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CHIRAL PROSTAGLANDIN SYNTHESES VIA CONJUGATE ADDITION OF (Z)-VINYLZINCATE INVOLVING KINETIC RESOLUTION AND ENANTIOFACE SELECTION.

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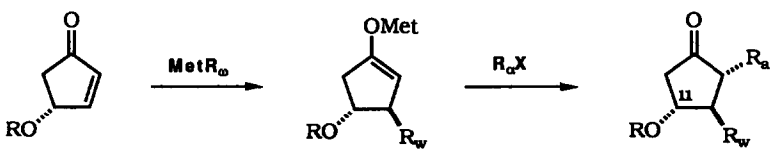
Summary: Chiral prostaglandins, PGE_2 and (-)-11-deoxy PGE_2, were synthesized via three component coupling process involving kinetic resolution of the *dl*-ω-chain and enantioface selection of the prochiral cyclopentenone, respectively.

Among many different routes to natural prostaglandins (PGs)[1] , the three component coupling process[2] (***Scheme 1***), using a chiral enone **1** and the ω-and α-chains, is one of the ideal approaches. This approach, however, involves two serious problems; rapid enolate exchange between **2** and **3** and immediate β-elimination of the 11-alkoxy group by a random enolate exchange, because the initially formed enolate **2** itself is sufficiently basic to cause rapid proton transfer at a rate faster than that of the regio-controlled enolate alkylation. Stork initially solved these problems by trapping the cuprate-generated enolate **2** with formaldehyde.[3] Recently, Noyori et al.[4] have succeeded in the direct alkylation of the zinc enolate **2** with $R_\alpha X$. We now report here[5] syntheses of chiral 11,15-O-bis(*t*-butyldimethylsilyl) PGE_2 methyl ester (**10**) and 11-deoxy PGE_2 methyl ester (**19**) via three component coupling process using conjugate addition of the (Z)-vinylzincate. During the conjugate addition (**1**→**2**), (1) a high degree of kinetic resolution[6] of the C-O chirality at C(15) in the *dl*-ω-chain **7** and (2) a high enantioface selectivity[6] of the prochiral cyclopentenone **11** were observed and a high degree of regioselectivity in the enolate-alkylation stage (**2**→**3**) was also attained.

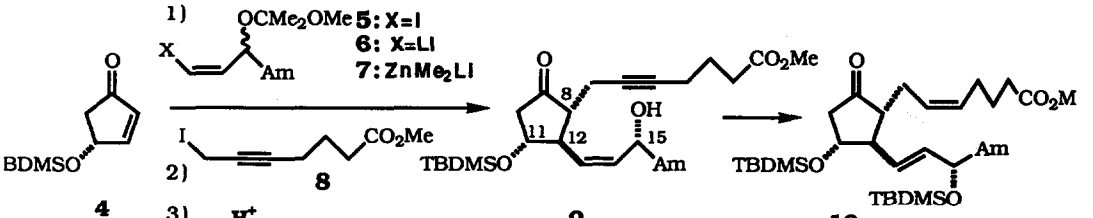


1 **2** **3**

Scheme 1

At first, the conjugate addition-enolate alkylation using lithium (*Z*)-vinyldimethyl-zincate (±)-**7**, enone (*R*)-**4**[7] and propargylic iodide **8**[8](***Scheme 2***) was carried out in order to examine whether (a) kinetic resolution of the (±)-ω-chain and (b) regioselective alkylation of the resulting kinetic enolate, could be realized. The iodide

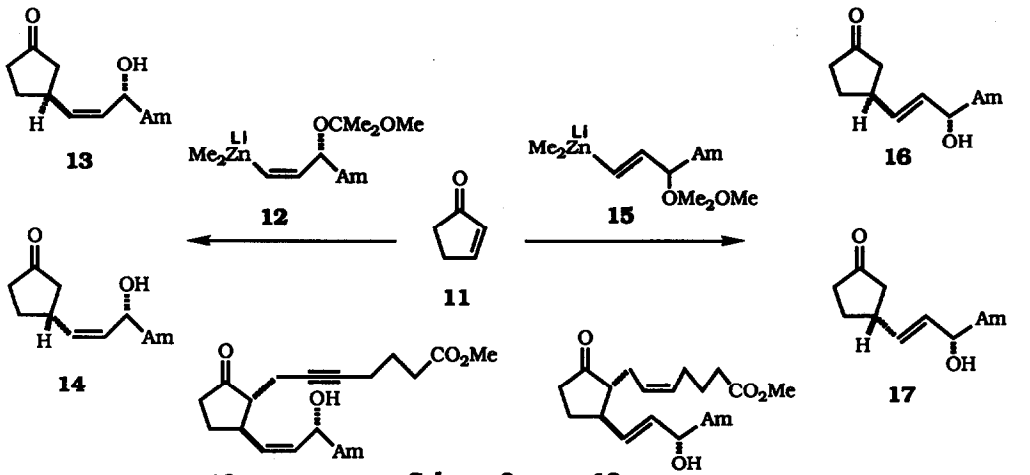
(±)-**5** [6a] (1.16 mmol) was metalated (-78 °C, 1 h under argon) in dry hexane with *t*-BuLi (1.20 mmol). Dimethylzinc was prepared[9] separately from $ZnCl_2$• TMEDA complex (1.17 mmol) and MeLi (2.43 mmol) in dry THF at -20 °C. The zincate (±)-**7** was prepared by addition of the lithiated **6** to a solution of $ZnMe_2$ in THF (in one portion at -78 °C, then at -50 °C for 1 h). The chiral enone (*R*)-**4** (0.39 mmol) in THF was added to the zincate **7** at -78 °C (dropwise for 30 min, then at -40 °C for 30 min) and HMPA (3.89 mmol) was added at -30 °C. After cooling the mixture to -78°C, the iodide **8** (1.99 mmol) in THF was added dropwise for 30 min and the reaction mixture was stirred for another 1 h (-78 °C ~ -50 °C). Usual work-up and hydrolysis of the alkylated product (50% aq. AcOH-THF, 30 min at 25 °C) gave the alcohol **9** ($[\alpha]^{25}_D$=14.4°(*c* 0.83, MeOH)) in 64% yield. We were unable to detect any undesired 15(*S*)-diastereomer and β-elimination product by direct comparison (TLC, HPLC) with the authentic samples. Thus, a high degree of kinetic resolution for 15(*R*)-alcohol of the racemic ω-chain during the conjugate addition as well as the regioselectivity in the enolate-alkylation was observed. The relative stereochemistry among C(8), C(11), C(12) and C(15) of the 13(*Z*)-allylic alcohol **9** was determined by converting the latter into 11,15-O-bis(*t*-butyldimethylsilyl) PGE_2 methyl ester (**10**) by the known sulfenate-sulfoxide rearrangement[6b] followed by hydrogenation of the triple bond ($Pd/BaSO_4/H_2$) and silylation of the 15(S)-allylic alcohol. Physical properties (NMR, IR, HPLC) of **10** derived by this rearrangement from **9** were identical with those of the reported **10**[8b].



Scheme 2

Based on the above kinetic resolution, enantioface selectivities in the reactions of (*Z*)- and (*E*)-zincates, (*R*)-**12** and (±)-**15**, to the enone **11** were examined (***Scheme 3***). The conjugate addition of (*R*)-**12** (1.2 equiv. to **11**), derived from the corresponding chiral (*Z*)-vinyl iodide,[10] to **11** and hydrolysis gave a 96 : 4 mixture of optically active diastereomers **13** and **14** in 67% combined yield.[11] On the other hand, the reaction of (*E*)-vinyl zincate (±)-**15** with **11** afforded a 59 : 41 mixture of the diastereomers (±)-**16** and (±)-**17** in 52% combined yield.[11] The stereochemistry of the much major product **13** was determined by the synthesis of 11-deoxy PGE_2 methyl ester (**19**) as follows. Conjugate addition of (*R*)-**12** to **11** and the enolate trapping with **8** (5 equiv to **11**) at -30 °C gave a 95 : 5 mixture of the alkylated- and non-alkylated products, **18**[11] ($[\alpha]^{25}_D$-37.7° (*c*, 0.1, MeOH)) and **13**, in 70% combined yield. The 13(*Z*)-allylic alcohol

18 was converted to the natural 13(*E*)-allylic alcohol **19** in the same manner as described above. Physical properties **19** thus obtained were identical with those of the reported 11-deoxy-PGE2 methyl ester.[12] Thus, a high enantioface selectivity in the reaction of (*Z*)-zincate (*R*)-**12** but not with (*E*)-zincate **15** was demonstrated.



Scheme 3

These high diastereo- and enantio-face selectivities in the conjugate addition can be rationalized as follows (***Fig. 1***). Assuming coordination of the C(15)-alkoxy group with zinc only for the (*Z*)-vinyl zincate, two possible transition states **20a** and **20b** for the reaction of (*R*)-**4** with (±)-**7** are considered. In **20a** there must be greater steric interactions between an alkyl group and a cyclopentenone ring than in **20b**. Consequently, the 1,4-addition proceeds via **20b** which gives the 15(*R*)-configuration as well as the trans relative stereochemistry between the silyloxy group and the ω–chain in **9**. Similarly, in the reaction of **11** with (*R*)-**12**, the transition state **21b** should be preferred over **21a**. Thus, the conjugate addition of (*R*)-**12** occurs from a β-face of the cyclopentenone to induce the 12(*S*)-configuration. Moreover, none of the enantioface selection in the reaction of (*E*)-zincate **15** is clear, since no template in coodination of the 15-alkoxy group with zinc exsists.

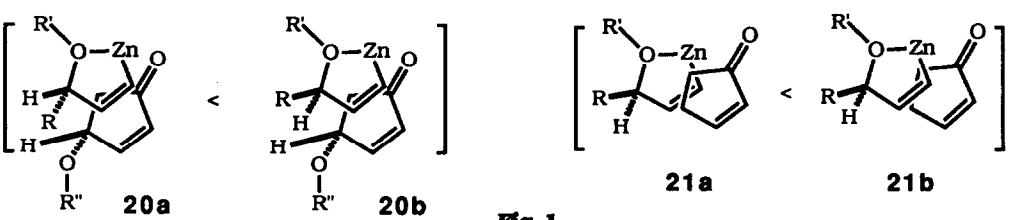


Fig. 1

Advantages for using the vinylzincates over the corresponding divinylcuprates in the three component coupling process for PGs syntheses are (1) a higher degree of

regioselecvtivity in the enolate-alkylation with little proton transfer, (2) to cut back on the number of equivalents of potentially valuable vinyl lithium needed, and (3) an easy purification of the product from excess side chains employed because of the absence of metallic by-products such as organocopper, stannane and phosphines after workup. Although chemical and structural properties of the vinylzincate are different from those of the divinylcuprate, high degree of both the kinetic resolution of ω-chain and the enantioface selectivity in the conjugate additions are emphasized.

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10) The chiral (Z)-vinyl iodide was prepared from 1,2,3,4,5,6-*O*-isopropylidene-*D*-mannitol. Details will be published elsewhere.

11) Satisfactory physical properties (NMR, IR, HPLC) of the compounds **13**, **14**, **16**,**17**, and **18** were obtained.

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