Asymmetric Reactions

DOI: 10.1002/anie.201209380

Pot Economy in the Synthesis of Prostaglandin A_1 and E_1 Methyl Esters**

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Dedicated to Professor E. J. Corey

The efficient total synthesis of natural products has always been a critical issue for organic chemists, especially when the molecule to be prepared possesses important biological activity and is difficult to obtain from natural sources. A lot of effort has been devoted to the development of the ideal synthesis.[1] Recently, when synthesizing molecules we not only have to consider efficiency but also sustainability, as indicated by terminology such as atom economy,[2] step economy[3] and redox economy.[4] Protecting-group-free[5] and toxic-metal-free syntheses would also contribute to sustainability, and catalytic reagents (as selective as possible) are regarded as superior to stoichiometric reagents according to the 12 principles of green chemistry.[6]

A one-pot reaction is an efficient method to achieve several transformations and form several bonds, while at the same time cutting out several purifications, minimizing the generation of waste chemicals, and saving time. Thus, a one-pot reaction can also be regarded as environmentally benign, and "pot economy" should be considered when planning a synthesis.[7]

The prostaglandins are known to act as local hormones; only trace amounts can control a multitude of important physiological processes, and some of their derivatives are used as medicines.[8] The scientific community has put a great deal of effort and ingenuity into their efficient synthesis because of their biological importance and limited availability from natural sources.[9] These molecules have inspired the chemical community to devise many different synthetic strategies, beginning with Corey's landmark synthesis[10] and continuing with more than 40 subsequent syntheses, but all the previous syntheses require many operations. Thus, it is still a synthetic challenge to synthesize a molecule of this complexity, that is, with three contiguous stereogenic centers, in a small number of steps and by a sustainable process. Moreover, the synthesis of the D and E series of prostaglandins, which contain a β-hydroxyketo moiety, is very difficult owing to their instability and facile dehydration resulting in their conversion into A-type and B-type prostaglandins in acidic and basic media, respectively.[11] Herein, we have accomplished a three-pot synthesis of prostaglandin E_1 methyl ester (**1**; see Scheme 1) and A_1 methyl ester (**2**; see Scheme 2) by using an organocatalyst.[12, 13] During the preparation of this manuscript, a short (seven steps) synthesis of prostaglandin $PGF_{2\alpha}$ has been described, for which the total yield is 2.2–3.3 %.[14]

Our strategy is completely different from any previous synthesis of prostaglandins: The first one-pot operation involves construction of a key chiral intermediate that contains all the carbon atoms of prostaglandin from three simple molecules, and subsequent reactions consist of only functional-group transformations.

The first key reaction relied on the use of diphenylprolinol silyl ether (**3**),[15] an effective organocatalyst developed independently by our research group[16] and that of Jørgensen.[17] The asymmetric Michael reaction of an aldehyde and an nitroalkene can be catalyzed by **3**, and this reaction has already been successfully employed in our two-pot synthesis of (−)-Oseltamivir[18] and one-pot synthesis of ABT-341.[19] Chiral cyclohexane derivatives can be synthesized by a domino reaction consisting of a Michael reaction mediated by organocatalyst **3** and a Henry reaction of aqueous tetrahydro-2H-pyran-2,6-diol.[20] We applied this domino reaction to the synthesis of the cyclopentane framework. Starting from the three simple fragments nitroalkene **4**, succinaldehyde (**5**), and Horner–Wadsworth–Emmons reagent **6**, the prostaglandin skeleton **7**, containing all the necessary carbon atoms, is constructed in a one-pot operation in good yield (81 %) with good diastereoselectivity and excellent enantioselectivity (Scheme 1). Of the eight possible diastereomers, three were generated in the ratio of 76:17:7. Although the relative stereochemistry was not determined at this stage, the relative and absolute configurations at C8 and C12 are highly controlled, as shown after conversion into the cyclopentene derivative **10** (see Scheme 2). This crucial sequence requires some elaboration: the first reaction is a Michael reaction mediated by diphenylprolinol silyl ether.[16] The sequential intramolecular Henry reaction is slow but is facilitated by $i\mathrm{Pr_2EtN}$, and subsequent addition of Horner–Wadsworth–Emmons reagent **6** to the same pot affords **7**, having the complete skeleton of the prostaglandins.

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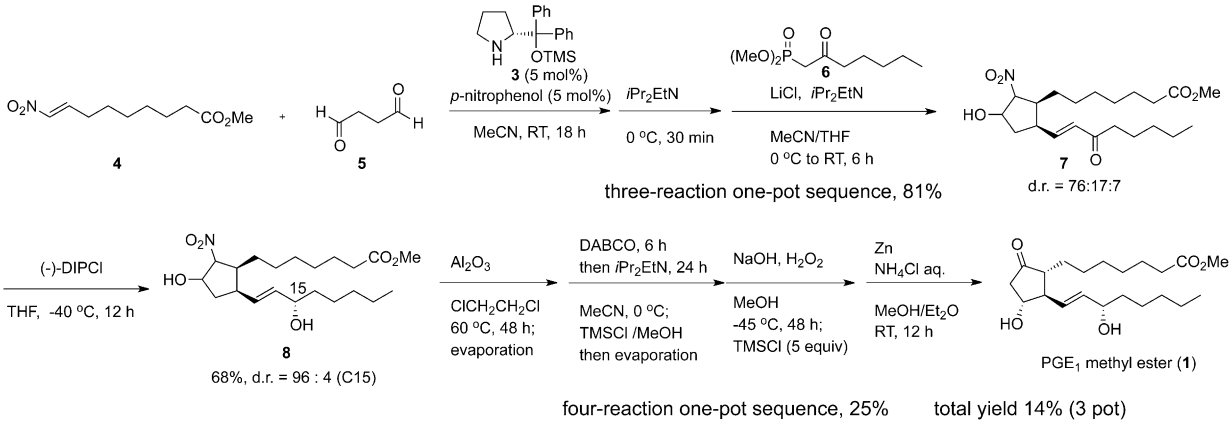
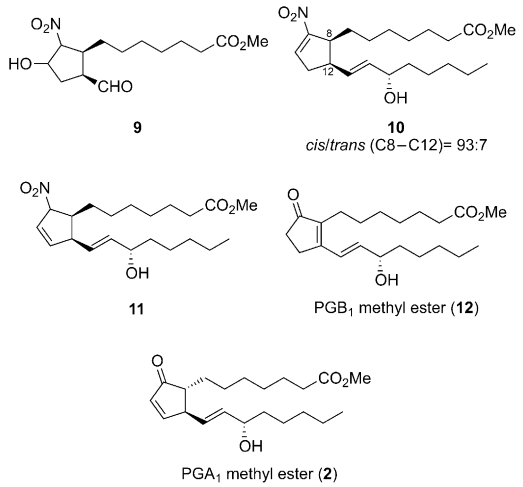
[**] This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from The Ministry of Education, Culture, Sports, Science and Technology (Japan). The authors thank Prof. Hayato Ishikawa at Kumamoto University, Dr. Takuya Seko, and Dr. Toru Maruyama at Ono pharmaceutical Co., Ltd. for their helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209380.



Scheme 1. Synthesis of PGE_1 methyl ester (**1**). DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = trimethylsilyl.



Scheme 2. Intermediates in the synthesis of PGE_1 (**1**) and PGA_1 (**2**) methyl esters.

The use of a one-pot procedure is beneficial, because when **9** (Scheme 2) was isolated before the addition of **6**, a lower yield was obtained as a result of the instability and ready epimerization of **9**. Only 5 mol% of catalyst **3** is needed and each reagent is added in succession to the same pot, thus making the one-pot synthesis of **7** practical.

The next reaction is the diastereoselective reduction of the ketone in the ω-side chain; this transformation was successfully achieved by treatment of **7** with (−)-diisopinocamphenyl chloroborane (DIPCl)[21] to afford allyl alcohol **8** in 68% yield and 96:4 d.r. at the C15 stereogenic center. It is not necessary to protect this hydroxy group, thus making the synthesis more efficient by removing the need for the usual protection/deprotection steps. Elimination of water proceeds upon treatment of **8** with acidic Al_2O_3[22] at 60 °C to provide 1-nitrocyclopentene **10**. The *cis* and *trans* isomers are separable, and are formed in a 93:7 ratio. The optical purity of the major *cis* isomer was determined to be 94% *ee* by HPLC analysis on a chiral column. These results indicate that the first Michael reaction mediated by organocatalyst **3** is highly diastereo- and enantioselective.

Prostaglandin A_1 (PGA_1) methyl ester (**2**) can be obtained from **10** by a base-promoted three-step transformation involving migration of the double bond to the neighboring position. Isomerization of the double bond of **10** to give 2-nitrocyclopentene **11** (see Scheme 2) proceeded in the presence of DABCO. It should be noted that 2-nitrocyclopentene **11** is stable and does not isomerize to conjugated 1-nitropentene **10** under basic conditions. Then, the addition of iPr_2EtN at 0 °C resulted in conversion of 2-nitrocyclopentene **11** into PGA_1 methyl ester (**2**), through a novel transformation of the nitro group into a carbonyl group, with subsequent epimerization of the α-side chain from the *cis* to *trans* orientation to the ω-side chain. The choice of base and temperature are key in this step, because isomerization of the double bond of **2** to give the more stable prostaglandin B_1 (PGB_1) methyl ester (**12**, see Scheme 2) is facile and occurs in the presence of stronger base or even just at room temperature. When the reaction is quenched at this stage, PGA_1 methyl ester (**2**)[23] can be isolated in 45% yield from **8** over four steps. Notably, the conversion of a nitroalkane into a carbonyl normally proceeds under strong acidic conditions and is known as the Nef reaction;[24] the similar base-promoted transformation is very rare.[25]

For the synthesis of **1**, instead of quenching the reaction, the reaction mixture was neutralized by the addition of TMSCl, the solvent was removed, and then a base-mediated epoxidation[26] in MeOH at −45 °C was performed to diastereoselectively provide an epoxyketone, without any unwanted hydrolysis of the methyl ester. This epoxyketone was treated with zinc[27] to afford PGE_1 methyl ester (**1**). As the intermediate epoxyketone is unstable, the one-pot procedure again gave better results compared to stepwise reactions. The transformations from **8** to give PGE_1 methyl ester (**1**) can be performed in a single pot in 25% yield over four steps (average 71% yield per step). The synthetic PGE_1 methyl ester (**1**) is identical in all respects to the natural product.[28]

An innovative total synthesis of prostaglandins has been accomplished by the use of diphenylprolinol silyl ether, thus demonstrating the power of organocatalysis in the synthesis of natural products and physiologically active compounds. This synthesis was made possible by the discovery of a novel transformation of a nitroalkene to α,β-unsaturated ketone under mildly basic conditions, a marked contrast to the

normal strong acidic conditions of the Nef reaction. Success was also due to the finding of mild reaction conditions, compatible with the labile functional groups, for several other steps. One-pot operations are essential for this synthesis as some of the intermediates are unstable, and therefore the omission of their isolation by use of a one-pot operation contributes to increasing the yield.

In summary, enantioselective total syntheses of PGE_1 methyl ester (**1**) and PGA_1 methyl ester (**2**) have been accomplished in 14% and 25% total yield, respectively, by using inexpensive and simple starting materials, and one-pot reactions. The present route is not only short and efficient but also possesses several noteworthy, sustainable features: 1) The total synthesis was performed in only three pots, including three isolations and three chromatographic purifications, which reduces the amount of solvent necessary and waste formed. 2) The key reaction is a highly selective catalytic reaction, involving an organocatalyst developed by our own group, and reduces the generation of waste. 3) Protection of the hydroxy group of **8** is not necessary, thus eliminating protection/deprotection steps. 4) The metal-based reagents employed in the present synthesis contain either alkali-metal ions (Na, Li) or nontoxic Zn. Thus, the present total synthesis is not only efficient for the synthesis of a wide variety of prostaglandins and other natural products with a cyclopentane skeleton, but is also environmentally benign.

Received: November 23, 2012
Published online: February 13, 2013

Keywords: asymmetric reactions · one-pot reactions · organocatalysis · prostaglandins · total synthesis

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