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Desymmetric hydrogenation of a *meso*-cyclic acid anhydride toward biotin synthesis

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ABSTRACT

Catalytic reactivity in the hydrogenation of a cyclic anhydride to a biotin synthetic intermediate has been investigated on the basis of Lyons' original method using Wilkinson Ru complex, revealing the high performance of DPPF and XANTPHOS diphosphines possessing wide bite angles. The results have shown a new trail for design of the corresponding asymmetric catalysts, and the potential utility of (*S*,*S*)-Et-FerroTANE and (*S*,*S*)-(*R*,*R*)-Ph-TRAP has been demonstrated.

1. Introduction

Cyclic anhydrides provide potentially useful hydrogenation substrates for the lactone synthesis.[1] The reaction is environmentally benign. The only coproduct is water, and the transformation exhibits a high atom economy.[2] The asymmetric version, particularly enantiotopos selective or desymmetric hydrogenation of *meso*-cyclic anhydrides,[3] should add a further value to the process. The water generated, however, sometimes causes the hydrolysis of anhydride to diacid, lowering the catalysis efficiency in terms of chemical yield, reactivity, and selectivity. This may be a reason for a sluggish development in the field, though over 35 years have passed since the first report on the homogeneous system in which Wilkinson Ru complex catalyzes hydrogenation of succinic anhydride to γ-lactone in 50% yield.[1a,4] Getting back to the Lyons' original report, we have reinvestigated the phosphine structure/reactivity/selectivity relationship only with the focus on the hydrogenation to a biotin synthetic intermediate (Fig. 1).[5] This paper reports the results together with the possibilities to the asymmetric version.

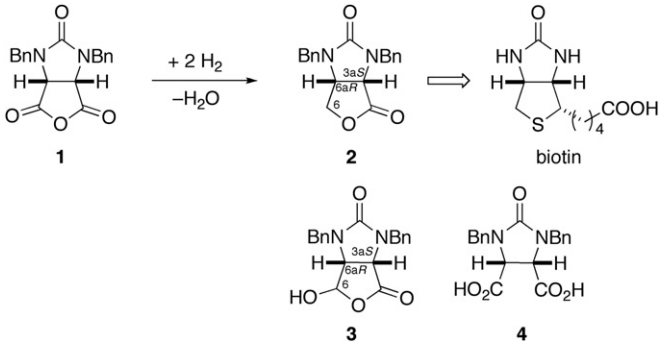

Fig. 1. Desymmetrization of *meso*-cyclic anhydride to a key intermediate for biotin synthesis.

2. Results and discussion

2.1. Reactivity

First of all, the catalytic reactivity of Ru–phosphine complexes in hydrogenation of *meso*-cyclic anhydride **1** was investigated under the fixed standard conditions ([**1**]=100 mM; [[$RuCl_2(C_6H_6)$]$_2$]=0.25 mM; [ligand]=0.5 mM; [*t*-C_4H_9OK]=0.5 mM; 100 atm H_2: toluene; 110 °C;

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12 h) with reference to the Lyons' report[1a] and our own results of ketone hydrogenations.[6] Table 1 lists the results in order of the bite angles (BA) of bidentate ligands used.[7] DPPE gave neither the desired lactone **2** nor hydroxy lactone **3**, while DPPP and DPPB gave **2** in ca. 50% yield. With DPPF, a remarkable enhancement of reactivity was recognized. The anhydride substrate **1** was completely converted to a >99:1 mixture of **2** and **3** without formation of diacid **4** via hydrolysis of **1**. Increase in the BA value to 112° by changing the ligand to XANTPHOS gave rise to quantitative hydrogenation to lactone **2** even with the substrate/catalyst (S/C) ratio of 2000.

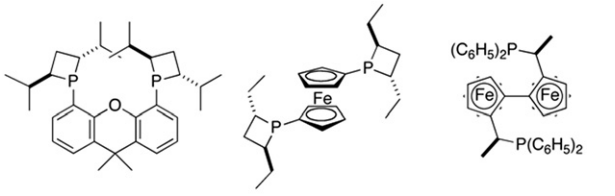
Table 1
Acceleration effect of diphosphine in hydrogenation of a *meso*-cyclic acid anhydride **1** using $[RuCl_2(C_6H_6)]_2$ as a catalyst precursor[a]

Entry	Ligand[b]	Bite angle[c]	S/C	% Yield[d]		
				2	**3**	**4**
1	DPPE	85	200	7	5	3
2	DPPP	91	200	52	48	<1
3	DPPB	98	200	51	49	<1
4	DPPF	96	200	>99	<1	<1
5	Xantphos	112	200	>99	<1	<1
6[e]	Xantphos	112	2000	>99	<1	<1

[a] All reactions were carried out under 100 atm of H_2 atmosphere in 0.2 mmol scale with the concentrations of [**1**]=100 mM, $[RuCl_2(C_6H_6)]_2$=0.25 mM, [ligand]=0.5 mM, and [*t*-C_4H_9OK]=0.5 mM in toluene at 110 °C for 12 h unless otherwise specified.
[b] See Ref. 7.
[c] The values are for the Ru complexes.
[d] Determined by ^1H NMR analysis with the S/N ratio of ca. 1000.
[e] $[RuCl_2(C_6H_6)]_2$=0.025 mM; [ligand]=0.05 mM; [*t*-C_4H_9OK]=0.05 mM; 48 h.

2.2. Asymmetric hydrogenation

With the acceleration effect of wide BA diphosphines in hand, three chiral ligands ^{i}Pr-XANTANE (**5**), Et-FerroTANE (**6**), and Ph-TRAP (**7**)[8] were adopted for the further examination on the desymmetrization of **1** under the standard conditions above. The results are shown in Table 2. (*R*,*R*)-^{i}Pr-XANTANE lost the high reactivity of the original achiral XANTPHOS, giving **2** and **3** in 10% and 60% yields, respectively, together with ca. 20% of diacid **4** (entry 1). The enantiomer ratio (er) of (3a*S*)- and (3a*R*)-**3** was 65:35.[9] Lowering the hydrogen pressure to 8 atm exerted little effect on the er of **3** and increase the degree of hydrolysis of **1** (entry 2). With the DPPF-based chiral ligand (*S*,*S*)-Et-FerroTANE, however, the desired lactone **2** became predominant (entries 3–7, 9, and 10). When the Ru precursor was changed to Ru(η^3-C_4H_7)$_2$(cod) at 100 atm, **2** was obtained in 97% yield as a 19:81 3a*S*/3a*R* mixture. Low-pressure hydrogenation increased the amount of hydroxy lactone **3** to 40%. Use of $RuCl_2$(nbd)py_2 improved both the reactivity and selectivity, giving **2** with a 14:86 er and in quantitative yield under either high or low pressure (entries 6 and 7). The reactivity without base was decreased in one-fifth (entry 8). Addition of 1–10 equiv of base relative to $RuCl_2$(nbd)py_2 completed the reaction (entries 9 and 10). (*S*,*S*)-(*R*,*R*)-Ph-TRAP having the largest BA and the trans chelating ability gave **2** with a 27:73 3a*S*/3a*R* ratio in 70% yield and **3** in 30% yield (entry 11). Decrease in the temperature to 25 °C stopped the reaction mainly at the first stage to give **3** in 85% yield as a 12:88 3a*S*/3a*R* mixture and **2** in 10% yield (entry 12). The side product **4** was obtained in ca. 5% yield. With an isolated complex, [RuCl(*p*-cymene)((*S*,*S*)-(*R*,*R*)-ph-trap)]Cl afforded a similar result (entry 15). At low pressure, however, the reactivity was lost even at 110 °C in contrary to Et-FerroTANE case (entries 7 and 13). In addition, a DPPE-based chiral ligand (*S*,*S*)-CHIRAPHOS[8] gave **2** with a 49:51 er in 40% yield, while a DPPB-based chiral ligand (*S*,*S*)-DIOP[8] with larger BA increased the yield to >99% but without significant increase in the er (38:62).



(*R*,*R*)-*i*Pr-XANTANE (**5**) (*S*,*S*)-Et-FerroTANE (**6**) (*S*,*S*)-(*R*,*R*)-Ph-TRAP (**7**)

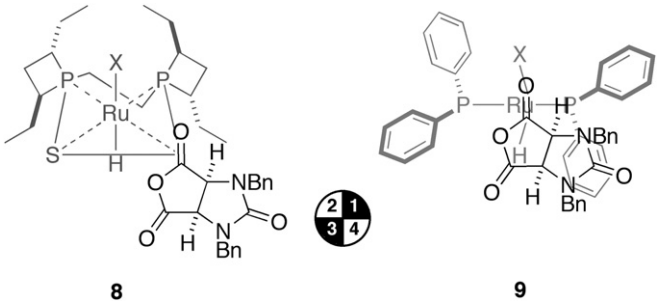
Table 2
Desymmetrization of *meso*-cyclic acid anhydride **1** using chiraldiphosphine–Ru complexes[a]

Entry	Ligand	Ru precursor	**2**		**3**		**4**
			% Yield[b]	3a*S*/3a*R*	% Yield[b]	3a*S*/3a*R*	% Yield[b]
1[c]	**5**	$[RuCl_2(C_6H_6)]_2$	10	—	60	65:35	20
2[c,e]	**5**	$[RuCl_2(C_6H_6)]_2$	20	—	40	64:36	30
3[d]	**6**	$[RuCl_2(C_6H_6)]_2$	80	23.5:76.5	20	—	0
4[d]	**6**	Ru(η^3-C_4H_7)$_2$(cod)	97	19:81	<3	—	0
5[d,e]	**6**	Ru(η^3-C_4H_7)$_2$(cod)	60	16:84	40	—	0
6[d]	**6**	$RuCl_2$ (nbd) py_2	>99	14:86	0	—	0
7[d,e]	**6**	$RuCl_2$ (nbd) py_2	>99	14:86	0	—	0
8[e,f]	**6**	$RuCl_2$ (nbd) py_2	20	—	40	—	<5
9[e,g]	**6**	$RuCl_2$ (nbd) py_2	>99	14:86	0	—	0
10[e,h]	**6**	$RuCl_2$ (nbd) py_2	>99	14:86	0	—	0
11	**7**	$[RuCl_2(C_6H_6)]_2$	70	27:73	30	—	0
12[i]	**7**	$[RuCl_2(C_6H_6)]_2$	10	12:88	85	12:88	<5
13[e]	**7**	$[RuCl_2(C_6H_6)]_2$	<1	—	<5	—	<5
14[e,i]	**7**	$[RuCl_2(C_6H_6)]_2$	0	—	0	—	0
15[d,i,j]	**7**	$[RuCl_2(p\text{-cymene})]_2$	<5	—	80	15:85	10

[a] All reactions were carried out under 100 atm of H_2 atmosphere in 0.2–1 mmol scale with the concentrations of [**1**]=100 mM, $[RuCl_2(C_6H_6)]_2$=0.25 mM, [ligand]=0.5 mM, and [*t*-C_4H_9OK]=0.5 mM in toluene at 110 °C for 12 h unless otherwise specified.
[b] Determined by ^1H NMR analysis.
[c] 32 h.
[d] [*t*-C_4H_9OK]=1.0 mM.
[e] 8 atm H_2.
[f] [*t*-C_4H_9OK]=0 mM.
[g] [*t*-C_4H_9OK]=0.5 mM.
[h] [*t*-C_4H_9OK]=5 mM.
[i] 25 °C.
[j] [RuCl (*p*-cymene)((*S*,*S*)-(*R*,*R*)-ph-trap)] Cl was used.

2.3. Supposed mechanisms of enantiotopos selection

Mechanism is not clear at the present stage. Possible reaction pathways from **1** to **2** are not simple,[3,10] but we assume that the most plausible route is the first hydrogenation of the anhydride carbonyl group of **1** followed by the second hydrogenation of aldehyde carbonyl group liberated from hydroxy lactone **3**. A route via acyl oxonium intermediate but not aldehyde carboxylic acid is also possible.[11] The reaction may proceed via Ru–H/C=O [2+2] metathesis.[12] Supposed mechanism of enantiotopos selection of two C=O of **1** by (*S*,*S*)-Et-FerroTANE– and (*S*,*S*)-(*R*,*R*)-Ph-TRAP–RuH complexes was illustrated in Fig. 2. In both cases, the chiral Ru–H species would first select one of four lone pairs of two C=O groups of **1** to give the corresponding substrate/catalyst complexes. These then move to the transition states (TS) by rotating the C=O bond in a clockwise or anticlockwise manner so as not to increase the steric repulsion between the substituents of ligand and substrate,[12a,b,d] resulting favorably in a species in which bicyclo [3.3.0] convex side is faced to the catalyst. Two phosphorous atoms of (*S*,*S*)-Et-FerroTANE should chelate to the central Ru(II) in a cis manner to open two diastereomeric coordination sites in the P–Ru–P plane ($X \neq H$). Among four possible TS, **8** would be the most stable and the hydride is supplied from Re face to give (3a*R*)-**3**, which will be lead to (3a*R*)-**2** via an aldehyde carboxylic intermediate.[13] The intermediate or the diacid **4** would serve as a carboxylato ligand to alter the structure of active species during the course of the hydrogenation. The formation of hydroxy lactone **3** under basic condition may play an important role to prevent the kind of product inhibition. (*S*,*S*)-(*R*,*R*)-Ph-TRAP–RuH complex would prefer trans chelation rather than cis one,[15] allowing only one coordination site for **1**. In the same way as above, the TS **9** are more favorable than the other diastereomeric TS because of the high degree of stereocomplementarity, giving (3a*R*)-**3** as the major enantiomer.[13]



8 9

Fig. 2. Supposed transition states in (*S*,*S*)-Et-Ferro TANE- and (*S*,*S*)-(*R*,*R*)-Ph-TRAP–Ru-catalyzed hydrogenation of **1**. The backbone of the ligand was omitted for clarity. X=H, Cl, etc.

3. Conclusion

We have revealed that XANTPHOS and DPPF show high reactivity in Ru-catalyzed hydrogenation of a *meso*-cyclic acid anhydride **1**. On the basis of the ligand structure/reactivity relationship that the ligands with the larger BA tend to give the higher reactivity, the potential utility of three chiral ligands ^{i}Pr-XANTANE, Et-FerroTANE, and Ph-TRAP have been investigated. Et-FerroTANE directly produces the lactone **2** with ca. 90:10 er at 8 atm, while Ph-TRAP affords the hydroxy lactone **3** with ca. 90:10 ratio at 100 atm. The enantioselectivity has been understood by stereocomplementary model.[12d] The performance of the present catalyst systems are not perfect yet, but the results should increase the utility of desymmetrization approach to biotin via enantiotopos hydrogenation of **1** or its related compounds in future.

4. Experimental section

4.1. General

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 spectrometer. The chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane or in ppm relative to $CHCl_3$, $CHD_2C(O)CD_3$ (δ 7.26, 2.05 in ^{1}H NMR; δ 77.0, 29.8 in ^{13}C NMR, respectively). Signal patterns of ^{1}H NMR are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad signal. High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-10AD instrument equipped with an SCL-10A system controller, a DGU-4A degasser, an SIL-10AXL autosampler, and a Shimadzu SPD-10A UV detector. Hydrogenation was conducted in an 80-mL glass autoclave for the 8-atm condition. The high-pressure reaction was carried out in a 50-mL glass vessel placed in a stainless steel autoclave.

4.2. Materials

Gases: H_2 gas of a 99.99999% purity grade was purchased from Nippon Sanso and used without purification. Argon gas obtained from Nippon Sanso was purified by being passed through a column of BASF R3-11 catalyst at 80 °C and then through a column of granular calcium sulfate.

Solvents: Toluene for hydrogenation was dried and degassed at reflux temperature in the presence of sodium benzophenone ketyl under an argon stream for 6 h and distilled into Schlenk flasks. The solvent was degassed by three freeze–thaw cycles before hydrogenation. Analytical grade solvents (acetone-d_6 and acetonitrile-d_3) were purchased from Cambridge Isotope Laboratories and used without further purification.

Silica gels: Analytical thin-layer chromatography (TLC) was performed using Merck 5715 indicating plates precoated with silica gel 60 F_{254} (layer thickness, 0.25 mm). The product spots were visualized with a solution of phosphomolybdic acid. Flash column chromatography was performed using Daiko AP 300 or nacalai tesque Silica Gel 60 (spherical, neutral).

Catalyst precursors: The following compounds were commercially available: $[RuCl_2(C_6H_6)]_2$ (Aldrich), $Ru(\eta^3\text{-}C_4H_7)_2(cod)$ (Acros). $RuCl_2(nbd)py_2$ was prepared by the reaction of $[RuCl_2(nbd)]_n$ and piperidine followed by reaction with pyridine.[16] $RuCl_2py_2$[(*S*,*S*)-Et-FerroTANE] was prepared by the reaction of $RuCl_2(nbd)py_2$ and (*S*,*S*)-Et-FerroTANE.[17]

Ligands: The following compounds were commercially available: DPPE (Tokyo Kasei), DPPP (Tokyo Kasei), DPPB (Tokyo Kasei), DPPF (Tokyo Kasei), XANTPHOS (Aldrich), (*S*,*S*)-Et-FerroTANE (Strem), (*S*,*S*)-CHIRAPHOS (Tokyo Kasei), (*S*,*S*)-DIOP (Tokyo Kasei). (*S*,*S*)-(*R*,*R*)-Ph-TRAP was prepared according to method previously reported.[8c] 4,5-Bis [(2R,4R)-2,4-diisopropylphosphetano]-9,9-dimethylxanthene was prepared by the reaction of 4,5-bisphosphino-9,9-dimethylxan-thene and cyclic sulfonate.[8a]

Substrate and authentic sample: Anhydride (**1**) was prepared by dehydration of dicarboxylic acid (**4**) according to the method previously reported.[5i] Lactone ((3a*S*)-**2**) of 99% ee is gift from Sumitomo Co. Ltd.

4.3. General procedure for hydrogenation of 1

The procedure is represented with XANTPHOS as diphosphine ligand. $[RuCl_2(C_6H_6)]_2$ (1.0 mg, 2.0 μmol), XANTPHOS (2.3 mg, 4.0 μmol), and toluene (8.0 mL) were placed into a dry, argon-filled 20-mL Schlenk tube with a Young's tap. The solution was degassed three times by freeze–thaw method and was heated at 100 °C for 1 h. After the resulting pale yellow-colored solution was cooled to

25 °C, a 25 mM THF solution of *t*-C_4H_9OK (0.16 mL, 4.0 μmol), which has been degassed by three freeze–thaw cycles was added to the mixture. One-quarter (2 mL, 1.0 μmol) of the solution was transferred via stainless cannula to a pre-dried 50-mL stainless autoclave containing **1** (67.3 mg, 0.2 mmol) under argon pressure. Hydrogen was initially introduced under 10 atm pressure with several quick release-fill cycles before being pressurized to 100 atm. The solution was vigorously stirred for 12 h at 110 °C. After carefully venting the hydrogen gas, the resulting orange-colored homogeneous solution was concentrated under reduced pressure to give reddish oil of the crude product. The ^{1}H NMR analysis (10:1 acetone-d_6/acetonitrile-d_3, 25 °C) showed that the conversion was 100% and the product ratio of lactone (**2**), hydroxy lactone (**3**), and dicarboxylic acid (**4**) was >99:<1:0. The yield was determined by ^{1}H NMR analysis of a reaction mixture after addition of a 24 mg (0.2 mmol) of mesitylene. The area of the methyl signal of mesitylene (δ 2.29, factor 1.00) and the following signals of the compounds were compared: substrate **1**, δ 4.63 (s, 2H, 2CH), factor 1.00; lactone **2**, δ 4.20 (d, 1H, *J*=15.2 Hz, CH*H*C_6H_5), factor 1.00; dicarboxylic acid, δ 4.10 (d, 2H, *J*=20.5 Hz, CH*H*C_6H_5), factor 1.21; hydroxy lactone **3**, δ 4.03 (d, 1H, *J*=15.0 Hz, CH*H*C_6H_5), factor 0.65. Physical properties of **2** and **3** were consistent with those previously reported.[5h,i] Physical properties of **4** were consistent with those of the commercially available sample.

4.4. Asymmetric hydrogenation of 1 using (*S*,*S*)-Et-FerroTANE (6) (Table 2, entry 6)

$RuCl_2$(nbd)py_2 (2.1 mg, 5.0 μmol), chiral ligand **6** (2.2 mg, 5.0 μmol), and toluene (10 mL) were placed into a dry, argon-filled 20-mL Schlenk tube with a Young's tap. The solution was degassed three times by freeze–thaw method and was heated at 100 °C for 1 h. After the resulting pale yellow-colored solution was cooled to 25 °C, the solution (10 mL, 5.0 μmol) was transferred via stainless cannula to a pre-dried 50-mL stainless autoclave containing **1** (336 mg, 1.0 mmol) and *t*-C_4H_9OK (1.1 mg, 10 μmol) under argon pressure. Hydrogen was initially introduced under 10 atm pressure with several quick release-fill cycles before being pressurized to 100 atm. The solution was vigorously stirred for 12 h at 110 °C. After carefully venting the hydrogen gas, the resulting orange-colored homogeneous solution was concentrated under reduced pressure to give reddish oil of the crude product. The ^{1}H NMR analysis showed that the conversion was 100% and the product ratio of **2**/**3**/**4** was >99:0:0. The product was purified by flash column chromatography (silica gel, 10 g; 1:2 hexane/ethyl acetate as eluent) to give (3a*R*)-**2** (319 mg, 99% isolated yield). The ratio of 3a*S*/3a*R* of **2** was 14:86. The enantiomeric excess of the products was determined by chiral HPLC analysis (Column, CHIRALCEL OD-H (4.6 mm×250 mm); eluent, hexane/2-propanol=6:4; flow rate, 1 mL/min; detection, 254-nm light; t_R of 3a*R* compound, 9.7 min; t_R of 3a*S* compound, 12.5 min).[5i] The absolute configuration was determined to be 3a*R* by comparison of the t_R of the authentic (3a*S*)-**2** of 99% ee. Physical properties were consistent with those of previously reported.[5h,i]

4.5. Asymmetric hydrogenation of 1 using (*S*,*S*)-(*R*,*R*)-Ph-TRAP (7) (Table 2, entry 12)

The procedure was the same as that for the asymmetric hydrogenation of anhydride (**1**). Listed below are the reaction conditions (amounts of anhydride (**1**); $[RuCl_2(C_6H_6)]_2$; chiral ligand **7**; *t*-C_4H_9OK; amount of toluene; H_2, atm; temperature, time), conversion of substrate, product ratio of **2**/**3**/**4** estimated by ^{1}H NMR measurement, the ratio of 3a*S*/3a*R* of **3**, and the physical property. Conditions (Table 2, entry 12): 0.2 mmol of **1**; 0.5 μmol of $[RuCl_2(C_6H_6)]_2$; 1 μmol of chiral ligand **7**; 1 μmol of *t*-C_4H_9OK; 2 mL of toluene; 100 atm of H_2; 25 °C; 12 h. Chiral ligand **7** and Ru precursor were aged at 100 °C for 1 h. Convn, >99%; **2**/**3**/**4**=10:85:<5. The ratio of 3a*S*/3a*R* of **3** was 12:88. Absolute configuration: 3a*R*. The enantiomeric excess and absolute configuration were determined by comparison of the HPLC after converting to lactone by the reported method.[5h] To a 1 mL methanol solution of the hydroxy lactone (15 mg, 0.04 mmol) was added $NaBH_4$ (3 mg, 0.08 mmol) at 0 °C. After the mixture was stirred at 25 °C for 20 min, the mixture was partitioned between CH_2Cl_2 (5 mL) and 6 M aqueous HCl (2 mL). The aqueous layer was extracted by two portions of CH_2Cl_2 (5 mL). The combined organic layers were dried on Na_2SO_4, filtered, and concentrated to give an oil (14 mg, 98% yield), which was subjected to the chiral HPLC analysis. Column, CHIRALCEL OD-H (4.6 mm×250 mm); eluent, hexane/2-propanol=6:4; flow rate, 1 mL/min; detection, 254-nm light; t_R of 3a*R* compound, 9.7 min; t_R of 3a*S* compound, 12.5 min.[5i] Physical properties were consistent with those of previously reported.[5h,i]

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9. The stereochemical relationship between C(6a)H and C(6)H of the hydroxy lactone **3** is supposed to be trans because the *J* value is 0.[5a,b,10a] (3a*S*)-**3** represents (3a*S*,6a*R*,6*R*)-**3**, while (3a*R*)-**3** does (3a*R*,6a*S*,6*S*)-**3**.
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13. The product in the first hydrogenation using (*S*,*S*)-Et-FerroTANE (**6**) or (*S*,*S*)-(*R*,*R*)-Ph-TRAP (**7**) should be (3a*R*,6a*S*,6*R*)-**3**[14] with cis C(6a)H/C(6)H relation. If the C=O reduction mechanism operates, this would be quickly isomerized to the more stable (3a*R*,6a*S*,6*S*)-**3** via an aldehyde carboxylic acid intermediate. Under the hydrogenation conditions ([**1**]=50 mM, $[[RuCl_2(C_6H_6)]_2]$=0.25 mM, [**7**]=0.5 mM, [*t*-C_4H_9OK]=0.5 mM, 20 atm H_2, toluene-d_8, 25 °C), however, the aldehyde signal was not observed in the ^1H NMR spectrum. Kinetic resolution of **3** is also not likely, because the ers of **2** and **3** in all cases in Table 2 are not significantly different each other.
14. The products enantiomeric to the natural biotin are obtained with (*S*,*S*)-**6** and (*S*,*S*)-(*R*,*R*)-**7**.
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