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FACILE SYNTHESIS OF 6a-CARBAPROSTAGLANDIN I_2

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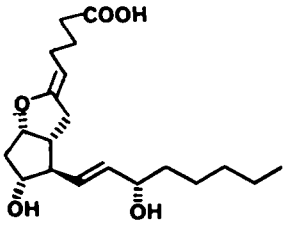
Abstract—The optically active 6a-carbaprostaglandin I_2 (2), a stable mimic of natural prostacyclin (1), was synthesized from the lactone 4 or the hydroxy acid 5, which were general synthetic intermediates for natural prostaglandins.

Prostacyclin (PGI_2, 1)[1] is one of the most interesting members in the prostaglandin family, and its biological activities have been investigated extensively.[2] Unfortunately, however, PGI_2 is an extremely unstable substance due to the enol-ether functionality, and it is not surprising that PGI_2 is rapidly hydrolyzed to the stable and less active 6-ketoprostaglandin $F_{1\alpha}$ in neutral or acidic aqueous media.[3] Although the biological activities of PGI_2 are quite important, the instability still remains as one of the greatest problems in its pharmacological use. Thus, great efforts to get stable prostacyclin analogues of hetero-atom substituted derivatives have been developed by a number of groups.[4] Recently, the desirable stability of carba-PGI_2 (2) (trivial names carbacyclin, carbaprostacyclin, and 9(O)-methanoprostacyclin) has received attention because of the rational substitution of 6,9-oxygen bridge of PGI_2 by methylene. Furthermore, the typical biological activities of PGI_2, e.g. inhibition of platelet aggregation, are well preserved in carba-PGI_2 itself.[5] Unfortunately, the reported routes to 2 are either lengthy or less practical despite the vast demand from biological research.[6] Therefore, the development of a more practical method to construct the molecule is the first priority. The straightforward preparation of the optically active bicyclic five membered ring system from a readily available starting material is necessary. Furthermore, such a method should be quite flexible to construct other carbacyclin analogues, e.g. the modification of the ω-chain. We describe herein the details of our total synthesis of carba-PGI_2 (2) following the strategy described in Scheme 1.

RESULTS AND DISCUSSION

The synthesis of the crucial intermediate 3 was summarized in Scheme 2. The optically active and readily available lactone 4, a general synthetic intermediate for natural prostaglandins,[8] was treated with aqueous base, then esterified by an ethereal diazomethane to give 7. The relactonization of the hydroxy ester 7 was quite rapid, so the crude ester 7 was used directly for the next reaction without any purification. Oxidation of 7 with chromyl chloride-*t*-butyl alcohol-pyridine complex[9] in dichloromethane at 35° for 2.5 hr afforded 8 in 79% overall yield from 4. Treatment of the ketone 8 with 3 equiv. lithiomethyl trimethylsilylacetate[10] in THF at −78° for 2 hr afforded the desired unsaturated ester 9 (46%; 69% based upon unrecovered 8), minor product 10 (14%; 21% based upon unrecovered 8), and recovered 8 (33%). It could be assumed that the moderate recovery of 8 in spite of the presence of excess anion was due to the enolization of the cyclopentanone. When the reaction mixture was warmed to 0°, the conjugated cyclopentanone derivatives due to the dehydropyranylation were obtained. The compound 10 was smoothly converted to the desired 9 in 76% yield by the treatment with potassium fluoride in methanol and subsequently with an ethereal diazomethane. Hydrogenation of 9 over palladium on carbon in ethanol afforded the diester 11 in 91% yield. In principle, two acetate appendages of 11 may be formed from this reaction, but 11 showed a single spot on tlc in several solvent systems. The stereochemical assignment was solved at the later stage of synthesis.

Ring closure of the diester 11 was effected by exposure to excess potassium *t*-butoxide in benzene at 75° for 4 hr. Two components were separated by chromatography on silica gel and the less polar materials consisted of a mixture of 12 and 14 (35%), and the more polar materials were shown to be the regio isomers of 14 (39%). Demethoxycarbonylation of the less polar materials proceeded smoothly at 175° for 15 min in HMPA to give a mixture of ketones 3 and 15 in 54 and 37% yields, respectively, after chromatography on silica



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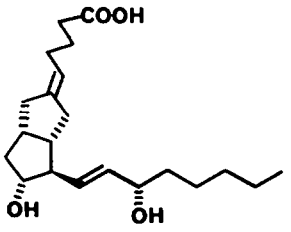

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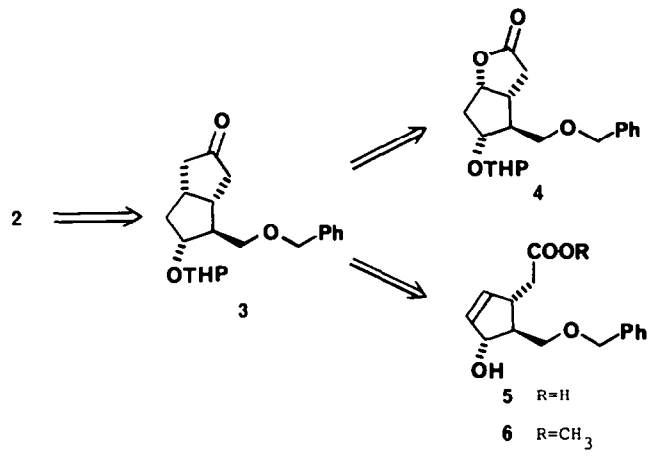
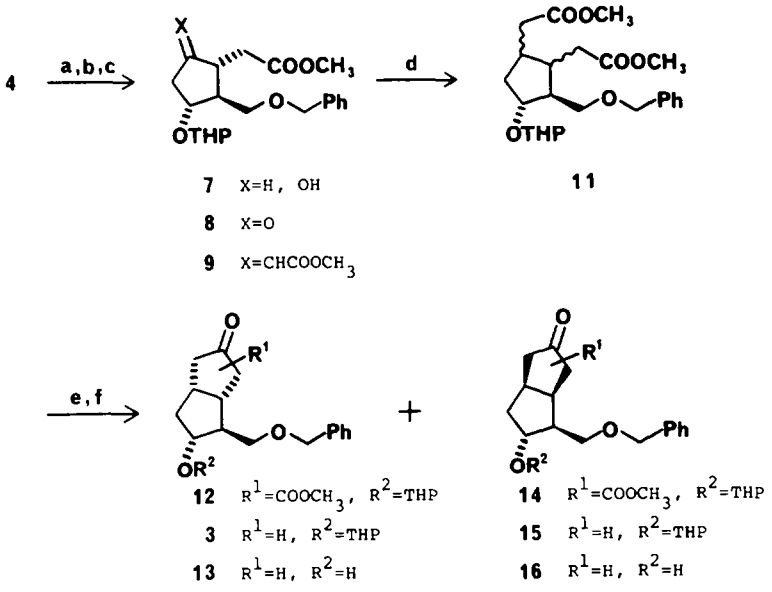


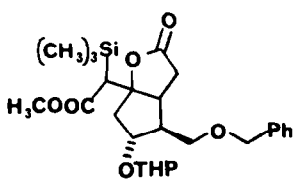
Scheme 1.



Scheme 2. (a), (i) NaOH, (ii) CH_2N_2; (b) CrO_2Cl_2, t-BuOH, py; (c) Me_3SiCH_2COOMe, LDA: (d) H_2, 5% Pd-C; (e) t-BuOK: (f) 175°, HMPA.

gel. Attempted demethoxycarbonylation of the more polar component was unsuccessful by the similar method. Judging from the IR spectrum of **14** (1760, 1730 cm^{-1}), which reveals no absorption of the enol form, the difficulty of the demethoxycarbonylation may not be surprising. However, after detetrahydropyranylation, refluxing the hydroxy keto-ester with LiI in pyridine for 16 hr afforded the ketone **16** in good yield.

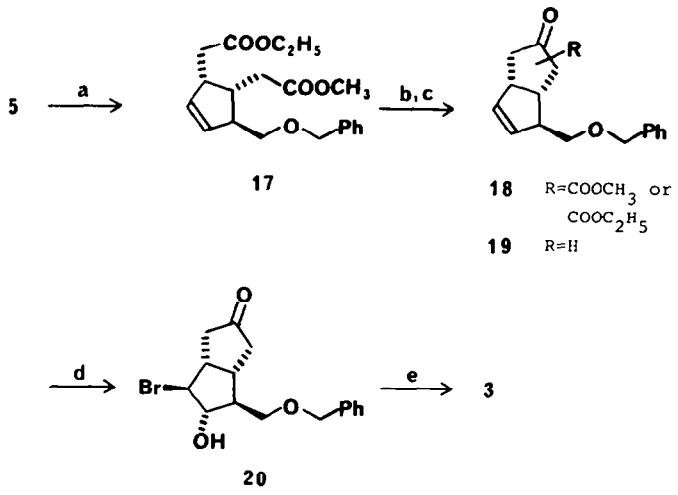
After deprotection of THP group, the α-configuration of **3** was confirmed by circular dichroism (CD) and



10

chemical transformations. Ketones **13** and **16** were indistinguishable by their NMR, IR and MS spectra, however, they were distinguished clearly by the analyses of their CD spectra. Thus, the CD curve of the ketone **13** showed a weak negative sign in contrast to a strong positive sign of that of the ketone **16**. From the octant rule,[11] it is reasonable to conclude that the structure of both ketones correspond to the ones illustrated in the figure respectively. The ketone **16** might be produced either by epimerization in the Wittig type reaction of **8** or during the hydrogenation of **9**. The structure of **3** was further confirmed by the following chemical transformations: (a) deprotection of THP group of diester **11**, (b) hydrolysis (KOH), (c) intramolecular lactonization (p-TsOH, benzene) followed by separation (33%), (d) hydrolysis (KOH), (e) esterification (CH_2N_2), (f) tetrahydropyranylation, (g) Dieckmann condensation, and (h) demethoxycarbonylation to form the ketone **3** as a sole product.

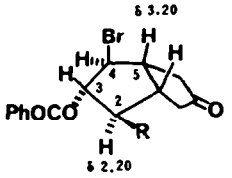
The necessary carbon skeleton of carbacyclin (**2**) was



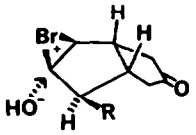
Scheme 3. (a), (i) CH_2N_2, (ii) $CH_3C(OC_2H_5)_3$; (b) t-BuOK; (c) 120°, DMSO, NaCl; (d) NBS, DMSO, H_2O; (e), (i) n-Bu_3SnH, (ii) DHP, p-TsOH.

now assembled. However, the low overall yield of **3** from **4** (*ca.* 12% yield) and the unexpected epimerization of C-8 and C-9 (PG numbering) required the alternative synthesis which was started from the optically active hydroxy acid **5** as shown in Scheme 3. The acid **5** was also a general synthetic intermediate for the synthesis of natural prostaglandins.[12] Esterification of **5** with methyl iodide in the presence of K_2CO_3 in acetone (35°, 16 hr) provided the hydroxy ester **6** in quantitative yield. Since the cyclopentanone ring might be prepared by Dieckmann condensation, and since a carboalkoxymethyl group would be required for our purpose, Claisen rearrangement may be the choice of the method. Thus, treatment of **6** with triethyl orthoacetate in the presence of hydroquinone[13] afforded a single isomer of diester **17** in 56% yield after chromatography on silica gel.

Dieckmann condensation of the diester **17** (potassium *t*-butoxide in benzene) followed by dealkoxycarbonylation in dimethyl sulfoxide (DMSO) containing water and NaCl led to the ketone **19** as a sole product in 79–84% yield. Our attention next turned to the introduction of the hydroxyl function to **19** in regio- and stereoselective fashion. Ranganathan reported the similar functionalization in the prostaglandin synthesis.[14] The modified procedure was applied to **19**; treatment of **19** with N-bromosuccinimide in DMSO-water (10:1) gave the single bromohydrin **20** exclusively in 77% yield after chromatography on silica gel. The regiochemistry of the benzoate **21** (m.p. 108–109°), which was prepared from the alcohol **20** (93%) using benzoyl chloride-pyridine in dichloromethane, was assigned by ^1H NMR ($J_{2,3} = J_{3,4} = J_{4,5} = 7$ Hz). Although the stereochemistry could not be determined by ^1H NMR, it is clear that bromonium cation may approach to the double bond of **19** from the *exo* side to produce the ion **22** which would be neutralized by hydroxy ion from the C-3 *endo* side. Irradiation of **20** with a high pressure mercury lamp in the presence of n-Bu_3SnH using AIBN as a sensitizer in benzene afforded **13** in 89% yield, which was identical in all respects with the tetrahydropyranylation product of **3** prepared by the method described in Scheme 2. These results clearly show that the hydroxyl function of **20** has desirable regio- and stereochemical configuration. Finally, the alcohol **13** was transformed to **3** quantitatively with 2,3-dihydropyran in the presence of *p*-toluenesulfonic acid in dichloromethane. Thus, the crucial synthetic intermediate **3** was readily prepared in large quantity from **5** in 30% overall yield without any careful chromatography for all intermediates.



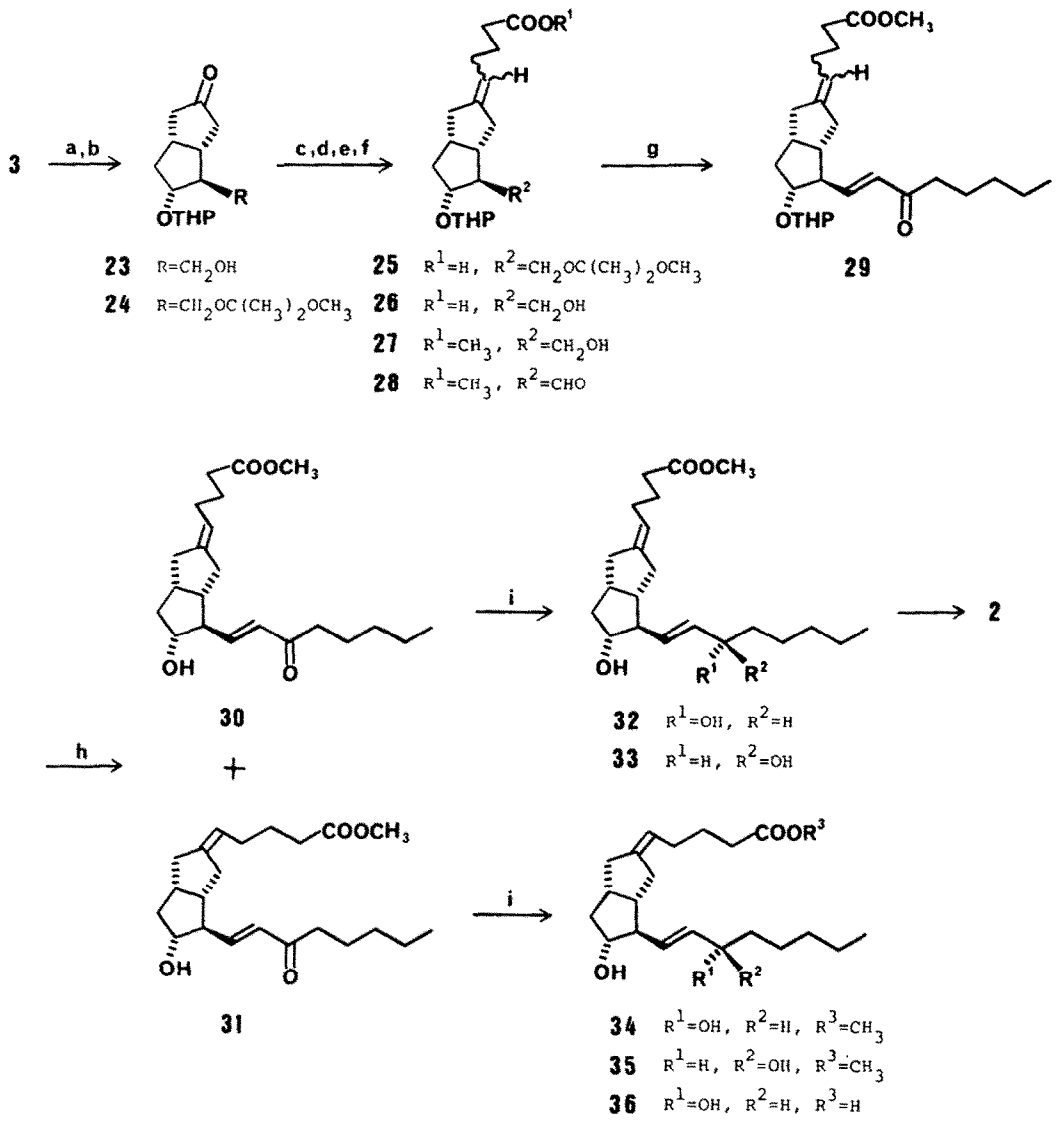
21 R=CH_2OCH_2Ph



22 R=CH_2OCH_2Ph

The final conversion of **3** to **2** was accomplished straightforwardly which was shown in Scheme 4. Deprotection of benzyl ether group by hydrogenolysis using palladium on carbon in AcOEt furnished the hydroxy ketone **23** (72% yield). Alternatively, hydrogenolysis in ethanol–acetic acid (10:1) gave **23** in 96% yield. Conversion of **23** to the methyl ester **27** was effected by the following sequence: (a) protection of the hydroxyl function by treating with 2-methoxypropene, (b) Wittig reaction with the ylide derived from (4-carboxybutyl-triphenylphosphonium bromide in DMSO at 35° for 16 hr, (c) selective deprotection of 2-methoxypropyl unit with 0.5 N HCl in THF at 0°, and (d) esterification with diazomethane (overall 77% yield). The alcohol **27** was oxidized to the aldehyde **28** using SO_3-pyridine complex[15] or DMSO-$(COCl)_2$[16] and thence transformed to enone **29** by Emmons–Horner method[17] (98 and 99% yield, respectively, from **27**).

Although the 5*E* and 5*Z* isomers of **25** to **29** were not able to separate, hydrolysis of THP group in the enone **29** produced a mixture of more polar material **30** and less polar material **31** (*ca.* 1:1 by TLC in 97% yield), which were readily separated by chromatography on silica gel. The Wittig reaction of the alcohol **23** gave a 1:2 mixture of 5*E* and 5*Z* isomers, which were readily separated by chromatography on silica gel after Emmons–Horner reaction. These two components may be due to the stereo isomers of C-5 double bond. Unfortunately spectral features of **30** and **31** were not good enough for the



Scheme 4. (a) H_2, 5% Pd-C; (b) $CH_2C(CH_3)OCH_3$, p-TsOH; (c) $Ph_3P{=}CH(CH_2)_3COO^-$; (d) 0.5 N HCl; (e) CH_2N_2; (f) SO_3-Py; (g) $(MeO)_2POCH_2COC_5H_{11}$, NaH; (h) 65% AcOH; (i) i-Bu_2AlH, t-$Bu_2C_6H_2$ $(CH_3)OH$.

stereochemical assignments and the assignment should wait until the construction of the whole structure of prostane. Stereoselective reduction of the enone **30** with diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide[18] in toluene at −78 to −10° furnished 15*S* alcohol **32** (83% yield) and 15*R* alcohol **33** (12% yield) after separation by chromatography on silica gel. 5*Z*, 15*S* and 5*Z*, 15*R* isomers, **34** and **35**, were also prepared in 79 and 18% yield, respectively, from the enone **31** in the same manner.

The stereochemical assignments at C-15 of **32** and **33** (**34** and **35**) were determined by the following two methods. The first was based on their relative tlc mobility. It is well known that PGI_2 methyl ester (**37**) and its 15*R* epimer **38** are clearly distinguished by tlc analysis. In several solvent systems (e.g. AcOEt-cyclohexane, 2:1 0.1% Et_3N), the 15*S* isomer **37** was more polar R_f (0.17) than the 15*R* isomer **38** (R_f 0.25). As well, (5*E*, 15*S*)-PGI_2 methyl ester (**39**) was more polar R_f (0.16) than the corresponding 15*R* epimer **40** (R_f 0.24). Therefore, it may be reasonable that the more polar diols **32** (R_f 0.20) and **34** (R_f 0.22), in the same solvent system, had 15*S* configurations, and that the less polar diols **33** (R_f 0.34) and **35** (R_f 0.36) might be 15*R* alcohols. Secondly, those were confirmed by stereoselective reduction of the enones **30** and **31** with a chiral binaphthyl-modified aluminum hydride reagent which was developed by Noyori *et al.*[19] This reagent reduced enone **30** to a mixture of **32** and **33** with ratio of 95.9:4.1, and also reduced enone **31** to a mixture of **34** and **35** with a ratio of 93.9:6.1. The ratio of isomers was determined by hplc; LiChrosorb RP-18, 5 μm, 250 mm × 4 mm; mobile phase acetonitrile/water (1:1, v/v); flow rate 0.9 ml/min; 20°; detected at 205 nm. These results clearly show that diols **32** and **34** had 15*S* configurations, and that diols **33** and **35** had 15*R* configurations.[19] These stereochemical assignments were further supported by the relative biological activities of the final carbacyclic stages.[6e]

Saponification of the ester **32** with aqueous base gave the crystalline acid diol **2** in 96% yield (m.p. 64.5–66.5°).

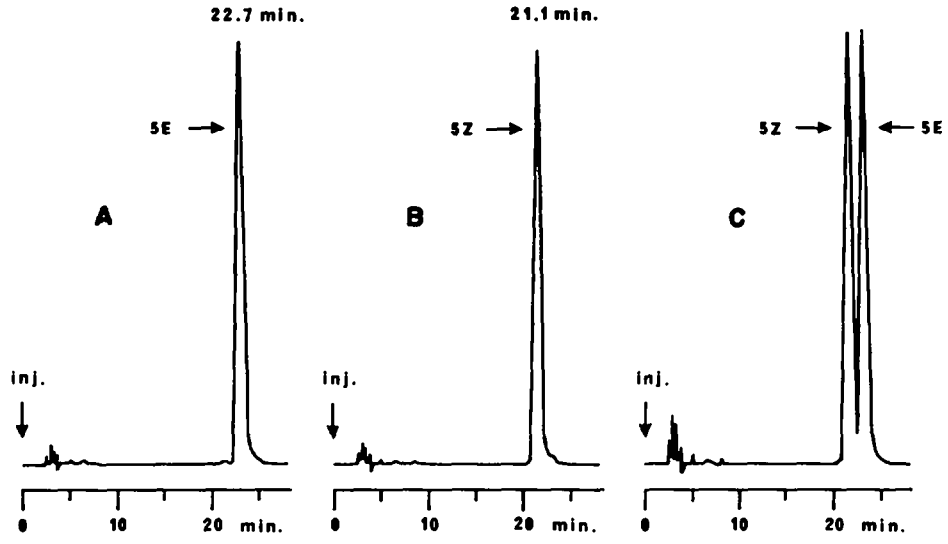
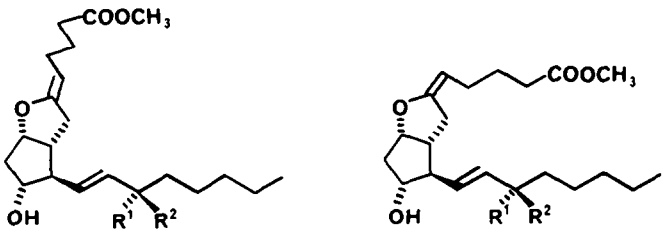


Fig. 1. Reversed phase hplc of 5*E*-carbacyclin (2) and 5*Z*-carbacyclin (36). (A) 5*E*-carbacyclin(2), (B) 5*Z*-carbacyclin (36), (C) mixture of 2 and 36. LiChrosorb RP-18, 5 μm, 250 mm × 4 mm; mobile phase 0.02 M KH_2PO_4/acetonitrile/isopropanol (450/335/75, v/v/v); flow rate 0.7 ml/min; 20°; detected at 205 nm.



37 R^1=OH, R^2=H
38 R^1=H, R^2=OH
39 R^1=OH, R^2=H
40 R^1=H, R^2=OH

Similarly, the 5*Z* isomer **36** (m.p. 113–114°) was obtained from **34** in 93% yield. The purities of **2** and **36** were determined to >99.5% by hplc as shown in Fig. 1.

Initially, the configurational assignments at C-5 for **30** and **31** have not been determined by a physical or chemical method owing to the close structual similarity. However, the biological activities of **2** and **36** reveal considerable contrast. Thus, **2** was two times more potent than PGE_1, whereas **36** was fifty times less potent in inhibitory effect on ADP-induced rat platelet aggregation *in vitro*. Therefore, 5*E*, 15*S* and 5*Z*, 15*S* were assigned to **2** and **36**, respectively by their biological potency. These methods used here to determine the stereochemistry of C-5 and C-15 are essentially same ones reported by Morton.[6e]

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 or 260–30 model and were calibrated with the 1610 cm^{-1} absorption of polystyrene. ^1H NMR spectra were obtained on a JEOL PMX-60 or a Varian XL-100 spectrometer in C^2HCl_3. Chemical shifts are reported as parts per million relative to internal tetramethylsilane. Mass spectra were measured on a JMS-01 SG double-focussing mass spectrometer. Circular dichroism spectra were obtained with a JASCO J-40 spectropolarimeter. High-pressure liquid chromatography was carried on a JASCO FLC-A20 instrument. Thin layer chromatography was conducted with Merck glass plates precoated with silica gel 60 F_{254}. Unless otherwise noted, column chromatography was carried out on silica gel (Merck, particle size 0.063–0.20 mm). All chromatography solvents were distilled prior to use.

Methyl 3α - hydroxy - 5 - oxo - 2β - benzyloxymethylcyclopentane - 1α - acetate tetrahydropyranyl ether (**8**). A mixture of 47 g (0.135 mol) of 3α,5α - dihydroxy - 2β - benzyloxymethyl - 1α - acetic acid γ-lactone 3-tetrahydropyranyl ether (**4**), 100 ml of 2N NaOH, and 160 ml of MeOH was stirred at room temp for 30 min. A reaction mixture was concentrated to half volume, then acidified with 15% HCl to pH 3 at 5°, and extracted with AcOEt (500 ml, 400 ml × 2). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to *ca* 1000 ml. To this soln at 5° was added an ethereal diazomethane until a yellow color persisted. The solvents were evaporated to give the hydroxy ester **7**, which was dissolved in 200 ml of CH_2Cl_2.

A 2 l four neck flask was charged with 650 ml of dry CH_2Cl_2, 35 ml (0.366 mol) of t-BuOH, and 44.5 ml (0.549 mol) of pyridine. The soln was cooled to −78° and a soln of 28.4 g (0.183 mol) of chromyl chloride in 70 ml of CCl_4 was added over 40 min. The resulting soln was warmed to room temp, then a soln of the above hydroxy ester **7** in 200 ml of CH_2Cl_2 was added in one portion. The reaction mixture was stirred at 35° for 2.5 hr, quenched by the addition of 2.5 ml of dimethylsulfide, stirred for 10 min, then concentrated to *ca.* 300 ml under the reduced pressure. The resulting soln was poured into 1000 ml of ether with vigorous stirring. The precipitate removed by filtration through Celite pad, and washed with 500 ml of ether. The filtrate was

washed with 1 N HCl, water and brine, dried over $MgSO_4$, concentrated to give an oil. This material was chromatographed on 700 g of silica gel using AcOEt-cyclohexane (1:5) as eluent to give **8** as a pale yellow oil: 40 g, 79%; tlc R_f 0.50 (AcOEt–benzene, 1:2); IR (film) cm^{-1} 1740, 1495, 1450, 1435, 1370, 1200, 970; NMR δ 7.20 (5H, s), 4.60 (1H, m), 4.50 (2H, s), 4.00–4.45 (1H, m), 3.60 (3H, s); MS for $C_{21}H_{28}O_6(M^+)$ *m/e* (calcd) 376.18858, *m/e* (found) 376.18786 (other ions at *m/e* 358, 345, 292, 274, 201, 185).

Methyl 3α - hydroxy - 2β - benzyloxymethyl - 5 - carbomethoxymethylenecyclopentane - 1α - acetate tetrahydropyranyl ether (**9**). To a stirred soln of diisopropylamine (44.6 ml, 0.32 mol) in dry THF (1000 ml) at −78° was added 1.55 M n-butyllithium in hexane (205 ml, 0.32 mol) under argon. After stirring at −78° for 15 min, methyl trimethylsilylacetate (50 g, 0.34 mol) was added into this soln at −78°. After stirring at −78° for 20 min, to this anion soln was added a soln of ketone **8** (38 g, 0.1 mol) in dry THF (100 ml) over 10 min. The mixture was stirred at −78° for 2 hr, quenched by the addition of 23 ml of AcOH at this temp. The reaction mixture was then warmed up to room temp, and the THF was removed in vacuo. The residue was partitioned between 200 ml of water and 500 ml of AcOEt, after separation of the phases, the aqueous phase was extracted with two additional 200 ml portions of AcOEt. The combined extracts were washed with 1 N HCl, water, and brine, dried over $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed on 800 g of silica gel using AcOEt-cyclohexane (1:6) as eluent to afford **9** (19.8 g 46%), **10** (7 g, 14%), and the recovered **8** (12.5 g, 33%). **9**:TLC R_f 0.58 (AcOEt-benzene, 1:2); IR (film) cm^{-1} 1740, 1720, 1655, 1495, 1440, 1210, 1030; NMR δ 7.20 (5H, s), 5.70 (1H, m), 4.60 (1H, m), 4.45 (2H, s), 4.10 (1H, m), 3.63 (3H, s); MS for $C_{23}H_{29}O_6$ (M^+–OCH_3) *m/e* (calcd) 401.19640, *m/e* (found) 401.19857 (other ions at *m/e* 348, 347, 241, 240, 222, 209, 207). **10**: tlc R_f 0.46 (AcOEt–benzene, 1:2); IR (film) cm^{-1} 1775, 1720, 1495, 1440, 1030, 850; NMR δ 7.20 (5H, s), 4.60 (1H, m), 4.40 (2H, s), 3.85–4.30 (5H, m), 3.60 (3H, s), 0.15 (3H, s).

A mixture of **10** (7 g, 14.3 mmol), KF (0.81 g, 14 mmol), and MeOH (50 ml) was stirred at room temp for 30 min. The reaction mixture was concentrated to *ca.* 20 ml, acidified with 1 N HCl to pH 4, extracted with AcOEt (200, 100 ml). The extracts were washed with brine, dried over $MgSO_4$. The filtrate was concentrated to ca. 100 ml, and then to this soln at 5° was added an ethereal diazomethane until a yellow color persisted. The solvents were evaporated *in vacuo*. The residue was chromatographed on 100 g of silica gel using AcOEt-cyclohexane (1:6) as eluent to give **9** (4.7 g, 76%).

Methyl 3α - hydroxy - 2β - benzyloxymethyl - 5ξ - carbomethoxymethylcyclopentane - 1ξ - acetate tetrahdropyranyl ether (**11**). The unsaturated ester **9** (29 g, 67 mmol) was hydrogenated on 10 g of 5% Pd–C in 600 ml of EtOH under the atmospheric pressure of hydrogen at room temp for 1.6 hr. When 67 mmol of hydrogen was absorbed, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on 500 g of silica gel eluting with AcOEt-cyclohexane (1:5) to afford **11** as a colorless oil (26.5 g, 91%): tlc R_f 0.52 (AcOEt-benzene, 1:2); IR (film) cm^{-1} 1740, 1495, 1440, 1020; NMR δ 7.20 (5H, s), 4.60 (1H, m), 4.40 (2H, s), 3.85–4.20 (1H, m), 3.60 (3H, s), 3.50 (3H, s); MS for $C_{23}H_{31}O_6$ (M^+–OCH_3) *m/e* (calc.) 403.21205, *m/e* (found) 403.21270 (other ions at *m/e* 349, 333, 332, 331, 259, 243, 241, 209, 193).

3α - Hydroxy - 7 - oxo - 2β - benzyloxymethylbicyclo[3.3.0]*octane tetrahydropyranyl ether* (**3**) *and the β-isomer* **15**. To a stirred soln of t-BuOK (27.4 g, 0.244 mol) in dry benzene (700 ml) at 30° was added a soln of diester **11** (26.5 g, 61 mmol) in dry benzene (100 ml) under argon. The mixture was stirred at 70° for 4 hr, and then cooled in an ice-water bath, quenched by the addition of AcOH (20 ml), and diluted with water (150 ml). The organic phase was separated. The aqueous phase was extracted with AcOEt (300 ml). The combined extracts were washed with water and brine, dried over $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed on 800 g of silica gel using AcOEt-cyclohexane (1:5) as eluent to afford the less polar materials **12** and **14** [8.45 g, 35%; R_f 0.38 homogeneous (AcOEt–cyclohexane, 1:2)], and the more polar materials **14** [9.53 g, 39%; R_f 0.28 homogeneous (AcOEt–cyclohexane, 1:2)].

The above less polar materials (a mixture of **12** and **14**, 8.45 g, 21 mmol) was dissolved in 20 ml of HMPA-water (19:1). The soln was stirred at 175° for 15 min, then poured into ice water (150 ml), extracted with ether (300, 200 ml × 2). The combined extracts were washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo* to give a yellow oil. This material was chromatographed on 350 g of silica gel eluting with AcOEt-cyclohexane (1:3) to obtain **3** as a colorless oil (3.9 g, 54%) and **15** as a colorless oil (2.7 g, 37%). **3**: tlc R_f 0.51 (AcOEt–cyclohexane, 2:3); IR (film) cm^{-1} 1740, 1495, 1455, 1405, 1360, 1200, 1120, 1080. 1025, 975: NMR δ 7.20 (5H, s), 4.60 (1H, m), 4.45 (2H, s), 4.05 (1H, m); MS for $C_{21}H_{28}O_4$ (M^+) *m/e* (calcd) 344. 19875, *m/e* (found) 344.20108 (other ions at *m/e* 261, 259, 253, 244, 242, 153, 136, 108, 91, 85. **15**; tlc R_f 0.57 (AcOEt–cyclohexane, 2:3); IR (film) cm^{-1} 1745, 1495, 1455, 1415, 1360, 1200, 1110, 1080, 1025, 970; NMR δ 7.20 (5H, s), 4.60 (1H, m), 4.45 (2H, s), 4.25 (1H, m); MS for $C_{21}H_{28}O_4$ (M^+) *m/e* (calcd) 344.19875, *m/e* (found) 344, 19878 (other ions at *m/e* 300, 261, 259, 253, 242, 237, 194, 192, 153, 149, 108, 91, 85).

3α - Hydroxy - 7 - oxo - 2β - benzyloxymethylbicyclo[3.3.0]*octane* (**13**). *Method A.* A mixture of **3** (100 mg, 0.29 mmol), 1 N HCl (1 ml), and THF (2 ml) was stirred at room temp for 2 hr, diluted with 5 ml of water, then extracted with AcOEt (10 ml × 2). The extracts were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on 5 g of silica gel using AcOEt–cyclohexane (1:2) as eluent to give **13** as a colorless oil (70 mg, 93%): tlc R_f 0.31 (AcOEt–cyclohexane, 2:1); IR (film) cm^{-1} 3450, 1740, 1495, 1455, 1405, 1365, 1100, 740, 705; NMR δ 7.33 (5H, s), 4.54 (2H, s), 4.11 (1H, q, J = 7.5 Hz), 3.65 (1H, dd, J = 9.0, 5.5 Hz), 3.48 (1H, dd, J = 9.0, 8.0 Hz); MS for $C_{16}H_{20}O_3$ (M^+) *m/e* (calc.) 260.14124, *m/e* (found) 260.14286 (other ions at *m/e* 242, 169, 154, 151, 136, 108, 91); CD (*c* 7.07×10^{-3}, MeOH) [θ] (nm) 0 (245), -6.40×10^2 (289, 297), -4.34×10^2 (sh, 307), -0.88×10^2 (sh, 319), 0 (330). *Method B.* A mixture of **20** (33 g, 97.6 mmol), n-Bu_3SnH (26.3 ml, 0.29 mol), azobisisobutyronitrile (280 mg, 2 mmol) and dry benzene (500 ml) was irradiated with high pressure mercury lamp under argon at room temp for 2 hr. The mixture was concentrated *in vacuo*. The residue was chromatographed on 400 g of silica gel using AcOEt–cyclohexane (1:2) as eluent to afford **13** as a colorless oil (22.5 g, 89%).

Tetrahydropyranylation of **13**. To a soln of 22.5 g (86.5 mmol) of **13** and 9.1 ml (0.1 mol) of 2,3-dihydropyran in 200 ml of dry CH_2Cl_2 at 10° was added 190 mg of p-toluenesulfonic acid monohydrate. The mixture was stirred at room temp for 30 min under argon. The reaction mixture was quenched by the addition of 2 ml of Et_3N, then concentrated *in vacuo*. The residue was chromatographed on 300 g of silica gel eluting with AcOEt–cyclohexane (1:5) to afford **3** as a colorless oil (28.9 g, 97%).

The β-isomer **16**. Tetrahydropyranyl ether **15** (100 mg, 0.29 mmol) was converted to 67 mg (90%) of **16** as a colorless oil by the same method described for the preparation of **13** (*Method A*). **16**: tlc R_f 0.31 (AcOEt–cyclohexane, 2:1); IR (film) cm^{-1} 3450, 1740, 1495, 1455, 1410, 1365, 1120, 1090, 1030, 740, 700; NMR δ 7.31 (5H, s), 4.53 (2H, s), 4.34 (1H, m), 3.63 (1H, dd, J = 9, 6 Hz), 3.52 (1H, dd, J = 9, 7 Hz); MS for $C_{16}H_{20}O_3$ (M^+) *m/e* (calc.) 260.14124, *m/e* (found) 260.14189 (other ions at *m/e* 242, 169, 153, 151, 108, 91); CD (c 7.60×10^{-3}, MeOH) [θ] (nm) 0 (235), $+1.51 \times 10^4$(sh, 287), $+1.66 \times 10^4$ (295), $+1.27 \times 10^4$ (sh, 305), $+0.46 \times 10^4$ (sh, 316), 0 (330).

Methyl 3α - hydroxy - 2β - benzyloxymethyl - 4 - cyclopentene-1α - acetate (**6**). To a well stirred soln of 3α - hydroxy - 2β - benzyloxymethyl - 4 - cyclopentene - 1α - acetic acid (**5**), 140 g, 0.534 mol) and CH_3I (165 ml, 2.65 mol) in acetone (460 ml) was added K_2CO_3 (147 g, 1.06 mol) at room temp. The mixture was stirred at 35° for 16 hr, then diluted with AcOEt (1000 ml). K_2CO_3 was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on 1 kg of silica gel using AcOEt-cyclohexane (1:4) as eluent to give **6** as a pale yellow oil (146 g, 99%): tlc R_f 0.45 (AcOEt–cyclohexane, 2:1); IR (film) cm^{-1} 3430, 1735, 1450, 1435, 1365, 1250, 1165, 1100, 1005, 740, 700; NMR δ 7.20 (5H, s), 5.70 (2H, m), 4.55 (1H, m), 4.45

(2H, s), 3.60 (3H, s); MS for $C_{16}H_{18}O_3$ (M^+–H_2O) *m/e* (calc.) 258.12559, *m/e* (found) 258.12837 (other ions at *m/e* 245, 167, 152, 135, 107, 91).

Methyl 2β - benzyloxymethyl - 5α - carboethoxymethyl - 3 - cyclopentene - 1α - acetate (**17**). A mixture of **6** (134 g, 0.485 mol), triethyl orthoacetate (360 ml, 1.95 mol), and hydroquinone (11 g, 0.1 mol) was stirred at 140° for 12 hr with removing EtOH formed by distillation, then cooled and concentrated *in vacuo*. The residue was chromatographed on 1.2 kg of silica gel eluting with AcOEt–cyclohexane (1:9) to give **17** as a pale yellow oil (94 g, 57%): tlc R_f 0.60 (AcOEt–cyclohexane, 2:1); IR (film) cm^{-1} 1735, 1370, 1260, 1160, 1100, 1030, 740, 700; NMR δ 7.20 (5H, s), 5.67(2H, m), 4.44(2H, s), 4.07(2H, q), 3.56 (3H, s), 3.40 (2H, m), 1.23 (3H, t); MS for $C_{20}H_{26}O_5$ (M^+) *m/e* (calc.) 346.17801, *m/e* (found) 346.17568 (other ions at *m/e* 228, 206, 192, 179, 165, 151, 105, 91).

7 - Oxo - 2β - benzyloxymethyl - 3 - bicyclo[3.3.0]octene (**19**). To a stirred soln of t-BuOK (72.3 g, 0.64 mol) in dry benzene (1300 ml) at 50° was added a soln of **17** (56 g, 0.16 mol) in dry benzene (100 ml) under argon. The mixture was stirred at 65° for 1.5 hr, then cooled in an ice-water bath, quenched by the addition of 50 ml of AcOH, and diluted with 260 ml of water. The organic phase was separated and the aqueous phase was extracted with AcOEt (500 ml). The combined extracts were washed with 1 N HCl, water, and brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was chromatographed on 800 g of silica gel eluting with AcOEt–cyclohexane (1:10) to give 41 g of **18** (a mixture of methyl and ethyl ester): tlc R_f 0.65, homogeneous (AcOEt-cyclohexane, 1:2).

The above keto-ester **18** (41 g) was dissolved in 150 ml of DMSO containing 3 ml of water and 740 mg (12.6 mmol) of NaCl. The resulting soln was stirred at 120° for 1.5 hr, then poured into 900 ml of ice–water, and extracted with AcOEt–ether (1:1, 500 ml × 3). The combined extracts were washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was chromatographed on 500 g of silica gel eluting with AcOEt–cyclohexane (1:6) to afford **19** as a colorless oil (31 g, 79% from **17**) which solidfied on standing at −20°. Recrystallization from ether-*n*-pentane gave pure **19** as a white needle: m.p. 35–36°; tlc R_f 0.45 (AcOEt-cyclohexane, 1:2); IR (film) cm^{-1} 1740, 1495, 1452, 1400, 1360, 1160, 1100, 1025, 740, 700; NMR δ 7.33 (5H, s), 5.72 (2H, m), 4.53 (2H, s), 3.47 (1H, dd, J = 9, 6 Hz), 3.34 (1H, dd, J = 9, 7 Hz), 3.30–3.60 (1H, m); MS for $C_{16}H_{18}O_2$ (M^+) *m/e* (calc.) 242.13067, *m/e* (found) 242.13180 (other ions at *m/e* 149, 121, 91, 79).

3α - Hydroxy - 4β - bromo - 7 - oxo - 2β - benzyloxymethylbicyclo[3.3.0]octane (**20**). To a stirred soln of **19** (31 g, 0.128 mol) in 700 ml of DMSO-water (10:1) at 15° was added NBS (44.5 g, 0.25 mol) in several portions. The mixture was stirred at room temp for 30 min, poured into 2000 ml of ice-water, extracted with AcOEt-ether (1:1; 700 ml × 3). the combined extracts were washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was chromatographed on 900 g of silica gel using AcOEt-cyclohexane (1:5) as eluent to give **20** as a colorless oil (33 g, 77%): tlc R_f 0.36 (AcOEt–cyclohexane, 1:1); IR (film) cm^{-1} 3420, 1735, 1450, 1400, 1360, 1250, 1175, 1105, 1045, 1030, 810, 740, 705; NMR δ 7.33 (5H, s), 4.54 (2H, s), 4.12 (1H, t, J = 9 Hz), 3.74 (1H, t, J = 9 Hz), 3.67 (1H, dd, J = 9.0, 5.5 Hz), 3.56 (1H, dd, J = 9, 6 Hz); MS for $C_{16}H_{19}BrO_3$ (M^+) *m/e* (calc.) 338.05180, *m/e* (found) 338.04999 (other ions at *m/e* 259, 249, 247, 241, 232, 230, 167, 151, 135, 107, 91).

3α - Hydroxy - 4β - bromo - 7 - oxo - 2β - benzyloxymethylbicyclo[3.3.0]octane benzoate (**21**). To a soln of **20** (180 mg, 0.53 mmol) and pyridine (0.161 ml, 2 mmol) in dry CH_2Cl_2 (3 ml) at room temp was added benzoyl chloride (0.116 ml, 1 mmol). The mixture was stirred at that temp for 16 hr, quenched by the addition of 0.1 ml of EtOH. After 20 min, the soln was diluted with 30 ml of ether, washed with 1 N HCl, water and brine, dried over $MgSO_4$, then concentrated *in vacuo* to leave a white solid. This material was chromatographed on 10 g of silica gel eluting with AcOEt–cyclohexane (1:5) to afford **21** as a white solid (218 mg, 93%). Recrystallization from AcOEt-*n*-hexane gave pure **21** as a white needle: m.p. 108–109°; tlc R_f 0.43 (AcOEt–cyclohexane, 1:2); IR (KBr) cm^{-1} 1730, 1710, 1600, 1450, 1397, 1310, 1280, 1170, 1120, 1095, 1065, 1020, 735, 705; NMR δ 8.04 (2H, m), 7.35–7.60 (3H, m), 7.20 (5H, s), 5.65 (1H, t, J = 7 Hz, C_3H), 4.53 (2H, s), 4.11 (1H, t, J = 7 Hz, C_4H), 3.74 (1H, dd, J = 9, 5 Hz). 3.63 (1H, dd, J = 9, 6 Hz); MS for $C_{23}H_{23}BrO_4$ (M^+) *m/e* (calc.) 442.07801, *m/e* (found) 442.07913 (other ions at *m/e* 353, 351, 339, 337, 257, 241, 149, 135, 123, 107, 105, 93, 91).

3α - Hydroxy - 7 - oxo - 2β - hydroxymethylbicyclo[3.3.0]octane 3 - tetrahydropyranyl ether (**23**). **3** (18 g, 52.3 mmol) was hydrogenated on 9 g of 5% Pd–C in 250 ml of AcOEt under the atmospheric pressure of hydrogen at room temp for 4 days. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed on 180 g of silica gel using AcOEt–cyclohexane (1:1) as eluent to obtain **23** as a colorless oil (9.6 g, 72%): tlc R_f 0.18 (AcOEt–cyclohexane, 3:1); IR (film) cm^{-1} 3450, 1740, 1410, 1360, 1205, 1160, 1140, 1080, 1025, 975; NMR δ 4.60 (1H, m), 4.05 (1H, m); MS for $C_{14}H_{22}O_4$ (M^+) *m/e* (calc.) 254.15180, *m/e* (found) 254.14991 (other ions at *m/e* 236, 226, 170, 153, 135, 107.

3α - Hydroxy - 2β - hydroxymethyl - 7 - (4-carbomethoxybutylidene)bicyclo[3.3.0]octane 3 - tetrahydropyranyl ether (**27**). To a stirred soln of **23** (12.3 g, 48.2 mmol) and 2-methoxypropene (11.3 ml, 0.122 mol) in dry CH_2Cl_2 (150 ml) at 10° was added dropwise a soln of 11 mg of p-toluenesulfonic acid in CH_2Cl_2–THF (9:1; 10 ml). The mixture was stirred at that temp for 10 min, quenched by the addition of 1 ml of Et_3N, then concentrated *in vacuo* to leave a pale yellow oil **24** (*ca.* 20 g).

A 2 M soln of sodiomethylsulfinyl carbanion (120 ml, 0.24 mol) in dry DMSO was dropped into a stirred soln of (4-carboxybutyl)triphenylphosphonium bromide (54.2 g, 0.122 mol) in dry DMSO (120 ml) at such a rate as to maintain the soln at 25° to yield the red soln of the ylide. To this ylide soln was added a soln of crude **24** (*ca.* 20 g) in dry DMSO (30 ml), and then the resulting soln was stirred at 35° for 16 hr. The mixture was poured into cold water (1500 ml) containing K_2CO_3 (*ca.* 15 g) and extracted with AcOEt–ether (1:1, 500 ml × 3). The aqueous phase was acidified carefully with oxalic acid to pH 4 and was extracted with AcOEt–ether (1:1, 600 ml × 3). The acidic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to leave crude product **25**.

Immediately, the above crude product **25** was dissolved in 120 ml of THF, cooled to 0°. To this stirred soln was added 60 ml of cold 0.5 N HCl. The mixture was stirred at that temp for 10 min, diluted with AcOEt (1000 ml), washed with water and brine, dried over $MgSO_4$, then concentrated *in vacuo* to leave crude **26**.

The above oil was dissolved in ether (150 ml) and an ethereal diazomethane was added until a yellow color persisted. The ether was evaporated *in vacuo*. The residue was chromatographed on 200 g of silica gel eluting with AcOEt–cyclohexane (1:3) to give **27** as a colorless oil (13 g, 77% from **23**): tlc R_f 0.50 (AcOEt–cyclohexane, 3:1); IR (film) cm^{-1} 3470, 1730, 1440, 1360, 1240, 1130, 1075, 1025, 975; NMR δ 5.22 (1H, m), 4.60 (1H, m), 3.60 (3H, s); MS for $C_{20}H_{32}O_5$ (M^+) *m/e* (calc.) 352.22496, *m/e* (found 352.22352 (other ions at *m/e* 334, 268, 250, 232, 219, 179).

3α - Hydroxy - 2β - formyl - 7 - (4-carbomethoxybutylidene)bicyclo[3.3.0]octane tetrahydropyranyl ether (**28**). To a stirred soln of **27** (4.6 g, 13 mmol) in dry DMSO (50 ml) and Et_3N (11 ml) at room temp was added a soln of SO_3-pyridine complex (6.2 g, 39 mmol) in dry DMSO over 5 min. The mixture was stirred at that temp for 10 min, poured into ice-water (500 ml), and extracted with ether (200 ml × 3). The combined extracts were washed with water and brine, dried over $MgSO_4$, then concentrated *in vacuo* to give **28** as a pale yellow oil (4.45 g, 98%): tlc R_f 0.53 (AcOEt–cyclohexane, 1:1); IR (film) cm^{-1} 1735, 1435, 1350, 1195, 1160, 1125, 1075, 1030, 975; NMR δ 9.73 (1H, m), 5.26 (1H, m), 4.60 (1H, m), 4.30 (1H, m), 3.66 (3H, s); MS for $C_{20}H_{30}O_5$ (M^+) *m/e* (calc.) 350.20931, *m/e* (found) 350.20885 (other ions at *m/e* 332, 319, 314, 306, 266, 248, 235, 222, 220, 217).

(5E and 5Z) - 15 - Dehydro - 6a - carbaprostaglandin I_2 methyl ester tetrahydropyranyl ether (**29**). To a stirred suspension of 443 mg (11.7 mmol) of a 63% NaH dispersion in dry THF (80 ml) at room temp was added dropwise a soln of dimethyl 2-oxo-

heptylphosphonate (2.72 g, 12.3 mmol) in dry THF (4 ml) under argon. After 30 min, a soln of **28** (3.9 g, 11.1 mmol) in dry THF (10 ml) was added. The mixture was allowed to stir at that temp for 1 hr, and the reaction mixture was quenched by the addition of 3 ml of AcOH. The precipitate was removed by filtration through a pad of silica gel, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on 100 g of silica gel eluting with AcOEt–cyclohexane (1:9) to give **29** as a pale yellow oil (5.0 g, 100%): tlc R_f 0.51 (AcOEt–cyclohexane, 1:2); IR (film) cm^{-1} 1740, 1697, 1675, 1625, 1440, 1200, 1170, 1130, 1080, 1040, 980; NMR δ 6.45–6.95 (1H, m), 5.80–6.25 (1H, m), 5.15 (1H, m), 4.60 (1H, m), 3.60 (3H, s); MS for $C_{22}H_{34}O_4$ (M^+-DHP) *m/e* (calc.) 362.24570, *m/e* (found) 362.24545 (other ions at *m/e* 344, 318, 313, 85).

(5E) - 15 - *Dehydro* - 6*a* - *carbaprostaglandin* I_2 *methyl ester* (**30**) *and* (5Z) - 15 - *dehydro* - 6*a* - *carbaprostaglandin* I_2 *methyl ester* (**31**). A mixture of **29** (3.17 g, 7.1 mmol), 65% AcOH (56 ml), and THF (5.6 ml) was stirred at 50° for 45 min. The mixture was cooled in ice–water bath, then neutralized with $NaHCO_3$, and extracted with AcOEt (150 ml × 2). The combined extracts were washed with water and brine, dried over $MgSO_4$, concentrated *in vacuo*. The residue was chromatographed on 70 g of silica gel eluting with AcOEt–cyclohexane (1:3) to give a mixture of **30** and **31** (2.49 g 97%; the ratio of **30**:**31** *ca.* 1:1 by tlc). The mixture of **30** and **31** were separated by chromatography with a Lober prepacked column (Merck, Art 10402, Grösse C) using the same eluent to afford **30** as a colorless oil (805 mg, 31%), **31** as a colorless oil (754 mg, 29%), and their mixture (710 mg, 28%). **30**: tlc R_f 0.28 (AcOEt–cyclohexane, 1:2, two developments); IR (film) cm^{-1} 3430, 1740, 1695, 1670, 1625, 1435, 1375, 1320, 1250, 1170, 1135, 1080, 985; NMR δ 6.77 (1H, dd, J = 15.5, 8.0 Hz), 6.17 (1H, d, J = 15.5 Hz), 5.25 (1H, m), 3.90 (1H, m), 3.66 (3H, s), 0.90 (3H, m); MS for $C_{22}H_{34}O_4$ (M^+) *m/e* (calc.) 362.24570, *m/e* (found) 362.24484 (other ions at *m/e* 344, 318, 313, 245, 179, 164, 147, 131, 129, 105). **31**: tlc R_f 0.32 (AcOEt–cyclohexane, 1:2, two developments); IR (film) cm^{-1} 3430, 1740, 1695, 1670, 1625, 1435, 1375, 1320, 1250, 1170, 1135, 1080, 985; NMR δ 6.78 (1H, dd, J = 15.5, 8.0 Hz), 6.18 (1H, d, J = 15.5 Hz), 5.26 (1H, m), 3.88 (1H, m), 3.66 (3H, s), 0.90 (3H, m); MS for $C_{22}H_{34}O_4$ (M^+) *m/e* (calc.) 362.24570, *m/e* (found) 362.24732 (other ions at *m/e* 344, 318, 313, 245, 179, 164, 147, 131, 129, 105.

(5E) - 6*a* - *Carbaprostaglandin* I_2 *methyl ester* (**32**) *and* (5E, 15R) - 6*a* - *carbaprostaglandin* I_2 *methyl ester* (**33**). *Method A*. To a stirred soln of 2,6-di-*t*-butyl-4-methylphenol (875 mg, 3.98 mmol) in dry toluene (7 ml) at 5° was added 1.5 ml (2.65 mmol) of diisobutylaluminum hydride (1.76 M soln in toluene) under argon. The resulting colorless soln was stirred at 5° for 1 hr, then cooled to −78°. To this soln was added slowly a soln of **30** (90 mg, 0.248 mmol) in dry toluene (1 ml). The soln was changed from colorless to orange. The mixture was gradually raise to −10° over 2.5 hr, and stirred at −10° for 15 min. The soln changed to pale yellow. The reaction was quenched by the addition of water (0.9 ml), and vigorously stirred at room temp for 30 min. The precipitate was removed by filtration, washed with AcOEt (15 ml). The filtrate was concentrated *in vacuo*. The residue was chromatographed on 7 g of silica gel using AcOEt–CH_2Cl_2 (1:1) as eluent to afford **32** as a colorless oil (75 mg, 83%) and **33** as a colorless oil (11 mg, 12%). **32**: tlc R_f 0.21 (AcOEt–cyclohexane, 2:1); IR (film) cm^{-1} 3370, 1740, 1435, 1250, 1170, 1080, 970; NMR δ 5.49 (2H, m), 5.23 (1H, m), 4.01 (1H, m), 3.66 (3H, s), 3.55–3.85 (1H, m), 0.89 (3H, m); MS for $C_{22}H_{34}O_3$ (M^+-H_2O) *m/e* (calc.) 346.25078, *m/e* (found) 346.25312 (other ions at *m/e* 328, 315, 302, 275, 232, 179, 149, 131, 119, 117, 105). **33**: tlc R_f 0.32 (AcOEt-cyclohexane, 2:1); IR (film) cm^{-1} 3370, 1740, 1435, 1250, 1170, 1080, 970; NMR δ 5.58 (2H, m), 5.23 (1H, m), 4.08 (1H, m), 3.66 (3H, s), 3.57–3.82 (1H, m), 0.89 (3H, m); MS for $C_{22}H_{34}O_2$ (M^+-H_2O) *m/e* (calc.) 346.25078, *m/e* (found) 346.25245 (other ions at *m/e* 328, 315, 302, 275, 232, 179, 131, 119, 117, 105).

Method B. To a stirred suspension of LAH (78 mg, 2.05 mmol) in dry THF (4.1 ml) at 5° was added 0.82 ml of a soln of EtOH in THF (2.5 M, 2.05 mmol) under argon over 10 min. Then a soln of (*S*) - (−) - 2,2' - dihydroxy - 1,1' - binaphthyl (586 mg, 2.05 mmol) in dry THF (1.8 ml) was added at 5° over 20 min. The resulting white, cloudy mixture was stirred at room temp for 1 hr, then cooled to −78°. To this mixture was added a soln of **30** (105 mg, 0.29 mmol) in dry THF (4 ml) over 30 min. After 1.5 hr, the reaction mixture was quenched at −78° by the addition of a soln of 0.5 ml of MeOH in THF (2 ml), then 0.22 ml of water was added. The mixture was stirred at room temp for 20 min. The precipitate was removed by filtration, washed with AcOEt (30 ml). The filtrate was washed with 0.5 N HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on 10 g of silica gel eluting with CH_2Cl_2–AcOEt (10:1, 5:1) and then 3% MeOH in AcOEt. The recovered **30** (55 mg, 52%) was eluted by the first solvent system, and **32** (50 mg, 47%; 99% based on consumed starting enone) 95.9% stereoisomeric purity) was obtained by the later.

(5*Z*) - 6*a* - *Carbaprostaglandin* I_2 *methyl ester* (**34**) *and* (5Z, 15R) - 6*a* - *carbaprostaglandin* I_2 *methyl ester* (**35**) were prepared in 79 and 18% yield, respectively, as colorless oils from enone **31** (150 mg, 0.414 mmol) in the same manner used in the preparation of **32** and **33** (*Method A*). **34** (33 mg; 93.9% stereoisomeric purity) was also obtained in 47% yield (91% yield based on starting enone consumed) in the same manner used in the preparation of **32** (*Method B*). **34** solidified to a white semisolid on standing at −20°. Attempts to recrystallize this material were not successful. **34**: R_f 0.22 (AcOEt–cyclohexane, 2:1), IR (film) cm^{-1} 3370, 1740, 1435, 1320, 1250, 1170, 1130, 1080, 1020, 970; NMR δ 5.50 (2H, m), 5.23 (1H, m), 4.03 (1H, m), 3.66 (3H, s), 3.55–3.85 (1H, m), 0.89 (3H, m); MS for $C_{22}H_{34}O_3$ (M^+-H_2O) *m/e* (calc.) 346.25078, *m/e* (found) 346.25163 (other ions at *m/e* 328, 315, 302, 275, 232, 179, 147, 145, 131, 119, 117, 105). **35**: R_f 0.33 (AcOEt-cyclohexane, 2:1); IR (film) cm^{-1} 3370, 1740, 1435, 1310, 1250, 1170, 1130, 1080, 1015, 970; NMR δ 5.59 (2H, m), 5.23 (1H, *m*), 4.10 (1H, m), 3.67 (3H, s), 3.55–3.85 (1H, m), 0.89 (3H, m); MS for $C_{22}H_{34}O_3$ (M^+-H_2O) *m/e* (calc.) 346.25078, *m/e* (found) 346.25293 (other ions at *m/e* 328, 315, 302, 275, 232, 179, 147, 145, 131, 119, 117, 105).

(5E) - 6*a* - *Carbaprostaglandin* I_2 (**2**). A mixture of **32** (865 mg, 2.37 mmol), 5% aqueous KOH (12 ml), and EtOH (12 ml) was stirred at 50° for 20 min. After cooling, the mixture was acidified with 1 N HCl to pH 4, then extracted with AcOEt (50 ml × 3). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on 25 g of silica gel (Mallinckrodt, Silic AR CC-7 special) eluting with AcOEt-cyclohexane (4:1) to afford **2** as a colorless oil (798 mg, 96%), which solidified on standing. Recrystallization from ether-*n*-hexane gave pure **2** as a white powder: m.p. 64.5–66.5° (m.p. 62.4–63.3°)[6e]; tlc R_f 0.25 (AcOEt–cyclohexane–AcOH, 75:25:2, two developments); IR (KBr) cm^{-1} 3460, 3330, 3150, 2630, 1725, 1625, 1450, 1430, 1350, 1225, 1170, 1130, 1090, 975; NMR δ 5.47 (2H, m), 5.23 (1H, m), 4.02 (1H, m), 3.68 (1H, m), 0.89 (3H, m); MS for $C_{21}H_{32}O_3$ (M^+-H_2O) *m/e* (calc.) 332.23513, *m/e* (found) 332.23756 (other ions at *m/e* 314, 288, 261, 243, 232, 218, 165). $[\alpha]_D^{20}$ +92.2° (*c* 0.515, MeOH).

(5Z)-6*a*-*Carbaprostaglandin* I_2 (**36**) was prepared in 93% yield from ester **34** (202 mg, 0.544 mmol) in the same manner used in the preparation of **2**. Recrystallization from acetone-*n*-hexane gave pure **36** as a white powder: m.p. 113–114° (m.p. 107.5–108.8°),[6e] tlc R_f 0.29 (AcOEt-cyclohexane-AcOH, 75:25:2, two developments); IR (KBr) cm^{-1} 3450, 3360, 2600, 1695, 1450, 1395, 1350, 1325, 1200, 1090, 1065, 975; NMR δ 5.49 (2H, m), 5.21 (1H, m), 4.00 (1H, m), 3.66 (1H, m), 0.89 (3H, m); MS for $C_{21}H_{32}O_3$ (M^+-H_2O) *m/e* (calc.) 332.23513, *m/e* (found) 332.23544 (other ions at *m/e* 314, 288, 261, 243, 232, 218, 165); $[\alpha]_D^{20}$ +40.1° (*c*, 0.535, MeOH).

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