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Asymmetric total synthesis of four bioactive lignans using donor–acceptor cyclopropanes and bioassay of (−)- and (+)-niranthin against hepatitis B and influenza viruses†

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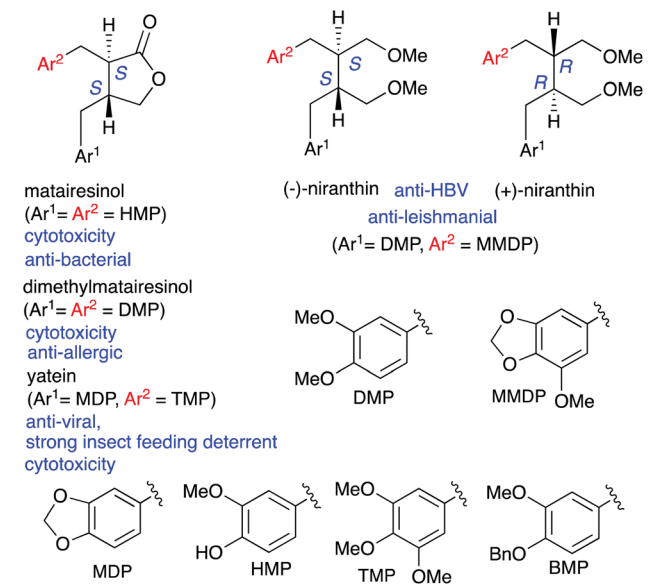
The asymmetric total synthesis of four lignans, dimethylmatairesinol, matairesinol, (−)-niranthin, and (+)-niranthin has been achieved using reductive ring-opening of cyclopropanes. Moreover, we performed bioassays of the synthesized (+)- and (−)-niranthins using hepatitis B and influenza viruses, which revealed the relationship between the enantiomeric structure and the anti-viral activity of niranthin.

Lignans are attracting considerable attention due to their widespread distribution in plants and their varied bioactivity.[1–5] For example, matairesinol,[2] dimethylmatairesinol,[3] yatein,[4] and niranthin[5] are found in nature and exhibit *e.g.*, cytotoxicity,[2b,d,3b,4b] anti-bacterial,[2c] anti-allergic,[3c] anti-viral,[4d,5b,e] anti-leishmanial,[5d] and strong insect-feeding-deterrent activity.[4c] Among these compounds, anti-viral compounds have received significant attention owing to the worldwide pandemic of coronavirus disease 2019 (COVID-19). Although niranthin exhibits anti-viral activity toward the hepatitis B virus (HBV),[5b,e] the enantiomeric SAR (structure–activity relationship) for the anti-viral activity of niranthin has not been revealed so far. To examine the SAR for a pair of enantiomers, an independent asymmetric synthesis of both enantiomers is necessary. However, the alternative synthesis of (−)- or (+)-niranthin has not been reported.[6] During our recent studies on the transformation of cyclopropanes,[7] we have reported a reductive ring-opening of enantioenriched donor–acceptor (D–A) cyclopropanes and its application to an asymmetric total synthesis of yatein.[7i] As a further extension of this synthetic method, we disclose here the asymmetric total synthesis of (−)-dimethylmatairesinol, (−)-matairesinol, (+)-niranthin, and (−)-niranthin. Moreover, the results of bioassays using (+)-niranthin and (−)-niranthin against HVB and influenza virus (IFV) are described (Scheme 1).

Scheme 2 outlines the enantioselective synthesis of optically active lactones **5a** and **5b**. Following our previous report,[7i] we attempted to synthesize the enantio-enriched bicyclic lactones **4a** and **4b**.

Initially, the cyclopropanation of enal **1** with dimethyl α-bromomalonate **2** using the Hayashi–Jørgensen catalyst afforded the desired optically active cyclopropylaldehydes **3a** and **3b** in good to high yield with high ee.[7c,e,h–j,8,9] The reduction of the



Scheme 1 Some examples of bioactive dibenzyl lignans.

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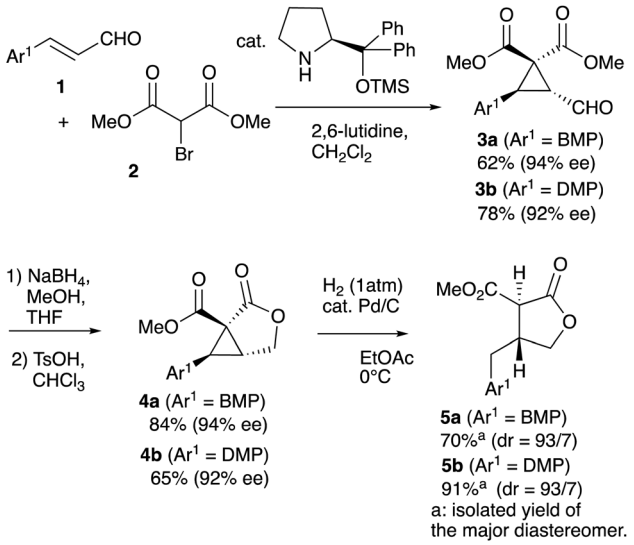
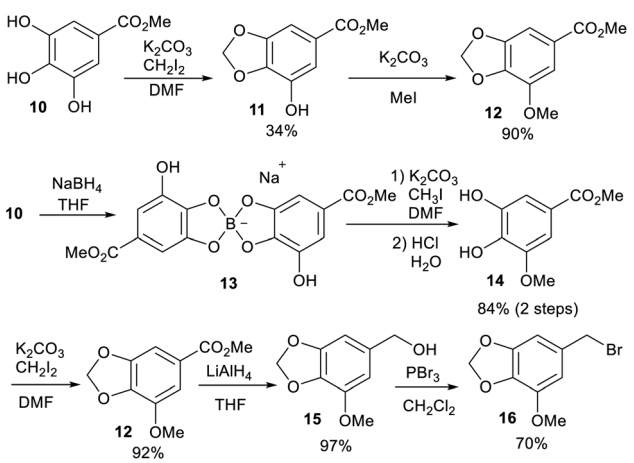


Scheme 2 Enantioselective synthesis of key intermediates **5a** and **5b**.

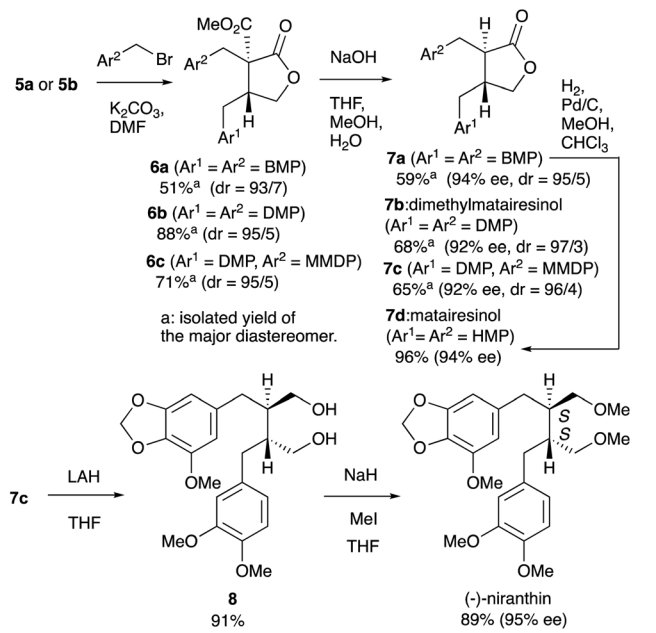
aldehydes to alcohols and subsequent lactonization with *p*-TsOH afforded lactones **4a** and **4b** in high yield with high ee. The optical purity of lactones **4a** and **4b** were determined using HPLC analyses on a chiral column, and the ee values of the enantioselective cyclopropanations were estimated based on these HPLC analyses. Next, treatment of bicyclic lactones **4a** and **4b** with hydrogen in the presence of a catalytic amount of Pd–C in AcOEt at 0 °C resulted in a regioselective reductive ring-opening to furnish benzyloxylactones **5a** and **5b** in good to high yield with high dr and high ee. In the hydrolysis step, debenzylation of the benzyloxyaryl group did not occur under these mild conditions, *i.e.*, in AcOEt at 0 °C.[7i]

For the α-benzylation of **5a** and **5b** to afford **6a–c**, the corresponding substituted benzylhalides were necessary. 3-Methoxy-4-benzyloxybenzylbromide and 3,4-dimethoxybenzylbromide were easily prepared by known methods (for details, see the ESI†); however, the preparation of 3,4-methylenedioxy-5-methoxybenzylbromide (**16**) required a modified procedure that involves the regioselective protection of the hydroxy group at the 3-position of 3,4,5-trihydroxybenzene (Scheme 3). The methylenedioxylation of gallic acid (**10**) during the first step resulted in a low yield of **11**.[10] Consequently, we successfully synthesized **12** using a cyclic boron-ester system.[11] Arylmethylbromide **16** was derived from ester **12** in two steps in good to high yield.

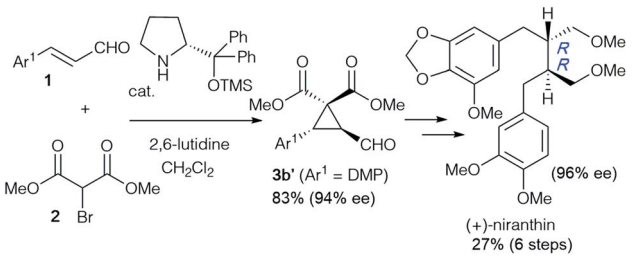


Scheme 3 Preparation of substituted benzylbromide **16**.

Next, enolates were generated from lactones **5a** and **5b** using K_2CO_3 in DMF, and successfully attacked the benzylhalides on the less-hindered side to afford α-benzyl lactones **6a–c** with excellent dr values (Scheme 4).[7i,12] The *trans*-α,β-disubstituted lactones **7a–c** were obtained *via* the hydrolysis of the α-methoxycarbonyllactones **6a–c** followed by decarboxylation. The transformation from the enol form to the keto form gave the thermodynamically favored *trans* products (**7a–c**) with excellent dr values.[7i,12] Finally, the debenzylation of **7a** using a catalytic amount of Pd–C in methanol under a hydrogen atmosphere afforded matairesinol (**7d**) in 96% yield. Thus, the total syntheses of dimethylmatairesinol (**7b**) and matairesinol (**7d**) were achieved, and spectral data of these natural products were consistent with reported data.[2e,3d] The absolute configuration of these compounds were determined using the known data of optical rotation values. The reduction of lactone **7c** using LAH afforded diol **8** in 91% yield (Scheme 4). Subsequent dimethylation of the resulting diol **8** using NaH and MeI furnished (−)-niranthin in 89% yield with 95% ee.[13] Spectral data of (−)-niranthin was also consistent with reported data.[5b,e,6] Following the total synthesis of (−)-niranthin, we also achieved the total synthesis of (+)-niranthin *via* an alternative enantioselective cyclopropanation using a different enantiomeric Hayashi–Jørgensen catalyst derived from D-proline instead of L-proline (Scheme 5).[14]



Scheme 4 Alternative asymmetric total synthesis of dimethylmatairesinol, matairesinol, and (−)-niranthin.



Scheme 5 Alternative asymmetric total synthesis of (+)-niranthin.

(−)-Niranthin has been reported to exhibit anti-HBV activity.[5b,e] Aiming to shed light on the relationship between its enantiomeric structure and activity, we performed a bioassay on the synthesized (−)- and (+)-niranthin against not only HBV, but also the influenza virus (IFV). The anti-HBV activity results are summarized in Fig. 1 and 2, while the anti-IFV activity is summarized in Fig. 3 (for details, see the ESI†).

Based on the assays using HBV-infected HepG2-hNTCP-C4 cells and HBV-replicating Hep38.7-tet cells, the amount of HBs antigen decreased in a concentration-dependent manner without apparent cytotoxicity. The 50% inhibition concentration (IC_{50}) in the HBV-infected cells was calculated to be 14.3 ± 0.994 μM for (−)-niranthin and 9.11 ± 0.998 μM for (+)-niranthin (Fig. 1), while the IC_{50} in the HBV-replicating cells was calculated to be 16.2 ± 0.992 μM for (−)-niranthin and 24.2 ± 0.993 μM for (+)-niranthin (Fig. 2). These results show that (−)-niranthin and (+)-niranthin exhibit anti-HBV activity, and that there is no remarkable difference between the anti-HBV activity of both enantiomers. In contrast, based on the bioassay of (−)- and (+)-niranthins against IFV using MDCK cells, cytotoxicity of (−)-niranthin appears at >400 μM judging that cell viability without IFV is less than 80%, and (−)-niranthin inhibited IFV-infection to cells in a concentration-dependent manner on the concentration range of non-cytotoxicity, and exhibits anti-IFV activity at 200–400 μM judging that cell viability with IFV is over 50% (Fig. 3). However, (+)-niranthin does not exhibit anti-IFV activity, and similarly to (−)-niranthin, cytotoxicity appears at >400 μM. Thus, the anti-

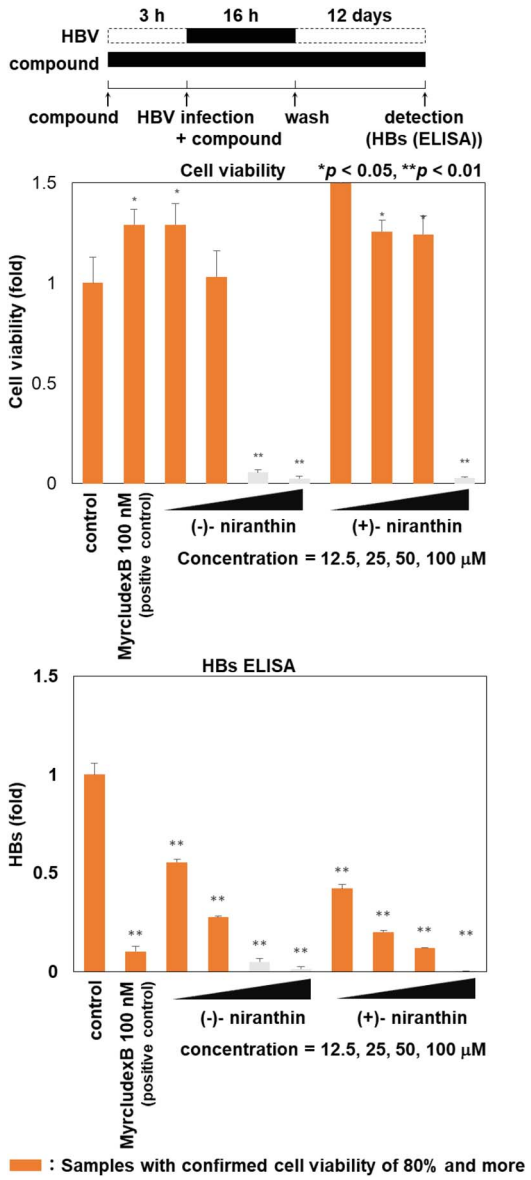


Fig. 1 HBV-infection assay using (−)- and (+)-niranthin.

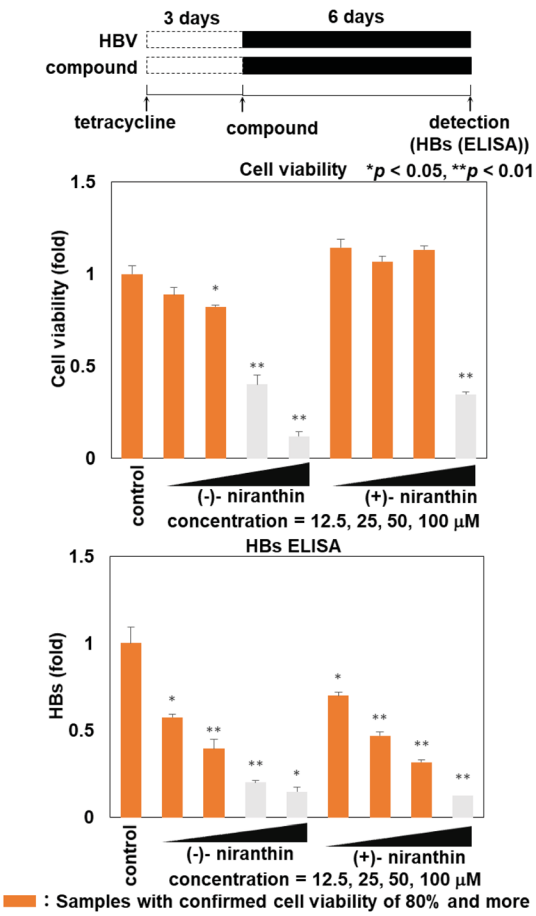


Fig. 2 HBV-replication assay using (−)- and (+)-niranthin.

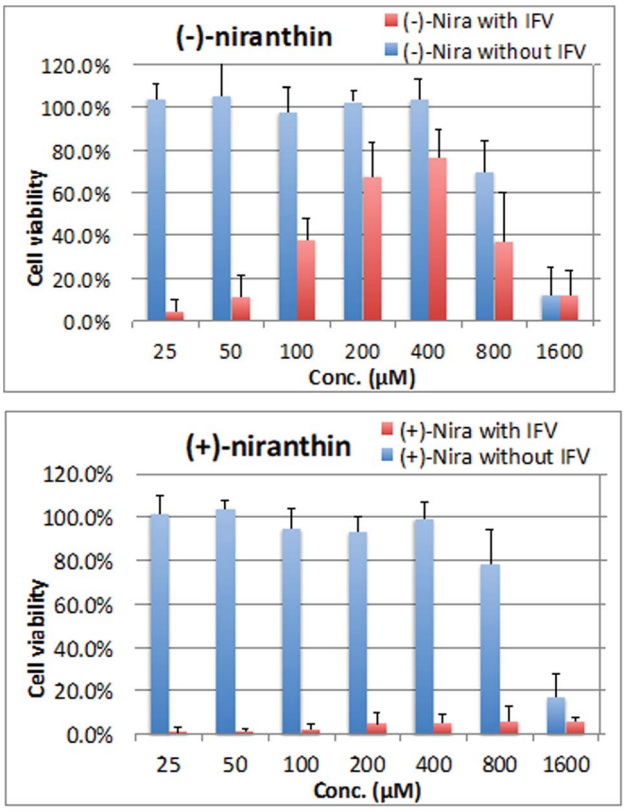
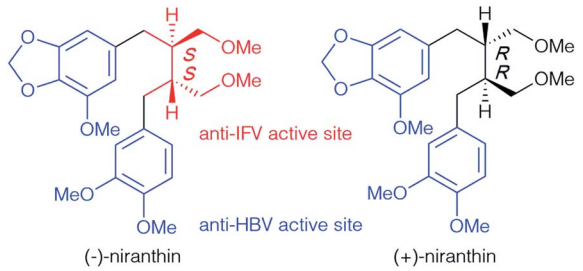


Fig. 3 Growth-inhibition assay of IFV using (−)- and (+)-niranthin.



Scheme 6 A speculation for the bioactive site of niranthin against HBV and IFV.

IFV activity between (−)- and (+)-niranthins is clearly different. Our findings suggest that the enantiomeric site in niranthin endows (−)-niranthin with more potent anti-IFV activity than (+)-niranthin. We speculated that the anti-HBV active site of niranthin might be a part of the molecular structure such as aromatic groups which are far from chiral centers. In contrast, anti-IFV active site of niranthin might be closer to the chiral centers (Scheme 6).

Conclusions

We achieved the asymmetric total syntheses of four bioactive lignans: matairesinol, dimethylmatairesinol, (−)-niranthin, and (+)-niranthin. Key reactions include the Pd-catalyzed reductive ring-opening reaction of enantioenriched cyclopropanes under a hydrogen atmosphere and a highly stereoselective decarboxylation. Thus, we have achieved the first alternative total synthesis of (−)-niranthin and (+)-niranthin. Using the synthesized niranthin enantiomers, we investigated the relationship between the enantiomer structure and its anti-viral activity against the hepatitis B virus (HBV) and the influenza virus (IFV). The results indicate that although the anti-HBV activity does not differ significantly between these two enantiomers, the anti-IFV activity of (−)-niranthin is more potent than that of (+)-niranthin. This result may be interpreted in terms of a different recognition of the enantiomeric structure of a bioactive compound among different virus species.

Author contributions

R. Ota: investigation for the synthesis of lignans. D. Karasawa: investigation for the synthesis of lignans. M. Oshima: investigation for bioassay of niranthin using HBV. K. Watashi: investigation for bioassay and writing original draft of bioassay using HBV. N. Shimasaki: investigation for bioassay and writing original draft of bioassay using IFV. Y. Nishii: methodology, investigation and writing – original draft.

Conflicts of interest

The authors declare no conflict of interest.

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13 During the isolation process, a recrystallization of (−)-niranthin increased the ee value from 92% ee to 95% ee.

14 Similar to (−)-niranthin, a recrystallization of (+)-niranthin increased the ee value from 94% ee to 96% ee.