Sequential Asymmetric Hydrogenation of Symmetric Bis-Cinnamic Acid Derivatives: Syntheses of the C_2-Symmetric Core Units of HIV Protease Inhibitors

Takayuki Doi, Kazunori Hirabayashi, Masaya Kokubo, Toshikazu Komagata, Keiji Yamamoto,* and Takashi Takahashi*

Department of Chemical Engineering, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152, Japan

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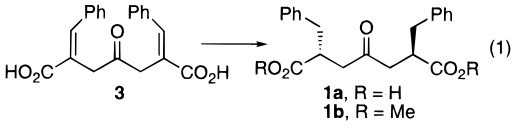
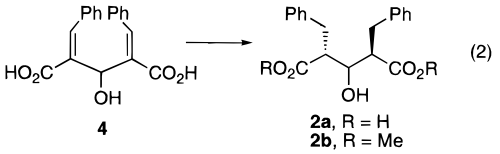
Asymmetric hydrogenation has been regarded as a synthetically useful and yet simple manipulation. Rhodium(I) and ruthenium(II) complexes with certain chiral bidentate phosphines are well known catalysts used to perform asymmetric hydrogenations with high enantiomeric bias.[1] Herein, we wish to report an approach to generate the chiral C_2-symmetric molecules **1a** and **2a** by sequential asymmetric hydrogenation of prochiral bis-cinnamic acid derivatives **3** and **4**, respectively, in one operation (eqs 1 and 2). The products **1a** and **2a** are the





C_2-symmetric core unit of the of HIV protease inhibitors[2] such as L-700,417[2a] and A-74704,[2b,c] respectively (Figure 1). They are not as effective as nonsymmetric inhibitors at the present time. Recently, however, the C_2-symmetric cyclic urea DM-323 has been reported as an effective inhibitor.[2d,e] Therefore, a method for preparing the C_2-symmetric core units in a chiral fashion would be useful in exploring new inhibitors. We expected that if each step of the sequential asymmetric hydrogenation of the symmetric dienes **3** and **4** occurred *independently*, the overall reaction could be performed with good overall asymmetric induction.[3−5] Thus, even though the asymmetric induction for each hydrogenation is moderate, for example, 60% ee (A:B = 4:1), the second hydrogenation

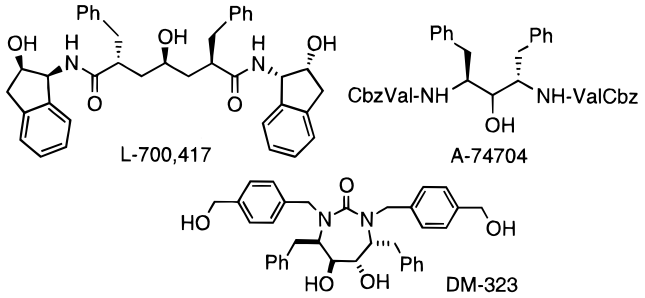
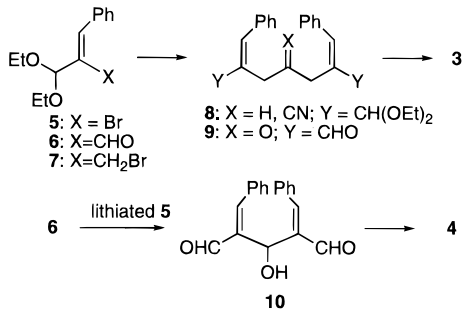


Figure 1.

Scheme 1



step would convert a portion of the minor enantiomer, formed by the initial hydrogenation step, into a meso compound. Therefore, the enantiomeric purity of the dually hydrogenated product would be enhanced to 88% ee (A^2:B^2 = 16:1) at the expense of the formation of the meso byproducts.

The bis-cinnamic acids **3** and **4** were prepared as shown in Scheme 1. Lithiation of (*Z*)-2-bromocinnamaldehyde diethyl acetal (**5**)[6] (BuLi, hexane), followed by the addition of DMF, provided enal **6** in 92% yield. Reduction ($NaBH_4$, MeOH) of **6** and bromination (MsCl, NEt_3, LiBr, THF) of the resulting allylic alcohol gave the allylic bromide **7** in 75% overall yield. Dialkylation by addition of $KN(TMS)_2$ (1.1 equiv for **7**) to a mixture of **7** and acetonitrile (0.58 equiv for **7**) in ether at 0 °C gave the adduct **8** in 86% yield.[7] The nitrile **8** was converted to the oxo bis-enal **9** in 71% yield by α-peroxidation−reduction[8] and hydrolysis ($LiNEt_2$, THF; O_2; $P(OEt)_3$; aqueous HCl; aqueous $NaHCO_3$). Oxidation ($NaClO_2$, NaH_2PO_4, *t*-BuOH−H_2O, 2-methyl-2-butene)[9] of the oxo bis-enal **9** afforded the desired oxo diacid **3** in 78% yield, which was purified by recrystallization from 2-propanol. The acid **4** was prepared starting from **5** and **6** as follows. Addition of lithiated **5**, shown above, to the enal **6** followed by hydrolysis ($CuSO_4$, MeOH−H_2O, 40 °C)[10] gave the bis-enal **10** in 53% yield. The oxidation[9] of **10** to diacid **4** (81%) was performed in the same manner as the preparation of **3** from **9**.

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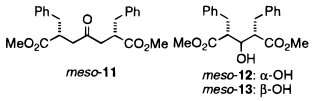
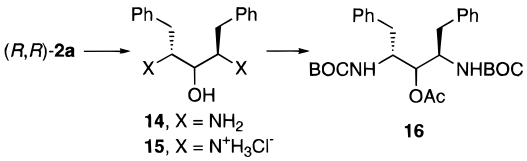
Table 1. Sequential Asymmetric Hydrogenation of 3 and 4

entry	compd	*T*/°C	H_2/atm	time/h	yield[c,d]/%		ratio/% (% ee)				
1	**3**[a]	35	30	24	93	(*R*,*R*)-**1b**	71 (93):	*meso*-**11**	29		
2		35	50	24	91		73 (93):		27		
3		35	50	80	84	*e*	70 (90):		30		
4		35	70	24	81		70 (90):		30		
5		25	50	48	92		69 (90):		31		
6	**4**[b]	50	50	70	>95	(*R*,*R*)-**2b**	62 (70):	*meso*-**12**	35:	*meso*-**13**	3
7		50	70	70	>95		80 (88):		15:		5
8		50	90	90	>95		80 (94):		19:		1
9		30	55	160	>95		80 (72):		19:		1
10		30	90	240	>95		65 (91):		34:		1

[a] 3 mol % $Ru(OAc)_2$[(*S*)-BINAP], 2 equiv of NEt_3. [b] 10 mol % $Ru(OAc)_2$[(*S*)-BINAP], 2 equiv of NEt_3. [c] Combined yield of **1b** and **11**. [d] Combined yield of **2b**, **12**, and **13**. [e] The selectivity was determined after reoxidation.



Scheme 2



The hydrogenation of diacid **3**[11] using a $Ru(OAc)_2$[(*S*)-BINAP] complex proceeded at 35 °C in 24 h, and the stereoselectivity and enantiomeric excess of products were determined by those dimethyl esters (Table 1, entries 1−5).[12−14] Both the stereoselectivity and the enantiomeric excess for **1b** are quite insensitive to changes in hydrogen pressure (entries 1, 2, and 4). Furthermore, there was no change in selectivity when the reaction was carried out at 25 °C for 48 h (entry 5). Reduction of the keto group was also observed when the reaction mixture was kept at 35 °C for 80 h (entry 3).[15] We presume that each step of the sequential asymmetric hydrogenation occurs quite independently with an asymmetric induction to the extent of 64−68% ee. Consequently, (*R*,*R*)-**1b**[16] and *meso*-**11** are obtained in a ratio of 70:30, while the optical purity of **1b** is markedly enhanced, 90−93% ee, as compared with that expected from a single hydrogenation.

In the case of hydrogenation of **4**, the diastereoselection directed by a hydroxyl group (substrate control), in addition to the chiral catalyst control for the bis-cinnamic acid moiety shown above, may have a significant influence on the enantiomeric excess of the desired product **2**. Hydrogenation of diacid **4** using $Ru(OAc)_2$[(*S*)-BINAP] as a catalyst and esterification of the reaction mixture gave a mixture of (*R*,*R*)-**2b**,[16] *meso*-**12**, and *meso*-**13** (Table 1, entries 6−10).[14] Although we had to use 10 mol % of the catalyst to substrate **4**, due presumably to the steric hindrance around the alkene moieties of **4**, the reaction was completed after 70 h at 50 °C. The enantiomeric excess as well as diastereoselectivity of **2b** were found to be highly dependent on the hydrogen pressure (entries 6−8).[1] Thus, the best chiral induction for (*R*,*R*)-**2b** (80% selectivity, 94% ee in entry 8) is slightly better than that observed for **1b**. Therefore, the catalyst control for the bis-cinnamic acid moiety was observed to override the directed control by the hydroxyl group in this particular case. Moreover, the minor enantiomers of the diastereomeric products in the initial step of the sequential hydrogenation would be preferentially converted to the meso diastereomers **12** and **13** in the second step, respectively, owing to the stereochemical preferences in the double asymmetric processes. When the reaction was conducted at 30 °C, however, inferior diastereoselectivities were obtained (entries 9 and 10).

The Curtius rearrangement of **2a** (DPPA/NEt_3/DMAP, THF, reflux; $Ba(OH)_2$, dioxane/H_2O = 1/2, reflux) gave the diamine **14** in 50% yield with complete retention of configuration (Scheme 2).[17] The diamine was purified as a hydrochloric acid salt **15**, whose purity was analyzed by HPLC and ^1H NMR of the corresponding diBOC acetate **16**.[18]

In conclusion, we have demonstrated that sequential asymmetric hydrogenation of the symmetric dienes **3** and **4** is an attractive method for generating the chiral C_2-symmetric molecules corresponding to the core units of the inhibitors of HIV protease.

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Supporting Information Available: NMR spectra and characterization data (30 pages).

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(11) The chiral induction by the rhodium-catalyzed asymmetric hydrogenation of **3**, as an analog of β-arylitaconic acid, failed due to the steric hindrance of the alkene moiety of **3**; see: Christopfel, W. C.; Vineyard, B. D. *J. Am. Chem. Soc.* **1979**, *101*, 4406. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735.

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(13) It has been reported that the asymmetric hydrogenation of (*E*)-α-methylcinnamic acid by a $Ru(OAc)_2$[(*S*)-H_8-BINAP] complex proceeds with good enantioselectivity (82% ee), while $Ru(OAc)_2$BINAP complex affords only 35% ee; see: Zhang, X.; Uemura, T.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Takaya, H. *Synlett* **1994**, 501.

(14) The diastereoselectivities were analyzed by HPLC. The enantioselectivities of **1b** and **2b** were determined by ^1H NMR in $CDCl_3$ using a chiral shift reagent Eu(hfc)$_3$ and Eu(dppm)$_3$, respectively.

(15) When the reaction was carried out at 60 °C, complete lactonization was observed in the product where the keto group was also hydrogenated.

(16) The absolute configuration was determined by conversion into (2*R*)-2-benzyl-1,3-propanediol 1-acetate, see: Atsuumi, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Ohkubo, M.; Yonezawa, T.; Funabashi, H.; Hashimoto, J.; Morishima, H. *Tetrahedron Lett.* **1990**, *31*, 1601.

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(18) None of the diastereomers due to epimerization was observed by HPLC and 270 MHz ^1H NMR analyses of its diBOC acetate **16**.