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ASYMMETRIC HYDROGENATION OF FURAN-CONTAINING KETONES OVER TARTARIC ACID-MODIFIED RANEY NICKEL CATALYST†

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Abstract—The hydrogenation of β-keto esters containing a furan unit at the conjugated position to the β-carbonyl group was carried out over a chiral heterogeneous catalyst, tartaric acid-modified Raney nickel. The hydrogenation first proceeds at the carbonyl to give optically active alcohols, but a simple substrate undergoes further hydrogenation of the furan part to produce a diastereomeric mixture of alcohols having a tetrahydrofuran moiety. This over-reduction was efficiently suppressed by substitutions of a substituent at the furan part. The optical yield at the hydroxy group is in the range of 40–90%.

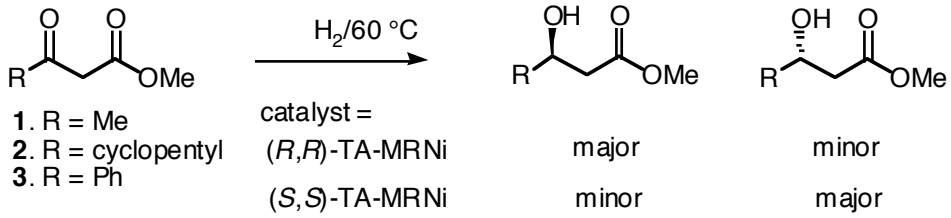
INTRODUCTION

Furan incorporated into synthetic intermediates is a versatile building block due to its weak aromaticity that provides a balance of moderate stability during the reaction of other functionalities and diverse reactivity of conversion of the furan element into various four-carbon units.[2] The importance of a furan-containing intermediate will be increased if it is readily available in an optically active form with the desired stereochemistry. Among such possible chiral intermediates, we focused our attention on furan analogues having a chiral hydroxylated carbon adjacent to the furan ring. Such compounds are potentially useful since the hydroxy group can be converted to different functional groups *via* ordinary stereospecific reactions, and it can also control the regio- and stereochemistries of the reactions at the furan element as well as at other parts of the molecule. A straightforward way to prepare such compounds is the reduction of the corresponding ketones, and for this conversion, we employed

†This paper is dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday.

asymmetric hydrogenation with a tartaric acid-modified nickel (TA-MNi), a heterogeneous catalyst which can be recovered and reused after the hydrogenation.[3]

TA-MNi is prepared from a nickel catalyst by soaking in an aqueous solution of a desired enantiomer of tartaric acid and NaBr. Hydrogenation of methyl acetoacetate (**1**) over TA-MNi at 100 °C results in an 83–91% ee depending on the nickel catalyst employed for the modification (Scheme 1). When the catalyst is prepared from ultrasound-irradiated Raney nickel after being developed by the W-2 method, the modified catalyst, TA-MRNi, has the highest activity among the TA-MNi's, while the enantio-differentiating ability is moderate with **1** (86% ee both at 60 and 100 °C).[4] The high catalytic activity of TA-MRNi allows the hydrogenation of less reactive substrates than **1** even at a lower temperature. By the hydrogenation over TA-MRNi at 60 °C, most alkyl substituted analogues of **1** were found to give better optical yields than that with **1** in the range of 94–98.6%; e.g., 95% with **2**.[5,6] An exception is a group of β-keto esters having an aromatic group at the conjugate position of the β-carbonyl, of which the hydrogenation results in poor optical yields; e.g., 52% with **3**. Recently, we have found that when an electron-donor such as a methoxy group is substituted on the phenyl ring of **3**, the optical yield can be improved to 70–72%.[7] In this context, β-conjugation to the carbonyl may not be a fatal problem and the effect of the conjugation can be relieved if the aromatic group is electron-donating like furan. We now report the asymmetric hydrogenation of furan-containing substrates over TA-MRNi to obtain optically active furans.[8]



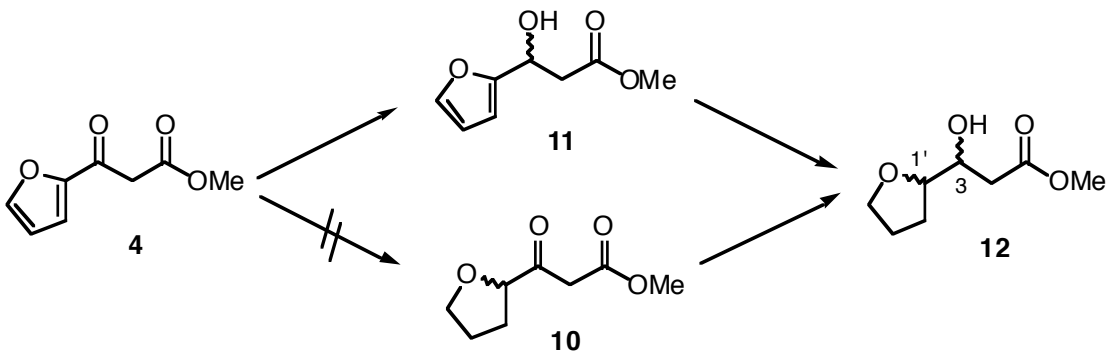
Scheme 1.

RESULTS AND DISCUSSION

Furan-containing ketones (**4**–**9**) and a reference compound (**10**) were employed for the hydrogenation over TA-MRNi. Substrates (**4**, **5**, **8**, and **9**) were prepared from the corresponding acetylfurans by methoxycarbonylation with dimethyl carbonate/sodium hydride in good yields (77–88%, method A[9]). The tetrahydrofuran analogue (**10**) was prepared from tetrahydro-2-furoic acid by a two-carbon extension; Meldrum's acid/DCC followed by thermolysis in methanol (67%, method B[10]). Substrate (**6**) was obtained from 5-*t*-butyl-2-furoyl chloride and the sodium salt of **1** followed by deacetylation in the

presence of aqueous ammonium chloride (78%, method C[11]). Substrate (**7**) is difficult to prepare by the conventional methods. Application of method A, B, or C resulted in no product (**7**). Only when potassium hydride was employed instead of sodium hydride in method A, a trace amount of **7** was obtained (less than 5% yield). The methoxycarbonylation of **4** at the 5'-position with sodium hydride, *sec*-butyllithium, and then dimethyl carbonate also afforded only a trace amount of **7**. A Friedel-Crafts approach with methyl 2-furoate and methyl malonyl chloride did not produce any **7**. Finally, **7** was obtained by the carbonylation of methyl 5-acetyl-2-furoate with methylmagnesium carbonate in DMF followed by methylation with diazomethane (20% for two steps).[12]

Hydrogenation over TA-MRNi was started with a simple furan-containing β-keto ester (**4**). When **4** was hydrogenated at 60 °C under the initial hydrogen pressure of 10^7 Pa (100 kg cm^{-2}) for 68 h, the product was not an expected one (**11**), but all three unsaturated bonds in **4** were fully reduced to produce a mixture of four stereoisomers of **12**. The isomer ratio determined by GLC with a chiral column was 7/45/4/44 in the order of retention times. The assignment of relative stereochemistry was achieved by the known stereoselectivity in the reduction of **10** with $NaBH_4$,[13] where two major products assigned to be *threo* have the shorter retention times than the *erythro* isomers in the GLC analysis. The absolute stereochemistry of the major enantiomers in both diastereomers at the 3-position is assigned to be *S*, as expected from the nature of the (*R*,*R*)-TA-MRNi catalyst, by converting the hydrogenation product to an ester with (*R*)-MTPACl, where both of the two major isomers show greater downfield shifts of the 2-proton on an NMR spectrometry. As summarized in Table 1, no diastereoselectivity is found in formation of *threo* and *erythro* isomers (52/48), but the ee values of the both diastereomers are high; 73% for *threo* and 82% for *erythro*. Overall, the enantiomeric excess at the 3-position is calculated to be 77% and that at the 1'-position is 2%.



Scheme 2.

Table 1. Stereoisomer ratio of **12** obtained by the hydrogenation of **4** and the possible intermediates over (*R*,*R*)-TA-MRNi

Subst.	React. time	3*R*,1'*R*/3*S*,1'*S*/3*R*,1'*S*/3*S*,1'*R*	*threo* /*erythro*	%ee of *threo*	%ee of *erythro*	%ee at 3-position	%ee at 1'-position
4	68 h	7.0 / 44.7 / 4.3 / 43.9	52/48	73	82	77	2
rac-**10**	68 h	13.8 / 41.1 / 9.1 / 36.0	55/45	50	60	54	–
rac-**11**	20 h	20.8 / 21.3 / 28.8 / 29.1	42/58	1	1	–	0

To examine the reaction pathway of the hydrogenation of **4** to **12**, the composition of the reaction mixture during the hydrogenation was analyzed by ^{1}H NMR spectrometry. The analysis was performed by the repeated hydrogenations for different reaction times under the same pressured conditions as the synthetic runs. In all cases, the concentrated reaction mixture contained intermediates (**10**) and (**11**), as well as **4** and **12**, but no other product was detected. The ratios of the four compounds at 2, 4, 6, 10, 12 hours are shown in Figure 2. In contrast to the low content (2.0–2.2 %) of **10** throughout the hydrogenation, a maximum content of the other intermediate (**11**) reached 30% at the 60% conversion of **4** (6 h). Thus, **12** must be mainly produced *via* **11**. The hydrogenation over TA-MRNi of the intermediates (**10**) and (**11**), independently prepared as racemic compounds, also resulted in the quantitative formation of **12.** The isomeric ratios of the product are given in Table 1. The hydrogenation of **11** is faster than that of **4** or **10** by *ca*. 2–4 times as deduced from the consumption rate of hydrogen, and then the conversion of **4** to **12** is confirmed to proceed through **11**. The opposite diastereoselectivity starting with **11** may attributable to the absence of the ketones, which can be adsorbed on the catalyst stronger than **11** during the hydrogenation.

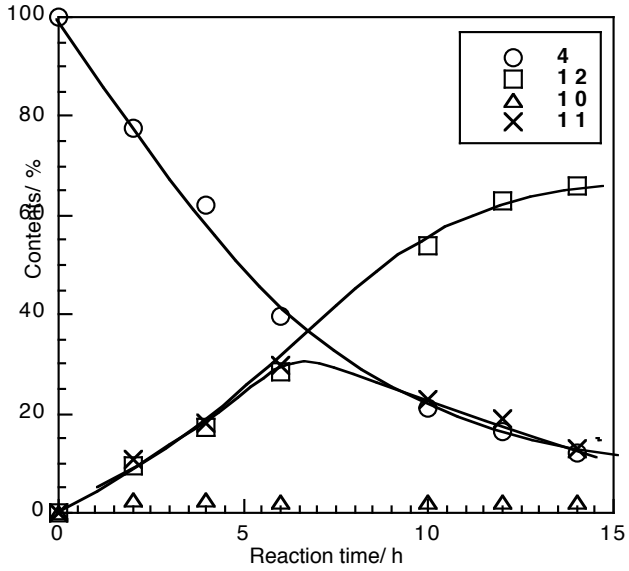


Figure 2. Composition of **4** and **10–12** as a function of the hydrogenation time.

Compared with the high stereoselectivity of the hydrogenation of **4** resulting in the 77% ee of **11**, that of **10** is much lower; 45% de (diastereomeric excess) from (1'*R*)-**10**, 64% de from (1'*S*)-**10**, and 54% ee equivalent overall. The difference between **4** and **10** in the stereoselectivities is reasonably understood as follows. Asymmetric hydrogenation over TA-MRNi allows enantio-differentiation of a β-keto ester using the ester part as an anchor to the chiral catalyst. An ether or hydroxy group can also be used as the anchor instead of the ester group in the β-keto ester to make α-hydroxy ketone or α-alkoxy ketone a suitable substrate.[2] If a substrate has such an oxy-function at both sides of the ketone to be hydrogenated, their anchoring effects will compete with and cancel each other. As a fact, when methyl 4-methoxy-3-oxobutanoate was hydrogenated over TA-MRNi at 60 °C, the product ee was only 51%, which is much lower than 86% ee with **1**, but similar to 54% ee with **10**. Since the mechanism of the anchoring is an interaction between the oxy-functions and the adsorbed sodium tartarate,[2,14] a more basic oxy-function in the substrate should work as a better anchor. As represented by the dipole moments, 0.66 Debye for furan and 1.70 Debye for tetrahydrofuran,[1] the furan oxygen is less basic than that of tetrahydrofuran due to the aromaticity. Hence, the furan-containing β-keto ester (**4**) is preferable for the TA-MRNi hydrogenation because of less interaction of the ether oxygen with the catalyst, but enough mesomeric donation of the furan ring compared with the phenyl in **3** to give 52% ee.[6]

To obtain optically active furans by the TA-MRNi hydrogenation, it is necessary to inhibit the furan part from hydrogenation. Since the reaction at the furan part during the hydrogenation of **4** is the overreaction that occurred after the hydrogenation of the carbonyl part, we first tried to suppress the hydrogenation of **11** by a change in the procedure. This change must be minimal because the stereoselectivity of the TA-MRNi hydrogenation is very sensitive to the reaction conditions as well as the catalyst preparation. Evaluation of the chemoselectivity was performed by interrupting the hydrogenation of **4** at *ca.* 50% consumption of the hydrogen. The compositions of the reaction mixtures obtained under various conditions were analyzed by ^{1}H NMR spectrum, and are given in Table 2. When the amount of NaBr employed as a co-modifier of the catalyst was increased while keeping the amount of tartaric acid, the catalytic activity of the modified catalyst was found to decrease as shown in Runs 1–6. However, this did not work to improve the chemoselectivity. As shown in Runs 7 and 8, a small change in the hydrogenation temperature did not have a significant effect on the selectivity. We then supposed that if the hydrogenation of the furan part in **11** was catalyzed at a separate site from that for the ketone, the coexisting furan can compete with **11** in the adsorption, and suppress the hydrogenation of **11**. However, the added furans showed little effect (Runs 9 and 10). Effects of acetic acid, which is regularly employed at *ca.* 1% of the reaction mixture, were also small to improve

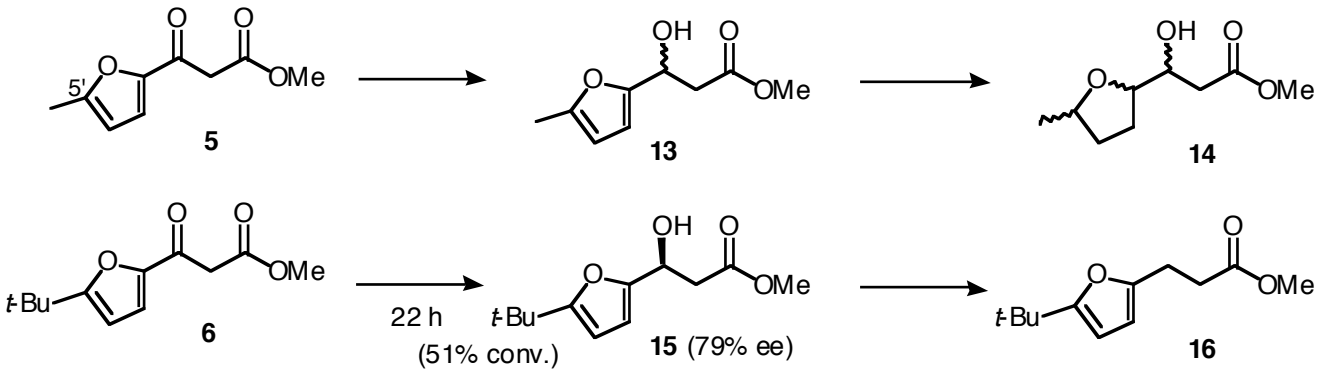
the chemoselectivity (Runs 11 and 12). Based on these, it was found that obtaining of an optically active furan analogue is difficult by the hydrogenation of **4** and some modification of the substrate structure is necessary.

Table 2. Composition of the hydrogenation products of **4** after partial conversion.[a]

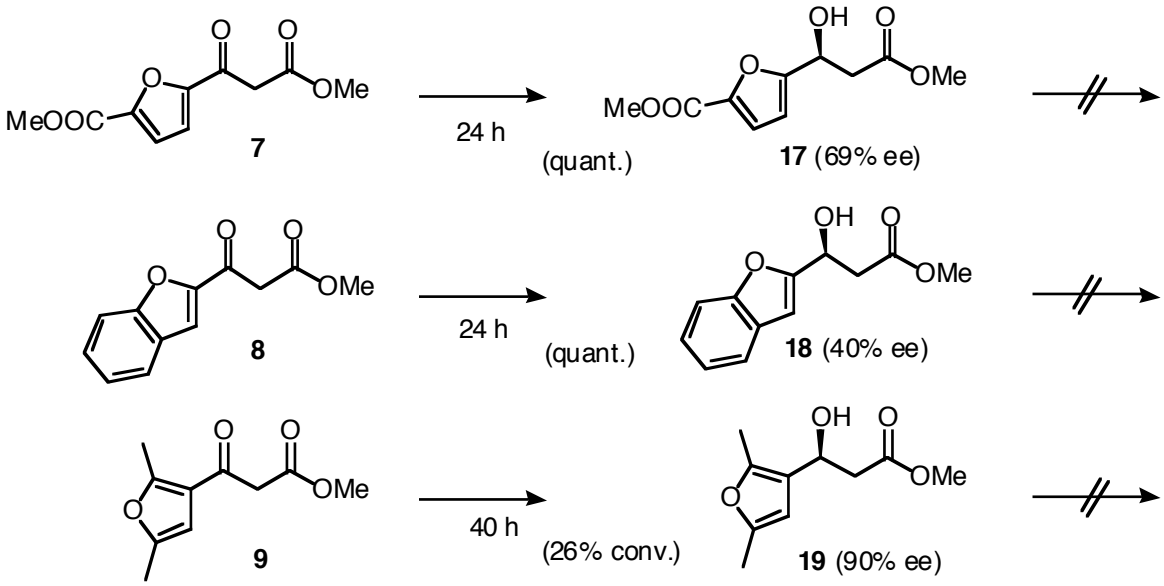
Run	Time /h	**4**	**12**	**10**	**11**	Variations [b]
1	4	38	49	5	8	NaBr = 2.5 g
2	6	31	58	3	8	NaBr = 2.5 g
3	6	77	9	3	11	NaBr = 10 g
4	8	62	19	5	14	NaBr = 10 g
5	12	57	37	5	1	NaBr = 20 g
6	18	37	58	4	1	NaBr = 20 g
7	12	41	43	3	13	at 50℃
8	24	6	89	<1	5	at 50℃
9	12	16	70	3	11	with furan (5 eq)
10	6	50	40	4	6	with 2-methylfuran (5 eq)
11	6	56	28	3	13	AcOH = 100 μl
12	6	24	57	2	17	AcOH = 0 μl

[a] The catalyst (0.4 g) was modified in a solution of tartaric acid (0.5 g) and NaBr (5 g) in water (50 mL). The hydrogenation was carried out by heating a solution of **4** (0.3 g) and acetic acid (20 μL) in THF (2 mL) at 60 °C. [b] The catalyst was prepared with different amounts of NaBr for Runs 1–6. The hydrogenations at lower temperature or with different additives are shown in Runs 7–12.

Some other furan-containing β-keto esters (**5**–**9**) were hydrogenated to examine the chemoselectivity as well as the stereoselectivity of the hydrogenation to provide the predominant formation of the desired optically active furan-alcohol free of an over-reduced tetrahydrofuran-alcohol. When the methyl-substituted substrate (**5**) was hydrogenated under the standard conditions for 6 h, only the desired **13** was produced at 12% conversion (Scheme 3). However, when the reaction time was extended to 12 h, the mixture consisted of three components in the ratio of **5**:**13**:**14** = 25:43:32, and only **14** was obtained after the 48 h hydrogenation. The effect of the 5'-methyl of **5** in suppressing the over-reduction is clear compared with the results of **4**, but it is insufficient to obtain predominantly the optically active furan (**13**). Hence, we did not study **5** in detail, but *t*-butyl substituted substrate (**6**) was examined, where the effect of the 5'-substituent should be greater than that in **5**. The hydrogenation of **6** was much slower than that of **5** resulting in only a 51% conversion after 22 h. The reaction mixture contained **15** of 79% ee, but no tetrahydrofuran analogue was detected at all, while another furan compound was produced in a trace amount as a byproduct. When the reaction time was extended to 44 h, 90% of **6** was consumed, and the ratio of **15** and the byproduct became 2:8. The structure of the byproduct was determined to be a dehydroxy analogue (**16**) at the 3-position deduced from the MS and ^{1}H NMR spectrum. The constant 79% ee of **15** at different conversions indicates the absence of the kinetic resolution of **15**.



Scheme 3.



Scheme 4.

The suppression of the furan hydrogenation can be achieved by other means than steric hindrance. The lower reactivity of **4** compared with **11** at the furan ring, as shown above, suggests that the carbonyl conjugation effectively reduces the hydrogenation rate of the furan unit. Substrate (**7**) in Scheme 4 should be hydrogenated first at the β-carbonyl like **4**, but the produced chiral furan (**17**) still has a carbonyl group at the 5'-position, and then the furan ring in **17** should be unreactive. As a matter of fact, the hydrogenation of **7** for 24 h at the standard temperature of 60 °C resulted in the quantitative formation of **17** that has the lower ee of 69% than that with the other furan substrates. Protection of the furan moiety also occurred by the condensation of benzene. The hydrogenation of **8** for 24 h resulted in **18** accompanied by a minimum overreaction (<2%) at the 100% conversion. Unfortunately, the produced **18** is only 40% ee. Substrate (**9**) was designed somewhat differently. The furan unit is connected at the 3'-position to the β-keto ester, and has two methyl groups at the 2' and 5'-positions. This substrate is much less reactive compared with the other furan-containing substrates, but ee of the product (**19**) reached 86–90% though the conversion was very low (20–26%, 40 h).

CONCLUSION

In the present study, it was shown that furan-containing β-keto esters can be applied as the first heterocyclic substrates to the asymmetric hydrogenation over TA-MRNi. The produced chirality at the 3-position has the higher stereochemical purity of 77–79% ee than 52% for **3**, or even higher than 72% ee with the 4'-methoxy analogue of **3**, the best aromatic-conjugated substrate before the present study. However, the results with **7** and **8**, 69% and 40% ee, respectively, suggest that the design of the substrate for TA-MRNi is not simple. The best ee of 90% using **9** is as high as those with aliphatic β-keto esters. This indicates that aromatic substrates are not always unsuitable for the TA-MRNi hydrogenation. The exceptionally high stereoselectivity with **9** may be attributed to a lower contribution of the furan oxygen to the coordination of the substrate onto the chiral catalyst during the hydrogenation. The optical purities are still not sufficiently high, but further studies with heteroaromatic substrates may reveal the additional potential of TA-MRNi as an asymmetrically modified heterogeneous catalyst.

EXPERIMENTAL

General. All the substrates and the hydrogenation products were characterized by NMR spectrometry using a JEOL EXcaliber-400 spectrometer at 400 MHz for the proton spectra and 100 MHz for the carbon spectra, and by IR with a JASCO IR-88 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 243B polarimeter. High resolution MS was obtained by a JEOL JMS-AX505HF. Analytical GLC was performed on a Shimadzu GC17A. Stereoisomer ratios of the produced alcohols were determined after acetylation (acetic anhydride/pyridine) with a CP-Chirasil DEX CB capillary column (25 m, 0.25 mm id, GL Science, Japan, flow rate: 30 cm/sec). Deionized water for the preparation of the catalyst was obtained from Kanto Chemicals, Japan. All solvents were purified by distillation with proper drying agents.

Methyl 3-(2-furyl)-3-oxopropanoate (4). Sodium hydride (28.02 g, 60% in oil, 700 mmol) was placed in a flask and washed with dry hexane (x3). Dimethyl carbonate (51.13 g, 568 mmol) and THF (150 mL) were added to this flask, and the mixture was heated for reflux. After the addition of a small portion of potassium hydride (in oil), a solution of 2-acetylfuran (25.02 g, 227 mmol) in THF (100 mL) was added over 30 min. The mixture was stirred for 1 h at the same temperature, and then cooled to 0 °C. After the addition of aqueous acetic acid (3 M, 284 mL, 875 mmol), the mixture was extracted (dichloromethane), dried ($MgSO_4$), and concentrated. The resulting oil was washed with hexane and dissolved in methanol. After decantation, the solution part was concentrated and distilled (5 mmHg, 113–115 °C) to give 15.5 g as a colorless oil (77.4%). IR (neat) 1740 and 1680 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.37 (s, 1H), 7.00 (d, J = 3.4 Hz, 1H), 6.28 (d, J = 3.4 Hz, 1H), 3.58 (s, 2H), 3.40 (s, 3H). ^{13}C NMR

($CDCl_3$) δ 180.1, 166.7, 151.2, 146.7, 118.0, 112.1, 51.7, 44.4. High resolution MS (*m*/*z*), calcd for $C_8H_8O_4$: 168.0423; found: 168.0411.

Methyl 3-(5-methylfuran-2-yl)-3-oxopropanoate (5). This compound was prepared by the same method as that of **4**. From 20.12 g (162 mmol) of 2-acetyl-5-methylfuran, 25.69 g of **5** was obtained as a colorless oil (87.5%). bp 105–109 °C (6 mmHg), IR (neat) 1740 and 1670 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.01 (d, *J* = 3.4 Hz, 1H), 6.02 (d, *J* = 3.4 Hz, 1H), 3.61 (s, 2H), 3.52 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 179.2, 167.0, 158.2, 150.1, 120.2, 109.1, 51.8, 44.4, 13.5. High resolution MS (*m*/*z*), calcd for $C_9H_{10}O_4$: 182.0579; found: 182.0577.

Methyl 3-(5-*t*-butylfuran-2-yl)-3-oxopropanoate (6). A mixture of 5-*t*-butyl-2-furoic acid (1.01 g, 6.00 mmol) and thionyl chloride (4.50 g, 37.8 mmol) was stirred for 20 min at rt, and then warmed up 55 °C for 25 min. Concentration of the mixture under vacuum, the addition of ether (25 mL), and then concentration gave the acid chloride as a reddish brown oil (1.14 g, 104%). Sodium hydride (0.79 g, 60% in oil, 20 mmol) was washed with hexane and suspended in THF (20 mL). To this suspension, methyl acetoacetate (**1**, 0.47 mL, 4.4 mmol) was added at 0 °C, and stirred for 40 min. After warming this mixture to rt, a solution of the acid chloride (1.14 g, 6.11 mmol) in THF (10 mL) was added over 30 min. The reaction mixture was allowed to stand for 100 min, and then stirred with an excess saturated aqueous ammonium chloride for 12 h. Extraction (ether) and column chromatography on silica gel (elution with 20% ethyl acetate in hexane) gave an yellow oil (0.997 g, 93% based on **1**). IR (neat) 1730 and 1670 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.16 (d, *J* = 3.4 Hz, 1H), 6.16 (d, *J* = 3.4 Hz, 1H), 3.79 (s, 2H), 3.12 (s, 3H), 1.30 (s, 9H). High resolution MS (*m*/*z*), calcd for $C_{12}H_{16}O_4$: 224.1049; found: 224.1008.

Methyl 3-(5-methoxycarbonylfuran-2-yl)-3-oxopropanoate (7). A solution of methyl 2-furoate (3.60 g, 28.5 mmol) and acetyl *p*-toluenesulfonate (7.0 g, 33 mmol) in benzene (60 mL) was heated to gentle reflux over 24 h. After cooling, the reaction mixture was poured into water (100 mL), and then saturated aqueous sodium bicarbonate (300 mL) was added to this mixture. The mixture was extracted with ether, dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (elution with 20% ethyl acetate in hexane) to give 0.76 g of a 5-acetyl product as a yellow solid (15.8%). When the amount of recovered methyl 2-furfurate (2.94 g, 25 mmol) is considered, the product yield becomes 86.6%. Magnesium (0.60 g) was placed in a flask under nitrogen, and heated to 130 °C for 2 h. After cooling, methanol (11.5 mL) was added, and the resulting mixture was heated to 50 °C until all the magnesium had reacted. A colorless solid obtained by removing excess methanol under vacuum was dissolved in DMF (8.75 mL), and stirred under a stream of carbon dioxide for 30 min. The mixture was gradually heated to 140 °C, and then cooled to 100 °C under a nitrogen atmosphere. After the addition of methyl 5-acetyl-2-furoate (760 mg, 4.52 mmol), the mixture was heated until reflux for 2 h. The

mixture was cooled to 0 °C, acidified with 0.5 M hydrochloric acid, and extracted with ether. The ethereal layer was extracted with 0.1 M aqueous sodium hydroxide (33 mL), and the aqueous layer was acidified with 2 M hydrochloric acid. The product was re-extracted with ether, and the ethereal layer was treated with a solution of diazomethane in ether at 0 °C. Concentration and recrystallization from ethyl acetate gave 138 mg of **7** as yellow prisms (20.1 %). mp 67–71 °C, IR (neat) 1740, 1720, 1680 cm^{-1}, ^1H NMR ($CDCl_3$) □ 7.26 (d, *J* = 3.4 Hz, 1H), 7.22 (d, *J* = 3.4 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.74 (s, 3H). High resolution MS (*m*/*z*), calcd for $C_{10}H_{10}O_6$: 226.0477; found: 226.0449.

Methyl 3-(5-benzofuryl)-3-oxopropanoate (8). This compound was prepared by the same method as that of **4** except for the use of column chromatography (SiO_2, elution with 20% ethyl acetate in hexane). From 10.05 g (6.28 mmol) of 5-acetylbenzofuran, 11.86 g of **8** was obtained as a yellow oil (86.6 %). IR (neat) 1730 and 1660 cm^{-1}, ^1H NMR ($CDCl_3$, for the keto form) □ 7.70 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.48 (tm-like, *J* = *ca*. 8.5 Hz, 1H), 7.30 (t-like, *J* = *ca*. 8.5 Hz, 1H), 3.99 (s, 2H), 3.74 (s, 3H). High resolution MS (*m*/*z*), calcd for $C_{12}H_{10}O_4$: 218.0579; found: 218.0550.

Methyl 3-(2,5-dimethylfuran-3-yl)-3-oxopropanoate (9). This compound was prepared by the same method as that of **4** except for the purification by the twice distillation. From 22.11 g (160 mmol) of 3-acetyl-2,5-dimethylfuran, 24.54 g of **9** was obtained as a yellow oil (78%). bp 112 °C (6–7 mmHg), IR (neat) 1740 and 1670 cm^{-1}, ^1H NMR ($CDCl_3$) □ 6.04 (s, 1H), 2.56 (s, 3H), 3.55 (s, 2H), 2.36 (s, 3H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$) □ 187.5, 167.3, 157.7, 149.9, 120.7, 105.2, 51.8, 47.5, 13.8, 12.7. High resolution MS (*m*/*z*), calcd for $C_{10}H_{12}O_4$: 196.0736; found: 196.0702.

Methyl 3-(2-tetrahydrofuryl)-3-oxopropanoate (10). To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldurum's acid, 5.76 g), tetrahydro-2-furoic acid (5.02 g, 43.2 mmol), and *N*,*N*-dimethylaminopyridine (0.5 g) in dichloromethane (150 mL), a solution of DCC (9.86 g, 47.8 mmol) in dichloromethane (100 mL) was added dropwise over 2 h at 0 °C. The mixture was stirred for 15 h at rt. After the addition of 50% aqueous acetic acid (2 mL), the mixture was dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in methanol (30 mL) and heated to reflux for 4 h. Concentration, silica gel column chromatography (elution with 30% ethyl acetate in hexane), and distillation (5 mmHg, 75-80 °C) gave **10** as a colorless oil (4.97 g, 67.1%). IR (neat) 1760 and 1670 cm^{-1}, ^1H NMR ($CDCl_3$) □ 4.36 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.84 (t-like, *J* = 6.4 Hz, 2H), 3.71 (s, 3H), 3.58 (s, 2H), 2.19 (m, 1H), 2.00 (m, 1H), 1.87 (m, 2H). High resolution MS (*m*/*z*), calcd for $C_8H_{12}O_4$: 172.0736; found: 172.0708.

Preparation of catalyst. Raney nickel (0.4 g) was prepared from 1.0 g of Raney nickel alloy (Ni/Al = 42/58, Kawaken, Japan) in an alkaline solution (4.5 g of NaOH in 20 mL of deionized water) heated at 100 °C for 1 h. To wash out the excess base and aluminum salts, a sufficient amount of deionized water was used under ultrasonic irradiation. The modifying solution was prepared by dissolving (*R*,*R*)-tartaric

acid (0.5 g) and NaBr (5 g) in deionized water (50 mL) followed by adjustment of the pH to 3.2 with aq. 1N NaOH. TA-MRNi was prepared by heating the RNi in the modifying solution at 100 °C for 1 h, followed by decantation, and washing with water (5 mL), methanol (15 mL x2), and THF (15 mL x2).

Hydrogenation. In a 100 mL autoclave (i.d. 36 mm x 100 mm), TA-MRNi (0.4 g) and a solution of the substrate (1.5 g) and acetic acid (0.1 mL) in THF (10 mL) were placed. Hydrogen was charged into the autoclave under the initial pressure of *ca.* 10^7 Pa (100 ± 2 kg cm^{-2}), and the autoclave was heated to 60±1 °C with reciprocating shaking. The autoclave was cooled and the excess hydrogen was released from it. Hydrogenation products were not isolated except for **17**, **18**, and **19**, but identified using the authentic (racemic) samples obtained by the reduction of the substrates with $NaBH_4$ in methanol. **rac-11**: IR (neat) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 7.36 (m, 1H), 6.32 (dd, *J* = 3.4, 1.9, 1H), 6.26 (dm, *J* = 3.4 Hz, 1H), 5.13 (m, 1H), 3.72 (s, 3H), 3.13 (d, *J* = 5.4 Hz, 1H, OH), 2.90 (dd, *J* = 16.6, 8.8 Hz, 1H), 2.82 (dd, *J* = 16.6, 4.4 Hz, 1H). High resolution MS (*m*/*z*), calcd for $C_8H_{10}O_4$: 170.0579; found: 170.0557. **rac-12**: IR (neat) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 4.01–3.90 (m, 1H), 3.87–3.72 (m, 2H), 3.70 (s, 3H), 2.83 (br s, 0.5 H, OH), 2.65–2.41 (m, 2H), 1.98–1.68 (m, 4H). High resolution MS (*m*/*z*), calcd for $C_8H_{14}O_4$: 174.0892; found: 178.0840. GLC retention times (120 °C); 15.5, 15.8, 18.7, and 19.0 min (= 32/32/18/18). **rac-13**: IR (neat) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 6.12 (d, *J* = 2.9 Hz, 1H), 5.89 (m, 1H), 5.07 (m, 1H), 3.72 (s, 3H), 3.02 (d, *J* = 4.9 Hz, 1H, OH), 2.89 (dd, *J* = 16.6, 8.8 Hz, 1H), 2.79 (dd, *J* = 16.6, 3.9 Hz, 1H), 2.26 (s, 3H). High resolution MS (*m*/*z*), calcd for $C_9H_{12}O_4$: 184.0736; : 184.0698. **rac-15**: IR (neat) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 6.13 (d, *J* = 3.3 Hz, 1H), 5.78 (d, *J* = 3.3 Hz, 1H), 5.07 (m, 1H), 2.95–2.70 (2H, m), 1.25 (s, 9H). High resolution MS (*m*/*z*), calcd for $C_{12}H_8O_4$: 226.1205; found: 226.1190. **17** (quantitative yield): $[□]_D^{20}$ = –30.8° (c 0.5, $CHCl_3$, 68.5% ee), IR (neat) 1740 and 1725 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 7.11 (d, *J* = 3.4 Hz, 1H), 6.41 (d, *J* = 3.4 Hz, 1H), 5.17 (ddd, *J* = 8.3, 5.4, 4.8 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.41 (d, *J* = 5.4 Hz, 1H, OH), 2.92 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.86 (dd, *J* = 16.6, 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) □ 172.8, 159.0, 158.9, 143.8, 118..7, 108.2, 64.6, 64.5, 52.0, 39.6. High resolution MS (*m*/*z*), calcd for $C_{10}H_{12}O_6$: 228.0634; found: 228.0662. **18** (quantitative yield): $[□]_D^{20}$ = –11.0° (c 1.0, $CHCl_3$, 39.6% ee), IR (neat) 1730 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 7.52 (d, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.28–7.18 (m, 2H), 6.66 (s, 1H), 5.26 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.73 (s, 3H), 3.32 (d, *J* = 5.4 Hz, 1H), 2.94–2.89 (m, 2H). ^{13}C NMR ($CDCl_3$) □ 171.8, 157.3, 544.6, 127.8, 124.1, 122.7, 121.0, 111.1, 102.8, 64.7, 52.0, 39.7. High resolution MS (*m*/*z*), calcd for $C_{12}H_{12}O_4$: 220.0736; found: 220.0712. **19**: (isolated by SiO_2 column chromatograph with 30% ethyl acetate in hexane), $[□]_D^{20}$ = –17.0° (c 1.1, $CHCl_3$, 89.3% ee), IR (neat) 1740 cm^{-1}, ^{1}H NMR ($CDCl_3$) □ 5.89 (s, 1H), 4.99 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 1H, OH), 2.77 (dd, *J* = 16.1, 9.3 Hz, 1H), 2.57 (dd, *J* = 16.1, 3.9 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$)

□172.3, 149.9, 146.1, 121.1, 104.1, 63.0, 51.6, 41.9, 13.2, 11.5. High resolution MS (*m*/*z*), calcd for $C_{10}H_{14}O_4$: 198.0892; found: 198.0900.

Hydrogenation of 4 (Figure 1 and Table 2).

The hydrogenation was carried out by heating a solution of **4** (0.3 g, 1.8 mmol) and acetic acid (20 □l) in THF (2 mL) in the presence of TA-MRNi (0.2 g) in a small autoclave (10 mL) under 10^7 Pa of H_2 at 60 °C. The composition of the reaction for the shorter time was determined by ^{1}H NMR spectral analysis as well as the GLC analysis (TC-WAX, 60 m, 0.25 mm id, flow rate: 30 cm/sec) using internal standard of methyl hexanoate for calibration of the sensitivities. The retention times at 150 °C are 4.0 min for the standard, 4.8 min for **10**, 5.7 min for **4**, 26.2 and 26.7 min for **12**, and 37.6 min for **11**.

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