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A short and enantioselective preparation of taxol A-ring fragment

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ABSTRACT

Two short preparations of the taxol A-ring fragment are described: one via organocatalyzed α-aminoxylation and the other via Sharpless asymmetric dihydroxylation (SAD). The former approach affords the A-ring fragment in 10 steps, and the latter approach involves eight steps to afford the new A-ring fragment in 91% ee, which is made enantiomerically pure through recrystallization. The new A-ring fragment bearing a bromoalkene is confirmed to be useful to form the carbocyclic eight-membered ring of a taxol model compound by palladium-catalyzed intramolecular alkenylation. The preparation of the new A-ring fragment will be beneficial for the total synthesis of taxol as well as other natural products

Taxol (Fig. 1) is an intriguing and synthetically challenging compound because of its complex structure and clinically important anticancer activity.[1–7] Although six total syntheses and one formal synthesis have been reported thus far, the distinguished structure and bioactivity of taxol still draw the attention of synthetic chemists.[8,9]

We have reported the enantioselective synthesis of compound **2** (Scheme 1),[8a] which contains the taxol A–B ring system, via the construction of an eight-membered ring through the palladium-catalyzed intramolecular alkenylation of methyl ketone **1**, which proceeded with excellent yield (96%). Although a benzene ring was used as a substitute for the C-ring moiety of taxol, this reaction would be potentially useful for the construction of the taxol B-ring.

However, one problem to be solved in this strategy is how to decrease the number of steps in preparing the A-ring fragment **4** (Scheme 2), because this requires 16 steps from the commercially available compound **3**.[8b]

Compound **4** was expected to be prepared from **5** (Scheme 3), which could be obtained through α-oxygenation of aldehyde **6**. Recent progress in organocatalysis suggests that chiral α-hydroxyaldehydes can be obtained via the proline- or its derivative-catalyzed α-aminoxylation of aldehyde with nitrosobenzene in high ee.[10] For example, the catalytic asymmetric α-aminoxylations of aldehydes using proline and nitrosobenzene, which were reported independently by Zhong,[11] MacMillan,[12] and Hayashi,[13] are useful methods for the preparation of chiral α-hydroxyaldehydes. However, to the best of our knowledge, the organocatalytic asymmetric α-oxygenation of α-branched aldehydes is limited. Jang and co-workers[14a] described the (*S*)-proline-catalyzed α-aminoxylation of an α-branched aldehyde (58%, 37% ee) in their report on prolinamide-catalyzed direct nitroso aldol reactions. Kim et al.[14b] reported the catalytic asymmetric α-hydroxyamination and α-aminoxylation of α-branched aldehydes using (*S*)-proline and its derivatives, and obtained α-hydroxyamination adducts with up to 90% ee. However, they obtained a mixture of α-hydroxyamination and α-aminoxylation products, and the ee of the α-aminoxylation products did not exceed 45%, probably because the enamine formed in situ through the organocatalytic reaction would be a mixture of geometric isomers. Recently, List and co-workers[14c] reported the organocatalytic asymmetric α-benzoyloxylation of α-branched aldehydes and enals, which afford α-benzoyloxy aldehydes in good yields and enantioselectivity. Unfortunately, this protocol cannot be applied for the preparation of **5** from **6**, because **5** decomposes via fragmentation under the reaction conditions for the removal of benzoate.

The enamine of aldehyde **6** with (*R*)-proline would prefer the *E*-isomer **8** (Scheme 4) owing to the steric repulsion between the

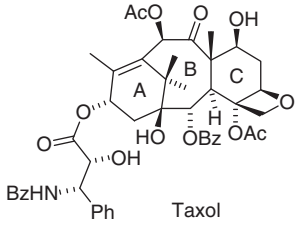

Figure 1. Structure of taxol.

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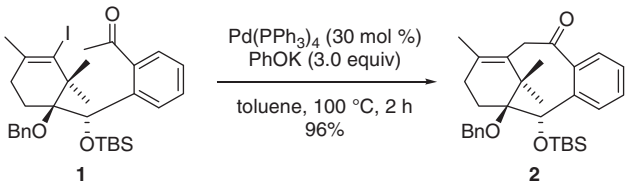
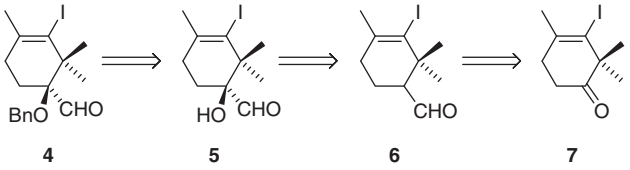
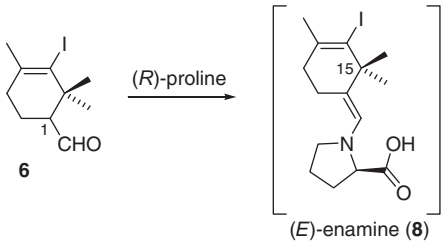


Scheme 1.

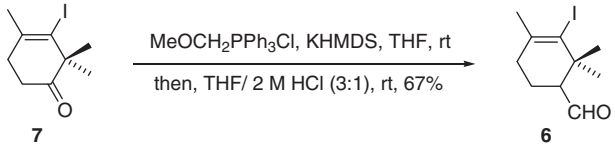
Scheme 2.



Scheme 3.



Scheme 4.

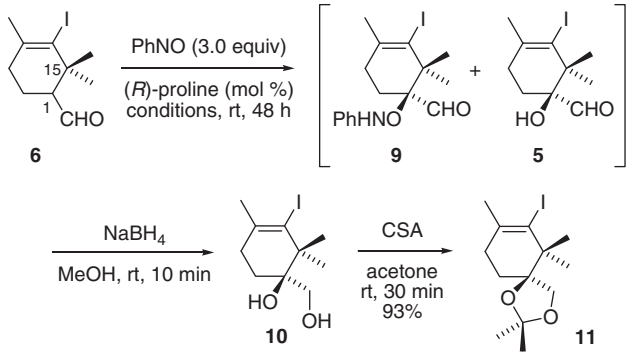


Scheme 5.

organocatalyst and the C15 quaternary carbon, and high enantioselectivity is expected. However, the α-aminoxylation of **6** is suspected to be slow because the C1 position is sterically hindered by the adjacent C15 quaternary carbon. Nonetheless, the enantioselective direct installation of an oxygen atom at the C1 position is attractive. Hence, for the exploration of the possibility of utilizing the α-aminoxylation of **6** to establish short access to **4**, the organocatalyzed asymmetric α-aminoxylation of **6** was examined.

Aldehyde **6** was obtained by the reaction of **7** with methoxymethylidene triphenylphosphorane and subsequent one-pot acid hydrolysis in 67% yield (Scheme 5). With **6** in hand, the organocatalyzed catalytic asymmetric α-aminoxylation of **6** was examined (Table 1). Considering the mechanism of the proline-catalyzed α-aminoxylation of **6** with nitrosobenzene, (*R*)-proline was used

Table 1
(*R*)-Proline-catalyzed α-aminoxylation of **6** with nitrosobenzene



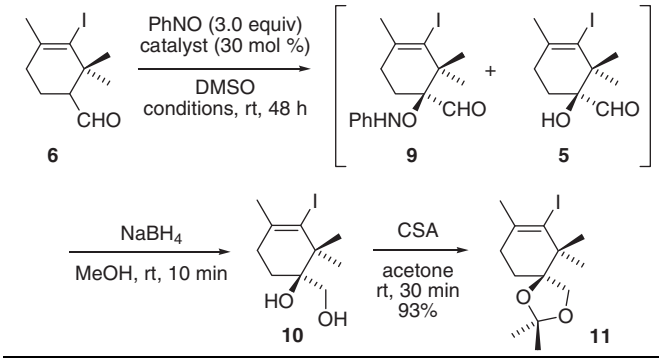
Entry	Catalyst (mol %)	Solvent	Yield[a] (%) **10**	ee[b] (%) **11**
1	10	DMSO	11	52
2	30	DMSO	45	86
3	100	DMSO	45	86
4	30 + 30[c]	DMSO	25	84
5	30	DMSO[d]	51	75
6	30	DMSO, additive[e]	23	—
7	30	DMF	22	75
8	30	NMP	20	79
9	30	MeCN	11	16
10	30	$MeNO_2$	Trace	—
11	30	CH_2Cl_2	5	38
12	30	$CHCl_3$	0	—
13	30	$(CH_2Cl)_2$	0	—
14	30	1,4-Dioxane	0	—
15	30	THF	0	—
16	30	EtOAc	0	—

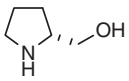
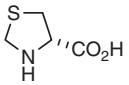
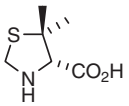
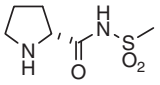
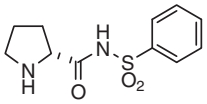
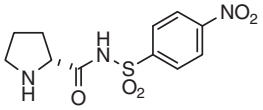
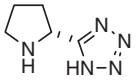
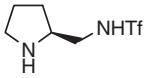
[a] Isolated yields.
[b] ee determined by HPLC (254 nm); CHIRALPAK OD-H, 0.46 cm $\varphi \times 25$ cm, hexane/*i*-PrOH = 300:1, 0.2 mL/min, 23.7 min (***ent*-11**), 25.5 (**11**).
[c] Another 30 mol % of (*R*)-proline was added after 24 h.
[d] The reaction was carried out at 50 °C.
[e] 1-(2-(Dimethylamino)ethyl)-3-phenylurea (30 mol %) was used.

to obtain the desired enantiomer. The reaction of **6** with nitrosobenzene (3.0 equiv) in the presence of 10 mol % of (*R*)-proline in DMSO at room temperature for 48 h afforded a mixture of **9** and **5** (entry 1). An extended reaction time did not improve the yield. The obtained mixture was reduced with $NaBH_4$ in a one-pot manner to give **10** in 11% yield (two steps). The ee of the product was 52%, as determined by HPLC analysis of the corresponding acetonide **11**. The use of 30 mol % of (*R*)-proline improved the yield and ee to 45% and 86%, respectively (entry 2), but the yield was not improved by an extended reaction time. The use of 100 mol % of (*R*)-proline did not change the yield and ee (entry 3), and the addition of another 30 mol % of (*R*)-proline after 24 h reduced the yield (entry 4). The reaction at 50 °C improved the yield slightly, but reduced the ee (entry 5). The use of the additive (1-(2-(dimethylamino)ethyl)-3-phenylurea),[15] which was reported to increase the rate of proline-catalyzed α-aminoxylations, was also ineffective (entry 6). The reactions were also examined in a variety of solvents; however, no improvement was observed (entries 7–16).

The organocatalyzed asymmetric α-aminoxylation of **6** was further examined using other catalysts (Table 2). The yield and the ee of the products were determined according to the method used in Table 1. The reactions in the presence of 30 mol % of **12**,[16a] **13**,[16b] **14**,[16c] and **15**[16e] gave no products (entries 1–4). The reactions using **16**[16e] and **17**[16d] afforded the desired products, but the yield and the ee were low (entries 5 and 6). The reaction with **18**,[16e,17] the acidity of which in a polar solvent is comparable to that of carboxylic acid, and subsequent reduction afforded **10** in 53% yield and with 85% ee (entry 7). Although the ee (85%) was almost the same as that in

Table 2
Organocatalyzed α-aminoxylation of **6** with nitorosobenzene using **12–19**



Entry	Catalyst (30 mol %)		Yield[a] (%) **10**	ee[b] (%) **11**
1		**12**	0	–
2		**13**	0	–
3		**14**	0	–
4		**15**	0	–
5		**16**	15	59
6		**17**	21	20
7[c]		**18**	53	85
8		**19**	28	−94[d]

[a] Isolated yields.
[b] ee determined by HPLC. For the conditions, see footnote to Table 1. For the determination of absolute configuration of **11**, see Ref. 19.
[c] 100 mol % of catalyst was used.
[d] Minus sign means ***ent*-11**.

entry 2 of Table 1, the yield (53%) was improved from 45%. The ee of the reaction catalyzed by **19**[18] afforded the product with 94% ee, but the yield was only 28%.

Considering both the yield and the ee of **10**, the conditions in entry 7 could be utilized for the preparation of the A-ring fragment because compound **10** has been converted into **4**, which is crystalline and its ee can be improved by recrystallization.[19] Compound **7** (Scheme 5) was prepared from commercially available compounds in five steps;[20] therefore, the number of synthetic steps required for the preparation of **4** was reduced to 10 steps from commercially available compounds, because compound **10** is converted into **4** in three steps (benzylidene formation, reductive cleavage of the benzylidene by DIBAL-H, and Dess–Martin oxidation).[8b]

The yield of the organocatalyzed α-aminoxylation of **6** with nitrosobenzene is unsatisfactory. Hence, we explored another possibility for the short preparation of the A-ring fragment **4**.

We first examined the Sharpless asymmetric dihydroxylation (SAD) of **24** (Table 3), which was prepared by the Wittig reaction of **7** ($Ph_3P{=}CH_2$, THF, reflux, 83%). The SAD of **24** using a catalytic amount of $(DHQ)_2PHAL$ and $K_2OsO_2{\cdot}2H_2O$ afforded **25** in 83% yield, but the ee was low (45% ee) (entry 1). The SAD of **24** using DHQ-PHN improved the ee; however, 76% ee was unsatisfactory (entry 2). Therefore, we decided to examine the SAD of silyl enol ether of **6**, which was expected to give good results, because the highly enantioselective SAD of a similar compound has been reported by Kuwajima and co-workers.[21]

In addition, we examined the SAD of silyl enol ether of **23** because **23** was prepared in three steps from commercially available compounds. That is, the Diels–Alder reaction of commercially available **20** and acryloyl chloride afforded **21**,[22] which was converted into aldehyde **23** via **22** (Scheme 6).[23]

TIPS enol ether **24a** was prepared as a single and stable (*E*)-isomer from **6**.[24] The SAD of **24a** using a catalytic amount of $(DHQ)_2PHAL$ (Fig. 2) and $K_2OsO_2{\cdot}2H_2O$ under the conditions given in Table 3 afforded **25a** in 86% yield and with 24% ee (entry 3). The use of an increased amount of $(DHQ)_2PHAL$ (10.0 mol %) did not improve the ee (entry 4), and reaction at 0 °C reduced the yield (entry 5).

The use of $(DHQ)_2PHAL$ resulted in a low ee; hence, the reaction using another ligand, Q-PHN (Fig. 2), was performed. As a result, the reaction proceeded faster than that using $(DHQ)_2PHAL$ and was completed after 26 h to afford **25a** in 71% yield with 85% ee (entry 6).

The SAD of a similar TIPS enol ether using DHQ-PHN (Fig. 2) was reported to afford the product with high yield and ee.[21] Hence, the SAD of **24a** using a catalytic amount of DHQ-PHN and $K_2OsO_2{\cdot}2H_2O$ was examined. The yield and the ee were slightly improved (entry 7) and the reaction was completed faster (12.5 h) than that with Q-PHN (26 h). The SAD of **24a** using DHQ-PHN (15.0 mol %) and $K_2OsO_2{\cdot}2H_2O$ (5.0 mol %) gave **25a** with 91% ee, but the yield was 64% (entry 8).

The SAD of **24b** was also examined using DHQ-PHN (15.0 mol %) and $K_2OsO_2{\cdot}2H_2O$ (5.0 mol %). The reaction was completed after 20 h to afford **25b** in 78% yield and with 88% ee (entry 9). Finally, the reaction with DHQ-PHN (10.0 mol %) and $K_2OsO_2{\cdot}2H_2O$ (5.0 mol %) afforded **25b** in 92% yield and with 91% ee (entry 10), which was reproducible in a gram-scale reaction.

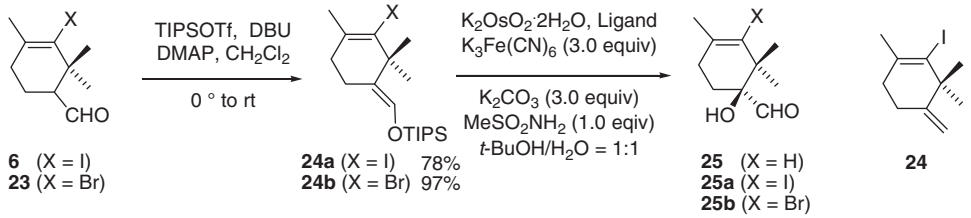
Compound **25b** was subjected to benzylidene formation to afford **26** (Scheme 7), followed by regioselective cleavage of benzylidene acetal by DIBAL-H, and subsequent Dess–Martin oxidation gave **27**. Gratifyingly, **27** was crystalline and an enantiomerically pure compound was obtained through recrystallization.[25]

Compound **27** was prepared from **20** in eight steps. Hence, the preparation of **27** via SAD could be the shortest preparation of our A-ring fragment. However, we must confirm whether methyl ketone **31** (Scheme 8), which could be prepared from **27**, is converted into **2** via palladium-catalyzed intramolecular alkenylation.

Compound **27** was converted into **31** and its palladium-catalyzed reaction was examined as follows. The reaction of **27** with lithiated **28** afforded **29** as a single isomer. This was followed by TBS formation, removal of ethoxyethyl ether, and Dess–Martin oxidation to give aldehyde **30**. The reaction of **30** with methylmagnesium bromide and subsequent Dess–Martin oxidation afforded methyl ketone **31**. The palladium-catalyzed intramolecular alkenylation of **31** was performed under the same conditions used for the reaction of compound **1**. As a result, **31** was converted successfully into **2** in 95% yield, which was comparable to the yield of the reaction of **1**, though the reaction required 4 h for completion.

In summary, two short preparations of the A-ring fragment of taxol, via organocatalyzed α-aminoxylation and Sharpless asymmetric dihydroxylation (SAD), were studied. The former approach afforded the A-ring fragment in 10 steps and the latter in eight

Table 3
Sharpless asymmetric dihydroxylation of **24**, **24a**, and **24b**



6 (X = I)
23 (X = Br)

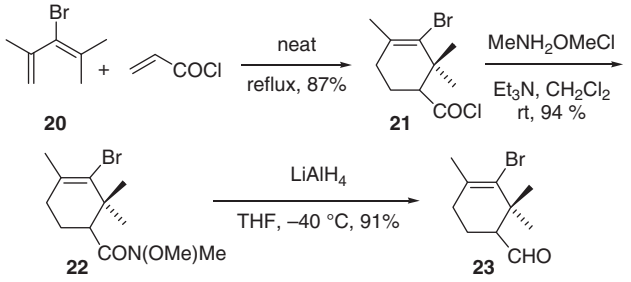
24a (X = I) 78%
24b (X = Br) 97%

25 (X = H)
25a (X = I)
25b (X = Br)

24

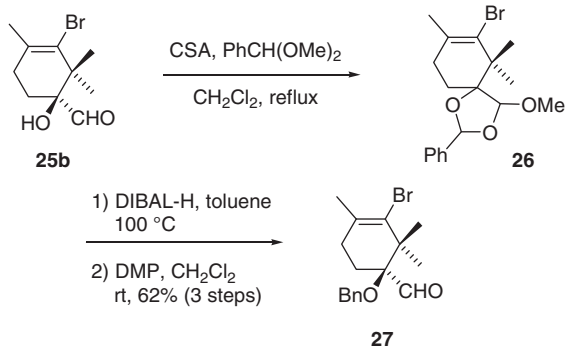
Entry	Substrate	Ligand (mol %)	$K_2OsO_2·2H_2O$ (mol %)	Temp (°C)	Time (h)	Yield[a] (%)	ee (%)
1	**24**	$(DHQ)_2PHAL$ (15.0)	5.0	0	3	83	45[b,c]
2	**24**	DHQ-PHN (15.0)	5.0	0	1.5	96	76[b,c]
3	**24a**	$(DHQ)_2PHAL$ (5.0)	2.5	rt	14	86	24[c,d]
4	**24a**	$(DHQ)_2PHAL$ (10.0)	2.5	rt	15	99	33[c,d]
5	**24a**	$(DHQ)_2PHAL$ (10.0)	2.5	0	50	59	45[c,d]
6	**24a**	Q-PHN (10.0)	2.5	0	26	71	85[c,d]
7	**24a**	DHQ-PHN (10.0)	2.5	0	12.5	73	87[c,d]
8	**24a**	DHQ-PHN (15.0)	5.0	0	18	64	91[c,d]
9	**24b**	DHQ-PHN (15.0)	5.0	0	20	78	88[e]
10	**24b**	DHQ-PHN (10.0)	5.0	0	35	92	91[e]

[a] Isolated yields.
[b] The product was oxidized to **25a** by Dess–Martin periodinane, which was used to determine the ee by HPLC. The HPLC (254 nm) analysis also confirmed the absolute configuration of **25** as shown above.
[c] CHIRALPAK IC, 0.46 cm $\varphi \times 25$ cm, hexane/*i*-PrOH = 19:1, 0.3 mL/min, 20.2 (***ent*-25a**), 22.0 (**25a**).
[d] Compound **25a** was converted into compound **11** to determine its absolute configuration by HPLC, which also confirmed the absolute configuration of **25a** shown above. For the conditions, see footnote to Table 1.
[e] Compound **25b** was converted into **27** for HPLC (254 nm); CHIRALCEL AS-H, 0.46 cm $\varphi \times 25$ cm, hexane/*i*-PrOH = 19:1, 0.3 mL/min, 17.8 (**27**), 21.7 (***ent*-27**). For the determination of absolute configuration of **27**, see Ref. 25.



Scheme 6.

steps. The organocatalyzed α-aminoxylation afforded the desired product with up to 86% ee (94% ee when ***ent*-19** is used), but the yield requires improvement. The SAD approach afforded the new A-ring fragment with 91% ee, which was made enantiomerically pure through recrystallization. The new A-ring fragment bearing a bromoalkene was confirmed to be useful for the palladium-catalyzed intramolecular alkenylation to form the carbocyclic eight-membered ring. The preparation of the new A-ring fragment will be beneficial to the total synthesis of taxol as well as other natural products.



Scheme 7.

Acknowledgments

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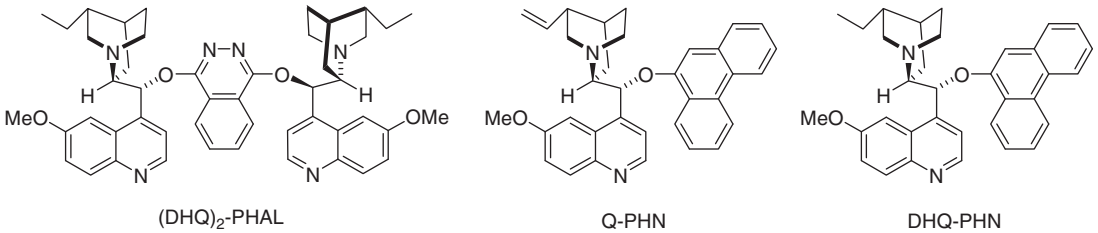
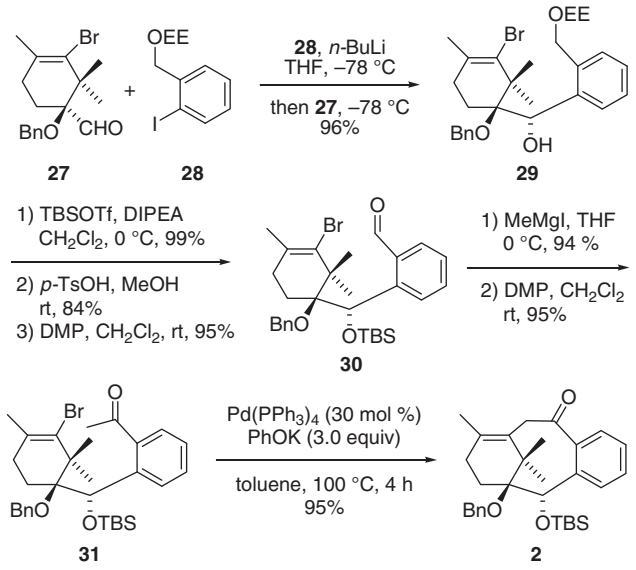


Figure 2. Structures of $(DHQ)_2$-PHAL, Q-PHN, and DHQ-PHN.



Scheme 8.

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19. *Compound* ***4****:* mp = 104–105 °C (recrystallization from hexane); R_f = 0.63 (hexane/EtOAct = 4/1); IR (KBr) ν_{max} 1724, 1458, 1094, 1049, 899, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.39–7.26 (m, 5H), 4.56 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 2.35–2.21 (m, 2H), 2.17–2.09 (m, 1H), 2.04–1.98 (m, 1H), 1.91 (s, 3H), 1.38 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 138.2, 137.1, 128.3, 127.5, 126.8, 114.2, 83.4, 66.2, 45.6, 30.9, 29.4, 27.5, 26.6, 20.8; HRMS (FAB) $[M+H]^+$ calcd for $C_{17}H_{22}O_2I$, 385.0664, found 385.0676; $[\alpha]_D^{32}$ +57.7 (*c* 1.03, $CHCl_3$, >99% ee). The plus sign in specific rotation of **4**, which was derived from **10**, was the same as that of the previously prepared **4** via baker's yeast reduction,[8b] indicating that the absolute configuration of **10** is as shown in Table 1.
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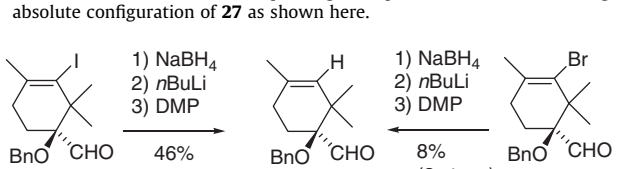
23. Rosemund reduction of **21** afforded **23**. However, the yield (71%) was inferior to the two-step sequence in Scheme 6 (86%, two steps) because reduction of the C–Br bond in **21** took place during the palladium-catalyzed reduction.
24. (*E*)-TBDPS enol ether of **6** was also prepared and subjected to the SAD, but the reaction proceeded very slowly at room temperature and only 17% of **25a** with 28% ee was formed after 12 h.
25. *Compound* ***27****:* mp = 92–93 °C (recrystallization from hexane, 39% from **27** (91% ee)); IR (neat) ν_{max} 2196, 1980, 1728, 1458, 1365, 1092, 1028, 904, 735, 696, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.41–7.20 (m, 5H), 4.56 (d, J = 11.7 Hz 1H), 4.40 (d, J = 11.7 Hz 1H), 2.29–2.17 (m, 2H), 2.17–2.07 (m, 1H), 2.07–1.95 (m, 1H), 1.83 (s, 3H), 1.42 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 138.5, 129.0, 128.5, 127.7, 127.0, 84.5, 66.3, 45.2, 29.1, 25.2, 24.5, 20.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{21}O_2BrNa$, 359.0623, found, 359.0622; $[\alpha]_D^{16}$ +90.0 (*c* 1.72, $CHCl_3$, >99% ee). Compounds **4** (>99% ee)[8b] and **27** (91% ee) were converted into compound **32** as shown below. Both compounds were found to have the same plus sign in specific rotation, confirming the absolute configuration of **27** as shown here.



from **4:** $[\alpha]_D^{22}$ +38.0 (*c* 0.10, $CHCl_3$)
from **27:** $[\alpha]_D^{22}$ +35.3 (*c* 0.17, $CHCl_3$)