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STEREOCONTROLLED SYNTHESIS OF 8-ISO-PROSTAGLANDIN E_1 AND E_2[1)]

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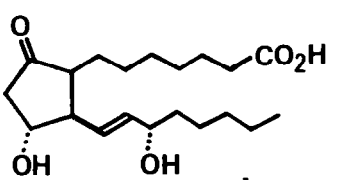
Interest in the unique biological properties[2)] of 8-iso-prostaglandin (PG) E_1 (1), which has been isolated by Daniels et al. in the biochemical transformation of 8,11,14-eicosatrienoic acid[3)], prompted us to synthesize a series of 8-iso-prostanoids. As the reported syntheses[4-6)] of 1 have not been stereochemically controlled, we have developed a new pathway to dl-1 and dl-8-iso-PGE_2 (2) utilizing the bicyclic cis-lactone 5 obtained by the intramolecular cyclopropanation and subsequent ring cleavage[7)] (3 → 4 → 5).



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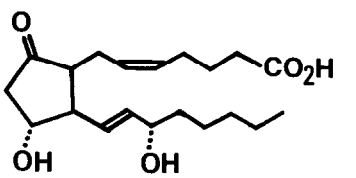

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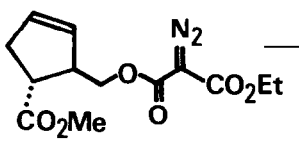

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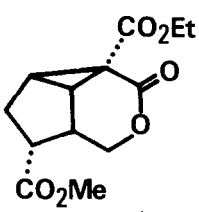

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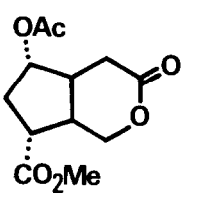

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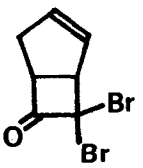
Reaction of dibromoketene with cyclopentadiene in n-pentane gave the adduct[8)] 6 (mp 23-24°, 77%). Ring opening[9)] of 6 with NaOMe (-5 ~ -10°) yielded the trans ester 7 [bp 87-90°/2 mmHg; 83%; NMR[10)], σ 5.85(1H, d., J=5 Hz, $-CHBr_2$)]. Isomeric cis ester 8 [bp 59-61°/0.01 mmHg; 89%; NMR, σ 6.30(1H, d., J=5 Hz, $-CHBr_2$)] was obtained by the similar reaction at -15°. Conversion of 8 to 7 by treatment with NaOMe at -5 ~ -10° confirmed the trans-configuration of 7. The dibromo ester 7 was partially reduced with Bu_3SnH (neat, 5-15°, 16 hr) to the monobromide 9[11)] [bp 104-106°/8 mmHg; 88%; NMR, σ 3.52(2H, m., $-CH_2Br$)]. The partial reduction of the dichloro ester corresponding to 7 was not successful.



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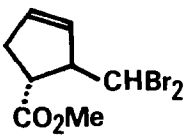

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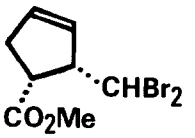

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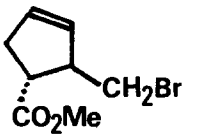

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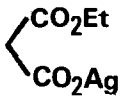

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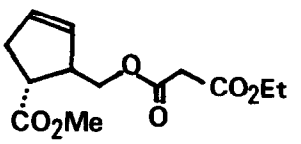

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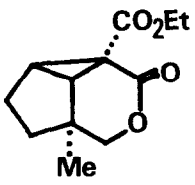

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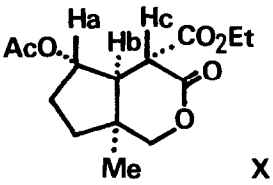

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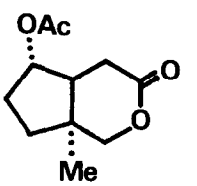

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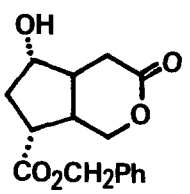

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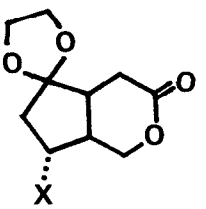
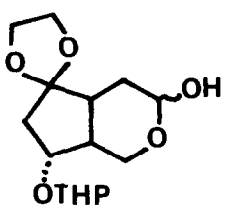


16 CO_2CH_2Ph → (H_2, Pd-C) → 17 CO_2H → (i) $(COCl)_2$ ii) Me_2CuLi in Et_2O-CH_2Cl_2) → 18 Ac → (CF_3CO_3H-Na_2HPO_4) → 19 OAc → (K_2CO_3, MeOH) → 20 OH → (DHP, p-TsOH) → 21 OTHP



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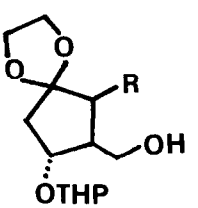

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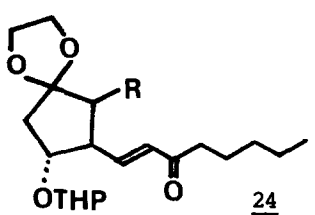
a: R = $(CH_2)_4CO_2Me$

b: R = $CH{=}CH(CH_2)_3CO_2Me$



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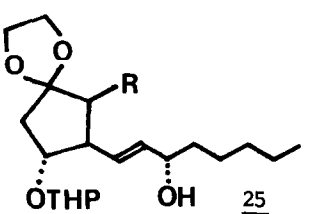

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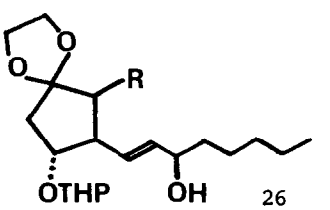

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Reaction of 9 with the silver salt 10 (prepared from ethyl potassium malonate and $AgNO_3$) in MeCN (reflux, 7 hr) gave the triester 11 (51%), which was converted to the diazo ester 3 (TsN_3, Et_3N in MeCN). Intramolecular cyclopropanation of 3 (Cu, xylene, 120-125°, 2.5 hr) afforded the tricyclic lactone 4 [mp 118.5-119.5°; 35%; MS(m/e), 268 (M^+)]. Heating of 4 in AcOH-H_2SO_4 (40:1) (110°, 2 hr) followed by esterification with CH_2N_2 provided the bicyclic lactone 5 [oil; 78%; NMR, σ 4.80 (1H, m., >CH-OAc)]. The 9α-acetoxy structure assigned to 5 was based on mechanistic consideration and supported by the following model experiments. Heating of the tricyclic lactone 12[7] in AcOH-H_2SO_4 at 60° afforded the intermediate 13 (48%) in addition to the final product 14 (20%). The analysis of 100 MHz NMR spectrum of 13 [Ha(σ 4.77, d.t.), Hb(2.39, d.d.), Hc(3.34, d.); Jab =4.5, Jbc=8.3 Hz; NOE (12±5%) between Ha and Hc] proved the structure indicated.

Transesterification of 5 in benzyl alcohol (K_2CO_3, r.t., 3 days) gave the hydroxy ester 15, which was sequentially oxidized (Collins reagent) and acetalized ($BF_3 \cdot Et_2O$-ethyleneglycol) providing the acetal 16 (mp 74-75°, 87%). Stepwise reactions[12] 16→17 (mp 182-184°)→18 (mp 139-140°)→19 (mp 152-153°)→20(mp 116-117°)→21, as indicated, afforded the tetrahydropyranyl ether 21 (mp 105-113°) in 55% overall yield.

Reduction of 21 with i-Bu_2AlH (-60°) gave the lactol 22, which was treated with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid to yield, after esterification with CH_2N_2, the hydroxy ester 23b (84% from 21). Catalytic hydrogenation gave the saturated ester 23a, quantitatively. Collins oxidation of 23a, followed by Wittig reaction with 2-oxoheptylidenetributylphosphorane provided the enone 24a (87%). The two isomeric alcohols, 25a and 26a, formed by the reduction of 24a ($NaBH_4$ in MeOH, -20°) were separated by silica gel column chromatography. The more polar 15α-ol 25a (37%) was treated successively with 5% aq. NaOH-MeOH (1:2) and 50% aq. AcOH (r.t., 16 hr) to yield 1 [mp 88-89°[13] (Et_2O-n-hexane), 57%]. The structure of 1 was confirmed by its conversion[4] to dl-PGE_1 (mp 112.5-113.5°).

By the similar reaction sequence, dl-2 [mp 90-92° (EtOAc-n-heptane); 100 MHz NMR in CD_3OD, σ 5.62 (1H, d.d., J=15.5 and 6.5 Hz, C_{14}-H), 5.40 (2H, m., C_5- and C_6-H), 5.33 (1H, d.d., J=15.5 and 9.5 Hz, C_{13}-H), 4.25 (1H, m., C_{11}-H), 4.00 (1H, d,t., J=6.5 and 6 Hz, C_{15}-H)] was synthesized from 23b, and also transformed to dl-PGE_2 (oil), whose spectral data in solution were identical with those of natural PGE_2.

Acknowledgements

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References and Notes

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10) All new compounds were characterized by IR, NMR, MS spectroscopy and elemental analyses. NMR spectra were taken in $CDCl_3$, if not otherwise noted.

11) After completion of this work (patent application in Japan; 4th April, 1977), similar transformation (6→7→9) was reported: W. Boland and L. Jaenicke, Chem. Ber., 110 1823 (1977).

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13) Reported mp 101-103° (ref. 4). This discrepancy may be attributed to the polymorphism observed in natural 1 (ref. 3).