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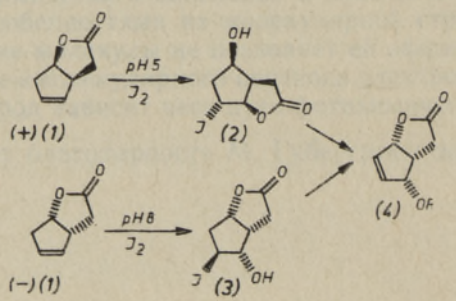
A SYNTHETIC WAY TO R(+)METHYL-7-(3-HYDROXY-5-OXO-1-CYCLOPENTENYL)-5(*Z*)--HEPTENOATE PGE_2 SYNTHON

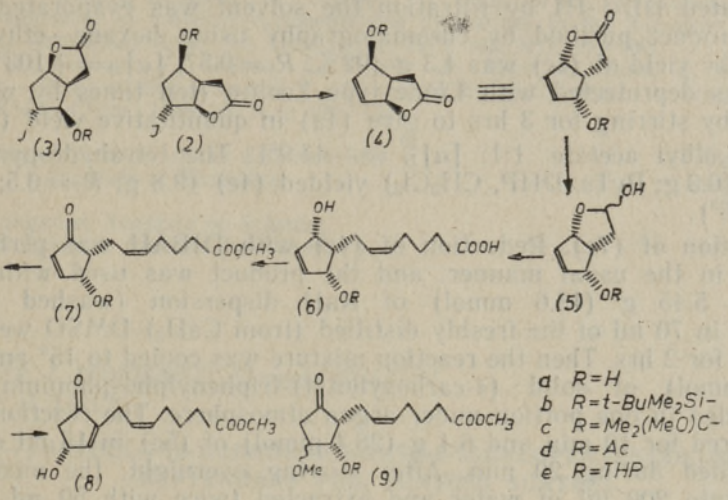
The enantiocomplementarity of unsaturated bicyclic lactone antipodes (1) in the iodolactonization reaction [1] conducted at different pH values gives them equal importance at least in the convergent prostaglandin synthesis [2].

Taking advantage of this opportunity we have developed a new version of the synthesis of the PGE_2 synthon (8) [3, 4] starting from (+)(1) which is a by-product in linear $PGE_{2\alpha}$ synthesis [5]. Iodolactonization of (+)(1) at pH 5 followed by the protection of the pertinent OH-group by either acetylation or tetrahydropyranylation led to a chromatographically inseparable product mixture of (2d), (2e) and (3d), (3e). However, the *t*-butyldimethylsilyl ((2b) and (3b)) or 2-methoxy-2-propyl ((2c) and (3c)) derivatives could be easily separated by column chromatography on silica gel. The amount of (2b) or (2c) was four times as high as that of (3b) or (3c) determined by HPLC or preparative column chromatography. The 2-methoxy-2-propyl protecting group was advantageous because of its acid sensitivity and economic considerations.



Dehydroiodination of (2c) with 1,8-diazabicyclo[5.4.0]undec-7-ene (1,5—5) (DBU) in dry tetrahydrofuran (THF) afforded the optically pure (4c) in high yield. To avoid the undesirable deprotection reaction during the workup of Wittig reaction product, the 2-methoxy-2-propyl protecting group was converted to tetrahydropyranyl (THP) by treating (4c) with Linde type Zeolite (H^+ form) in CH_2Cl_2, followed by the protection of the (4a) with 2,3-dihydropyrane (DHP). When the deprotection of (4c) was carried out in methanol in the presence of a catalytic amount of pyridinium tosylate (PyTs), a rapid racemization took place.

The following steps are in common in prostaglandin chemistry [4]: reduction of (4e) with diisobutylaluminium hydride (DIBAH), Wittig reaction with the corresponding ylide prepared from (4-carboxybutyl)--triphenylphosphonium bromide and dimsyl-sodium in dimethylsulphoxide



(DMSO), esterification of the Wittig product with diazomethane ((6e) was formed), oxidation of (6e) with pyridinium chlorochromate (PCC) in CH_2Cl_2 in the presence of anhydrous sodium acetate ((7e) was formed).

The THP group of (7e) has to be removed in acetic acid. When deprotection was performed in methanol with PyTs as a catalyst, a large quantity of the 11-methoxy-substituted (according to the prostaglandin numeration) product (9a) was isolated. The optically pure PGE_2-synthon (8) was obtained from (7a) by Stork's method [6] or by isomerization on an aluminium oxide surface [7]. The synthon (8) prepared by the method described above was used in the synthesis of (—)PGE_2 and (—)15-keto PGE_2 [8].

Continuing our research work in this field we are engaged in determining the stereochemistry of the base-catalysed conjugate 1,4-addition to the conjugate system (7) and in finding a way to 11-substituted PGE_2 synthons.

Experimental

Satisfactory combustion data, IR and ^1H NMR spectra (published partly in [2]) were obtained for all new compounds. The intermediates were purified using low-pressure flash column chromatography. The $[\alpha]_D$ values were measured in methanol (C=1, POLAMAT, GDR), R_f values refer to the Kieselgel 60 F_{254} type plate (Merck).

Preparation of (4c) and (4e). 10.0 g of (+)(1) were dissolved in 95 ml of 1 n NaOH and after stirring for 3 hrs the pH was adjusted to 5 by 1 n $NaHSO_4$. Then 22.9 g I_2 were added in one portion, and the reaction mixture was stirred overnight. After extraction with ethyl acetate, the excess of iodine was destroyed with $Na_2S_2O_3$, the organic phase was dried over $MgSO_4$ and evaporated to give (2a) and (3a) (19 g, 94%). The mixture was treated with 2 eqs of 2-methoxy-1-propene and a catalytic amount of PyTs in 60 ml of CH_2Cl_2. After stirring for 6 hrs, the reaction mixture was quenched with triethylamine and the solvent was evaporated. Purification and separation of the isomers (2c) and (3c) was performed

by chromatography on silica gel using hexane—ethyl acetate (2:1; 0.5% NEt_3). 16.9 g of (2c) (R_f=0.33, $[\alpha]_D^{20}$ =+17.1°) were obtained. 7.5 g of the protected iodolactone (2c) were dissolved in 25 ml of THF, and 1 eq of DBU was added. The reaction mixture was stirred at room temperature for 8 hrs, and then 20 ml of ether were added. After removal of the precipitated DBU·HI by filtration the solvent was evaporated and the crude product purified by chromatography using hexane—ethyl acetate (1:1). The yield of (4c) was 4.3 g (92%, R_f=0.57, $[\alpha]_D$=+103°. Lactone (4c) was deprotected with Linde type Zeolite (ten times by weight) in CH_2Cl_2 by stirring for 3 hrs to give (4a) in quantitative yield (R_f=0.25; hexane—ethyl acetate 1:1; $[\alpha]_D^{20}$ =—44.9°). The tetrahydropyranylation of (4a) (6.3 g; PyTs, DHP, CH_2Cl_2) yielded (4e) (9.8 g; R_f=0.5; $[\alpha]_D$= =+50.5°).

Preparation of (7c). Reduction of (4c) with DIBAH was performed in toluene in the usual manner, and the product was used without purification. 5.45 g (13.6 mmol) of NaH dispersion (washed with dry hexane) in 70 ml of the freshly distilled (from CaH_2) DMSO were heated at 65 °C for 2 hrs. Then the reaction mixture was cooled to 15° and 25.16 g (56.8 mmol) of solid (4-carboxybutyl)-triphenylphosphonium bromide were added in one portion under argon atmosphere. The reaction mixture was stirred for 10 min and 6.4 g (28.4 mmol) of (5c) in 15 ml of DMSO were added during 20 min. After stirring overnight, the mixture was poured into 200 ml of water and extracted twice with 50 ml of ether. The water phase was acidified to pH 3—4 with $NaHSO_4$ and extracted four times with 50 ml of ether. The ethereal solution was washed twice with 30 ml of brine and dried over $MgSO_4$. After keeping in the refrigerator overnight, the precipitated Ph_3PO was filtered and the solution quenched with diazomethane. The ether was evaporated and the crude product was purified on silica gel using hexane—ethyl acetate (1:1). The yield of (6c) was 4.4 g (49%, R_f=0.45). 4.4 g (13.7 mmol) of (6c) were dissolved in 50 ml of CH_2Cl_2 and 2.2 g (27.5 mmol) of anhydrous NaOAc, and 6.0 g (27.5 mmol) of PCC were added. After 4 hrs the reaction mixture was filtered through a short column containing 20 g of silica gel to remove the dark precipitate. After purification on silica gel, 3.1 g of (7c) were gained (R_f=0.54; hexane—ethyl acetate 1:1; $[\alpha]_D^{20}$=—40.9°).

Preparation of (8). (7c) was deprotected in a mixture of acetic acid—water—THF (20:10:3; room temperature; 40 hrs) in a 80% yield (R_f= =0.24; hexane—ethyl acetate 1:1) and converted to (8) by Stork's method [5]. The PGE_2 synthon (8) ($[\alpha]_D^{20}$ =+13.5°; R_f=0.22; hexane—ethyl acetate 1:1) was identical to that prepared by another method [3].

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R(+)METÜÜL-7-(3-HÜDROKSÜ-5-OKSO-1-TSÜKLOPENTENÜÜL)-5(*Z*)-HEPTENOAAT PGE_2 SÜNTONI SÜNTEES

Bitsüklilisest Grieco laktoonist on võimalik sõltuvalt jodolaktonisatsioonireaktsiooni pH-st sünteesida kaks erinevat jodolaktooni. See asjaolu lubab seni vähekasutatavast (+) Grieco laktoonist sünteesida naturaalsete E_2 seeria prostaglandiinide lähtesüntonit — R(+)metüül-7-(3-hüdroksü-5-okso-1-tsüklopentenüül)-5(*Z*)-heptenoaati. On toodud andmed selle ühendi sünteesi kohta.

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М. ЛОПП, Ю. ЛИЛЛЕ

МЕТОД СИНТЕЗА R(+)МЕТИЛ-7-(3-ГИДРОКСИ-5-ОКСО-1-ЦИКЛОПЕНТЕНИЛ)-5(*Z*)-ГЕПТЕНОАТА — СИНТОНА $ПГЕ_2$

В зависимости от pH среды йодолактонизация лактона Грико приводит к различным йодолактонам. Это обстоятельство позволяет получать исходный синтон натуральных простагландинов серии E_2 из (+)лактона Грико. Приводятся данные о синтезе этого синтона — R(+)метил-7-(3-гидрокси-5-оксо-1-циклопентенил)-5(*Z*)-гептеноата.