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Asymmetric Hydrogenation of Tetrasubstituted Cyclic Enones to Chiral Cycloalkanols with Three Contiguous Stereocenters

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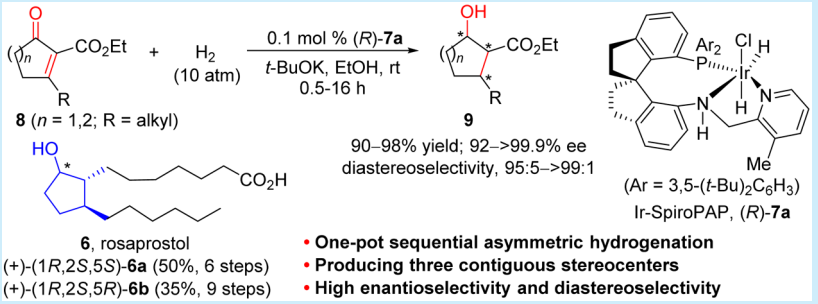
Supporting Information



ABSTRACT: A highly efficient iridium-catalyzed asymmetric hydrogenation of tetrasubstituted cyclic enones has been developed for the enantioselective synthesis of chiral cycloalkanols with three contiguous stereocenters. The C═O and C═C bonds of the enone substrates were hydrogenated sequentially in one pot with excellent enantioselectivity (92 to >99% ee) and diastereoselectivity (dr 95:5 to >99:1). The reaction provided a practical approach to all of the stereoisomers of the antiulcer drug rosaprostol.

Chiral cycloalkanols, particularly chiral cyclopentanols with contiguous stereocenters, are prevalent structural motifs in natural products, pharmaceuticals, and other bioactive molecules. Estradiol (**1**, the primary female sex hormone),[1] longeracemine (**2**, a daphniphyllum alkaloid),[2] and dipulchellin A (**3**, a sesquiterpene lactone dimer)[3] contain a chiral cyclopentanol unit with three contiguous stereocenters, one of which is an alkyl-substituted tertiary stereocenter (Figure 1). Prostaglandins and their analogues such as prostaglandin F2α (**4**, PGF2α, used to induce labor and as an abortifacient),[4] lantanoprost (**5**, used to treat increased pressure inside the eye),[5] and rosaprostol (**6**, used to treat gastric and duodenal ulcers),[6] which are widely used as pharmaceuticals,[7] are the most prominent examples of compounds with chiral core cyclopentanol structures with three or four contiguous stereocenters, in which the β-tertiary stereocenter linked with an alkyl group. Thus, the enantioselective synthesis of chiral cycloalkanols with contiguous stereocenters including a β-alkyl-substituted tertiary stereocenter have been the focus of study in organic synthesis.[8]

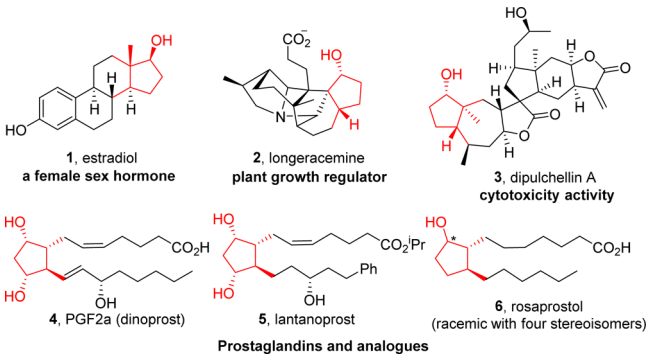


Figure 1. Representative natural products and pharmaceuticals containing cyclopentanol units with contiguous stereocenters.

Undoubtedly, transition-metal-catalyzed asymmetric hydrogenation of configurationally labile α-substituted ketones via dynamic kinetic resolution (DKR) is a reliable method for the syntheses of optically active chiral alcohols with contiguous stereocenters.[9] However, the asymmetric hydrogenation of cyclic ketones to chiral alcohols with three contiguous stereocenters remains a challenge. Recently, we have found that asymmetric hydrogenations of racemic disubstituted cyclohexanones and cyclopentanones with two configurationally labile α- or β-stereocenters catalyzed by chiral spiro ruthenium or iridium catalysts via DKR produce chiral alcohols with three contiguous stereocenters in high yield with high enantioselectivity and diastereoselectivity.[10] However, those reactions cannot be used to direct prepare chiral cyclic alcohols with a β-alkyl-substituted tertiary stereocenter because the β-C−H of the tertiary stereocenter of the ketone substrates is not

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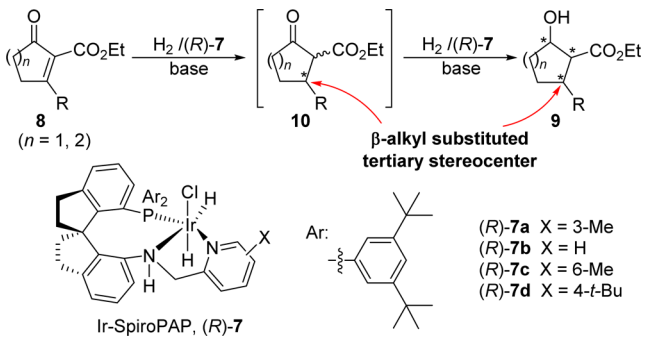
Org. Lett. XXXX, XXX, XXX−XXX

acidic enough to be epimerized under the DKR reaction conditions.

To develop an efficient method for the enantioselective synthesis of chiral cycloalkanols, especially those containing a β-alkyl-substituted tertiary stereocenter, we studied the catalytic asymmetric hydrogenation of β-alkyl-α-ethoxycarbonylcycloalkenones **8** to obtain chiral cycloalkanols **9** with three contiguous stereocenters (Scheme 1). We envisioned that the

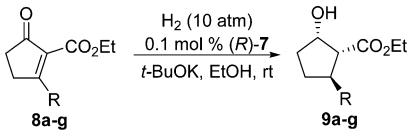
Scheme 1. Our Envisioned One-Pot Sequential Asymmetric Hydrogenation Strategy for the Synthesis of Chiral Cycloalkanols with Three Contiguous Stereocenters



asymmetric hydrogenation of the C=C bond of cycloalkenones **8** could install the β-alkyl-substituted tertiary stereocenter and followed by asymmetric hydrogenation of the C=O bond of the resulting β-ketoesters **10** via DKR chiral cycloalkanols **9** with three contiguous stereocenters could be achieved. Thus, a one-pot sequential asymmetric hydrogenation of tetrasubstituted cyclic enones could provide an efficient approach to chiral cycloalkanols with three contiguous stereocenters. Herein, we report our detailed investigations on the catalytic asymmetric hydrogenation of **8** to chiral cyclic alkanols **9** with excellent enantioselectivity and diastereoselectivity and the application of this method for the enantioselective syntheses of the stereoisomers of rosaprostol (**6**). It should be mentioned that, although the asymmetric hydrogenations of separated ketones and olefins have been well-explored, the asymmetric hydrogenation of α,β-unsaturated enones, especially the enones with tetrasubstituted olefin to saturated chiral alcohols, is still an unrealized goal in asymmetric catalysis.[11]

We chose β-methyl-α-ethoxycarbonylcyclopentenone (**8a**) prepared from a γ-ketoacid[12] as a model substrate to evaluate various chiral spiro iridium catalysts Ir-(*R*)-SpiroPAP, (*R*)-**7**.[13] The reaction was carried out under mild conditions: 0.1 mol % of catalyst and 10 mol % of *t*-BuOK as the base in EtOH under 10 atm of H_2 at room temperature (Table 1). When the catalyst (*R*)-**7a** was used, the hydrogenation of **8a** for 0.5 h afforded chiral alcohol β-methyl-α-ethoxycarbonylcyclopentanol (**9a**) in 93% yield with 97% ee and >99% *cis,trans*-selectivity (entry 1). The absolute configuration of **9a** was determined to be 1*R*,2*S*,5*S* by X-ray diffraction analysis of the crystal structure of its 3,5-dinitrobenzoyl derivative (Figure 2, left). This result shows that both the C=O and C=C bonds of the substrate were hydrogenated by catalyst (*R*)-**7a**. Thus, this reaction constitutes a one-step procedure for hydrogenation of two different functional groups, generating three contiguous stereocenters with excellent enantioselectivity and diastereoselectivity. Catalysts (*R*)-**7b–d** gave almost the same results as (*R*)-**7a** (entries 2–4). By using catalyst (*R*)-**7a**, a variety of cyclopentenones **8b–g** with different β-alkyl groups were

Table 1. Asymmetric Hydrogenation of β-Alkyl-α-ethoxycarbonylcyclopentenones 8a–g with (*R*)-7[a]



entry	R	(*R*)-7	9	time (h)	yield[b] (%)	ee[c] (%)
1	Me (**8a**)	(*R*)-**7a**	**9a**	0.5	93	97
2	Me (**8a**)	(*R*)-**7b**	**9a**	0.5	91	97
3	Me (**8a**)	(*R*)-**7c**	**9a**	0.5	92	97
4	Me (**8a**)	(*R*)-**7d**	**9a**	0.5	92	97
5	Et (**8b**)	(*R*)-**7a**	**9b**	0.5	92	98
6	*n*-Pr (**8c**)	(*R*)-**7a**	**9c**	2	90	93
7[d]	*i*-Pr (**8d**)	(*R*)-**7a**	**9d**	0.5	92	>99
8	*n*-Hex (**8e**)	(*R*)-**7a**	**9e**	0.5	94	97
9	$C_6H_5CH_2CH_2$ (**8f**)	(*R*)-**7a**	**9f**	0.5	95	>99
10[e]	$EtOC(O)CH_2$ (**8g**)	(*R*)-**7a**	**9g**	16	90	92

[a]Reaction conditions: 1.0 mmol scale, (*R*)-**7**/**8**/*t*-BuOK = 1/1000/100, [**8**] = 0.2 M, 10 atm H_2, EtOH, room temperature (25–30 °C), 0.5–16 h, 100% conversion, *cis,trans*-selectivity is >99:1 determined by HPLC. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase (see the Supporting Information). [d]*cis,trans*/*trans,cis* = 95:5 (*cis,cis*-isomer was not observed). [e]50 atm H_2, 40 °C.

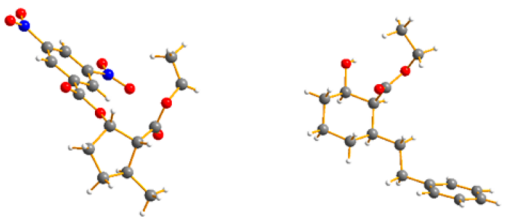


Figure 2. Crystal structures of the 3,5-dinitrobenzoyl derivative of **9a** (left) and the product **9m** (right).

hydrogenated to the corresponding cyclopentanols **9b–g** in high yield, excellent enantioselectivity, and diastereoselectivity (entries 5–10).

Encouraged by these results, we investigated the asymmetric hydrogenation of β-alkyl-substituted cyclohexenones **8h–n** with Ir-(*R*)-SpiroPAP catalysts. When the catalyst (*R*)-**7a** was used, the β-methyl-α-ethoxycarbonylcyclohexanone (**8h**) was hydrogenated to the cyclohexanol **9h** in 0.5 h in 94% yield with 99% ee and >99% *cis,cis*-selectivity (Table 2, entry 1). The *cis,cis*-(1*S*,2*R*,6*S*) configuration of **9h** was determined by ^{1}HNMR spectroscopy and optical rotation compared with the literature data.[14] The catalysts (*R*)-**7b–d** were evaluated, and also, almost the same results were observed (entries 2–4). With catalyst (*R*)-**7a**, other cyclohexenones **8i–n** with different β-alkyl groups were hydrogenated, producing cyclohexanols **9i–n** in high yields (90–98%) with excellent enantioselectivity (96 to >99% ee) and excellent diastereoselectivity (*cis,cis*-isomer: > 99%) (entries 5–10). A crystal of **9m** was grown, and the single-crystal X-ray diffraction analyses showed that the absolute configuration of **9m** is 1*S*,2*R*,6*R* (Figure 2, right).

To rationalize the stereochemistry of the reaction, we monitored the progress of the hydrogenation of **8a** by gas chromatography (Scheme 2). The product of C=C bond hydrogenation, *trans*-**10a**, predominated during the early stage of the reaction (Figure 3). Fully hydrogenated product (1*R*,2*S*,5*S*)-**9a** formed slowly at the beginning of the reaction

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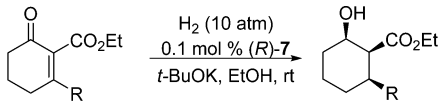
Table 2. Asymmetric Hydrogenation of β-Alkyl-α-ethoxycarbonylcyclohexenones 8h–n with (*R*)-7[a]

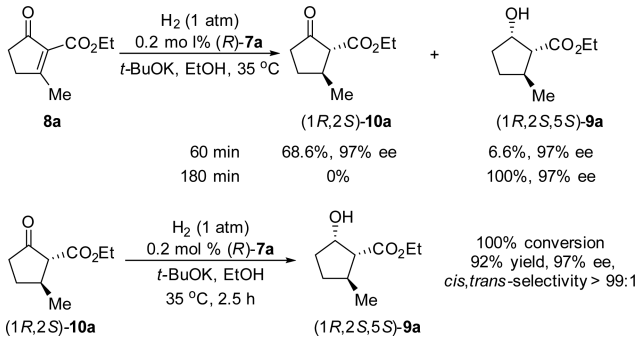


8h-n 9h-n

entry	R	(*R*)-7	9	time (h)	yield[b] (%)	ee[c] (%)
1	Me (**8h**)	(*R*)-**7a**	**9h**	0.5	94	99
2	Me (**8h**)	(*R*)-**7b**	**9h**	0.5	92	99
3	Me (**8h**)	(*R*)-**7c**	**9h**	0.5	93	99
4	Me (**8h**)	(*R*)-**7d**	**9h**	0.5	94	99
5	Et (**8i**)	(*R*)-**7a**	**9i**	0.5	92	>99
6	*n*-Pr (**8j**)	(*R*)-**7a**	**9j**	0.5	98	>99
7	*n*-Bu (**8k**)	(*R*)-**7a**	**9k**	0.5	98	98
8	*i*-Bu (**8l**)	(*R*)-**7a**	**9l**	0.5	96	96
9	$C_6H_5CH_2CH_2$ (**8m**)	(*R*)-**7a**	**9m**	2	95	99
10	$EtOC(O)CH_2$ (**8n**)	(*R*)-**7a**	**9n**	16	90	99

[a]Reaction conditions: 1.0 mmol scale, (*R*)-7/**8**/*t*-BuOK = 1/1000/100, [**8**] = 0.2 M, 10 atm H_2, EtOH, 25–30 °C, 0.5–16 h, 100% conversions, *cis*,*cis*-isomer is >99% determined by HPLC. [b]Isolated yield. [c]Determined by GC or HPLC on a chiral stationary phase (see the Supporting Information).

Scheme 2. Process of Hydrogenation of 8a with (*R*)-7a



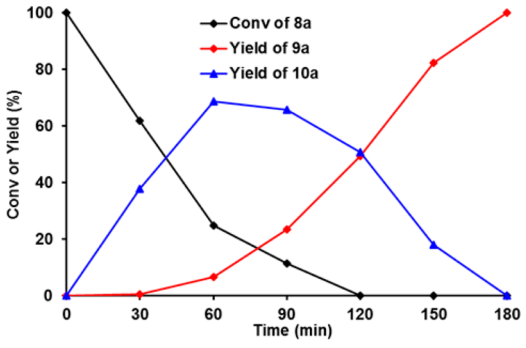
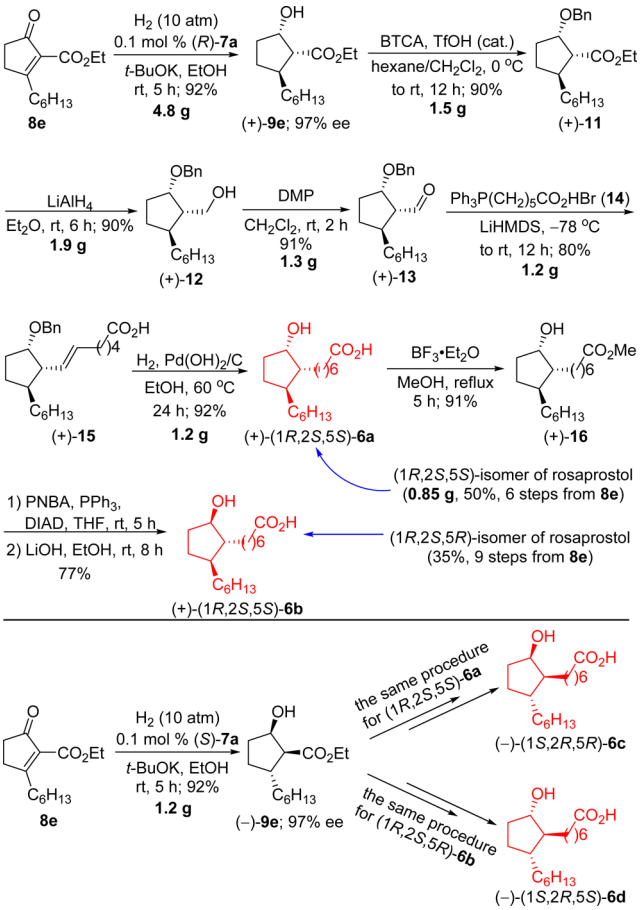


Figure 3. Plots of the process of hydrogenation of **8a** with (*R*)-**7b** (reaction conditions: 1.0 mmol scale, (*R*)-**7b**/**8a**/*t*-BuOK = 1/500/50, [**8a**] = 0.2 M, 1 atm of H_2, EtOH, 35 °C, conversions determined by GC).

but eventually became the major product and finally the only product. We isolated *trans*-**10a** from the reaction mixture and found it to have the same ee as the final product (1*R*,2*S*,5*S*)-**9a**. These results suggested that the hydrogenation proceeds through hydrogenation of the C=C bond of **8a** to form β-ketoester (1*R*,2*S*)-**10a**, followed by hydrogenation of the C=O bond of (1*R*,2*S*)-**10a** via DKR to afford (1*R*,2*S*,5*S*)-**9a**. Similar progress was also observed for the asymmetric hydrogenation of cyclohexanone **8h** (see the Supporting Information).

With this highly efficient, selective method for construction of chiral cyclic alcohols with three contiguous stereocenters in hand, we investigated the catalytic enantioselective synthesis of the stereoisomers of rosaprostol (**6**), which exhibit gastric antisecretory activity and cytoprotective action without the undesired side effects common to other prostanoids (e.g., diarrhea, hypotension, and uterine stimulation[15]) and is used to treat gastric and duodenal ulcers under the brand name Rosal.[6] However, owing to the lack of efficient methods for enantioselective construction of the chiral core cyclopentanol structure of rosaprostol,[16] the drug is used as a racemic sodium salt (that is, a mixture of racemic *trans*,*cis* and *trans*,*trans* diastereomers), and the active stereoisomer remains unknown. Using catalyst (*R*)-**7a**, the cyclopentenone **8e** was hydrogenated to cyclopentanol (+)-**9e** in 92% yield with 97% ee on a gram scale (Scheme 3). Protection of the hydroxyl group of (+)-**9e**

Scheme 3. Enantioselective Syntheses of the Stereoisomers of Rosaprostol



with benzyl 2,2,2-trichloroacetimidate (BTCA) yielded (+)-**11** in 90% yield. Reduction of (+)-**12** with $LiAlH_4$, followed by oxidation with Dess–Martin periodinane (DMP), afforded aldehyde (+)-**13** in 82% yield for two steps. Reaction of (+)-**13** with Wittig reagent **14** provided the acid (+)-**15** in 80% yield without epimerization at C-1. Finally, hydrogenation of (+)-**15** over $Pd(OH)_2/C$ yielded target molecule (+)-**6a** in 92% yield. Because no change in configuration occurs during the transformation of (+)-**9e** to (+)-**6a**, we synthesized

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Org. Lett. XXXX, XXX, XXX–XXX

(+)-(1*R*,2*S*,5*S*)-rosaprostol from cyclopentenone **8e** in six steps in 50% overall yield on a gram scale.

With (+)-(1*R*,2*S*,5*S*)-**6a** as a chiral starting material, we then synthesized the (1*R*,2*S*,5*R*)-isomer of rosaprostol, (+)-(1*R*,2*S*,5*R*)-**6b** (Scheme 3). Esterification of (+)-(1*R*,2*S*,5*S*)-**6a** with MeOH in the presence of $BF_3{\cdot}Et_2O$ furnished the corresponding methyl ester (+)-**16** in 91% yield. The ester (+)-**16** was then reacted with *p*-nitrobenzoic acid (PNBA) in the presence of triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate under normal Mitsunobu esterfication conditions and followed by hydrolysis with LiOH in one pot according to the procedure reported by Mikołajczyk et al.[15] to afford (1*R*,2*S*,5*R*)-**6b** in 77% yield. Thus, the rosaprostol stereoisomer (+)-(1*R*,2*S*,5*R*)-**6b** was obtained in 70% yield over three steps including a Mitsunobu inversion of the configuration of the C-5 hydroxyl group. In addition, we also carried out (*S*)-**7a**-catalyzed asymmetric hydrogenation of **8e** and obtained (−)-**9e** in 91% yield with 97% ee (Scheme 3). By using the same procedure as that for the syntheses of the rosaprostol stereoisomers (+)-(1*R*,2*S*,5*S*)-**6a** and (+)-(1*R*,2*S*,5*R*)-**6b**, the other two stereoisomers of rosaprostol, (−)-(1*S*,2*R*,5*R*)-**6c** and (−)-(1*S*,2*R*,5*S*)-**6d**, can undoubtedly be obtained from (−)-**9e**. Thus, we have established an efficient catalytic method for the enantioselective syntheses of all stereoisomers of rosaprostol. This represents the first example of catalytic asymmetric synthesis of the stereoisomers of rosaprostol.

In conclusion, we have developed a highly efficient iridium-catalyzed asymmetric hydrogenation of *β*-alkyl cyclic enones for the synthesis of chiral cyclic alcohols with three contiguous stereocenters. During the reaction, the C═O and C═C bonds of the enone substrates were hydrogenated sequentially in a single step with excellent enantioselectivity and diastereoselectivity. This practical protocol served as the key step in the syntheses of the stereoisomers of the antiulcer drug rosaprostol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01343.

Experimental procedures and characterization of the substrates and products (PDF)
X-ray data for compound **9m** (CIF)
X-ray data for the dibitrobenzoyl derivative of **9a** (CIF)

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Notes

The authors declare no competing financial interest.

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