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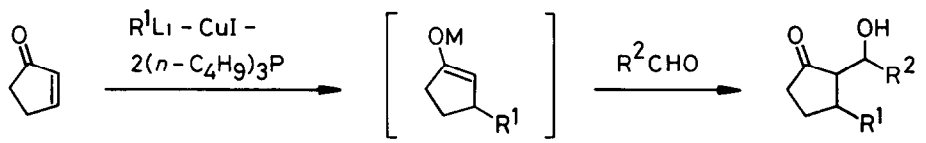
A FACILE SYNTHESIS OF (-)-PROSTAGLANDIN E_1 VIA A THREE-COMPONENT COUPLING PROCESS[1]

M. Suzuki, T. Kawagishi, T. Suzuki, and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Summary. A very short synthesis of chiral prostaglandin E_1 methyl ester is described.

Although a number of efficient synthetic routes to prostaglandins (PGs) have been explored,[4,5] the three-component coupling process, viz., consecutive introduction of the two side-chains to 4-hydroxy-2-cyclopentenone, is evidently the simplest converging synthesis.[5] The major obstacles to this attractive route have been the difficulty in the control of absolute stereochemistries at C-11 and C-15 (PG numbering) and lack of the reliable recipes which allow regiospecific vicinal carba-condensation[6] with 2-cyclopentenones. Now with efficient methods for the enantioselective reduction of α,β-unsaturated ketones[7] and nucleophilic/electrophilic vicinal carba-condensation of enones secured, this strategy holds considerable promise as a straightforward entry to various primary PGs and their analogues. Described herein is a very short synthesis of PGE_1 methyl ester in optically active form.

The key operation is the clean trapping by aldehydes of enolate intermediates generated by the organocopper conjugate addition to α,β-unsaturated ketones. Although the conjugate addition/aldehyde quenching is obviously a promising way of achieving vicinal carba-condensation, the existing methods which utilize lithium diorganocuprates (Gilman reagents)[8] are not satisfactory mainly because (1) the initially formed enolates, depending on the structure of starting enones and the efficiency of the trapping reaction, tend to equilibrate to form the regioisomers,[9] and (2) the complex nature of the reaction system, particularly the presence of excess organometallic nucleophiles, requires the use of a large amount of the aldehyde trap and, as a consequence, leads frequently to very complicated reaction mixtures. The only successful example reported utilized very reactive formaldehyde.[10,11] We elaborated a facile operation which rests on the stoichiometric use of an organometallic entering group and an aldehyde trap (eq 1). The reaction is carried out with equal quantities of the enone 1 and an organocopper reagent formed from an organolithium, copper(I) iodide, and tributylphosphine (1 1 2—3 mol ratio),[2] and therefore, when the initial conjugate addition proceeds ideally, the resulting enolate species 2 becomes the only strong nucleophile



(1)

1 **2**, M = Li or Cu **3**

Table I. Vicinal Carba-condensation with 2-Cyclopentenone[a]

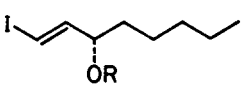
entry	β-entering group	trapping aldehyde	conditions: temp, °C	conditions: time, min	% yield of 3[b]
1	n-C_4H_9	$CH_3CH_2CH_2CHO$	-78	5	98[c]
2	n-C_4H_9	$(CH_3)_2CHCHO$	-78	10	93[c]
3	n-C_4H_9	$(CH_3)_3CCHO$	-78	60	71[c]
4	n-C_4H_9	C_6H_5CHO	-78	10	91[d]
5	n-C_4H_9	(E)-C_6H_5CH=CHCHO	-78	10	94[d]

[a] The alkylcopper-phosphine complex was prepared in situ by mixing copper(I) iodide, butyllithium, and tributylphosphine in 1:1:2 mol ratio in ether. The conjugate addition to 2-cyclopentenone was carried out at -78 °C for 10 min. All new compounds gave consistent ^{1}H NMR and IR characteristics and correct elemental analysis and/or mass spectral data. [b] Isolated yield after silica gel column chromatography. [c] A single isomer. However, ^{1}H NMR does not allow definite stereochemical assignment for this five-membered compound. [d] A mixture of two stereoisomers.

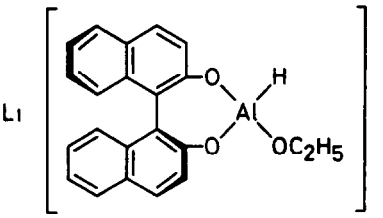
present in the reaction system and this intermediate should be trapped efficiently by one equivalent of an aldehyde to give an aldol 3. Some examples of the present three-component coupling method are given in Table I.[12] The side-chain incorporation occurs in a regiospecific manner via kinetically defined, nonequilibrated enolates, as confirmed, for example, by comparison of samples of 2-benzylidene-3-butylcyclopentanone, an aldol dehydration product, prepared by this method and an independent route.[3] No α',β-condensation products associated with possible enolate equilibration were detected in the reaction mixture.

The chiral building blocks requisite for the PG synthesis are readily accessible by the asymmetric reduction of enones by the binaphthol-modified lithium aluminum hydride (BINAL-H) reagent.[7] The levorotatory ω side-chain alcohol, (S)-4, can be obtained in 97% ee by the reduction of (E)-1-iodo-1-octen-3-one by the chiral hydride (S)-6.[7,13] The enantioselective reduction of cyclopent-4-ene-1,3-dione with (S)-6 led to the dextrorotatory enone, (R)-7 (94% ee). Alternatively (R)-7 is accessible by efficient optical resolution using the resolving agent 9.[14-16,18]

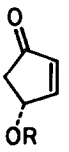
The newly devised three-component joining process using these chiral units allows direct construction of a PG basic skeleton. The vinylic iodide, (S)-5 ($[\alpha]_D^{22}$ -65.9° (c 1.05, CH_3OH)), was first converted to the organocopper reagent by the sequential treatment at -95 to -78 °C with 2 equiv of t-butyllithium, 1 equiv of copper(I) iodide, and 2.6 equiv of tributylphosphine in ether. Reaction of this reagent with the enone (R)-8[16] (1 equiv, -78 °C, 1 h) and then with 6-methoxycarbonylhexanal (1 equiv, -78 °C, 15 min) resulted in the formation of the aldol 10[19] ($[\alpha]_D^{22}$ -52.3° (c 1.02, CH_3OH), two stereoisomers) in 83% yield. Dehydration of 10 with methanesulfonyl chloride (2.5 equiv) and 4-dimethylaminopyridine (5 equiv) in CH_2Cl_2 at 18—45 °C gave the enone 11, $[\alpha]_D^{22}$ +29.5° (c 1.01, CH_3OH), in 92% yield. Exposure of 11 to excess zinc dust in 95:5 2-propanol—CH_3COOH at 25 °C, giving the saturated product in 78%, and removal of the tetrahydropyranyl protective groups under the standard conditions (3:1:1 CH_3COOH—THF—H_2O, 45 °C, 3 h) completed the synthesis of (-)-PGE_1 methyl ester (12), $[\alpha]_D^{23}$ -53.8° (c 1.04, CH_3OH).[20,21] This product was homogeneous as assayed by high performance liquid chromatography (HPLC) analysis



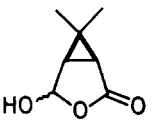
(S)- **4**, R = H
(S)- **5**, R = THP



(S)- **6**



(R)- **7**, R = H
(R)- **8**, R = THP



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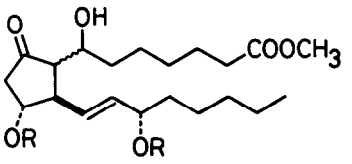
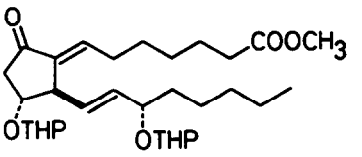


10, R = THP



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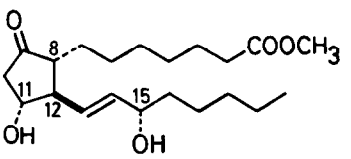

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and the spectroscopic and chromatographic behavior was identical with that of the authentic material (^{1}H and ^{13}C NMR, IR, MS, TLC, and HPLC)

PGE_1 possesses four asymmetric carbons. Here the absolute configurations at C-11 and C-15 are inherently determined in the starting materials, and the mutual trans relationship of the C-11 hydroxyl group and the C-12 and C-8 side-chains is established automatically through the overall vicinal side-chain incorporation This expeditious route is synthetically flexible and obviously allows the synthesis of a variety of PG derivatives

Acknowledgment A generous gift from Sumitomo Chemical Co of chrysanthemic acid for the preparation of 9 is acknowledged We are also grateful to Ono Pharmaceutical Co for providing authentic sample of PGE_1

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19. Secure stereochemical assignment could not be made on the basis of the ^1H NMR spectrum. The deprotected product 10 (R = H) exhibits potent inhibitory effect on platelet aggregation.
20. Reaction of commercial PGE_1 with diazomethane followed by HPLC (Develosil column, hexane: ethyl acetate:methanol = 1:9:0.05) afforded a sample showing $[\alpha]_D^{23}$ -54.0° (c 1.08, CH_3OH).
21. The methyl ester 12 can be easily converted to PGE_1 using an enzymatic process, see ref 13.

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