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A New Approach to Asymmetric Synthesis of Stork's Prostaglandin Intermediate

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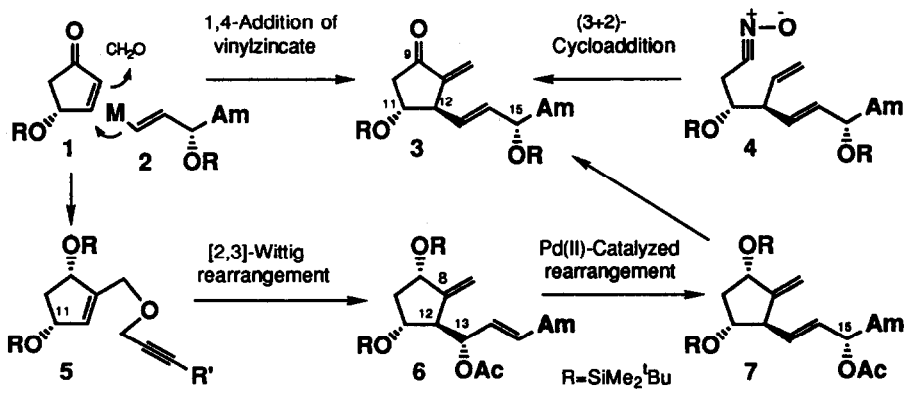
Summary : A stereocontrolled approach to asymmetric synthesis of Stork's prostaglandin intermediate **3** has been developed which involves the [2,3]-Wittig rearrangement and the Pd(II)-catalyzed allylic acetate rearrangement as the key steps.

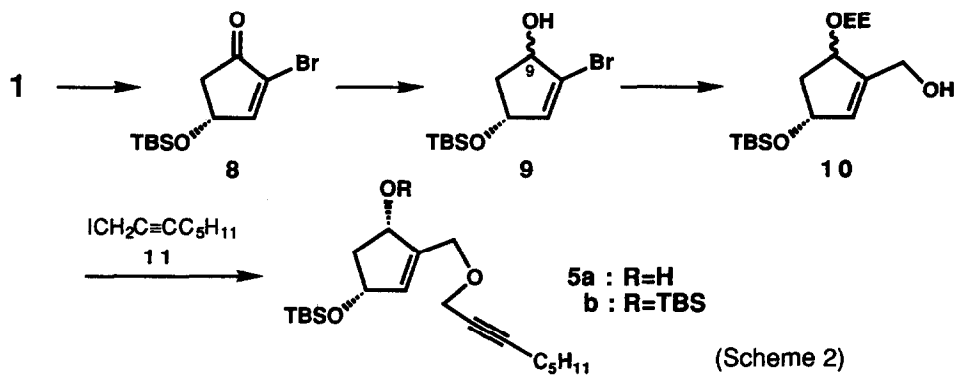
Among many synthetic intermediates for natural and unnatural prostaglandins,[1] the Stork intermediate **3**[2] is undoubtedly an ideal one. Recently, one of the author groups has reported two entries for **3**; one employs the three-component coupling process using vinylzincate **2**[3,4] instead of the vinylcuprate and the other one is based on the intramolecular (3+2)-cycloaddition of nitrile oxide **4**.[5] In these syntheses, the two stereogenic centers C11(*R*) and C15(*S*) are employed. Herein we disclose a new strategy (Scheme 1), wherein the C11(*R*) chirality in **5** derived from the commercially available cyclopentenone **1** is exploited to control the rest of chiralities in **3** via the [2,3]-Wittig rearrangement[6] (**5**→**6**) and the Pd(II)-catalyzed allylic rearrangement[7] (**6**→**7**).



(Scheme 1)

The key features of the present synthesis are two-fold. First, the [2,3]-Wittig rearrangement of **5** proceeds in a highly stereoselective fashion to establish the C12(*R*) and C13(*R*) configurations, together with the formation of the C8-exocyclic double bond in **6**. Second, the C13(*R*) chirality thus created is specifically transmitted to the desired C15(*S*) chirality in **7** by means of the Pd(II)-catalyzed rearrangement of the allylic acetate **6**. Thus, the overall transformation permits ready access to the desired configurations at C12, C13 and C15, as well as the required exo-methylene at C8.

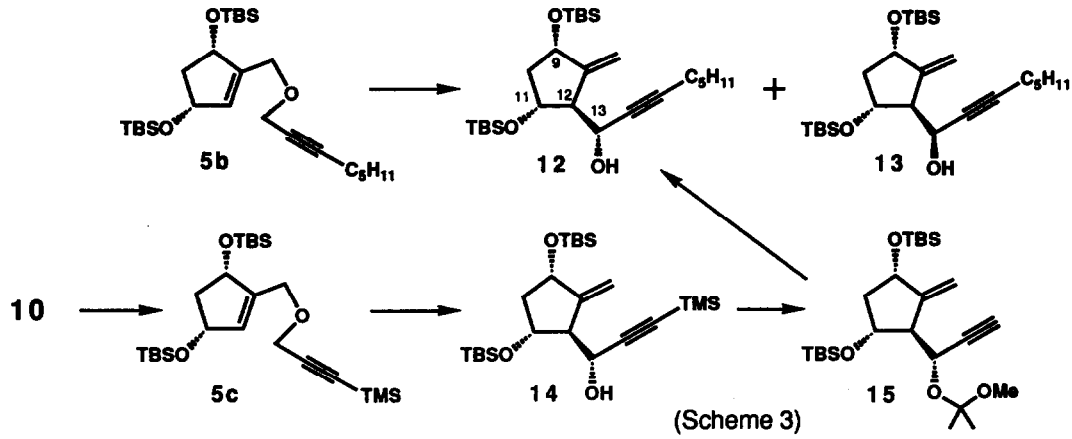
The propargylic ether **5b**, serving as a precursor to the prostaglandin skeleton, was prepared as outlined in Scheme 2. Reaction of (+)-enone **1** (>99% ee) with bromine (CCl_4, 0 °C) followed by treatment of the resulting dibromide with triethylamine gave bromoenone **8** which was then reduced ($NaBH_4/CeCl_3 \cdot 7H_2O$[8], MeOH, -20 °C) to afford a mixture of the 9α- and 9β-alcohol **9** (9α : 9β = 86 : 14) in 96% overall yield. Without separation of these isomers, **9** was converted to the allylic alcohol **10** in 75% overall yield via protection of the hydroxy group in **9** with ethyl vinyl ether and generation of the vinylic lithium (*n*-BuLi, THF, -78 °C) followed by addition of formaldehyde. Etherification of **10** with propargylic iodide **11** (KOH/*n*-Bu_4NI, benzene, 0 °C; 92%) followed by removal of the ethoxyethyl group (PPTS, MeOH; 56%) gave, after separation of the C9-epimer, the 9α-alcohol **5a**[9] which was treated with *t*-butyldimethylsilyl chloride (TBSCl) to give ether **5b** in 92% yield.



(Scheme 2)

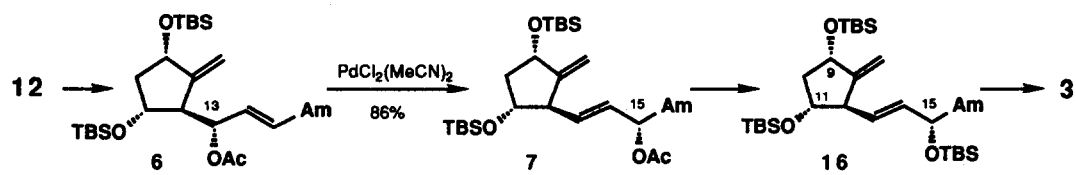
The [2,3]-Wittig rearrangement of **5b** was carried out with *t*-BuLi under the standard conditions (THF, -78 °C, 1h) to afford a mixture of the stereoisomers **12** and **13** (75 : 25) in 78% yield.[10] To improve the stereoselectivity in the [2,3]-Wittig process, we chose the trimethysilyl(TMS) derivative **5c** as the substrate which was prepared from **10** in four steps[11] (Scheme 3). The [2,3]-Wittig rearrangement of **5c** with *n*-BuLi was found to afford 90% yield of the single stereoisomer **14** which was then converted to the amyl derivative **12** as follows. Selective deprotection of the TMS group of **14** ($AgNO_3$, EtOH; 83%) followed by protection of the hydroxy group with 2-methoxypropene gave alkyne **15**. Alkylation of **15** (*n*-BuLi, THF/HMPA, *n*-$C_5H_{11}I$, -20

°C) followed by deprotection of the acetal moiety (PPTS, MeOH, 0 °C) afforded the amyl derivative **12** in 89% yield.



(Scheme 3)

Construction of the ω-side chain from the [2,3]-Wittig product **12** was carried out via the Pd(II)-catalyzed 1,3-rearrangement[12] of allylic acetate **6**. Acetate **6** was prepared in 78% yield from **12** by trans reduction of the triple bond (Red-Al®, 40 °C) followed by acetylation (Ac_2O, Py). The Pd(II)-catalyzed rearrangement of **6** [$PdCl_2(MeCN)_2$ (4 mol%), THF, reflux] gave rise to a 27 : 73 mixture[13] of the allylic acetates **6** and **7**[14] in 86% combined yield. In this rearrangement, neither the C13(*Z*)- nor the C15(*R*)-isomers was detected. Conversion of **7** to Stork's intermediate **3** (R=TBS) required two operations; (1) reprotection of the allylic acetate to the TBS group and (2) selective oxidation of the 9-hydroxyl to carbonyl group. Thus, hydrolysis of the acetate group of **7** (K_2CO_3, MeOH) followed by protection of the resulting alcohol (TBSCl, imidazole) gave the tri-TBS derivative **16** in 80% overall yield. Acid treatment of **16** (80% aq. AcOH, r.t.) produced a mixture of the di-TBS derivatives (C11,15-di-TBS : C9,11-di-TBS = 2 : 1). The desired 9-hydroxy derivative was isolated and oxidized (MnO_2, *n*-hexane) to furnish the desired enone **3** in 75% yield. The spectral data (NMR, IR) of **3** are identical with the literature values.[2g] Further improvement of the present approach is in progress.



(6 : 7 = 27 : 73)

(Scheme 4)

Acknowledgment. We are grateful to Sumitomo Chemical Co. and Teijin Co. for providing the optically active enone **1.**

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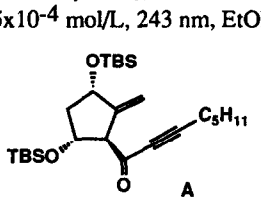
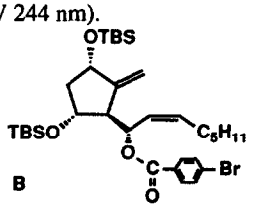
9) The absolute stereochemistry at C_9 in **5a** was determined by the CD spectrum of the p-bromobenzoate derivative; $[\Theta]=-5.04\times10^4$ (7.88×10^{-5} mol/L, 243 nm, EtOH; UV 246 nm).
10) The relative stereochemistry over C_{11}, C_{12} and C_{13} in the major product **12** was determined by the following way. The individual oxidation of **12** and **13** with MnO_2 gave the same ketone **A**. This result indicates that the [2,3]-Wittig rearrangement gave the single stereochemistry at C_{12} but diasteromers at C_{13}. The absolute stereochemistry at C_{13} in **12** was determined by the CD spectrum of the allylic benzoate **B**; $[\Theta]=-6.66\times10^3$ (1.65×10^{-4} mol/L, 243 nm, EtOH; UV 244 nm).



A



B

11) 1) NaH, propargyl bromide, HMPA, 87%; 2) EtMgBr, TMSCl; 3) PPTS, MeOH, 41%; 4) TBSCl, imidazole, 90%.
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13) Based on the assumption of a thermodynamically controlled process for the Pd(II)-catalyzed allylic acetate rerrangement, MM2 calculations on MACROMODEL (ver. 2.5) considering a Boltzman distribution at 67°C suggest that allylic acetates **6** and **7** would exist in a ratio 20 : 80. We are grateful to Professor Clark Still for providing a copy of MACROMODEL (ver. 2.5).
14) The absolute stereochemistry at C_{15} in the product **7** was determined by the CD spectrum of the p-bromobenzoate derivative; $[\Theta]=1.78\times10^5$ (4.78×10^{-5} mol/L, 244 nm, EtOH; UV 244 nm).

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