this model since the reaction of other electrophilic reagents (HOBr, PhSeCl, $Hg(OAc)_2$, B_2H_6) gave rise to all possible regioisomeric products[15] in comparable amounts. Similarly, the addition of OsO_4 followed a stereochemical pattern of low "exo - endo" selectivity affording both *endo-cis-diol* (**7**) and *exo-cis-diol* (**8**) nearly in equal yields (**7 : 8** = 43 : 57)[16].

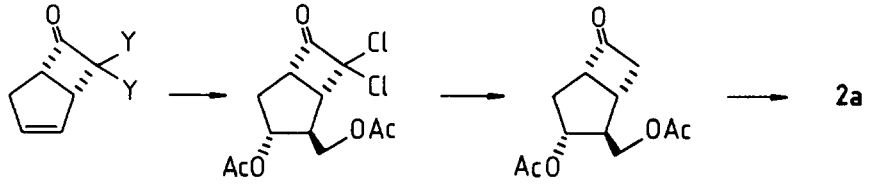


1 **7** **8**

Scheme 3.

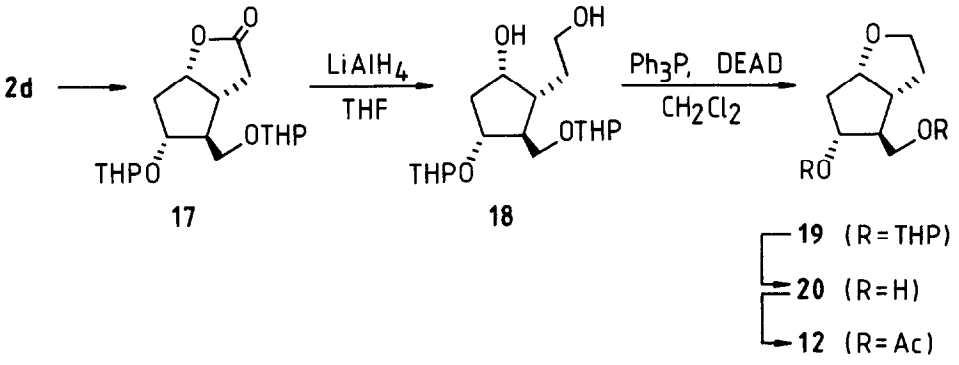
To form an idea of the scope of this favourable Prins reaction we extended our examinations to several other related models (**9 - 11**). With the exception of **11** each model gave a mixture of products considerably more complex than that obtained in the case of **1**. The main products *(Scheme 4.)* formed in rather poor yields were accompanied by extensive tar formation.





Scheme 4.

2-Oxabicyclo[3.3.0]oct-6-ene (**9**) showed reactivity comparable to that of **1**. After 24 hours at 80 °C no unchanged starting material (**9**) could be detected in the reaction mixture by TLC. Repeated chromatography on silica gel column resulted in the separation of three pure main products (**12** - **14**) accompanied by several minor fractions of incompletely resolved materials. The assignment of structure and configuration to **12** and **14** was made by comparison with authentic samples prepared, *e. g.*, from **2d** *(Scheme 5.)*. An analogous sequence of reactions led to authentic **14**.



Scheme 5.

In **13** the homonuclear decoupling experiments did not provide unambiguous assignment of the protons since some of the vicinal couplings were about of the same magnitude as the long range *(w)* ones (0.5 - 3.5 Hz). Structure and stereochemistry was deduced from the NOE difference experiments where irradiation of the H-6 proton (2.80 ppm) showed enhancement on the resonance of H-2 and H-8_B demonstrating that these protons are on the same face of the molecule. Irradiation of H-11 resulted in NOE effects of H-8_A, H-10_A, H-7 and H-1 protons. Finally, saturation of H-7 had no effect on H-1 proton thus the coupling between H-7 and H-1 must be of long range origin.

Bicycloheptenone **10** afforded an extremely complex mixture of products as evidenced by TLC analysis. On the contrary, the dichloro derivative **11** reacted like **1** although more sluggishly in such a way that the extent of conversion reached only 40% after reaction of 120 hours at 75-80 °C in a sealed tube. Chromatography on silica gel afforded unreacted **11** (60%) and **15** as the main product in 21% yield (52.5% based on unrecovered **11**) together with small amounts of unseparable more polar fractions. The structure and stereochemistry of **15** was assigned on the basis of its conversion into **2a** by dechlorination with zinc in acetic acid and subsequent oxidation with 3-chloroperbenzoic acid in dichloromethane.

Experimental

Infrared spectra were obtained on a Perkin-Elmer 225 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian XL-100 and XL-400 spectrometers in $CDCl_3$ solutions containing Me_4Si as internal standard. Optically active **1** (m. p. 41-42 °C; $[\alpha]_D$ -104 (c 1.1, MeOH)) and racemic **10, 11** were prepared as described in the literature[17]. Racemic **9** was prepared from racemic **1** via an analoguos procedure as described for **12** below. Optically active **4** was generously donated by Dr. I. Szekely (Chinoin Pharmaceuticals, Budapest).

Prins Reaction. Representative Procedure.

A mixture of 3 g paraformaldehyde, 30 ml glacial acetic acid, 1 ml sulfuric acid, and 3.85 g unsaturated lactone **1** was stirred and slowly warmed to 50 °C in an oil-bath until the paraformaldehyde had completely dissolved. The flask was then stoppered and the temperature of the bath raised to 75-80 °C. (***Warning!*** The slight pressure which evolves at this temparature can be compensated by fastening the stopper with two light springs, however, uncontrolled increase of the temperature above 100 °C may cause considerable overpressure. We used a 50 ml round bottomed flask to reduce the volume of the vapour-space above the solution. The flask should be immersed as deep as possible into the oil-bath to avoid unwanted clogging caused by polymerization of formaldehyde on cool places.) After 21 - 24 hours at 75 - 80 °C the consumption of **1** (R_f : 0.72) was complete. TLC (ethyl acetate) revealed one main spot (R_f : 0.55) and three minor ones (R_f : 0.45, 0.42, and 0.25). The deep brown reaction mixture was cooled, 4 g sodium acetate was added and the mixture stirred for 30 min to neutralize sulfuric acid. After removal of acetic acid on a rotary evaporator the residue was dissolved in ethyl acetate (50 ml) and washed with saturated aq $NaHCO_3$ (pH = 8.5), brine and dried ($MgSO_4$). The residue obtained after evaporation of the solvent was applied to a silica gel column (130 g) and eluted with hexane : ethyl acetate (1 : 1) at 0.25 mPa pressure. The evaporation of appropriate fractions afforded **2a** (4.76 - 5.56 g, 60 - 70%), **3** (0.54 g, 9.5%), **2c** (0.19 g, 3%), and **2b** (0.53 g, 8%)

2a, $[\alpha]_D$ - 57.6 (c 0.93, $CHCl_3$); IR (film): 2950, 1775, 1740, 1360, 1230, 1160 cm^{-1}. ^{13}C NMR (100 MHz): 20.79, 21.05, 35.75, 38.10, 40.56, 51.35, 63.96, 76.95, 84.01, 170.80, 171.15, 176.75.

2b, ^1H NMR (400 MHz): 2.04 (s, 3H), 2.09 (s, 3H), 2.20 (t, 1H), 2.22 (m, 1H), 2.39 (m, 1H), 2.50 (dd, 1H, J = 16.5 + 1.3 Hz), 2.84 (m, 1H), 2.87 (dd, 1H, J = 16.5 + 9 Hz), 3.59 (dd, 1H, J = 11.5 + 5.2 Hz), 3.65 (dd, 1H, J = 11.5 + 5 Hz), 4.99 (m, 1H), 5.10 (m, 1H).

2c, ^1H NMR (400 MHz): 2.07 (m, 1H), 2.08 (s, 3H), 2.15 (m, 1H), 2.32 (d, 1H, J = 5 Hz), 2.39 (m, 1H), 2.56 (dd, 1H, J = 16.5 + 2 Hz), 2.67 (m, 1H), 2.83 (dd, 1H, J = 16.5 + 10 Hz), 4.09 (dd, 1H, J = 11.5 + 5.5 Hz), 4.12 (m, 1H), 4.13 (dd, 1H, J = 11.5 + 6.5 Hz), 4.97 (m, 1H).

3, ^{13}C NMR (25 MHz): 33.8, 38.8, 40.5, 45.2, 65.1, 79.0, 85.3, 93.0, 176.5; ^1H NMR (100 mHz): 1.65 (m, 1H), 2.05 (m, 1H), 2.35 (dd, 1H, J = 17.5 + 2 Hz), 2.40 (m, 1H), 2.82 (dd, 1H, J = 17.5 + 9 Hz), 3.31 (m, 1H), 3.96 (m, 2H), 4.21 (m, 1H), 4.64 (d, 1H, J = 6.5 Hz), 4.97 (d, 1H, J = 6.5 Hz), 5.13 (m, 1H).

The analoguos reaction in the case of racemic **10** afforded (yields are in parantheses):

12 (17%); ^1H NMR (400 MHz): 1.74 (m, 1H), 1.8 (m, 1H), 2.02 (s, 3H), 2.04 (m, 1H), 2.06 (s, 3H), 2.09 (m, 1H), 2.40 (m, 1H), 2.48 (m, 1H), 3.85 (m, 1H), 3.91 (m, 1H), 4.10 (d, 2H, J = 5.5 Hz), 4.39 (m, 1H), 4.89 (q, 1H, J = 7.8 Hz).

13 (6%); ^1H NMR (400 MHz): 1.93 (m, 1H), 2.04 (s, 3H), 2.12 (m, 1H), 2.32 (m, 1H), 2.51 (m, 1H), 2.80 (m, 1H), 3.54 (m, 2H), 3.59 (m, 1H), 3.69 (dd, 1H, J = 10.5 + 3 Hz), 3.82 (dd, 1H, J = 11 + 3 Hz), 4.05 (m, 1H), 4.45 (d, 1H, J = 7.5 Hz), 4.87 (dd, 1H, J = 0.5 + 0.5 Hz); ^{13}C NMR (100 MHz): 21.3, 32.3, 46.3, 47.0, 47.1, 69.0, 70.5, 72.4, 82.1, 86.3, 170.5.

14 (4%); ^1H NMR (400 MHz): 1.58 (m, 1H), 1.63 (m, 1H), 1.76 (m, 1H), 2.04 (m, 1H), 2.23 (dd, 1H, J = 15 + 7.2 Hz), 3.09 (m, 1H), 3.79 (m, 1H), 3.87 (m, 1H), 3.93 (dd, 1H, J = 11.8 + 2.8 Hz), 3.98 (dd, 1H, J = 11.8 + 1.5 Hz), 4.19 (m, 1H), 4.61 (d, 1H, J = 6.5 Hz), 4.71 (m, 1H), 4.97 (d, 1H, J = 6.5 Hz).

The analogous reaction in the case of racemic **11** afforded **15** (52.5%); IR (film): 2960, 1805, 1735, 1330, 1220, 1150, 740, 720 cm^{-1}; ^1H NMR (100 MHz): 1.82 (m, 1H), 2.05 (s, 3H), 2.09 (s, 3H), 2.11 (m, 1H), 2.28 (m, 1H), 2.39 (m, 1H), 2.68 (m, 1H), 4.10 (d, 2H, J = 5.2 Hz), 4.92 (m, 1H)

*Authentic lactone diol diacetate (**2a**).*

To the solution of 1.76 g iodolactone **4** in 10 ml dichloromethane and 1 ml pyridine was added 0.44 ml acetyl chloride. After stirring for 2 hours, the mixture was diluted with 20 ml dichloromethane, washed with water, saturated aq $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave **5** (1.93 g, 98%) as a pale yellow syrup which was then dissolved in ether (20 ml) and treated dropwise with a 0.5 molar solution of tributyltin hydride in ether (10 ml) at room temparature. After completion of the reaction (1.5 hrs) the solvent was evaporated and the residue was purified by chromatography on silica gel (50 g) using hexane : ethyl acetate (3 : 1) as eluent to afford **6** (1.2 g, 89%) which was dissolved in acetic anhydride (10 ml), cooled in ice water and treated with 10 drops of boron trifluoride etherate. After stirring for 20 min the reaction was allowed to warm up to 23 °C and maintained at this temperature for an additional 2 hrs. The reaction was quenched by the addition of 2 ml water followed by stirring for 30 min. The bulk of the acetic acid was evaporated and the residue was dissolved in ethyl acetate (40 ml) and successively washed with saturated aq $NaHCO_3$, water, brine and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography furnished pure lactone diol diacetate (0.868 g, 86%) which proved to be identical to **2a** in every respect.

*Methanolysis of lactone diol diacetate **2a** to lactone diol **2d**.*

Into the solution of **2a** (5.12 g) in dry methanol (30 ml) was added 9 g Amberlite IR 120 resin (H^+-form, 28 - 35 mesh) and the mixture was gently stirred at 70 °C for 8 hrs. The resin was filtered off, washed with 2x5 ml portions of dry methanol and concentrated to about 15 ml by evaporation of the solvent. Addition of ether (30 ml) to this solution caused rapid crystallization of **2d** (2.82 g, 82%, m. p. : 117.5 - 118 5 °C, $[\alpha]_D$ -43.4 (c 1.12, methanol).

*Characterization of Monoacetyl Derivatives (**2b,c**).*

A solution of **2b** (107 mg) in dichloromethane (6 ml) was treated with 4-dimethylaminopyridine (122 mg) and acetic anhydride (0.94 ml). The reaction was complete in several minutes (TLC) and was quenched by the addition of 1 ml methanol. Evaporation of the solvent followed by chromatography (silica gel, hexane : ethyl acetate, 2 : 1) afforded **2a** (112 mg, 88%). A similar procedure gave **2a** from **2c** in 91% yield. Methanolysis carried out as described above afforded **2d** both from **2b** and **2c** (86 and 82%, resp.).

A mixture of **6** (501 mg) and palladium on activated carbon (Pd content 10%, 200 mg) in ethyl acetate (15 ml) was stirred under hydrogen held slightly above atmospheric pressure (0.6 kPa). The consumption of hydrogen (40 ml) reached saturation after 11 hrs. TLC (ethyl acetate) showed the appearance of a single new spot of R_f : 0.25 identical to that of **2b**. Usual work up and subsequent chromatography on silica gel (50 g, ethyl acetate) furnished pure **2b** (251 mg, 72%).

*Characterization of m-Dioxane Derivative **3**.*

A solution of **3** (184 mg) and p-toluenesulfonic acid (10 mg) in dry methanol (30 ml) was strirred at 75 - 80 °C so as to allow slow distillation of the solvent (5 ml/h) through a short column (25 cm) together with the methylal formed. The reaction was complete in 4 hours. Triethylamine (0.2 ml) was added and the solvent was removed by evaporation. Chromatography of the residue on silica gel (15 g) using ethyl acetate : methanol (10 : 1) as eluent afforded **2d** (134 mg, 78%).

A slurry of **2d** (235 mg) and a small drop of $POCl_3$ in methylal (10 ml) was stirred at room temperature until dissolution of **2d** became complete (ca 8 hrs). Triethylamine (0.5 ml) was then added followed by evaporation of the solvent. Chromatography on silica gel (20 g) eluting with hexane : ethyl acetate (1 : 2) furnished **2a** (181 g, 72%).

Authentic **12.**

A solution of **17**[18] (560 mg) in dry THF (10 ml) was added dropwise into a stirred slurry of $LiAlH_4$ (160 mg) in dry THF (10 ml) at 0 °C. After completion of the reaction (30 min), 0.16 ml water, 0.64 ml 2N aq NaOH, and 0.2 ml water were successively added and stirring was continued for another 40 min. The solid precipitate was filtered off, washed with dry THF (2x5 ml) and concentrated to leave an oil (**18**, 534 mg, 94%) which was dissolved in dry dichloromethane (10 ml). Triphenylphosphine (626 mg) and diethyl azodicarboxylate (0.4 ml) were then added into the cooled (0 °C) solution and stirring was continued for 1 hr at 0 °C and for 1 hr at room temperature. After evaporation of the solvent, the residue was purified by chromatography on silica gel (30 g, hexane : ethyl acetate 3 : 1) to give **19** (430 mg, 85%). The solution of **19** (380 mg) and p-toluenesulfonic acid (15 mg) in dry methanol (20 ml) was stirred at ambient temperature to remove THP-protection (5 hrs). The reaction was quenched by the addition of dry pyridine (1 ml) and evaporated to dryness. The residue was dissolved in dichloromethane (10 ml), 4-dimethylaminopyridine (320 mg) and acetic anhydride (0.25 ml) were successively added and the mixture was stirred for 40 min at room temperature. Excess of the reagent was decomposed by the addition of methanol (1 ml) followed by evaporation of the solvent. Chromatography on silica gel (25 g, hexane : ethyl acetate, 2 : 1) afforded pure diacetate (213 mg, 76%) which was identical to **12** in every respect.

Conversion of **15** *into* **2a.**

A solution of **15** (998 mg) in acetic acid (10 ml) was treated with zinc dust (2 g) added in small portions over a period of 2 hrs. After stirring overnight, TLC (hexane : ethylacetate, 2 : 1) showed complete consumption of **15** (R_f : 0.41) resulting in the formation of **16** (R_f : 0.23) together with a very small amount of incompletely reduced monochloroketone (R_f : 0.30). The mixture was diluted with water (40 ml) then with ether (60 ml) and filtered through a small cotton plug. The ethereal solution was washed successively with satd aq $NaHCO_3$ (5x10 ml), water (2x10 ml), brine (10 ml) and dried over $MgSO_4$. The residue obtained by evaporation of the solvent was dissolved in dry dichloromethane (20 ml) and treated in portions with 3-chloroperbenzoic acid (80% purity, 610 mg) while stirring at 0 °C. The reaction was complete in 30 min as reflected by TLC (hexane : ethyl acetate, 1 : 1), R_f : 0.46 (**16**), 0.31 (**2a**). Usual work up and subsequent chromatography on silica gel (40 g, hexane : ethyl acetate, 2 : 1) afforded pure **2a** (520 mg, 63%, overall).

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References

1. Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977,** 661-672
2. March, J. *Advanced Organic Chemistry*; John Wiley & Sons, Inc.: New York, **1985**; pp. 856-858.
3. Fodor, G.; Kovács, Ö.; Tömösközi, I.; Szilágyi, J. *Bull. Soc. Chim. France* **1957,** 357-361
4. Yang, N. C.; Yang, D-D. H.; Ross, C. B. *J. Am. Chem. Soc.* **1959,** 81, 133
5. Dolby, L. J. *J. Org. Chem.* **1962,** 27, 2971

6. Dolby, L. J.; Liese, D. N.; Rosencrantz, D. R.; Schwarz, M. J. *J. Am. Chem. Soc.* **1963**, 85, 47
7. Dolby, L. J.; Schwarz, M. J. *J. Org. Chem.* **1963**, 28, 1456; *ibid.* **1965**, 30, 3581
8. Schwollen, K. B.; Smissman, E. E.; Schwollen, R. L. *J. Org. Chem.* **1968**, 33, 1873
9. Dolby, L.J.; Meneghini, F.A.; Koizumi, T. *J. Org. Chem.* **1968**, 33, 3060
10. Wilkins, C. L.; Marianelli, R. S.; Pickett, C. S. *Tetrahedron Lett.* **1968**, 5109
11. Smissman, E. E.; Schnettler, R. A.; Portoghese, P. S. *J. Org. Chem.* **1970**, 35, 797
12. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, 91, 5675; Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *ibid.***1970**, 92, 397; Corey, E. J.; Albocino, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *ibid.* **1971**, 93, 1491
13. Tömösközi, I.; Gruber, L.; Kovács, G.; Székely, I.; Simonidesz, V. *Tetrahedron Lett.* **1976**, 4639-4642
14. Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, 95, 7171
15. Béres, J.; Sági Gy.; Tömösközi, I.; Gruber, L.; Gulácsi, E.; Ötvös, L. *Tetrahedron Lett.* **1988**, 29, 2681-2684
16. Tömösközi, I.; Gruber, L.; Béres, J. Galambos, G. Stereospecific introduction of the lowerchain of prostanoids. (*Organic Synthesis : Modern Trends*; Chizov, O. Editor; Blackwell Scientific Publ., **1987**, pp. 221-227)
17. Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, 95, 6832; Gruber, L.; Tömösközi, I.;Major, E.; Kovács, G. *Tetrahedron Lett.* **1974**, 3729-3730, and references cited therein
18. Béres, J.; Sági, Gy.; Baitz-Gács, E.; Tömösközi, I.; Ötvös, L. *Tetrahedron* **1989**, 44, 6207-6216