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A short diastereoselective synthesis of *cis*-(2*S*,4*S*) and *cis*-(2*R*,4*R*)-4-hydroxyprolines

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ABSTRACT

A concise synthesis of (2*R*,4*R*)-4-hydroxyproline (**1**) and (2*S*,4*S*)-4-hydroxyproline (**2**) has been developed in enantiomerically pure form from commercially available starting materials with excellent diastereoselectivity. The tightly bound chelation controlled transition state formed during the 5-*exo*-*tet* ring closure reaction is assumed to be the origin of high diastereoselectivity.

3- and 4-Hydroxyprolines have attracted widespread attention in the recent past as a useful chiral building block in organic synthesis. These chiral building blocks were extensively used for the synthesis of glycopeptides,[1] antimetabolite of glutamic acid, ACE inhibitors,[2] and 1-β-methylacarbapenem antibiotics. 3- and 4-Hydroxyprolines are also used in the agrochemical industry.[3] Recently the application of *cis*-4-hydroxyproline in topical medication is also disclosed.[4] One of the key structural fragments of naturally occurring phalloidine alkaloid is *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**).[5] Chirally pure 4-hydroxyproline was first isolated from gelatin hydrolyzates[6] and Luechs et al. reported the first synthesis of racemic 4-hydroxyproline in 1937.[7] Subsequently numerous methodologies were reported in the literature for the synthesis of racemic 4-hydroxy-prolines.[8] The diastereo as well as enantioselective synthesis of (2*R*,4*R*)-hydroxyproline (**1**) and (2*S*,4*S*)-4-hydroxyproline (**2**) are rarely disclosed in the literature.

Papaioannou et al.[9] and Seki et al.[10] reported the synthesis of (2*R*,4*R*)-4-hydroxy-proline **1** by the inversion of a stereocenter in (2*R*,4*S*)-4-hydroxyproline under Mitsunobu reaction conditions. The synthesis of **1** is also reported by Thirring et al.[11] from (−)-menthyl ester of hippuric acid.[12] However; both syntheses use the separation techniques for enriching the de of the required *cis* isomer. The enantioselective synthesis of **1** through stereocontrolled 1,4-*trans* alkylation of (6*S*)-methyl-4-(1*S*)-phenylethyl-1,4-morpholine-2,5-diones is a noteworthy approach.[13] Syntheses of **1** and **2** are also reported from the amino acid,[14a] carbohydrates,[14b] and 4-oxo-1,2-pyrrolidinedicarboxylic acid dimethyl ester.[15] Recently Kimura et al. demonstrated the synthesis of both enantiomers of *cis*-4-hydroxyproline using Wittig olefination protocol (Fig. 1).[16]

Though some of these syntheses commenced with chirally pure starting materials, the product 4-hydoxyproline is obtained with low diastereomeric excess. The lengthy synthetic sequence, use of complex and expensive reagents, and tedious purification procedures adapted for enriching the diastereomeric excess in these synthesis demand efficient protocols for the preparation of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) and *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**) in a minimum number of stages. As a part of our efforts to develop new methodologies for the total synthesis of natural products,[17] herein we disclose our successful efforts toward the development of a concise and highly diastereoselective synthesis of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) and *cis*-(2*S*,4*S*)-4-hydroxyproline (**2**).

The retro synthetic approach for the diastereoselective synthesis of *cis*-(2*R*,4*R*)-4-hydroxyproline (**1**) is outlined in Scheme 1. The deprotection of *N*-Boc/*N*-benzyl proline ester **3** under standard deprotection conditions could easily generate (2*R*,4*R*)-4-hydroxyproline (**1**). The required proline ester **5** could be obtained from enantiomerically pure amino epoxide **6** under intramolecular 5-*exo*-*tet* ring closure conditions (*path A*) from a highly chelated Zn(II) or Mg(II) complexes. The reaction of optically pure

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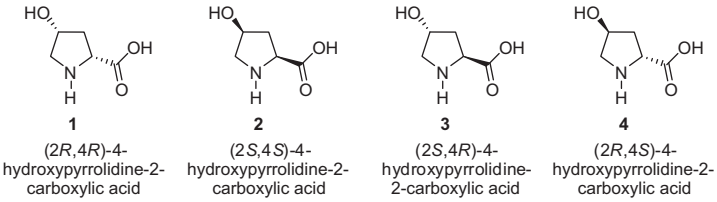
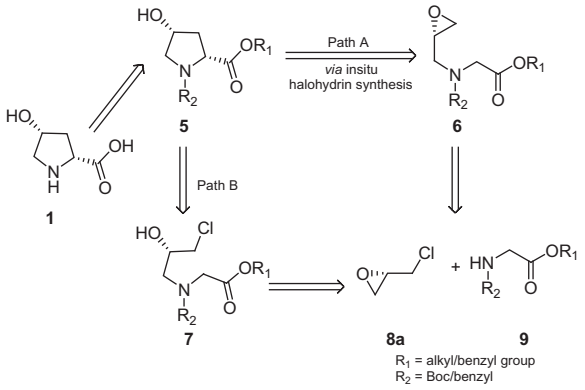


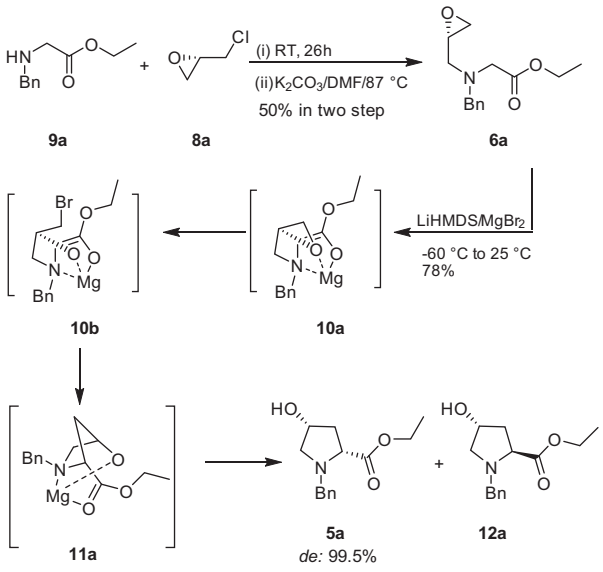
Figure 1. Stereoisomer's of 4-hydroxyproline.



Scheme 1. Retro synthetic analysis of *cis*-4-hydroxyproline.

(*S*)-epichlorohydrin (**8a**) and glycine ester **7** would generate chiral epoxide **6**. In Path-B, (2*R*,4*R*)-4-hydroxyproline (**1**) is envisaged to be obtained from chirally pure chlorohydrins **7** by using the memory of chirality protocol.[18] Chlorohydrins **7** required for the synthesis of **1** could easily synthesized by the reaction of epichlorohydrin **8a** with glycine ester **9**.

The synthesis of **1**was initiated using commercially available enantiomerically pure (*S*)-epichlorohydrin (**8a**) and *N*-benzyl glycine ethyl ester **9a** (Scheme 2). *N*-Benzyl glycine ethyl ester **9a**reacted with (*S*)-epichlorohydrin **8a** at ambient temperature to yield chlorohydrin **7a**, which was then in situ converted to the amino epoxide **6a** using potassium carbonate and DMF at elevated temperature in 50% yield.[19] The key step, the intramolecular oxirane ring opening of **6a** leading to the formation of ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was designed under 5-*endo-tet* ring opening reaction conditions. Thus, amino epoxide **6a** was reacted with bases like NaH, KO^{t}Bu, NaOEt, and LDA over a wide range of temperatures; however these reactions failed to yield the required product **5a**. The oxirane ring opening in **6a**, was also attempted with 1.5 equiv of LiHMDS in THF in the temperature range of −60 °C to 0 °C, however, this reaction also resulted in the formation of a complex mixture of products. The experiments conducted with higher equiv of LiHMDS at different temperatures in solvents like 2-MeTHF, CPME, toluene, as well as in MTBE also failed to yield 4-hydroxypyrrolidine-2-carboxylate **5a**. The inability of the oxirane **6a** to undergo disfavored 5-*endo-tet* ring closure reaction prompted us to use oxophilic metal halide as an additive in the reaction to stabilize the lithium enolate as well as for the in situ generation of halohydrin (Scheme 2). Thus, when the oxirane ring opening was carried out in presence of Zn(II), Mg(II), Li(I), as well as Cu(II) halides, the required product **5a** was obtained in various percentages as summarized in Table 1. The best diastereoselectivity and yield were obtained when the oxirane ring opening in **6a**, was attempted with 1.5 equiv of LIHMDS in the presence of 1 equiv of $MgBr_2$. The product hydroxypyrrolidine-2-carboxylate **5a** with SOR $[\alpha]_D^{20}$ +37.9° (c 1.0, $CHCl_3$)[20] was isolated in 78% yield with 99.5% de.[21] In-order to check the chiral purity of the ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) by the HPLC method, other diastereomers were synthesized as per the reported literature protocols.



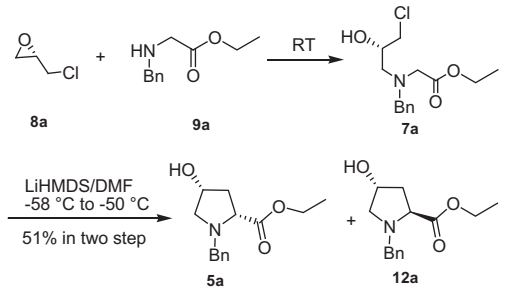
Scheme 2. Synthesis of *cis*-4-hydroxyproline from chiral epoxide **6a**.

The diastereoselective intramolecular 5-*exo-tet* ring closure reaction of **6a** leading to the formation of ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) is assumed to proceed via tightly bound chelation controlled transition states. The lithium enolate formed from chiral epoxide **6a** by deprotonation with LiHMDS forms a highly stabilized magnesium enolate with $MgBr_2$ along with the liberation of halide ion. The magnesium enolate then activates the epoxide via coordination and forms halohydrin **10b**. The hydroxyl oxygen of halohydrin, enolate oxygen, and tertiary amine together forms a tricoordinate complex with the magnesium ion. The metal coordinated transition states such as **10a**, **10b**, and **11a** ensure that the enolate oxygen and the hydroxyl oxygen will have *syn* facial orientation. The formation of these tightly

Table 1
Synthesis of *cis*-4-hydroxyproline from chiral epoxide **6a**

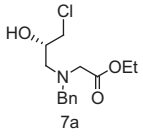
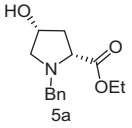
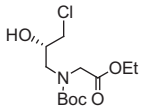
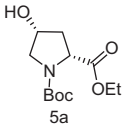
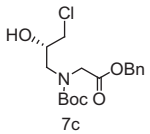
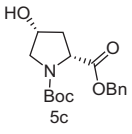
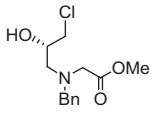
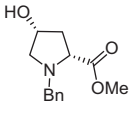
Entry	Substrate	Metal halide	Equiv of LiHMDS/ metal halide	Yield (%)	de (%)
1	**6a**	$ZnBr_2$	1.5/1.0	55[a]	98.5
2	**6a**	ZnI_2	1.5/1.0	63[a]	99.5
3	**6a**	$MgBr_2$	1.5/1.0	78[a]	99.5
4	**6a**	LiBr	1.5/1.0	30[b]	98.0
5	**6a**	LiCl	1.5/1.0	<5%	Not analyzed
6	**6a**	$CuCl_2$	1.5/1.0	<5%	Not analyzed

[a] The reaction terminated after 4 h.
[b] The reaction terminated after completion as per TLC.



Scheme 3. Synthesis of *cis*-4-hydroxyproline from chlorohydrin **7a**.

Table 2
Synthesis of **3** from halohydrin **7** in DMF/THF at −50 °C

Entry	Substrate	Product	de (%)	Yield (%)
1	 7a	 5a	99.5	51
2	 7b	 5a	88.0	72
3	 7c	 5c	77.3	54
4	 7d	 5d	99.0	49

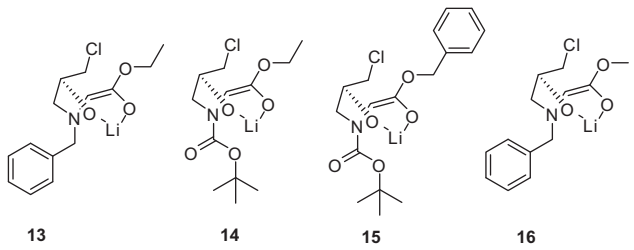
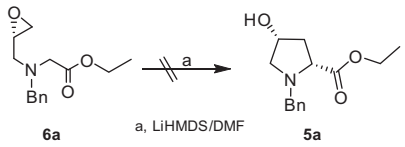


Figure 2. Transition state for the formation of **5a**, **5b**, **5c**, and **5d**.

bound magnesium coordinate complexes **10a**, **10b**, and **11a** drives the diastereoselectivity in the reaction (Scheme 2).

To get more mechanistic insight about the diastereoselective synthesis of (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**), we decided to use chiral chlorohydrin **7** instead of the epoxide **6** in the synthesis. For the synthesis of key intermediate ethyl-(*S*)-*N*-benzyl-*N*-(3-chloro-2-hydroxypropyl)glycinate(**7a**), ethyl benzyl glycinate **9a** was reacted with (*S*)-epichlorohydrin (**8a**) in neat conditions at 25–30 °C. When the 5-*exo tet* ring closure was attempted with LiHMDS in DMF at −60 °C, the required product (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was obtained approximately in 15% yield. Encouraged by this result, the reaction was attempted to optimize to improve the yield of required product **5a**. The use of excess equiv of LiHMDS did not improve the



Scheme 4. Attempted Synthesis of 4-hydroxyproline from epoxide **6a**.

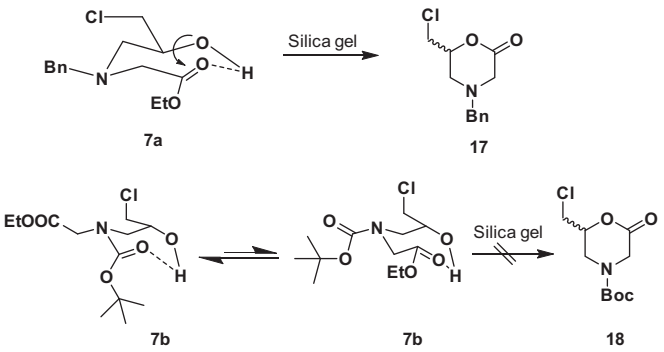
yield of the reaction further. Surprisingly, when the reaction was conducted at slightly higher temperature (−50 °C), the required product (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (**5a**) was isolated in 51% yield with 99.5% de. The ring closure reaction went equally well when conducted in THF with LiHMDS at −50 °C and further maintenance at −5 °C over a period of 4 h. The moderate yield as well as high diastereoselectivity achieved in this reaction is believed to occur by the *syn* complexation between the lithium enolate with –OH group, which is further stabilized by the coordinating solvents like DMF. (Scheme 3) Further variations in reaction conditions, and mol equiv of reagents did not improve the yield of *cis*-4-hydroxy proline derivative **5a**. The synthesis of benzyl (*S*)-*N*-(tert-butoxycarbonyl)-*N*-(3-chloro-2-hydroxypropyl)glycinate (**7c**) was carried out by reacting glycine benzyl ester tosylate salt with (*S*)-epichlorohydrin (**8a**) in IPA followed by in situ Boc-protection in 51% overall yield (Table 2).

To understand the impact of protecting groups in 4-hydroxypyrrolidine-2-carboxylate (**5**) synthesis, the reaction was carried out with different amine and acid protecting groups as described in Table 2. Among the protecting groups, the best yield (72%) of *cis*-proline derivative **5b** was obtained when the amine and acid functionality were protected with Boc and ethyl ester respectively; however a diminished de of 88% was obtained with these substrates.

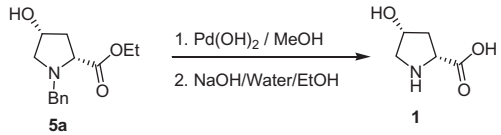
The formation of hydroxyl proline ester **5b** and **5c** with lesser de are probably due to the increased steric repulsion between the bulky amine and acid protecting groups which partially block the *syn* facial metal complexation between the lithium enolate and hydroxyl groups in the transition states of **14** and **15**, respectively (Fig. 2).

The chiral epoxide **6a** when subjected to hetero annulation reaction using DMF/LiHMDS/THF, failed to yield *cis*-4-hydroxy proline derivative **5a**, which clearly proves that the reaction did not proceed as per less preferred 5-*endo tet* Baldwin cyclization pathway. React IR studies were also conducted to check the intermediacy of epoxide **6a** during the conversion of halohydrin **7a** to *cis*-4-hydroxy proline derivative **5**. These studies clearly rule out the intermediacy of epoxide **6a** during the conversion of chlorohydrin **7a** to *cis*-proline derivative **5a** and the reaction proceeds through the preferred Baldwin's 5-*exo tet* pathway[22] (Scheme 4).

Interestingly, during the course of the purification of halohydrin **7a** by silica gel column chromatography, lactone **17** was isolated in 20% yield. This silica gel assisted lactonization of **7a** is probably due

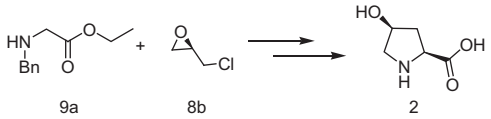


Scheme 5. The lactonization of chlorohydrin **7a**.



5a 1

Scheme 6. Synthesis of (2*R*,4*R*)-4-hydroxy-proline (**1**).



9a 8b 2

Scheme 7. Synthesis of (2*S*,4*S*)-4-hydroxy-proline (**2**).

to the favored conformational orientation of **7a** via hydrogen bonding between the carbonyl carbon of ethyl ester and the hydroxyl group, which favors the intramolecular lactonization. Halohydrin **7b** has failed to yield lactone **18** even after stirring **7b** with silica gel in various percentages of hexane and ethyl acetate mixture (Scheme 5) on prolonged time, as well as at elevated temperature.

Ethyl (2*R*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate **5a** was then converted to (2*R*,4*R*)-4-hydroxy-proline (**1**) by debenzylation with $Pd(OH)_2$ followed by hydrolysis of ester with aqueous sodium hydroxide in 80% yield (Scheme 6) over two steps. The SOR, spectral and analytical data of (2*R*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid **1** thus obtained are identical to the values reported in the literature.

In a similar way, (2*S*,4*S*)-4-hydroxypyrrolidine-2-carboxylic acid **2** was also synthesized in high de (99.5%) in moderate yields starting from (*R*)-epichlorohydrin **8b** and glycine ester **9a** as described in Scheme 7.

In conclusion, a concise and highly diastereoselective synthesis of (2*R*,4*R*)-4-hydroxyprolineand (2*S*,4*S*)-4-hydroxyprolinein with high de have been developed from readily accessible starting materials in moderate yields. The high de observed in the synthesis of *cis* 4-hydroxyproline is probably due to the highly chelated complex formed during the *exo tet* ring closure process, as well as via the stabilization of the enolate by coordinating solvent. The application of this methodology for the diastereoselective synthesis of densely functionalized diverse products is under progress and will be reported in due course of time.

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Supplementary data

Supplementary data (detailed experimental analysis and spectral analysis including ^1H, ^{13}C, and HRMS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.03.119.

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19. *(S)-Ethyl 2-(benzyl (oxiran-2-ylmethyl)amino)acetate) (**6a**):* pale yellow viscous liquid. (Yield = 50%) ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.26 (t, *J* = 7.3 Hz, 3H), 2.47 (dd, *J* = 2.9 Hz, 1H), 2.63–2.73 (m, 2H), 2.98 (dd, *J* = 3.4, 1H), 3.01–3.11 (m, 1H), 3.45 (s, 2H), 3.81 (d, *J* = 13.7 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 1H), 4.14 (q, *J* = 7.4 & 6.8 Hz, 2H), 7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.2, 44.69, 51.08, 54.66, 56.03, 58.76, 60.24, 127.17, 128.27, 128.89, 138.55, 171.27. IR: 3685, 3019, 2400, 1732, 1520, 1495, 1477, 1214, 775, 669. HRMS (ESI): Calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1433. $[\alpha]_D^{25}$ 1.22° (c 0.5, $CHCl_3$).
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21. *Procedure for the synthesis of **5a**:* a solution of (*S*)-ethyl 2-(benzyl (oxiran-2-ylmethyl)amino)acetate) **6a** (500 mg, 2.01 mmol) in THF (7.5 mL, 15 vol) was cooled to −60 °C and was added 1.5 equiv of 1 M LiHMDS in THF (3 mL, 3.01 mmol). The reaction mixture was then allowed to warm to −15 °C for 10 min and cooled to −60 °C. $MgBr_2$/etherate (622 mg, 2.41 mmol, 1 equiv) or Zn(II)I_2 (1 equiv) in THF (2.5 v) was added into the reaction mixture over a period of 30 min. The reaction mixture was then maintained at room temperature and was stirred for 3 h. It was then cooled to −10 °C, quenched with aqueous saturated NH_4Cl solution (50 mL) and diluted with ethyl acetate (25 mL). The layers were separated, the aqueous layer extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water, 10% brine solution, dried over sodium sulfate and evaporated. Crude product was then purified by column chromatography on silica gel (230–400 mesh) using ethyl acetate and hexane (1:4) to afford 390 mg of title compound as a pale yellow liquid. Yield: 78% ($MgBr_2$), 63% (ZnI_2). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.21 (t, *J* = 7.4 Hz, 3H), 1.9–2.0 (m, 1H), 2.33–2.4 (m, 1H), 2.64 (dd, *J* = 3.9 and 4.4 Hz, 1H), 3.01 (d, *J* = 9.8 Hz, 1H), 3.2 (br s, 1H), 3.33 (dd, 3.5 and 3.4 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.87 (d, *J* = 13.2 Hz, 1H), 4.07 (m, 2H), 4.24 (m, 1H), 7.2–7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.06, 39.11, 58.07, 60.96, 61.78, 63.39, 70.91, 127.18, 128.2, 128.92, 138.01, 175.10. IR: 3451, 1729, 1454, 1376, 1216, 756, 700. HRMS (ESI): Calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1436. $[\alpha]_D^{20}$ +39.04° (c 1.0, $CHCl_3$), $[\alpha]_D^{20}$ +37.9° (c 1.0, $CHCl_3$). % de (HPLC) = 99.5.
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