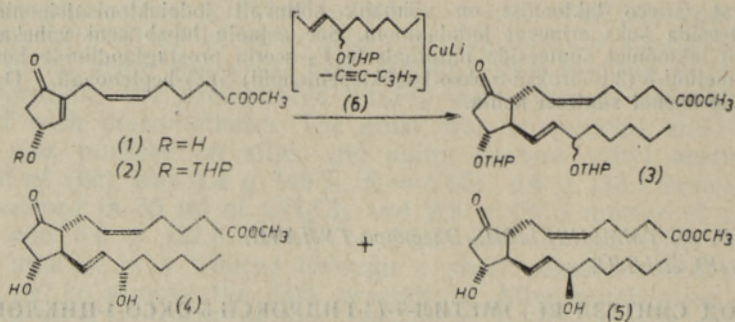


УДК 577.1

Anne PAJU, T. VALIMAE, Eleonora GULACSI,
 L. GRUBER, M. LOPP, Ü. LILLE

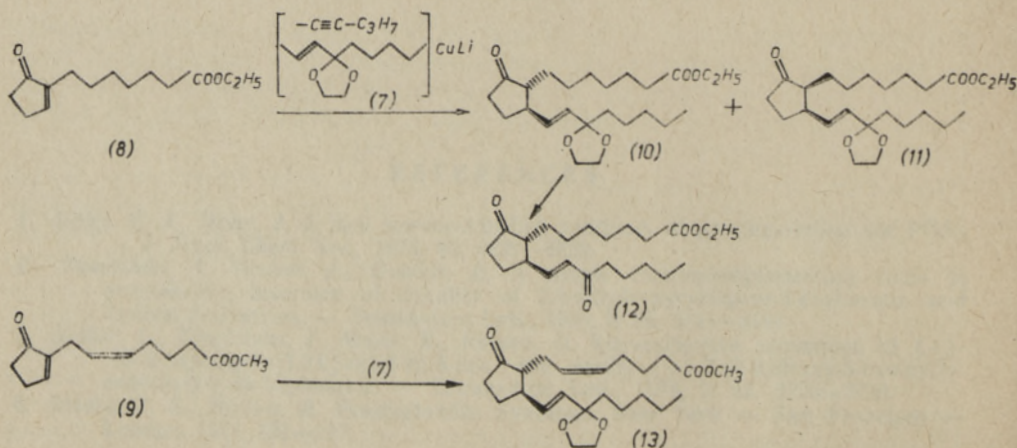
SYNTHESIS OF (–)PGE₂ METHYL ESTER AND (–)15-KETO PGE₂ METHYL ESTER

The addition of various cuprate reagents to optically active enone synthon is a simple and convenient method for preparing optically active prostaglandins and their analogs. Starting from optically active (–) (1) [1] using the known method [2], (–)PGE₂ (4) with $[\alpha]_D^{20} = -18.6^\circ$ in a 24.6% overall yield was synthesized (NMR ¹³C shifts in the Figure).



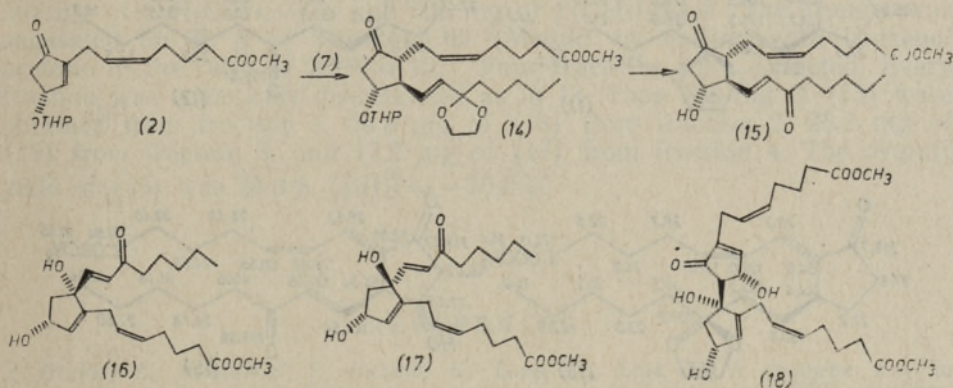
The use of racemic cuprate (6) always leads to a mixture of epimers (4) and (5). In our case the ratio of these isomers was 55:45.

An interesting possibility for the synthesis of several analogs of PGE₂ and PGE_{2α} overcoming the above-mentioned problem is the use of unchiral ketale cuprate (7) with chiral enone synthon (2).



To examine the scope and limitation of the use of cuprate (7) in this reaction, the enones (8) and (9) were allowed to react with cuprate (7) under usual conditions. The 1,4-addition reaction occurs in a 50–80% yield. Enone (8) with the cuprate (7) gave (10) in a 60% yield together with 10–15% of the *cis*-addition product (11).

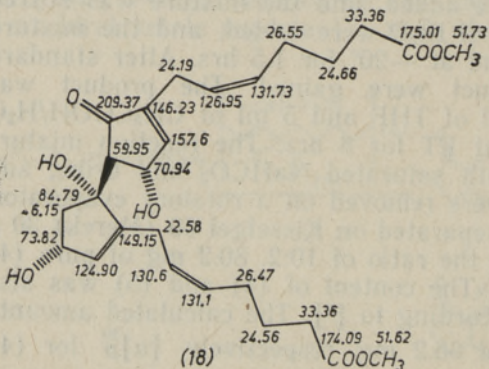
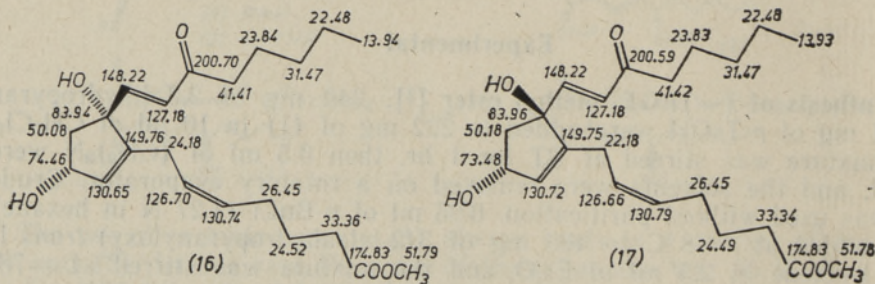
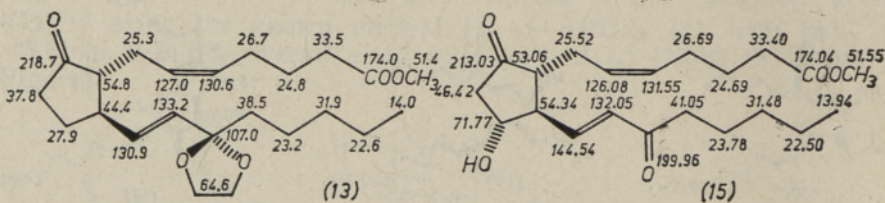
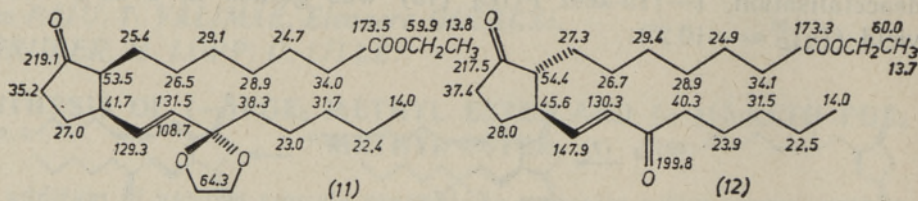
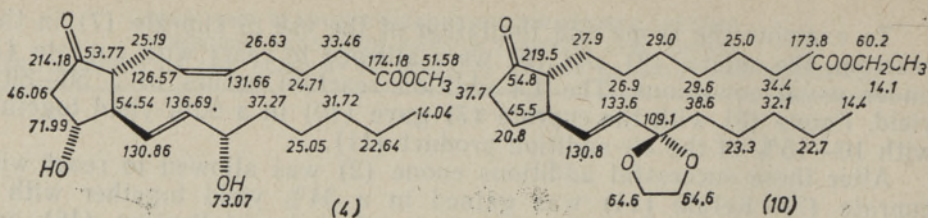
After these successful additions enone (2) was allowed to react with cuprate (7). Ketal (14) was gained in a 34% yield together with a certain amount of 1,2-addition product (after deacetalisation (16) and (17)) and a condensation product (after deacetalisation (18)). After deacetalisation, (–)-15-keto PGE₂ (15) was gained in a 30% overall yield ($[\alpha]_D^{20} = -10.2^\circ$).



Experimental

1) Synthesis of (–)PGE₂ methyl ester [2]. 240 mg of 2,3-dihydropyran and 1 mg of *p*-TsOH were added to 222 mg of (1) in 10 ml of CH₂Cl₂. The mixture was stirred at RT for 1 hr, then 0.5 ml of (CH₃)₃N were added, and the solvents were removed on a rotatory evaporator. Crude (2) was used without purification. 0.95 ml of *n*-BuLi (1.27 N in hexane) were added at –78°C to 406 mg of 3(2-tetrahydropyranyloxy)-*trans*-1-iodo-1-octene in 2.5 ml of Et₂O, and the mixture was stirred at –78° for 1.5 hrs. The complex of 157 mg of C₃H₇C≡C–Cu and 392 mg of [(CH₃)₂N]₃P in 7 ml of Et₂O were added, and the mixture was stirred at –78° for 1 hr. Now (2) in 2 ml of Et₂O were added, and the mixture was stirred at –78° for 20 min and at –20° for 1.5 hrs. After standard workup, 350 mg of crude product were gained. The product was deacetalised in a mixture of 0.5 ml of THF and 5 ml of CH₃COOH/H₂O in the ratio of 65:35 by stirring at RT for 8 hrs. The reaction mixture was diluted with Et₂O, washed with saturated NaHCO₃ and brine, and dried over Na₂SO₄. The solvents were removed on a rotatory evaporator. 314 mg of the crude product were separated on Kieselgel 60 (Merck) 30 g by eluting with benzene/acetone in the ratio of 10:2. 80.2 mg of pure (4) and 70.4 mg of (5) were received. The content of (4) and (5) was also determined by UV spectroscopy according to [3]. The calculated amounts of (4) and (5) were 80.2 mg and 66.2 mg, respectively. $[\alpha]_D^{20}$ for (4) was –18.6°.

2) Synthesis of 11-deoxy-15-keto PGE₁. Analogously to 1), 1175 mg of crude product were gained from 610 mg of enone (8), 782 mg of *trans*-1-iodo-1-octene-3-one ethylene ketal, 2.9 ml of *n*-BuLi (0.92 N in hexane), 335 mg of C₃H₇C≡C–Cu and 854 mg of [(CH₃)₂N]₃P. The separation of isomers on 45 g of silica gel L 40–100 μ (Czechoslovakia),



^{13}C chemical shifts in ppm downfield from internal TMS.

eluating by benzene/ethyl acetate 0—35% ethyl acetate, yielded 668 mg of (10) and 118 mg of (11). The total yield of the addition based on (8) was 78%. Deacetalisation of (10) by stirring for 2 hrs at RT in 5 ml of CH_2Cl_2 together with 0.4 ml of 10% oxalic acid and 3 g of silica gel [4] yielded 550 mg of (12) after the usual workup.

3) **Synthesis of 11-deoxy-15-keto PGE₂**. Analogously to 1), 328 mg of (13) were gained in a 50.6% yield from 444 mg of enone (9), 588 mg of *trans*-1-iodo-1-octene-3-one ethylene ketale, 2.4 ml of *n*-BuLi (0.86 N in hexane), 260 mg of $\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}$ and 716 mg of $[(\text{CH}_3)_2\text{N}]_3\text{P}$.

4) **Synthesis of (–)15-keto PGE₂**. Analogously to 1), 0.8 g of crude product were gained from 437 mg of enone (2), 503 mg of *trans*-1-iodo-1-octene-3-one ethylene ketale, 1.22 ml of *n*-BuLi (1.27 N in hexane), 202 mg of $\text{C}_3\text{H}_7\text{C}\equiv\text{C}-\text{Cu}$ and 506 mg of $[(\text{CH}_3)_2\text{N}]_3\text{P}$. The product was separated on 30 g of Kieselgel 60 (Merck) by eluting with benzene/acetone in the ratio of 20:1 to 10:1. Four fractions were collected. Every fraction was separately deacetalised as in 1). Thus 150 mg of (15) were obtained from fraction 1, 26.8 mg of (18) from fraction 2, 25.8 mg of (16) from fraction 3, and 17.2 mg of (17) from fraction 4. The overall yield of (15) was 30.3% ($[\alpha]_D^{20} = -10.2^\circ$).

REFERENCES

1. Gruber, L., Tömösközi, I., Gulácsi, E., Lopp, M., Lille, Ü. A synthetic way to R(+)methyl-7-(3-hydroxy-5-oxo-1-cyclopentenyl)-5(Z)-heptenoate PGE₂ synthon. — Proc. Acad. Sci. ESSR. Chem., 1986, 35, N 2, 134—137.
2. Sih, C. J., Heather, J. B., Soid, R., Price, P., Peruzzotti, C., Hsu Lee, L.-F., Lee, S. S. Asymmetric total synthesis of (–)-prostaglandin E₁ and (–)-prostaglandin E₂. — J. Amer. Chem. Soc., 1975, 97, 865—874.
3. Andresen, N. H. Dehydration of prostaglandins; study by spectroscopic method. — J. Lipid Res., 1969, 10, 320—325.
4. Huët, F., Lechevallier, A., Pellet, M., Conia, J. M. Wet silica gel: a convenient reagent for deketalization. — Synthesis, 1978, 63—65.

Academy of Sciences of the Estonian SSR,
Institute of Chemistry

Received
Nov. 1, 1985

Hungarian Academy of Sciences,
Central Research Institute for Chemistry

Anne PAJU, T. VALIMÄE, Eleonora GULÁCSI,
L. GRUBER, M. LOPP, Ü. LILLE

PROSTAGLANDIINIDE (–)E₂ JA (–)15-keto E₂ METUOLESTRITE SUNTEES

Prostaglandiinide ω-ahelatele vastavate oktenoonkupraatide 1,4-liitumisel optiliselt aktiivsele R(+)metüül-7-(3-hüdroksü-5-okso-1-tsüklopentenüül)-5(Z)-heptenoaadile sünteesiti prostaglandiinid (–)E₂ ja (–)15-keto E₂, saagis vastavalt 24,6% ja 30%. Reaktsioonide põhi- ja kõrvalproduktid iseloomustati TMR ¹³C tuumade nihetega.

Анне ПАЮ, Т. ВЯЛИМЯЭ, Элеонора ГУЛАЧИ,
Л. ГРУБЕР, М. ЛОПП, Ю. ЛИЛЛЕ

СИНТЕЗ МЕТИЛОВЫХ ЭФИРОВ ПРОСТАГЛАНДИНОВ (–)E₂ И (–)15-КЕТО E₂

1,4-Присоединением соответствующих октеноновых купратов к оптически активному R(+)метил-7-(3-гидрокси-5-оксо-1-циклопентенил)-5(Z)-гептеноату синтезированы метиловые эфиры простагландинов (–)E₂, (–)15-кето E₂ с выходом 24,6 и 30% соответственно. Целевые продукты и основные примеси синтезов охарактеризованы сдвигами ядер ¹³C в ЯМР-спектрах.