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Enantioselective Total Synthesis of Beraprost Using Organocatalyst

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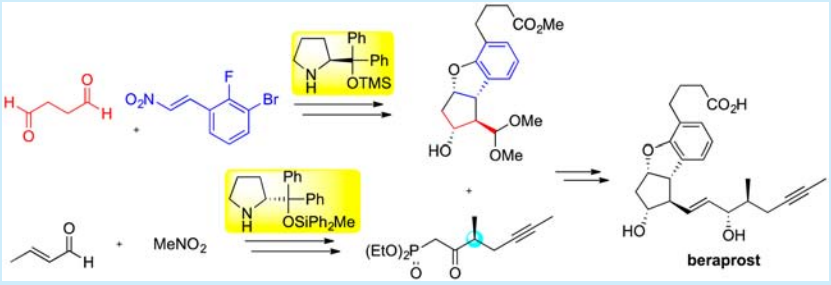
Supporting Information



ABSTRACT: A convergent and enantioselective total synthesis of the most active isomer of beraprost was achieved in 17 pots. A unique tricyclic core in beraprost was synthesized efficiently by utilizing the asymmetric organocatalyst-mediated formal [3 + 2] cycloaddition reaction of succinaldehyde with nitroalkene as a key step. The synthesis of the optically active Horner–Wadsworth–Emmons reagent for the construction of the ω-side chain was also established by means of the enantioselective Michael reaction of crotonaldehyde with nitromethane catalyzed by the organocatalyst developed by our group.

The prostaglandins are essential natural products for human life controlling a wide array of physiological processes as local hormones.[1] Numerous chemical syntheses of prostaglandins and derivatives have been reported owing to their attractive biological activities.[2]

Prostaglandin (PG) I_2 (**1**) is a physiologically active natural product, which can inhibit platelet aggregation and vasodilation (Figure 1).[3] As PGI_2 can also promote axonal remodeling of

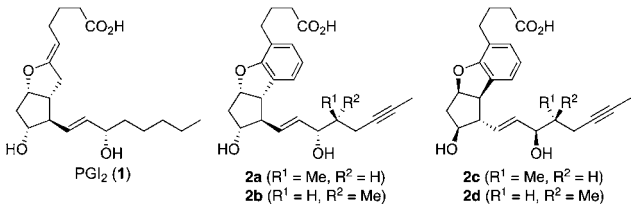


Figure 1. Structure of PGI_2 (**1**) and beraprost (**2**).

injured neuronal networks,[4] it is thus considered as a fascinating drug candidate. However, **1** is highly unstable and hydrolyzed even under neutral aqueous conditions because of its highly reactive enol ether functionality.[5] Since the hydrolyzed product has no pharmacological activity,[6] more stable analogs of **1** have been pursued for decades.

Toray Industries Inc. have developed beraprost, which is a mixture of four isomers (**2a**, **2b**, **2c**, and **2d**), bearing six stereogenic centers and a unique benzofuran ring system instead of the sensitive enol ether moiety (Figure 1).[7] Beraprost is a more stable and less cytotoxic analog than PGI_2 whose sodium salt is used as an antiplatelet aggregation drug.

On the other hand, a selective synthesis of **2a** is highly important for reducing undesired pharmacological activities because these isomers in beraprost (**2a**, **2b**, **2c**, and **2d**) have different biological activities respectively, and **2a** is known as the most biologically active isomer.[7f] Toray's group reported the enantioselective synthesis of **2a**, combining the tricyclic core and side chain, but it required a total of 27 pots.[7f] Requirements for an ideal synthesis of **2a** are as follows: (1) A suitable methodology for high yielding construction of the tricyclic core is required. (2) A catalytic and asymmetric reaction introducing the stereogenic center(s) in the core skeleton must be developed. (3) An efficient and enantioselective preparation of the ω-side chain unit is needed.

Several asymmetric syntheses of the common tricyclic core in **2a** have been developed, which are summarized in Scheme 1 including the number of pots for the synthesis of this moiety.

In Toray's synthesis, an intramolecular S_N2' reaction with a Grignard reagent and copper iodide furnished a tricyclic product. An optical resolution produced enantiopure carboxylic acid in 30% over two steps (Scheme 1a).[7e,f] Chandrasekhar and co-workers took advantage of an enzymatic optical resolution, and an intramolecular oxy-Michael reaction of an enone formed a key benzofuran ring (Scheme 1b).[8a] The Takemoto group demonstrated that an enantioselective intramolecular oxy-Michael addition of an α,β-unsaturated amide by an organocatalyst afforded a chiral amide (Scheme 1c).[8b] An intramolecular C–H insertion of a diazo compound followed by reduction gave a tricyclic substrate in a useful yield. Most

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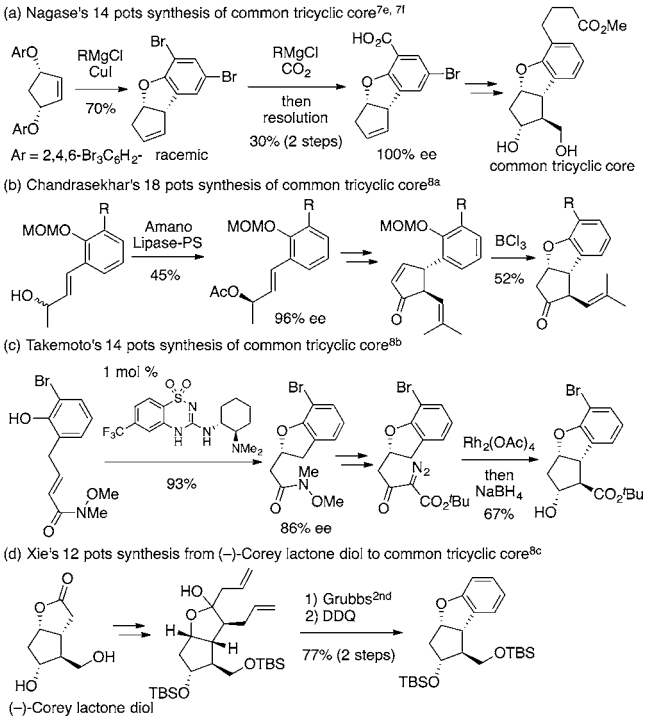
Scheme 1. Syntheses of the Tricyclic Core in Beraprost

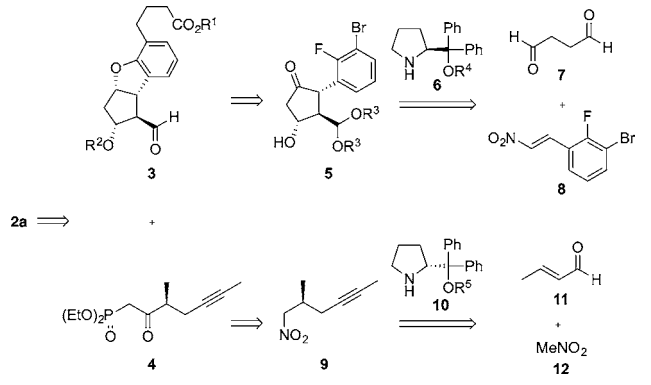


recently, Xie and co-workers described that a diolefin substrate prepared from the commercially available (−)-Corey lactone diol was converted into a tricyclic system via olefin metathesis and oxidation (Scheme 1d).[8c]

These methods can produce the chiral common tricyclic intermediate, but still require long sequences (over 14 pots) and/or include low yielding manipulations, such as optical resolutions. Moreover, a catalytic construction of the C-16 stereogenic center has not been reported. Only one method controlling this stereocenter by using an optical resolution is introduced by the Toray research group.[7g] Indeed, most of the previous work did not control the C-16 stereogenic center. There is thus a significant synthetic challenge to prepare the complex tricyclic core and the ω-side chain unit in an efficient and fully stereocontrolled fashion. Here, an enantioselective total synthesis of **2a** in 17 pots utilizing two organocatalyzed asymmetric reactions and an amenable benzofuran ring formation via an intramolecular S_NAr reaction is described.

Our retrosynthetic analysis of **2a** is illustrated in Scheme 2. The desired product **2a** could be disconnected into tricyclic

Scheme 2. Retrosynthetic Analysis of 2a

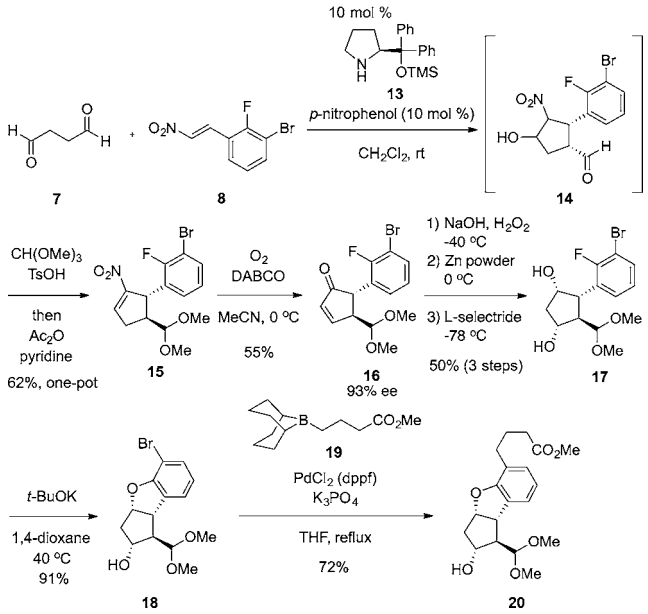


core **3** and phosphonate **4**. We proposed that the benzofuran ring in aldehyde **3** could be prepared from β-hydroxyl ketone **5** through a diastereoselective reduction, followed by an intramolecular S_NAr reaction. According to our previous synthesis of prostaglandin E_1 methyl ester,[9] ketone **5** would be derived from two simple starting materials, succinaldehyde (**7**) and commercially available nitroalkene **8**, by means of an asymmetric formal [3 + 2] cycloaddition reaction[10] catalyzed by diphenylprolinol silyl ether.[11]

On the other hand, we also envisioned that the optically active Horner−Wadsworth−Emmons reagent **4** could be synthesized by an organocatalyzed asymmetric reaction as a key step. A simple nitroalkane **9** would be considered as a suitable precursor toward **4**. We assumed that nitroalkane **9** could be prepared from crotonaldehyde (**11**) and nitromethane (**12**) with high enantioselectivity by utilizing our catalytic enantioselective Michael reaction[12] in the presence of diphenylprolinol silyl ether.

The synthesis of the key tricyclic core **20**, as outlined in Scheme 3, commenced with succinaldehyde (**7**) which is easily

Scheme 3. Synthesis of the Key Intermediate 20



obtained from inexpensive 2,5-dimethoxytetrahydrofuran. The formal [3 + 2] cycloaddition reaction afforded a highly substituted cyclopentane **14** in good yield. After dimethylacetal protection followed by dehydration under acetylation conditions, nitroalkene **15** was obtained in 62% yield as single isomer. In the acetalization step, the complete epimerization of α-position of the formyl group occurred to furnish the *trans* product. Notably, these three-step sequences can be engineered in one pot[13] and multigram scale.

An oxygen-promoted Nef reaction by DABCO produced enone **16** in 55% yield,[14] and the enantiomeric excess of **16** was determined by HPLC analysis (93% ee). A base-mediated epoxidation[15a,b] of **16** followed by a reductive epoxide opening reaction using zinc powder under mildly acidic conditions gave the corresponding unstable β-hydroxyketone. A successive L-selectride reduction of this crude product was performed immediately to give diol **17** in 50% yield over three steps.[16] The minor diastereomer generated in the epoxidation could be

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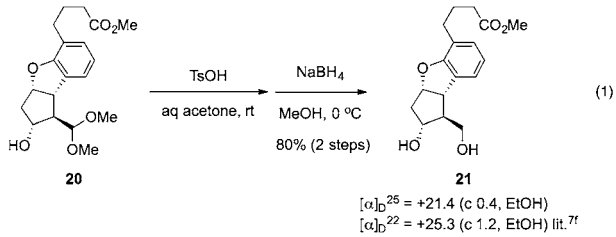
separated at this stage. Next, we conducted a crucial formation of the benzofuran ring system. Fortunately, the desired product **18** was successfully afforded in excellent yield by simple treatment of **17** with *t*-BuOK in 1,4-dioxane.[17] The alkyl side chain on the aromatic ring was subsequently installed by the Suzuki–Miyaura coupling with alkylborane **19**, prepared from methyl but-3-enoate and 9-BBN to afford a key intermediate **20**.[18] The chiral functionalized tricyclic key intermediate **20** was constructed in only seven pots.

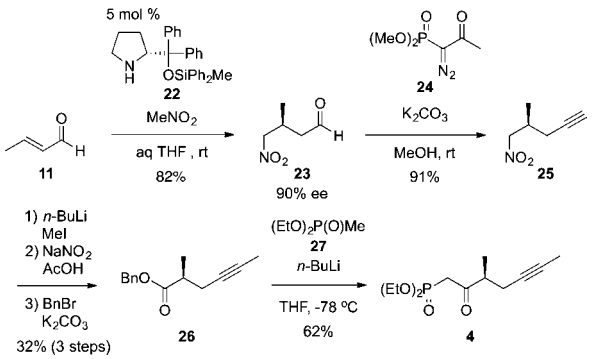
In order to determine the absolute configuration of **20**, a known compound **21** in the Toray's synthesis was accessed through hydrolysis of dimethoxyacetal moiety and a sequential reduction of the generated aldehyde (eq 1). All spectral data and the optical rotation of our synthetic diol **21** matched those in the reported literature.[7f]



(1)

Next, we carried out the enantioselective Michael reaction of crotonaldehyde (**11**) with nitromethane, which was an essential step for preparing the chiral Horner–Wadsworth–Emmons agent **4** (Scheme 4). We selected secondary amine **22**

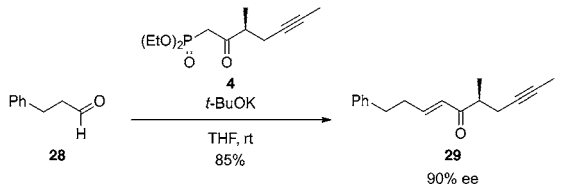
Scheme 4. Preparation of Chiral Phosphonate 4



developed by the Seebach group as the best catalyst,[19] which provided better asymmetric induction than the corresponding TMS catalyst in Michael reactions via iminium ion intermediates.[12,20] The yield of **23** was dramatically improved when the reaction was carried out in aqueous THF[21] instead of MeOH.[12] Ultimately, the catalyst loading was able to be reduced to only 5 mol % and the desired product was obtained in 82% yield with 90% ee.

With an adequate amount of the optically active nitroalkane **23** accessible, we started to investigate transformations toward phosphonate **4**. Treatment of **23** with the Ohira–Bestmann reagent **24** furnished the corresponding terminal alkyne **25** in 91% yield.[22] Three-step transformations including a selective methylation in **25**, a Nef reaction,[23] and a benzyl esterification provided ester **26** in 32% yield over three steps. The resulted benzyl ester was converted into the desired **4** by a Claisen-type reaction with diethylmethane phosphonate (**27**) in 62% yield.

As partial racemization was expected in the preparation of **4**, we confirmed the enantiomeric enrichment of **4** by conversion into the corresponding enone using 3-phenylpropanal (**28**) as a model (eq 2). The desired product **29** was obtained in 85%

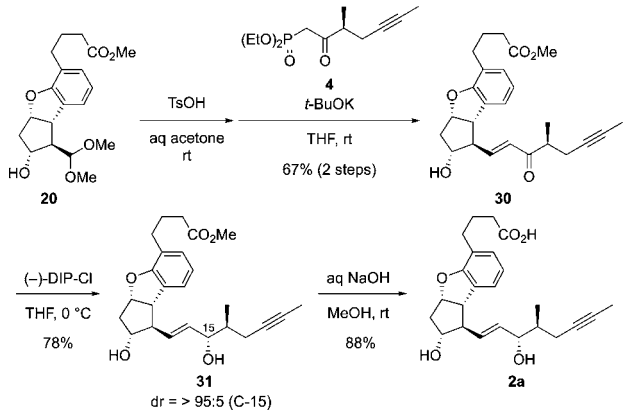


(2)

yield along with 90% ee under standard conditions. No racemization was observed under several acidic and basic conditions (Nef reaction, benzyl esterification, Claisen-type reaction, and Horner–Wadsworth–Emmons reaction).

With the two chiral fragments in hand, the total synthesis of **2a** was completed in Scheme 5. Hydrolysis of dimethylacetal **20**

Scheme 5. Completion of Enantioselective Total Synthesis of 2a



under the acidic conditions gave the corresponding aldehyde, which was used directly after an aqueous workup. The subsequent Horner–Wadsworth–Emmons reaction proceeded smoothly to deliver enone **30** in 67% yield over two steps together with perfect *E*-selectivity. A diastereoselective 1,2-reduction of **30** using (−)-*B*-chlorodiisopinocampheylborane (DIP-Cl) provided diol **31** (dr = >95:5 at C-15) possessing all requisite stereogenic centers.[24] Finally, hydrolysis of methyl ester was achieved under basic conditions to afford beraprost (**2a**) in 88% yield.

In summary, we have developed a concise, highly stereoselective, and short total synthesis of **2a**, which is the most biologically active isomer of beraprost, from simple starting materials. The present synthesis has several notable features: (1) A formal asymmetric [3 + 2] cycloaddition reaction catalyzed by diphenylprolinol silyl ether **13** was suitable to install stereogenic centers. (2) An asymmetric Michael addition of crotonaldehyde with nitromethane in the presence of diphenylprolinol silyl ether **22** furnished the appropriate chiral building block toward the ω-side chain unit. This is the first example controlling the C-16 stereogenic center in a catalytic manner. It is noteworthy that diphenylprolinol silyl ether catalysts facilitate two key asymmetric reactions that allow assembling the complex setting of beraprost in 17 pots. (3) The intramolecular S_NAr reaction of **17** successfully provided the tricyclic system in excellent yield. Moreover, our synthetic

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method of highly functionalized cyclopentane **17** would be useful for preparing prostaglandin derivatives bearing an aryl group at the α-side chain because it is difficult to access cyclopentanes such as **17** by conventional prostaglandin syntheses based on the Corey lactone[25] or Noyori's three-component strategy.[26]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00134.

Experimental procedure, analytical data (^{1}H and ^{13}C NMR, IR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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