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Two-pot synthesis of chiral 1,3-*syn*-diols through asymmetric organocatalytic aldol and Wittig reactions, followed by domino hemiacetal/oxy-Michael reactions

Yujiro Hayashi,*[a] Takanobu Saitoh,[a] Hiromu Arase,[a] Genki Kawauchi,[a] Naohiro Takeda,[a] Yasuharu Shimasaki,[a] and Itaru Sato[a, b]

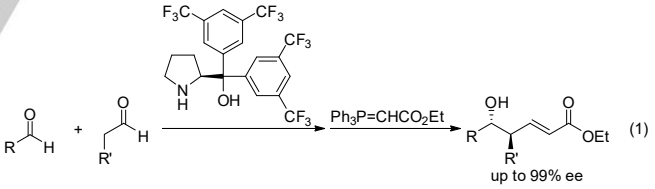
Abstract: A two-pot synthetic method to construct the chiral *syn*-1,3-diol unit has been developed from three aldehydes and either Wittig or Horner–Wadsworth–Emmons reagents. In the first pot, chiral δ-hydroxy α,β-unsaturated ketones are synthesized with excellent enantioselectivity by the organocatalyst-mediated asymmetric direct aldol reaction of two different aldehydes, followed by either Wittig or Horner–Wadsworth–Emmons reactions. In the second pot, domino acetalization with an aldehyde and subsequent oxy-Michael reaction proceeds in the presence of $NaClO_4$ and a catalytic amount of $Bi(OTf)_3$ to provide the chiral 1,3-*syn*-diol derivative with excellent diastereoselectivity. Diospongin C and yashabushidiol A have been synthesized efficiently using the present method as a key step.

Introduction

The 1,3-*syn*-diol unit is found in many natural products and drugs, and its efficient preparation is an important synthetic challenge. There are several methods for its synthesis, with *syn*-selective Narasaka reduction of β-hydroxy ketone[1] being one of the most useful. Although 1,2-addition reaction of β-alkoxy or β-siloxy aldehyde is another method, in general, *anti*-adducts are major products under chelation control,[2] and successful syntheses of *syn*-adducts are limited to intramolecular reactions,[3] the reaction of unprotected β-hydroxy aldehyde,[4] and some specific substrates with additional functional groups.[5] 1,3-*syn*-Diol units are also synthesized through acetalization followed by oxy-Michael reaction of δ-hydroxy α,β-unsaturated carbonyl compounds: D. A. Evans reported the base-catalyzed intramolecular conjugate addition of hemiacetal-derived alkoxide as an intermediate,[6] and P. A. Evans developed the $Bi(NO_3)_3$-catalyzed hemiacetal/oxy-Michael addition reaction for construction of the 1,3-*syn*-diol unit.[7] Recently, the enantioselective domino acetalization/oxy-Michael reaction was employed to form β-hydroxy ketone derivatives through organocatalysts.[8, 9]

In terms of the efficiency of the synthesis of the 1,3-diol unit, the availability of the required starting material is also very important. Especially considering the demand for chiral molecules, it is necessary to develop an efficient synthetic method for the construction of chiral 1,3-*syn*-diol building blocks from easily available starting materials in a small number of pots in terms of the pot economy.[10]

We have previously reported the asymmetric cross-aldol reaction of two different aldehydes catalyzed by diarylprolinol substituted with a trifluoromethyl group to afford β-hydroxy aldehyde.[11] Subsequent treatment of the aldol product with a Wittig reagent such as (ethoxycarbonylmethylidene)triphenylphosphorane provided the corresponding δ-hydroxy α,β-unsaturated ester in good yield with excellent enantioselectivity in a one-pot operation (Eq. 1). Given that the δ-hydroxy α,β-unsaturated carbonyl compound is a precursor of the *syn*-β,δ-diol carbonyl unit (via hemiacetal formation), which can undergo intramolecular conjugate addition, the chiral 1,3-diol unit would be constructed in only two pots from readily available starting materials (Eq. 2). In this paper, we will describe the realization of this scenario.



Results and Discussion

6-(*p*-Nitrophenyl)-6-hydroxyhex-3-ene-2-one (**1a**) was selected as a model δ-hydroxy α,β-unsaturated ketone, which was synthesized easily with excellent enantioselectivity by using the previously described one-pot procedure.[11a] Namely, cross-aldol reaction of *p*-nitrobenzaldehyde and acetaldehyde proceeded smoothly in the presence of a catalytic amount of diarylprolinol to provide the aldol product, which was treated with acetylmethylene triphenylphosphorane in the same reaction vessel to afford the desired (*E*)-δ-hydroxy α,β-unsaturated

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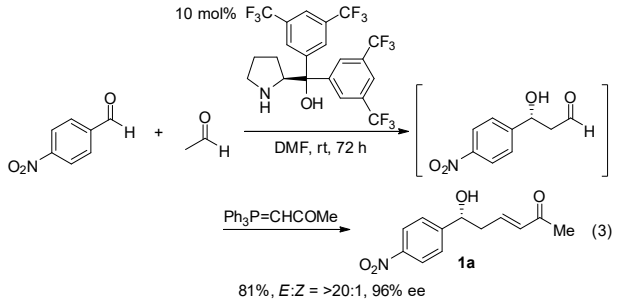
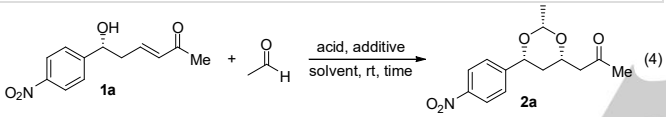
ketone **1a** in good yield with excellent enantioselectivity (96% ee, Eq. 3).



81%, *E*:*Z* = >20:1, 96% ee

The hemiacetal/oxy-Michael reaction was then investigated using acetaldehyde as an aldehyde partner. First, we employed the conditions developed by P. A. Evans using $Bi(NO_3)_3{\cdot}5H_2O$,[7] which afforded the desired product **2a** as a single isomer in good yield (Table 1, entry 1). Given that the reaction required 72 h to reach completion, we investigated the additive in more detail to facilitate the reaction with respect to time economy.[12]

Table 1. The effect of acid, additive, and solvent in the hemiacetal/oxy-Michael reaction[a]



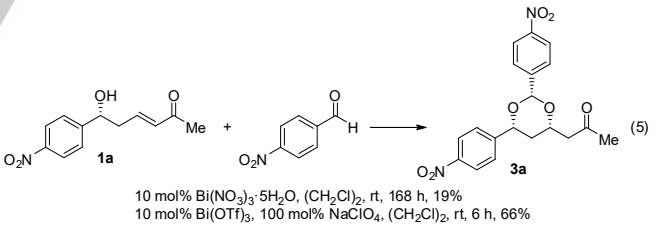
Entry	Acid	Additive	Solvent	Time [h]	Dr[b]	Yield [%][c]
1	$Bi(NO_3)_3{\cdot}5H_2O$	none	$(CH_2Cl)_2$	72	>20:1	78
2	$Bi(NO_3)_3{\cdot}5H_2O$	$LiClO_4$	$(CH_2Cl)_2$	3.5	>20:1	98
3	none	$LiClO_4$	$(CH_2Cl)_2$	72	nd[d]	<5
4	$Bi(NO_3)_3{\cdot}5H_2O$	$LiNO_3$	$(CH_2Cl)_2$	72	>20:1	90
5	$Bi(NO_3)_3{\cdot}5H_2O$	LiOTf	$(CH_2Cl)_2$	5	>20:1	quant.
6	$Bi(NO_3)_3{\cdot}5H_2O$	$NaClO_4$	$(CH_2Cl)_2$	2	>20:1	quant.
7	$Bi(OTf)_3$	none	$(CH_2Cl)_2$	1.5	>20:1	quant.
8[e]	$Bi(OTf)_3$	$NaClO_4$	$(CH_2Cl)_2$	0.17	>20:1	quant.
9	$Bi(OTf)_3$	$NaClO_4$	CH_2Cl_2	0.17	>20:1	90
10	$Bi(OTf)_3$	$NaClO_4$	CH_3CN	0.5	>20:1	quant.
11	$Bi(OTf)_3$	$NaClO_4$	Toluene	0.25	>20:1	quant.
12[f]	$Bi(OTf)_3$	$NaClO_4$	$(CH_2Cl)_2$	0.5	>20:1	quant.

[a] Unless noted otherwise, reaction was performed by employing **1a** (0.3 mmol, 96% ee), acetaldehyde (6.0 mmol), Bi reagent (0.03 mmol), and additive (0.3 mmol) in solvent (3 mL) at room temperature for the indicated time. [b] Diastereomer ratio was determined by ^{1}H-NMR. [c] Isolated yield of **2a**. [d] nd = not determined. [e] The enantiomeric excess of the product was 96% ee. [f] $Bi(OTf)_3$ (5 mol%, 0.015 mmol) and $NaClO_4$ (15 mol%, 0.045 mmol) were employed.

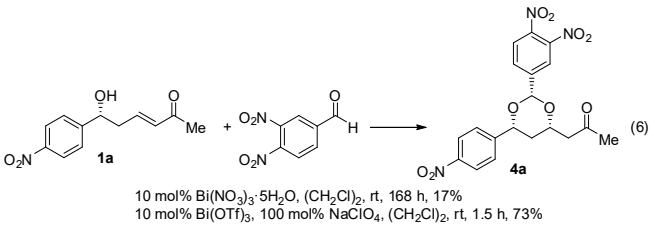
We found that the reaction was dramatically accelerated by the addition of $LiClO_4$; with this additive, only 3.5 h were required for the reaction to reach completion (entry 2) compared with the reaction in the presence of only $Bi(NO_3)_3{\cdot}5H_2O$. $LiClO_4$ alone did not promote the reaction (entry 3). Other salts were examined and it was found that whereas $LiNO_3$ was not effective, the use of LiOTf and $NaClO_4$ accelerated the reaction (entries 4–6). We also noted that $Bi(OTf)_3$ is more reactive than $Bi(NO_3)_3{\cdot}5H_2O$ (entry 7). The combination of $Bi(OTf)_3$ and $NaClO_4$ was very effective (entry 8), with the reaction reaching completion within 10 minutes. The reaction proceeded successfully in solvents such as 1,2-dichloroethane, dichloromethane, acetonitrile, and toluene (entries 8–11). Furthermore, the loading of $Bi(OTf)_3$ could be reduced to 5 mol%, with the reaction reaching completion within 30 minutes in the presence of 15 mol% $NaClO_4$ (entry 12). A combination of $Bi(OTf)_3$ and $NaClO_4$ would produce $Bi(ClO_4)_3$, which is considered to be an active catalyst in the reaction. The optical purity of 1,3-dioxane **2a** was 96% ee, which indicates that the enantiomeric purity was maintained during the reaction (entry 8).

In addition to acetaldehyde, the reaction was also applicable to *p*-nitrobenzaldehyde and 3,4-dinitrobenzaldehyde to provide the products **3a** and **4a** in 66% and 73% yield, respectively, as single isomers. The yield was not satisfactory under the conditions developed by P. A. Evans, even with an extended reaction time (Eqs 5 and 6). Unfortunately, acetone and benzaldehyde were not suitable carbonyl compounds for the present reaction.

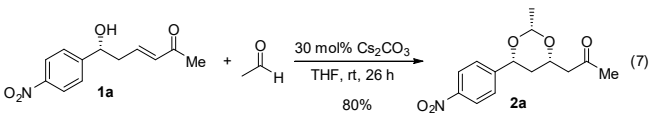
Notably, successive hemiacetalization and oxy-Michael reaction proceed under both acidic conditions and basic conditions.[6] Product **2a** was obtained as a single isomer in 80% yield when the reaction was catalyzed by a catalytic amount of Cs_2CO_3, although the reaction was slower and required 26 h to reach completion (Eq. 7).



10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, $(CH_2Cl)_2$, rt, 168 h, 19%
10 mol% $Bi(OTf)_3$, 100 mol% $NaClO_4$, $(CH_2Cl)_2$, rt, 6 h, 66%

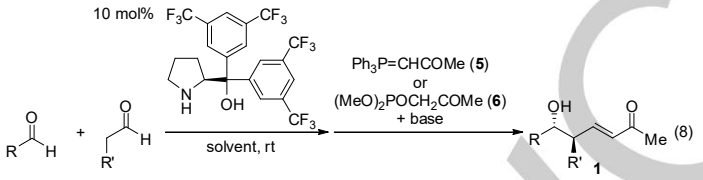


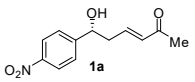
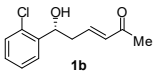
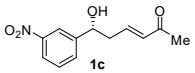
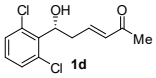
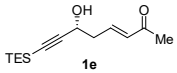
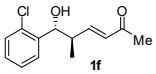
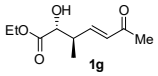
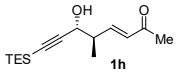
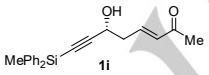
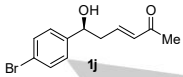
10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, $(CH_2Cl)_2$, rt, 168 h, 17%
10 mol% $Bi(OTf)_3$, 100 mol% $NaClO_4$, $(CH_2Cl)_2$, rt, 1.5 h, 73%



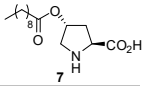
Having optimized the reaction conditions, the generality of the two-pot conversion from aldehyde into 1,3-diol unit was investigated. The first-pot reaction involving the asymmetric catalytic cross-aldol reaction, followed by the olefination reaction using either acetylmethylene triphenylphosphorane **5**[13] or dimethyl 2-oxopropylphosphonate **6**[14] was examined (Table 2). According to the combination of electrophilic aldehyde and nucleophilic aldehyde, the best reaction conditions for the cross-aldol reaction are slightly different.

Table 2. Sequential asymmetric aldol and olefination reaction for the formation of δ-hydroxy α,β-unsaturated methyl ketone[a]



Entry	Product	Solvent	Condition[b]	Time [h][c]	Yield [%][d]	*E*:*Z* [e]	*anti*:*syn*[e]	Ee [%][f]
1	 1a	DMF	1	72	81	>20:1		96
2	 1b	DMF	1	72	82	>20:1		96
3	 1c	DMF	1	72	71	>20:1		98
4	 1d	DMF	2	72	71	>20:1		95
5	 1e	1,4-dioxane	3	51	62	>20:1		89
6[g]	 1f	H_2O	3	70	73	>20:1	10:1	99
7[h]	 1g	CH_3CN	3	24	98	>20:1	7:1	98
8[i]	 1h	1,4-dioxane	3	8	77	>20:1	10:1	82
9	 1i	1,4-dioxane	3	51	56	>20:1		93
10[j]	 1j	DMF	3	96	64	>20:1		97

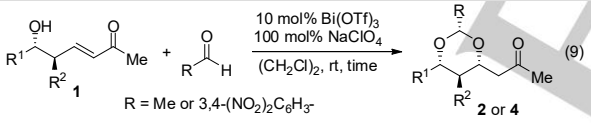
[a] Unless noted otherwise, reaction was performed by employing aldehyde (0.5 mmol), acetaldehyde (2.5 mmol), diarylprolinol (0.05 mmol) in solvent (0.5 mL) a room temperature for the indicated time. [b] Olefination conditions. Condition 1: Wittig reaction using **5** (1.5 mmol) was conducted at 50 °C for 2 h. Condition 2: HWE reaction was conducted using **6** (1.5 mmol) LiCl (1.5 mmol) and *i*Pr_2EtN (1.5 mmol) at rt for 30 min. Condition 3: After Aldol reaction, $MgSO_4$ was added Then, HWE reaction was conducted using **6** (1.35-2.85 mmol) and NaH (1.25-2.75 mmol) at rt for 30 min. See supporting information in detail. [c] Time of the aldol reaction. [d] Isolated yield of α,β-unsaturated ketone. [e] Ratio was determined by ^{1}H NMR [f] Determined by HPLC analysis on a chir column material. [g] Catalyst **7** (0.05 mmol), propanal (2.5 mmol), and H_2O (9 mmol) was used. Detail was shown on supporting info. [h] Propanal (0.75 mmol) was used. [i] Propanal (1.0 mmol) was used. [j] Enantiomer of catalyst (30 mol%) was employed.

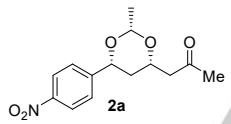
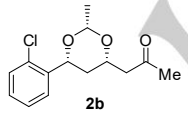
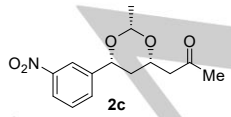
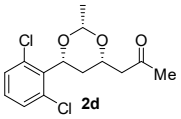
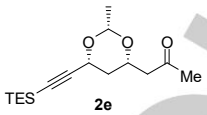
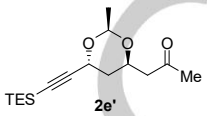
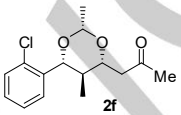
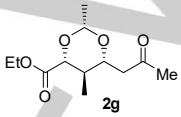
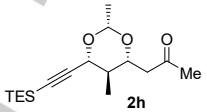
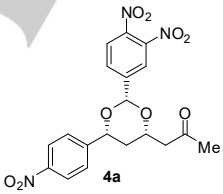
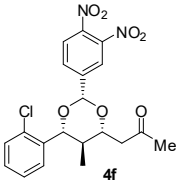
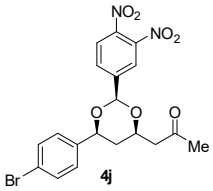

7

The aldol reaction of acetaldehyde with aromatic aldehyde proceeded well in DMF, catalyzed by diarylprolinol with trifluoromethyl substituent (entries 1–4, 10).[11a] Olefination also proceeded with Wittig reagent to provide 6-aryl-6-hydroxyhex-3-en-2-one in good yield with excellent enantioselectivity and high *E*-selectivity (entries 1–3). The reaction of triethylsilylpropinal or diphenylmethylsilylpropinal with acetaldehyde also proceeded in the presence of diarylprolinol in 1,4-dioxane to provide the desired α , β -unsaturated ketone in moderate yield with excellent *E*-selectivity and enantioselectivity after the Horner–Wadsworth–Emmons reaction (entries 5, 9).[11h, 15] It should be noted that the Horner–Wadsworth–Emmons reaction was employed in some cases because of the low yield of the corresponding Wittig reaction (entries 4, 5, 9, 10).

The aldol reaction of *o*-chlorobenzaldehyde and propanal was conducted in the presence of water without organic solvent, and catalyzed by surfactant and proline-conjugated catalyst **7**, which was developed in our group (entry 6).[16] Although proline catalyzes this aldol reaction, the *anti*/*syn* selectivity was not sufficient. As for the olefination reaction of the aldol product of propanal, Horner–Wadsworth–Emmons reagent was employed because of the higher reactivity and *anti*/*syn* selectivity (entries 6–8). All organocatalyst-mediated asymmetric aldol reactions and subsequent Wittig or Horner–Wadsworth–Emmons reactions proceeded successfully to provide δ-hydroxy α,β-unsaturated methyl ketone in good yield with excellent *E*-selectivity and excellent enantioselectivity in a one-pot operation.

Table 3. Hemiacetal formation/oxy-Michael reaction catalyzed by $Bi(OTf)_3$ and $NaClO_4$[a]



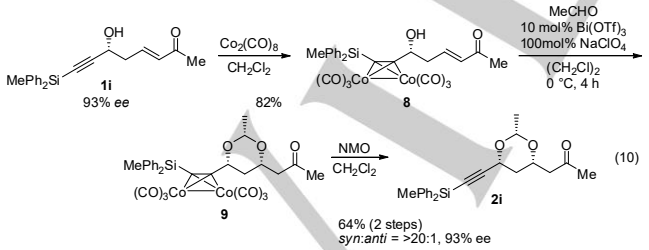
Entry	Product	Time [min]	dr[b]	Yield [%][c]
1[d]	 **2a**	10	>20:1	quant.
2	 **2b**	10	>20:1	quant.
3	 **2c**	10	>20:1	quant.
4	 **2d**	10	>20:1	quant.
5	 **2e**  **2e'**	15	1:1	quant.
6	 **2f**	10	>20:1[e]	quant.
7	 **2g**	90	>20:1[f]	77
8	 **2h**	10	>20:1[g]	70
9[h]	 **4a**	90	>20:1	73
10[h]	 **4f**	40	>20:1[e]	79
11[h]	 **4j**	120	>20:1	65

[a] Unless noted otherwise, reaction was performed by employing δ-hydroxy α,β-unsaturated methyl ketone (0.3 mmol), acetaldehyde (6.0 mmol), $Bi(OTf)_3$ (0.03 mmol), and $NaClO_4$ (0.3 mmol) in solvent $(CH_2Cl)_2$ (3 mL) at room temperature for the indicated time. [b] Diastereomer ratio of the newly generated chiral center was determined by ^1H NMR. [c] Isolated yield of methyl ketone. [d] The enantiomeric excess of the product was 96% ee. [e] *anti*:*syn* Ratio of the starting material is 9.6:1 and the final compound also possess same *anti*:*syn* diastereomer. [f] *anti*:*syn* Ratio of the starting material is 9.9:1 and the final compound also possesses same *anti*:*syn* diastereomer. [g] As *anti*:*syn* ratio of the starting material is >10:1 and the final compound

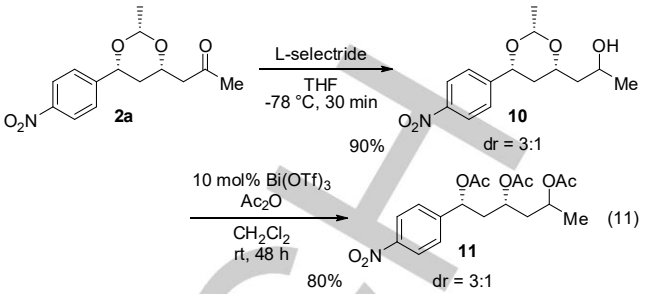
also possess same *anti:syn* diastereomer. [h] 3,4-Dinitrobenzaldehyde (0.36 mmol) was employed instead of acetaldehyde.

Given that δ-hydroxy α,β-unsaturated methyl ketones were obtained with excellent enantioselectivity, the generality of the second-pot reaction involving hemiacetal formation/oxy-Michael reaction for the formation of the 1,3-*syn*-diol unit was investigated (Table 3). As for the δ-substituent of the δ-hydroxy α,β-unsaturated methyl ketone, not only *p*-nitrophenyl but also *o*-chlorophenyl, *m*-nitrophenyl, and 2,6-dichlorophenyl were also suitable substituents, affording the 1,3-*syn*-adducts **2** with excellent diastereoselectivity in 10 minutes (entries 1–4). In the reaction of the alkynyl substituent, two diastereomers **2e** and **2e′** are generated. The stereochemistry was determined by ^{1}H-NMR spectroscopic analysis after reduction of the alkyne moiety (entry 5). For substrates with *anti* γ-methyl δ-hydroxy α,β-unsaturated ketones, excellent 1,3-*syn* chiral induction was observed, with the generation of three contiguous chiral centers with excellent diastereoselectivity. In this case, as for the δ-substituent, *p*-chlorophenyl, ethoxycarbonyl, and alkynyl were successfully employed to provide the synthetically useful chiral 1,3-diol with a 2-methyl substituent with excellent diastereoselectivity (entries 6–8). δ-Hydroxy α,β-unsaturated methyl ketones **1** react with not only acetaldehyde, but also 3,4-dinitrobenzaldehyde to provide the corresponding 1,3-*syn* products **4a**, **4f**, and **4j** with excellent diastereoselectivity (entries 9–11).

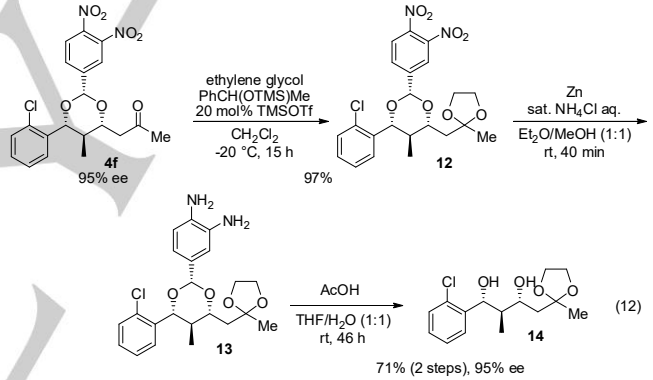
The diastereoselectivity of substrate **1e**, derived from alkynyl aldehyde and acetaldehyde, was not satisfactory (Table 3, entry 5). This is likely because of the small substituent of the alkynyl moiety.[17] To increase the diastereoselectivity, the reaction with alkyne cobalt complex[18] **8** was examined; the latter was easily prepared from the corresponding alkyne **1i** in good yield (Eq. 10). The domino acetalization and oxy-Michael reactions proceeded smoothly with excellent diastereoselectivity. 1,3-*syn*-Diol **2i** was obtained in 64% yield with 93% ee as a single isomer from **8** over two steps after removal of the cobalt moiety by treatment with NMO,[19] without decreasing the enantioselectivity during these transformations.



We then investigated the transformation of the 1,3-dioxane moiety into the 1,3-diol unit. There are several methods for the deprotection of ethylidene acetal.[20] Reduction of ketone with L-selectride afforded alcohol **10**, which was treated with Ac_2O and a catalytic amount of $Bi(OTf)_3$ to give triacetoxy derivative **11** in 80% yield (Eq. 11).



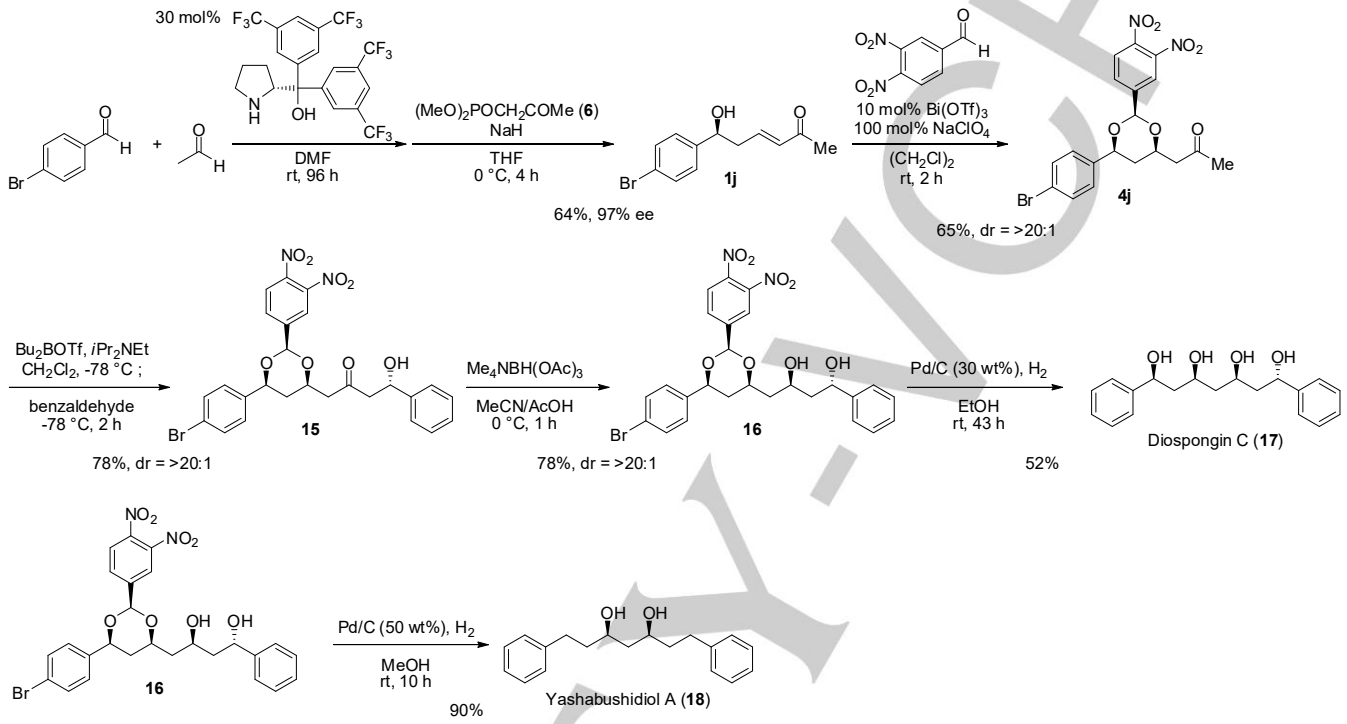
In general, rather strong acidic conditions are necessary to deprotect ethylidene acetal, which causes problems in the presence of acid-labile functional groups. Compared with ethylidene acetal, (3,4-dinitrophenyl)methylidene acetal[21] can be removed under milder acidic conditions after conversion of the nitro moiety into amine by reduction. For instance, **4f** was converted into the corresponding 1,3-dioxolane **12**,[22] and reduction of **12** with Zn provided diamine **13**. Acid treatment of **13** with AcOH afforded diol **14** in 71% yield over two steps, without decreasing the enantioselectivity (Eq. 12). It should be noted that the 1,3-dioxolane moiety is inert under these reaction conditions.



We then applied our new synthetic method for the generation of the 1,3-*syn*-diol unit to the total syntheses of diospongin C (**17**)[23] and yashabushidiol A (**18**).[24] These compounds are members of the biaryl heptanoid class of natural products and the former has been reported to exhibit antiosteoporotic activity,[23] whereas the latter has shown significant antiproliferative activity on human leukemia and melanoma cell lines.[24]

The synthesis started from the asymmetric aldol reaction of *p*-bromobenzaldehyde and acetaldehyde catalyzed by diarylprolinol to afford β-hydroxyaldehyde, which was treated with dimethyl 2-oxopropylphosphonate **6** to afford γ-hydroxy-α,β-unsaturated ketone **1j** in 64% yield with 97% ee in a one-pot operation (Scheme 1). When benzaldehyde was employed instead of *p*-bromobenzaldehyde in this first reaction, the yield was not satisfactory (20%). Domino acetalization and oxy-Michael reaction proceeded smoothly when **1j** was treated with 3,4-dinitrobenzaldehyde in the presence of $NaClO_4$ and a catalytic amount of $Bi(OTf)_3$ to provide **4j** with excellent diastereoselectivity (dr = >20:1). 1,5-Asymmetric induction was observed in the aldol reaction of **4j** with benzaldehyde under the conditions developed by D. A. Evans[25] to afford **15** in 78% with excellent diastereoselectivity. 1,3-*anti*-Reduction was

conducted with $Me_4NBH(OAc)_3$ by using D. A. Evans' protocol[26] to provide diol **16** in 78% yield. Reduction of the nitro group and Br to amine and H, respectively, was catalyzed by Pd/C (30 wt%) under H_2 atmosphere, and subsequent deprotection of the acetal moiety occurred in the same pot to afford diospongin C (**17**) in 52% yield. When the reaction of diol **16** was performed in the presence of Pd/C (50 wt%), further reduction at the benzylic hydroxyl group occurred to provide yashabushidiol A (**18**) in 90% yield.



Scheme 1. Syntheses of diospongin C and yashabushidiol A

Conclusions

We have established a two-pot synthesis of the chiral 1,3-*syn*-diol unit. In the first pot, chiral δ-hydroxy α,β-unsaturated ketones are synthesized by the asymmetric direct aldol reaction of two different aldehydes catalyzed by organocatalyst, followed by either Wittig or Horner–Wadsworth–Emmons reactions. In the second pot, domino acetalization and oxy-Michael reactions proceed in the presence of $NaClO_4$ and a catalytic amount of $Bi(OTf)_3$ to provide chiral 1,3-*syn*-diols with excellent diastereoselectivities. This two-pot synthesis of 1,3-*syn*-diols has a wide generality and generates several synthetically useful chiral building blocks efficiently. Diospongin C and yashabushidiol A are synthesized with excellent diastereo- and enantioselectivities by applying the present synthesis of the 1,3-diol unit as a key step as well as 1,5- and 1,3-asymmetric inductions.

Experimental Section

The typical procedure of asymmetric aldol / Wittig reaction (Table 2, Entry 1): To a mixture of (*S*)-2-(bis-[3,5-bis(trifluoromethyl)phenyl]hydroxymethyl) pyrrolidine (26 mg, 0.05 mmol), DMF (0.50 mL) and 4-nitrobenzaldehyde (76 mg, 0.50 mmol) was added acetaldehyde (110 mg, 2.5 mmol) in the sealed test tube (IWAKI, product number TE-32) at 6 °C. After the reaction mixture was stirred for 72 hours at room temperature, acetylmethylene triphenylphosphorane (478 mg, 1.5 mmol) was added. The resulting suspension was stirred for 2 h at 50 °C. Upon completion of the Wittig reaction, the reaction mixture was passed through a short silica gel pad, and concentrated *in vacuo*. Purification by silica gel column chromatography (ethyl acetate: hexane = 1 : 1) gave corresponding α,β-unsaturated ketone **1a** in 81% yield. The enantiomeric excess was determined by HPLC with a CHIRALCELL AS-H column (*i*PrOH : hexane = 1 : 10, λ = 214 nm; flow rate: 1.0 mL / min; minor enantiomer t_R = 54.3 min, major enantiomer t_R = 61.5 min).

The typical procedure of hemiacetal/oxy-Michael reaction (Table 3, Entry 1): To a mixture of a δ-hydroxy-α,β-unsaturated ketone **1a** (70.6 mg, 0.3 mmol) and acetaldehyde (264.3 mg, 6 mmol) in 1,2-dichloroethane (3.0 mL) in the sealed test tube (IWAKI, product number TE-32) was added $NaClO_4$ (36.7 mg, 0.3 mmol) and $Bi(OTf)_3$ (19.7 mg, 0.03 mmol). After the reaction mixture was stirred for 10 min at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the organic materials were extracted with ethyl acetate three times. The combined organic layer was dried by Na_2SO_4, filtrated and concentrated *in vacuo*. Purification by silica gel column chromatography (ethyl acetate:

hexane = 1 : 3) afforded the acetal **2a** in quantitative yield with excellent diastereoselectivity (>20 : 1).

Acknowledgements

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Keywords: organocatalyst • Michael reaction • 1,3-diol • asymmetric synthesis • diastereoselective reaction

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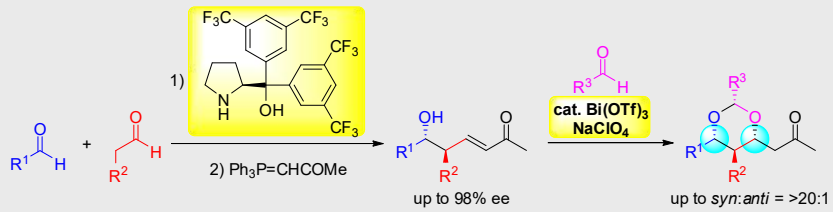

2 pot synthesis of chiral 1,3-*syn*-diol unit

Yujiro Hayashi, Takanobu Saitoh, Hiromu Arase, Genki Kawauchi Naohiro Takeda, Yasuharu Shimasaki, Itaru Sato*

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Two-pot synthesis of chiral 1,3-*syn*-diols through asymmetric organocatalytic aldol and Wittig reactions, followed by domino hemiacetal/oxy-Michael reactions

A two-pot synthetic method to construct the chiral *syn*-1,3-diol unit has been developed from three aldehydes and Wittig reagent using organocatalyst mediated aldol reaction, $Bi(OTf)_3$ mediated domino acetalization, and oxy-Michael reaction as key steps.