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Formal synthesis of J-type prostaglandins based on enantiopure polyfunctional cyclopentenol derivative

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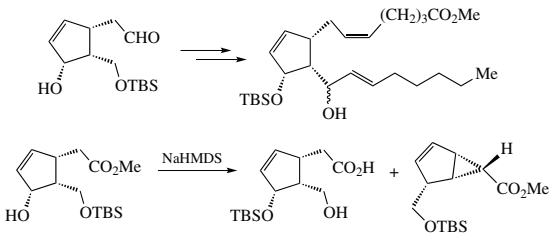
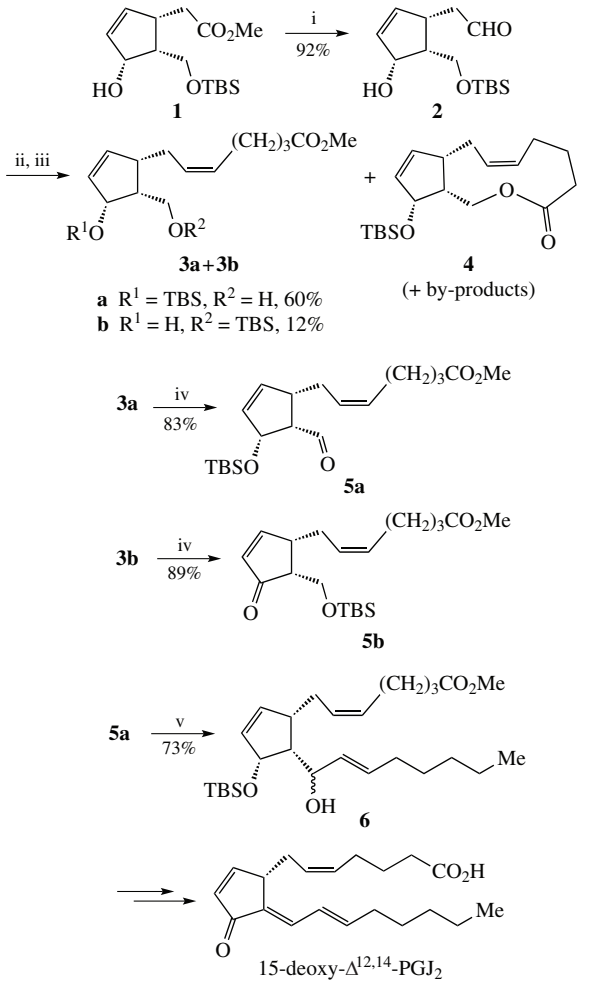
The Wittig reaction of {(1*S*,4*R*,5*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-4-hydroxycyclopent-2-en-1-yl}acetaldehyde is accompanied by the migration of silyl protective group from the primary hydroxy group to the secondary one, which enables further synthesis of J-type prostaglandins. Study of this phenomemon on model relative ester comprising base variation revealed formation of unusual functionalized bicyclo[3.1.0]hex-2-ene-6-carboxylate derivative.



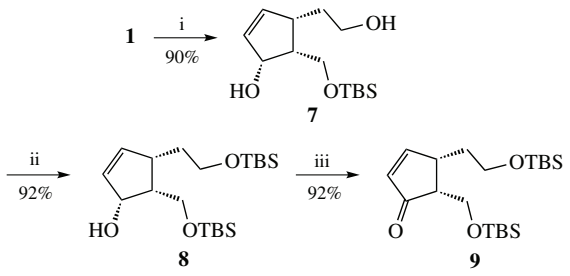
Keywords: 15d-prostaglandin J2, silyl migration, macrolactonization, cyclopropanation, Wittig reaction.

The valuable and unique cytotoxic properties of cross-conjugated prostaglandins stimulated intense efforts on their synthesis[1–13] Previously,[14] we described an original method for the preparation of chiral bicyclic allylsilane and its enantiomer, potential precursors for bioactive cyclopentanoids. Subsequently, in the course of the total synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2, we prepared allylsilane block from lactone in five stages and presented a model version of a two-stage construction of the prostaglandin α-chain. Acid containing the upper prostaglandin chain with the required *Z*-configuration was obtained after reducing the ester to the aldehyde followed by Wittig olefination with 5-phosphoniopentanoate derivative.[15] However, the presence of the double bond in the chain imposed considerable restrictions on the conversion of the allylsilane to the allylic alcohol. One of the possible solutions to this problem involved a synthesis of compound **1** (Scheme 1) by epoxidation of allylsilane-containing block with dimethyldioxirane generated *in situ* to give epoxides that are unstable in acidic media.[16–18]

Herein we found that the Wittig reaction of (cyclopent-2-enyl)acetaldehyde **2** bearing OH and CH_2OTBS groups was accompanied by migration of the TBS protection onto secondary alcohol group (see Scheme 1). In this case, in the **1** → **3a** transformation, we simultaneously achieve the protection of the secondary hydroxy group and unblocking of the primary one. This looks a good challenge for subsequent incorporation of the required substitutent at the lower chain. Similar examples of migration of silyl protective groups through a pentacoordinated state were reported,[19] not only with the use of strong bases such as dimsyl sodium[20] but also with milder DBU.[21] In our case, the steric factor should have been the driving force of this process due to shielding the *cis*-substituents in cyclopentene of type **1**. Thus, reduction of **1** with 2 equiv. DIBAL-H in CH_2Cl_2 at –78 °C afforded the desired aldehyde **2** in high yield. The reaction performed at higher temperatures simultaneously gave significant amounts of a product of over-reduction **7** whose yield reached 90% at –30 °C (Scheme 2). Compound **2** was tested under typical Wittig olefination conditions with an ylide prepared by the reaction of 9 equiv. NaHMDS with 4 equiv. 5-(triphenylphos-



Scheme 1 *Reagents and conditions*: i, DIBAL-H (2 equiv.), CH_2Cl_2, –78 °C, 30 min; ii, $HO_2C(CH_2)_4P^+Ph_3\ Br^-$ (4 equiv.), NaHMDS (9 equiv.), THF, –78 → 20 °C, 1 h; iii, CH_2N_2, Et_2O, ~5 °C, 3 h; iv, Collins reagent, CH_2Cl_2, room temperature, 3 h; v, *E*-1-iodoheptene/BuLi (1.7 equiv.), THF, –78 °C, 30 min.



Scheme 2 *Reagents and conditions*: i, DIBAL-H (3 equiv.), CH_2Cl_2, –30 °C, 30 min; ii, TBSCl (2 equiv.), imidazole (2 equiv.), CH_2Cl_2, room temperature, 3 h; iii, Dess–Matrin periodinane (2.5 equiv.), CH_2Cl_2, room temperature, 8 h.

phonio)pentanoic acid (see Scheme 1). This reaction, followed by work-up and methylation of the crude material with CH_2N_2 gave derivatives **3a**,**b** in 5 : 1 ratio in good yield (see Online Supplementary Materials, Table S1, entry 1). Along with the target compounds, a certain amount of side macrolactone **4** was formed. Unfortunately, we failed to isolate compound **4** by column chromatography in the pure state. However, the formation of lactone is indirectly consistent with NMR and IR data that confirm the absence of hydroxy group and methyl ester. Moreover, alkaline hydrolysis of the product mixture containing **4** followed by methylation afforded compound **3a** as the main product. Compounds **3a** and **3b** were further oxidized with the Collins reagent to give the corresponding desired aldehyde **5a** and cyclopentenone **5b**. The reaction of aldehyde with *E*-1-lithioheptene (generated from *E*-1-iodoheptene) may be a reasonable subsequent transformation, for example, in the synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2. The system of conjugated double bonds required in the target structure of derivative **6** can be generated by converting the hydroxy group at C(12) into a good leaving group (OMs, OTs, OTf) followed by treatment with a base.

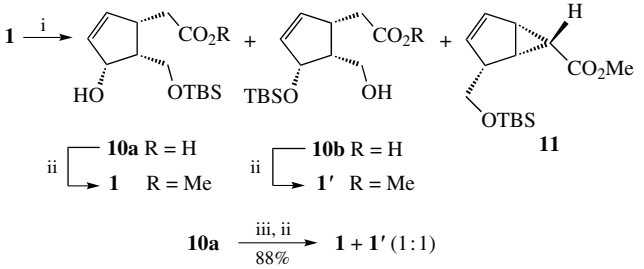
When we applied Bu^{t}OK as the base in the Wittig olefination, the reaction resulted in almost comparable amounts of compounds **3a**, **3b** and **4** with other impurities (see Online Supplementary Materials, Table S1, entry 4). We conducted a series of experiments to study the effect of the reaction conditions on the migration of the silyl group and to establish the reasons for the formation of side products (for further details, see Online Supplementary Materials, Scheme S1). The use of a larger excess of the base decreased the overall product yield and the fraction of migration product **3a**, along with an increase in the yield of side compounds (see Table S1, entry 2). At lower temperature of the Wittig olefination, no migration product was formed, and the conversion of the starting aldehyde dropped to 50% (entry 3), while the yield of compound **3b** was relatively low, apparently due to side processes that impacted the starting aldehyde. To clarify the reason for the decrease in the yield of the migration product with an increase in the base excess, compounds **3a** and **3b** were subjected to treatment with NaHMDS. In these experiments, the starting compounds disappeared rapidly in both cases. However, in the case of derivative **3b** side products were detected while final workup and methylation gave some recovered reactant **3b** with no traces of isomer **3a** (entry 6). The very compound **3a** was extremely labile under these conditions and was recovered only in trace amounts along with formation of side products (entry 5). If dimsyl sodium was used as the base, compound **3b** underwent only 70% migration in good yield (entry 8). In the case of Bu^{t}OK, this process took much longer, *e.g.*, after 10 h the transformation occurred by only 30%, and side compounds were formed simultaneously (entry 7).

We performed additional studies to determine more optimal conditions for migration of the silyl group in the course of **2** → **3a** conversion. The process was examined with substrates of less complicated structures, namely, compounds **1** and **7** (see Scheme 2). Under typical conditions, compound **7** did not undergo any changes after keeping it for 24 h in the presence of excess NaHMDS. Furthermore, the allylic hydroxy group clearly showed no activity in the silylation of compound **7** that exclusively gave diether **8**. The secondary allylic hydroxy group of this compound was oxidized, which afforded enone **9**.

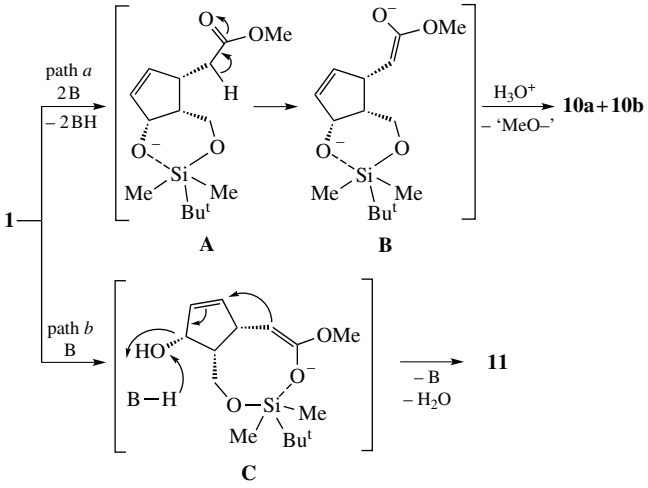
We also studied the migration activity of compound **1** (Scheme 3). The reaction of **1** with one equivalent of NaHMDS in THF at 0 °C resulted in its fast consumption and after a short exposure and acidification the corresponding acid **10a** was detected in the reaction mixture (see Online Supplementary Materials, Table S2, entry 1). The consequent reaction with diazomethane gave only the original ester **1**, which indicated that hydrolysis of an ester group was more preferable than the formation of an alkoxide anion. Interesting results were obtained using 2 equiv. or more of a base (entries 2, 3) when the expected migration was accompanied by the formation of cyclopropane derivative **11**. The best result for this transformation was achieved using 3 equiv. NaHMDS when the **1**/**1′**/**11** ratio was 1 : 2.5 : 20 (entry 3). It should be noted here that compound **11** was detected at all stages of the process, *i.e.*, its ester group was resistant to the action of the base. The ratio of the resulting compounds **1**/**1′** was 1 : 2.5 which looked optimal for these substrates under these conditions. With other bases such as dimsyl sodium, NaH, Bu^{t}OK, *etc*., formation of cyclopropane derivative **11** was not observed (entries 4–12).

As for the possible pathway for the formation of cyclopropane **11**, note that when the analogue of compound **1** with MOM-protected hydroxy group was treated with NaHMDS, no cyclopropane formation was observed and only ester hydrolysis occurred (see Online Supplementary Materials, compound **1″**). This high propensity for elimination of the hydroxy group in comparison to the $–OCH_2OMe$ one indicates the existence of intra- or intermolecular assistance. The reactions of substrate **1** with a base can occur in two directions (Scheme 4, pathways *a* and *b*). Pathway *a* includes the dianion formation which undergoes two parallel reactions. First, the alkoxide anion is involved in a pentacoordinated state with a silicon atom (**A**). In another part of the molecule, deprotonation of the ester group results in the corresponding enolate (**B**). However, a medium-sized lactone is not formed due to steric factors. As a result, the hydrolysis of intermediate **B** gives two products **10a**,**b**. Unlike this process, intermolecular cyclopropanation is more preferred (pathway *b*). Here, the S_N2' substitution of the allylic alcohol part in intermediate **C** by the ester enolate occurs as the oxygen atom of the enolate anion may be involved in a pentacoordinated silicon eight-membered ring. The *endo*-configuration (determined by NOESY experiment) of the ester group is also in favor of the suggested mechanism.

The formation of a macrolactone in the mixture of side products **4** (see Scheme 1), unlike in the case of **1**, may occur *via*

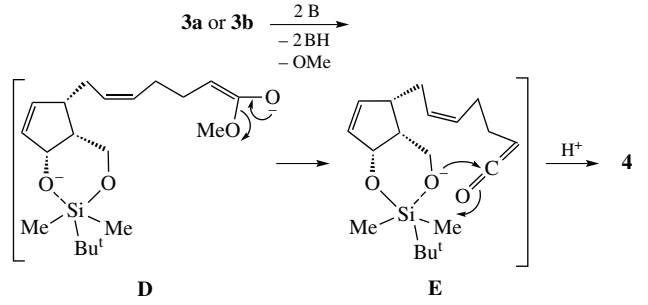


Scheme 3 *Reagents and conditions*: i, base [NaHMDS, $MeS(O)CH_2Na$, Bu^{t}OK or NaH], solvent (see Online Supplementary Materials); ii, CH_2N_2, Et_2O; iii, Bu^{t}OK, THF, room temperature, 3 h.



Scheme 4

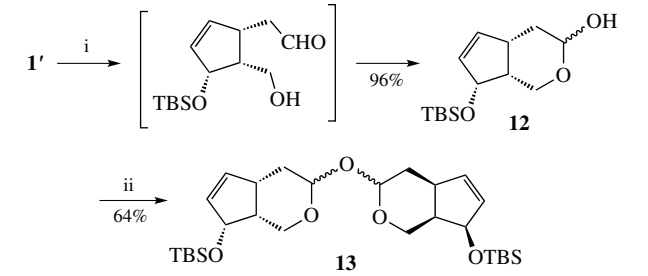
the corresponding ketene **E**. Such variants of transformation of enolate of type **D** at temperatures of 0–20 °C have been reported.[22] However, here the length and orientation of the α-chain are suitable for the reaction with the resulting alkoxide anion in **E** followed by the formation of cyclic ester **4** (Scheme 5). This mechanism is also confirmed by the fact that if one equivalent of a base was used, the reaction resulted only in the hydrolysis of the ester group. Thus, like in the case of compound **1**, the formation of the alkoxide anion occurred only with excess amounts of bases.



Scheme 5

We also attempted to involve ester **1′** into the sequence for building the upper prostaglandin chain. However, lactol **12** obtained by the DIBAL-H reduction of the ester group was found to be inert under standard Wittig olefination (0 → 20 °C). Raising the temperature to reflux conditions gave dimer **13** in good yield (Scheme 6). Therefore, a potent scheme for the prostaglandin synthesis comprising the silyl migration in ester precursor **1** at the first stage and ester reduction at the second stage is unpractical.

In conclusion, chiral polyfunctional cyclopentene derivative **1** can be successfully used in the J-type prostaglandin total synthesis. Initially, the ester should be reduced into the aldehyde, with the next Wittig reaction being accompanied by really wanted migraion of the silyl group. Reverse of silyl migration onto the first stage of the synthetic scheme turned to be unpractical. The discovered conversion of compound **1** into bicyclo[3.1.0]hex-2-ene derivative **11** seems rather unusual and may be attributed to specific assistance of silicon protective group.



Scheme 6 *Reagents and conditions*: i, DIBAL-H (2 equiv.), CH_2Cl_2, –78 °C, 30 min; ii, $HO_2C(CH_2)_4P^+Ph_3\ Br^-$ (4 equiv.), NaHMDS (9 equiv.), THF, –78 °C to reflux, 5 h.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.031.

References

1 C. A. Rouzer and L. J. Marnett, *Chem. Rev.*, 2003, **103**, 2239.
2 F. A. Fitzpatrick and M. A. Wynalda, *J. Biol. Chem.*, 1983, **258**, 11713.
3 J. Lefils-Lacourtablaise, M. Socorro, A. Géloën, P. Daira, C. Debard, E. Loizon, M. Guichardant, Z. Dominguez, H. Vidal, M. Lagarde and N. Bernoud-Hubac, *PLoS One*, 2013, **8**, e63997.
4 D. S. Straus and C. K. Glass, *Med. Res. Rev.*, 2001, **21**, 185.
5 E. M. Brunoldi, G. Zanoni, G. Vidari, S. Sasi, M. L. Freeman, G. L. Milne and J. D. Morrow, *Chem. Res. Toxicol*., 2007, **20**, 1528.
6 K. Uchida and T. Shibata, *Chem. Res. Toxicol.*, 2008, **21**, 138.
7 V. Pande and M. J. Ramos, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4057.
8 A. K. Kudva, N. Kaushal, S. Mohinta, M. J. Kennet, A. August, R. F. Paulson and K. S. Prabhu, *PLoS One*, 2013, **8**, e80622.
9 V. V. Loza, A. M. Gimazetdinov and M. S. Miftakhov, *Russ. J. Org. Chem.*, 2018, **54**, 1585 (*Zh. Org. Khim*., 2018, **54**, 1575).
10 J. Li, T. S. Ahmed, C. Xu, B. M. Stoltz and R. H. Grubbs, *J. Am. Chem. Soc.*, 2019, **141**, 154.
11 J. Li, B. M. Stoltz and R. H. Grubbs, *Org. Lett.*, 2019, **21**, 10139.
12 K. C. Nicolaou, K. K. Pulukuri, S. Rigol, Z. Peitsinis, R. Yu, S. Kishigami, N. Cen, M. Aujay, J. Sandoval, N. Zepeda and J. Gavrilyuk, *J. Org. Chem.*, 2019, **84**, 365.
13 B. K. Goering, *PhD Thesis*, Cornell University, 1995.
14 A. M. Gimazetdinov, S. S. Gataullin, I. S. Bushmarinov and M. S. Miftakhov, *Tetrahedron*, 2012, **68**, 5754.
15 A. M. Gimazetdinov, A. Z. Al'mukhametov and M. S. Miftakhov, *Russ. J. Org. Chem.*, 2019, **55**, 831 (*Zh. Org. Khim*., 2019, **55**, 938).
16 A. Z. Al'mukhametov, A. M. Gimazetdinov and M. S. Miftakhov, *Mendeleev Commun.*, 2020, **30**, 10.
17 A. Z. Al'mukhametov, A. M. Gimazetdinov and M. S. Miftakhov, *Mendeleev Commun.*, 2018, **28**, 362.
18 A. M. Gimazetdinov, A. Z. Al'mukhametov, V. V. Loza, L. V. Spirikhin and M. S. Miftakhov, *Mendeleev Commun.*, 2018, **28**, 546.
19 T. W. Greene and P. G. Wuts, *Greene's Protective Groups in Organic Synthesis,* 4th edn., Wiley, New York, 2007, p. 166.
20 Y. Torisawa, M. Shibasaki and S. Ikegami, *Tetrahedron Lett.*, 1979, **21**, 1865.
21 S. S. Jones and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1979, 276.
22 D. F. Sullivan, R. P. Woodbury and M. W. Rathke, *J. Org. Chem.*, 1977, **42**, 2038.

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