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Stereocontrolled Total Synthesis of Hedyotol A

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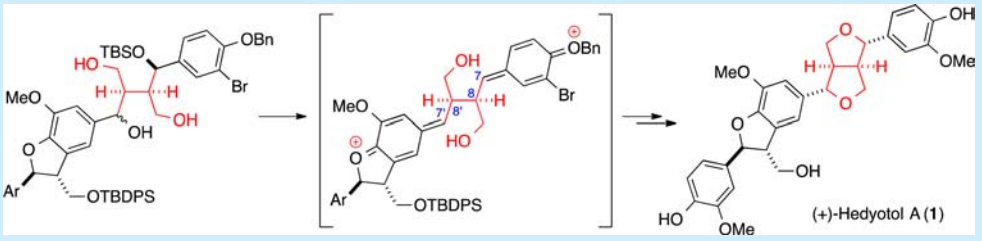
Supporting Information



ABSTRACT: The total synthesis of hedyotol A (**1**), a natural product isolated from *Hedyotis lawsoniae* (DC.) Wight *et* Arn. (Rubiaceae), was accomplished in a highly stereocontrolled manner. Key steps include an L-proline-catalyzed cross-aldol reaction and the biomimetic construction of a furofuran lignan skeleton through a quinomethide intermediate.

Hedyotols A (**1**) and B (**2**), which were isolated from *Hedyotis lawsoniae* (DC.) Wight *et* Arn. (Rubiaceae) by Kikuchi and co-workers in 1985, are constituents of plants used as folk medicines in Sri Lanka.[1] Structurally, hedyotols belong to a class of hybrid natural polyphenols and contain highly electron-rich aromatic rings, four contiguous stereogenic centers on an *exo-exo* type asymmetric furofuran lignan skeleton, and a 7″,8″-*trans*-configured dihydrobenzofuran neolignan skeleton (Figure 1).

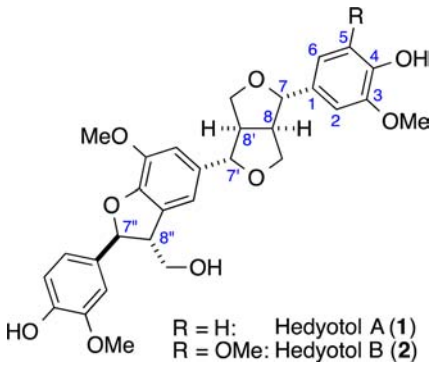
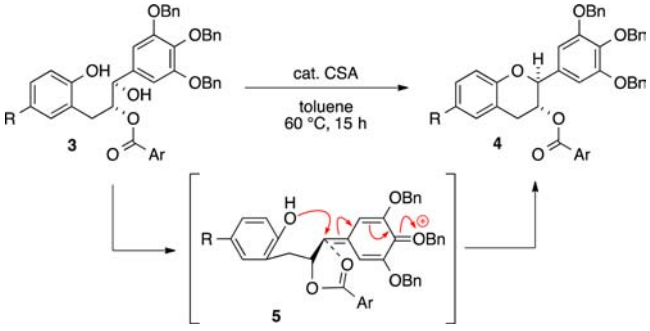


Figure 1. Structures of hedyotols A (**1**) and B (**2**).

Although the bioactivity of **1** and/or **2** has not been reported to date, the unique chemical structure of this hybrid compound prompted us to embark on the total synthesis of **1**. Herein, we report the first total synthesis and determination of the absolute configuration of hedyotol A (**1**).

We have previously reported the stereocontrolled construction of a dihydrobenzofuran ring during the total synthesis of dehydroconiferyl alcohol,[2] and this was expected to be relevant to the total synthesis of **1**, in which a crucial step would be the stereoselective synthesis of the *exo-exo* type furofuran ring. During the course of our synthetic study of tea polyphenol catechin derivatives,[3] we established an efficient synthetic method for the construction of dihydrobenzopyrans through the formation of quinomethide intermediates **5** (Scheme 1).

Scheme 1. Cyclization via Quinomethide Intermediate



Upon treatment of an electron-rich benzyl alcohol **3** with a catalytic amount of CSA in toluene at 60 °C, the stereoselective ring-closing reaction proceeded smoothly to provide **4** as a single diastereomer. Since this biomimetic cyclization reaction can be carried out under mild reaction conditions, we envisioned that this method would be applicable to the efficient and concise construction of the furofuran skeleton of **1**.

The heart of our synthetic plan for **1** is illustrated in Scheme 2. Although there have been many synthetic investigations on furofuran lignans, there are a few reports of the efficient construction of unsymmetrically substituted furofuran lignans.[4]

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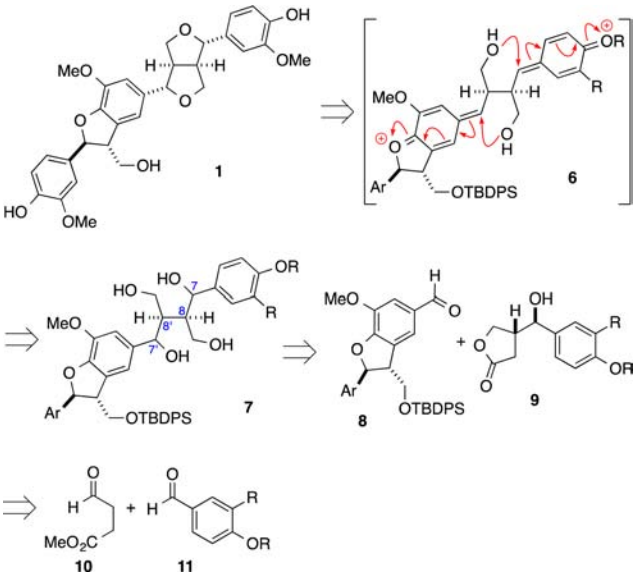
Scheme 2. Retrosynthetic Plan for Hedyotol A (1)

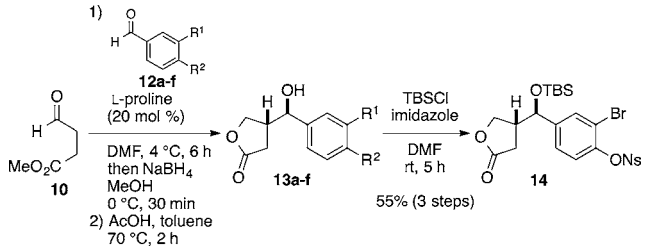


On the basis of our previous work, we expected that the acid-catalyzed double cyclization of the quinomethide intermediate **6** would enable the single-step construction of the furofuran core bearing the four consecutive chiral centers. Since this cyclization would provide a thermodynamically stable compound with the C-7, C-8 and C-7′, C-8′-*trans*-configurations, stereocontrolled construction of the C-8 and C-8′ positions of the cyclization precursor **7** would be a significant task. After an intermolecular aldol reaction between aldehyde **8** and lactone **9**, reduction of the carbonyl moiety should provide tetraol **7** with the correct stereochemistry. The dihydrobenzofuran ring of **8** would be synthesized by means of our original diastereoselective C−H insertion reaction.[2,5,6] The lactone **9** could be prepared by a cross-aldol reaction between **10** and **11** followed by chemoselective reduction of the resultant aldehyde.[7]

In the L-proline-catalyzed cross-aldol reactions of aliphatic aldehyde **10**[7] and 3,4-dihydroxybenzaldehyde derivatives **12a−e**, a significant increase in the reactivity was obtained by incorporation of an electron-withdrawing group at the phenol position (Table 1). The reaction of **10** with the electron-rich aldehyde derivatives **12a** (R^1 = OMe, R^2 = OH) and **12b** (R^1 = OMe, R^2 = OBn) failed to provide adducts **13a** and **13b**.[8] However, when the protecting groups were changed to benzoyl (Bz) and 2-nitrobenzenesulfonyl (Ns)[9] the desired aldol reaction of **10** with **12d** (R^1 = R^2 = OBz) and **12e** (R^1 = R^2 = ONs) proceeded smoothly under the same conditions.[10] Without isolation of the labile aldol adduct, successive reduction with $NaBH_4$ and treatment with AcOH gave the lactones **13d** and **13e**, respectively. Although the cross-aldol reaction with **12e** gave the best results, selective methylation of the catechol moiety was difficult. Thus, we selected **12f** (R^1 = Br, R^2 = ONs) as a precursor, expecting that the bromo atom would be sufficiently electron-withdrawing to activate the aldehyde and that it would be a suitable handle for incorporation of the methoxy group. The L-proline-catalyzed cross-aldol reaction of **10** and **12f** proceeded in a highly enantioselective manner (dr = >10:1, 99% ee).[11] After a two-step sequence, the resulting secondary alcohol was protected with a TBS group to afford the desired lactone **14** in 55% yield (three steps).

As shown in Scheme 3, aldehyde **17** was prepared from optically active dihydrobenzofuran derivative **15** (82% de),[2]

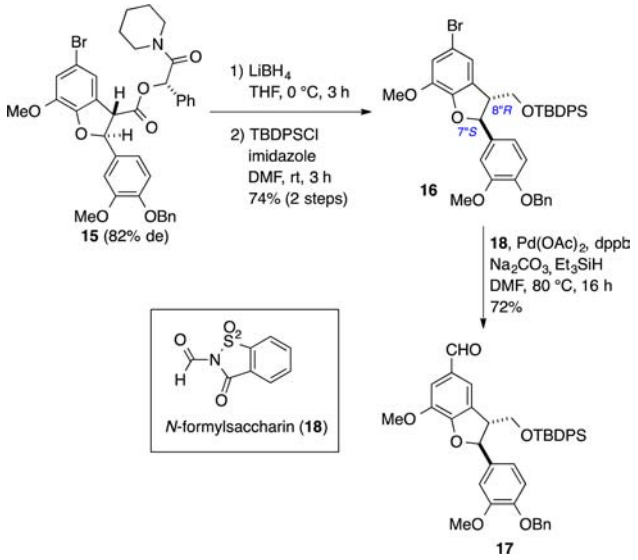
Table 1. Aldol Reaction of 10 with Electron-Rich Aldehydes (12a−12f)



entry	benzaldehyde	product	yield (%)
1	**12a** (R^1 = OMe, R^2 = OH)	**13a**	no reaction
2	**12b** (R^1 = OMe, R^2 = OBn)	**13b**	no reaction
3	**12c** (R^1 = OMe, R^2 = ONs)	**13c**	no reaction
4	**12d** (R^1 = R^2 = OBz)	**13d**	43[a]
5	**12e** (R^1 = R^2 = ONs)	**13e**	63[a]
6	**12f** (R^1 = Br, R^2 = ONs)	**14**	55[b]

[a]Isolated yield (two steps). [b]Isolated yield after conversion to the TBS ether (three steps).

Scheme 3. Synthesis of Dihydrobenzofuran Unit 17



which was efficiently synthesized by a rhodium-catalyzed intramolecular C−H insertion reaction[2,5] using our mandelic amide-type chiral auxiliary.[6] After its removal by reduction with $LiBH_4$, protection of the resulting hydroxyl group with a TBDPS group gave dihydrobenzofuran **16**. The incorporation of a formyl group into **16** was troublesome, since formylation did not proceed in the presence of usual Pd catalysts even under 500 psi of pressure of carbon monoxide. Surprisingly, however, we found that the desired reaction was accomplished in the presence of a Pd catalyst and Et_3SiH by utilizing *N*-formylsaccharin (**18**),[12] developed by Manabe and co-workers as a CO source, to give aldehyde **17** in 72% yield.

Since single-step removal of the protecting groups in the final step is highly attractive, the Ns group of **14** was changed to a benzyl group in one step to afford **19** in 82% yield. With the requisite aldehyde **17** and lactone **19** in hand, we then turned our attention to the coupling reaction and construction of the furofuran framework (Scheme 4). Upon treatment of **17** and **19** with LiHMDS, the desired aldol reaction occurred predominantly from the less-hindered *β*-face of the lactone ring to

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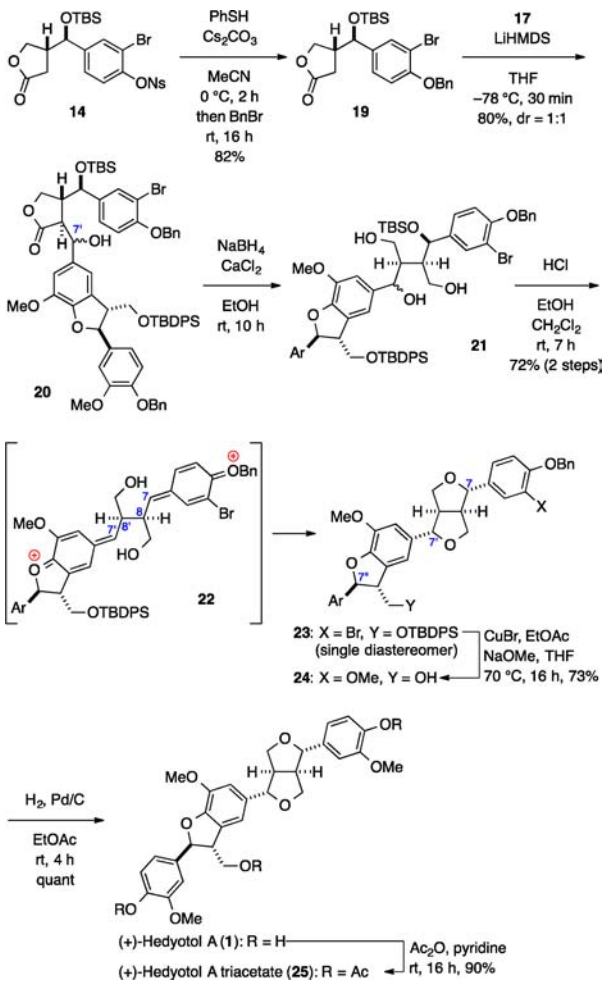
Scheme 4. Completion of the Total Synthesis of Hedyotol A (1)



provide **20** in 80% yield. Although the stereochemistry generated at C-7′ was a 1:1 mixture, both isomers could be converted to the desired furfuran ring (vide infra). Complete reduction of the lactone group of **20** to give triol **21** was achieved by treatment with $Ca(BH_4)_2$,[13] which was generated in situ from $NaBH_4$ and $CaCl_2$. The next challenge was construction of the furofuran ring. Treatment of **20** with HCl in a mixture of EtOH and CH_2Cl_2 efficiently promoted biomimetic cyclization[4c,14] through the quinomethide intermediate **22** to afford *exo-exo* furofuran **23** as a single diastereomer in 72% yield (two steps). Although the dihydrobenzofuran ring of **21** also potentially gives the quinomethide intermediate, no decomposition was observed during the cyclization sequence. Having succeeded in obtaining the key intermediate **23** containing the full hexacyclic skeleton of **1** with the correct stereochemistry, we next examined substitution of the bromo group with a methoxy group. Conversion from **23** to the methyl ether **24** was achieved by a copper-catalyzed coupling reaction with CuBr and NaOMe in THF at 80 °C.[15] Finally, hydrogenolysis of the benzyl ether of **24** with hydrogen and Pd/C in EtOAc gave (+)-hedyotol A (**1**) in a quantitative yield without any reductive cleavage at the C-7, C-7′, and C-7″ positions. Structural confirmation of the synthetic sample was performed after conversion to the triacetate **25**. All spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) of the synthetic **25** were in full agreement with reported values.[1] Furthermore, the absolute configuration of **25** derived from natural hedyotol A (**1**) was also determined by comparison of its specific rotation with that of the synthetic material: $[\alpha]_D$ +29.0 (*c* 1.00, $CHCl_3$, natural); $[\alpha]_D$ +34.0 (*c* 0.30, $CHCl_3$, synthetic). Based on these data, we concluded that the absolute and relative configurations of **1** are as shown in Figure 1.[16]

In conclusion, we have accomplished an efficient, stereocontrolled total synthesis of (+)-hedyotol A (**1**). Our synthesis features an L-proline-catalyzed cross-aldol reaction of **10** and **12f** and the biomimetic construction of the furofuran skeleton through the quinomethide intermediate. Since the optically active segments **14** and **17** were synthesized via organo- and transition-metal-catalyzed asymmetric reactions, it should be straightforward to obtain other stereoisomers. Further synthetic studies and biological investigations of other furofuran lignans as well as related hybrid natural products are in progress at our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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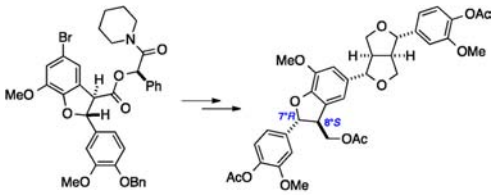
(16) In the NMR measurements, the furofuran part may have only a weak interaction with the benzofuran part. Thus the NMRs of **25** and other epimers are expected to be similar, and the data listed in the original paper are considered to be insufficient to distinguish them. Among the possible stereoisomers, we synthesized the 7″*R* and 8″*S* epimer **27**, since the enantiomer of **15** was readily obtained by employing enantiomers of the Rh catalyst and the chiral auxiliary for the C−H insertion reaction. The absolute configuration of **15** has already been confirmed by leading it to the natural product. This synthesis allowed a clearer comparison of the ^{1}H NMR spectra between **25** and **27**. Although their difference in ^{1}H NMR is not large, we could strictly confirm that the proposed relative stereochemistry is correct. Furthermore, we were able to determine the absolute stereochemistry by the comparison of the $[\alpha]_D$ data. Detailed synthetic procedures and spectral data are given in the Supporting Information.



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