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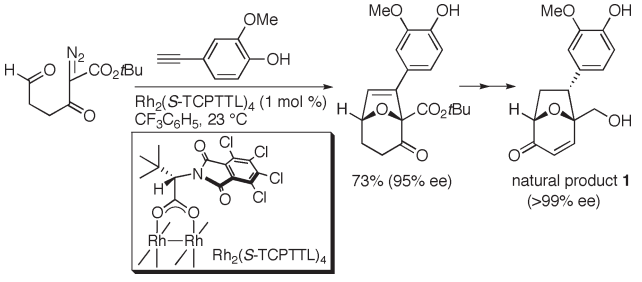
Catalytic Asymmetric Synthesis of the *endo*-6-Aryl-8-oxabicyclo[3.2.1]oct-3-en-2-one Natural Product from *Ligusticum chuanxing* via 1,3-Dipolar Cycloaddition of a Formyl-Derived Carbonyl Ylide Using Rh_2(*S*-TCPTTL)$_4$

Naoyuki Shimada,[†] Taiki Hanari,[†] Yasunobu Kurosaki,[†] Koji Takeda,[†] Masahiro Anada,[†] Hisanori Nambu,[†] Motoo Shiro,[‡] and Shunichi Hashimoto*,[†]

[†]*Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan, and* [‡]*Rigaku Corporation, Akishima, Tokyo 196-8666, Japan*

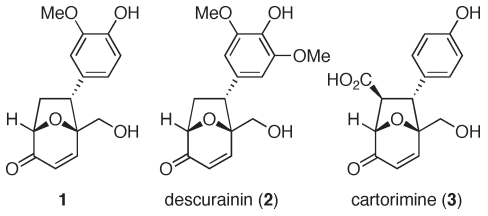
hsmt@pharm.hokudai.ac.jp

Received June 16, 2010



The reaction of a six-membered cyclic formyl-carbonyl ylide derived from α-diazo-*β*-ketoester with phenylacetylene derivatives under the catalysis of dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TCPTTL)$_4$, provides cycloadducts containing an 8-oxabicyclo[3.2.1]octane ring system in up to 97% ee. This represents the first example of an enantioselective 1,3-dipolar cycloaddition of a cyclic formyl-carbonyl ylide. Using this catalytic process, an asymmetric synthesis of *endo*-6-aryl-8-oxabicyclo[3.2.1]oct-3-en-2-one natural product **1** from *Ligusticum chuanxing Hort.* has been achieved.

In 1986, Wen, He, Xue, and Cao reported isolation of the *endo*-6-aryl-8-oxabicyclo[3.2.1]oct-3-en-2-one natural product **1** from *Ligusticum chuanxing Hort.*,[1] which is much used as a traditional Chinese medicine to promote blood circulation. Descurainin (**2**)[2] and cartorimine (**3**),[3] possessing the same ring system, were isolated from *Descurainia sophia* (L.) Webb ex Prantl and *Carthamus tinctorius* L. by the Li and He groups, respectively. Recently, Snider and Grabowski reported concise total syntheses of natural products (±)-**1**−**3**, in which the fully functionalized 8-oxabicyclo[3.2.1]-octenone skeletons were efficiently constructed by a possibly biomimetic [5 + 2] cycloaddition of oxidopyrylium ion.[4]



The 8-oxabicyclo[3.2.1]octane skeleton is a key structural unit found in a large and diverse array of biologically interesting and medicinally important natural products.[5] Although several strategies have been developed to achieve the asymmetric synthesis of this ring system,[6,7] catalytic enantioselective variants have been limited to date. Davies and co-workers developed an asymmetric entry to 8-oxabicyclo[3.2.1]octadienes by using a tandem cyclopropanation/Cope rearrangement between vinylcarbenoides and furans in the presence of the chiral dirhodium(II) catalyst Rh_2(*S*-TBSP)$_4$ (**5**) (Figure 1), in which enantioselectivities up to 80% ee were achieved.[8] The Harmata[9] and Hsung[10] groups recently reported that enantioselective [4 + 3] cycloaddition reactions of oxyallyl cation equivalents with furans catalyzed by chiral amine or chiral Lewis acid gave synthetically useful 8-oxabicyclo[3.2.1]oct-6-en-3-ones[6a] in up to 90% and 99% ee, respectively.

The dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction sequence represents one of the most efficient methods for the rapid assembly of complex oxapolycyclic systems.[11] The exceptional power of the carbonyl ylide cycloaddition

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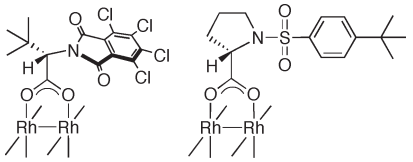
DOI: 10.1021/jo101175b Published on Web 08/11/2010

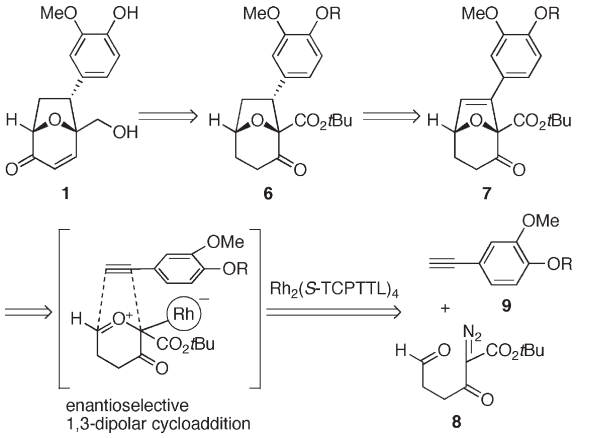


Rh_2(*S*-TCPTTL)$_4$ (**4**) Rh_2(*S*-TBSP)$_4$ (**5**)

FIGURE 1. Chiral dirhodium(II) complexes.

strategy has recently been demonstrated by an increasing number of syntheses of diverse natural products.[12,13] Over the past decade, an enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has also been realized in some selected reactions.[14−16] Recently, we reported that catalytic enantioselective cycloadditions of 2-diazo-3,6-diketoester-derived carbonyl ylides with arylacetylene, alkoxyacetylene, and styrene dipolarophiles using dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TCPTTL)$_4$ (**4**),[17,18] provide 8-oxabicyclo[3.2.1]octane derivatives in good to high yields and with enantioselectivities of up to 99% ee as well as with perfect *exo* diastereoselectivity for styrenes.[19] In order to demonstrate the utility of this catalytic process, we addressed asymmetric synthesis of natural product **1**, focusing on the cycloaddition of a formyl-derived cyclic carbonyl ylide with phenylacetylene derivatives under the catalysis of Rh_2(*S*-TCPTTL)$_4$ (**4**).

SCHEME 1. Retrosynthetic Analysis of Natural Product 1



1 **6** **7** **9** **8**

Our synthetic strategy for **1** based on the enantioselective 1,3-dipolar cycloaddition is outlined retrosynthetically in Scheme 1. We envisaged that natural product **1** would be accessible from bicyclic compound **6** bearing all of the stereogenic centers of **1**. It was anticipated that **6** might be formed by a catalytic hydrogenation of appropriately protected 8-oxabicyclo[3.2.1]oct-6-en-2-ones **7** in a stereocontrolled manner.[20] As mentioned above,[19] we envisioned that Rh_2(*S*-TCPTTL)$_4$-catalyzed reaction of *tert*-butyl 2-diazo-5-formyl-3-oxopentanoate (**8**) with phenylacetylene derivative **9** would provide cycloadducts **7**. While a variety of 1,3-dipolar cycloadditions of keto- or ester-derived cyclic carbonyl ylides have been reported,[11] only one example of a cyclic formyl-carbonyl ylide cycloaddition has been reported so far. Padwa and co-workers reported that the cycloaddition of benzannulated formyl-carbonyl ylide with dimethyl acetylenedicarboxylate in the presence of dirhodium(II) tetrakis(trifluoroacetate), Rh_2(tfa)$_4$, provided cycloadduct in 82% yield.[21] However, the use of $Rh_2(OAc)_4$ as the catalyst gave an unusual dimer as the sole product in 63% yield. The authors suggested that the $Rh_2(OAc)_4$-catalyzed reaction produces a mixture of both the six-membered ring dipole and the C−H aldehydic insertion product. Consequently, the

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SCHEME 2. Preparation of Formyl-Derived Carbonyl Ylide Precursor 8

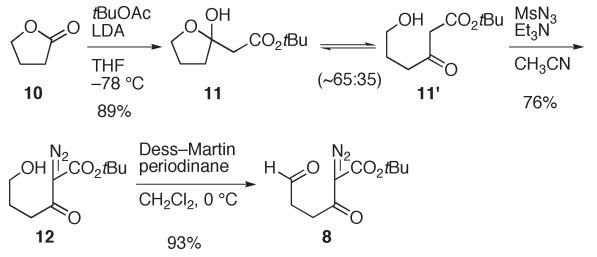
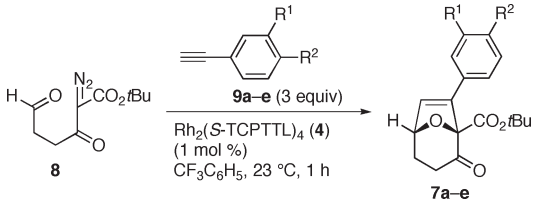


TABLE 1. Enantioselective 1,3-Dipolar Cycloaddition of Formyl-Derived Carbonyl Ylide from 8 with 9a–e Using Rh_2(*S*-TCPTTL)$_4$ (4)



	dipolarophile			product		
entry		R^1	R^2		yield[a] (%)	ee[b] (%)
1	**9a**	H	H	**7a**	75	97
2	**9b**	OMe	OTBS	**7b**	50	35
3	**9c**	OMe	OAc	**7c**	66	81
4	**9d**	OMe	OBn	**7d**	72	88
5	**9e**	OMe	OH	**7e**	73	95

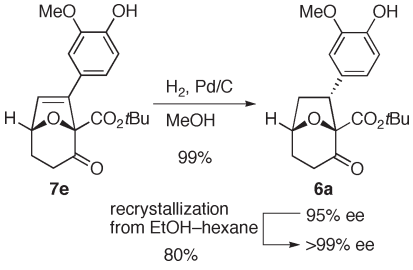
[a]Isolated yield. [b]Determined by HPLC. See the Supporting Information for details.

development of an enantioselective cycloaddition of formyl-derived cyclic carbonyl ylide with phenylacetylene derivatives has become a challenging objective.

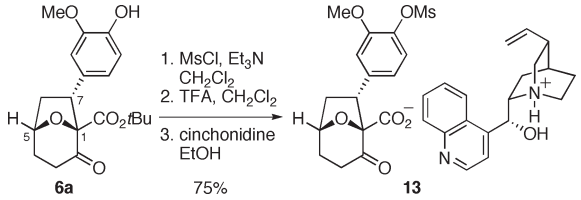
Toward this end, the formyl-derived cyclic carbonyl ylide precursor **8** was prepared from γ-butyrolactone (**10**) as shown in Scheme 2. Claisen condensation of **10** with the lithium enolate of *tert*-butyl acetate in THF gave an equilibrium mixture of hemiketal and keto tautomers **11** and **11′** in 89% yield,[22] which, upon diazo transfer with methanesulfonyl azide, produced α-diazo-β-ketoester **12** in 76% yield.[23] Oxidation of **12** with Dess–Martin periodinane afforded aldehyde **8** in 93% yield.[24]

On the basis of our previous work,[19] we initially evaluated the reaction of α-diazo-β-ketoester **8** with phenylacetylene (**9a**) (3 equiv) as a model system using 1 mol % of Rh_2(*S*-TCPTTL)$_4$ (**4**). The reaction in α,α,α-trifluorotoluene at 23 °C proceeded smoothly to give cycloadduct **7a** in 75% yield (Table 1, entry 1). The enantiomeric excess of **7a** was determined to be 97% by HPLC using a Chiralcel OD-H column. Encouraged by this result, we next examined the reaction of **8** with a variety of 4-hydroxy-3-methoxyphenylacetylenes **9b–e** as dipolarophiles. The use of *tert*-butyldimethylsilyl (TBS)-protected phenylacetylene **9b** resulted in a noticeable drop in both product yield and enantioselectivity (50% yield, 35% ee, entry 2). We found that switching the dipolarophile to acetyl- or benzyl-protected phenylacetylenes **9c** and **9d** afforded the corresponding cycloadducts **7c** and **7d** in higher yields (66% and 72%) and enantioselectivities (81% and 88% ee, respectively) than those found with **9b** (entries 3 and 4). Gratifyingly, the reaction with phenylacetylene **9e** bearing a free phenolic hydroxy group gave cycloadduct **7e** in 73% yield with 95% ee (entry 5). These results suggest that the use of phenylacetylenes bearing sterically less-demanding substituents at the *para* position on the benzene ring is crucial for a high level of enantioselectivity in this reaction.

SCHEME 3. Stereoselective Reduction of 7e



SCHEME 4. Determination of Absolute Configuration of 6a



Hydrogenation of **7e** provided exclusively the desired *endo*-bicyclic compound **6a** as a single diastereomer in 99% yield (Scheme 3).[20] A single recrystallization of **6a** from ethanol–hexane produced optically pure material [mp 105.5–106.5 °C, $[\alpha]^{24}_D$ +103.4 (*c* 1.02, $CHCl_3$)] in 80% yield.

The absolute configuration of **6a** was determined to be (1*R*,5*R*,7*R*) by single-crystal X-ray analysis of the corresponding carboxylic acid cinchonidine salt **13** (Scheme 4).[25]

With optically pure compound **6a** in hand, the stage was now set for completion of the asymmetric synthesis of natural product **1** as illustrated in Scheme 5. Protection of the phenolic hydroxy group in **6a** as the *tert*-butyldiphenylsilyl (TBDPS) ether gave **6b** in 99% yield. Treatment of ketone **6b** with NaHMDS at −78 °C followed by addition of $PhNTf_2$ and subsequent palladium-catalyzed reduction of the resulting enol triflate[26] furnished alkene **14** in 75% yield. Reduction of *tert*-butyl ester **14** with $LiAlH_4$ and subsequent silylation provided bis-TBDPS ether **16** in 85% yield. Allylic oxidation of **15** with SeO_2 gave alcohol **16** as a single diastereomer in 77% yield, which, upon oxidation with MnO_2, produced enone **17** in 83% yield. Finally, removal

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(25) CCDC-778842 (for **13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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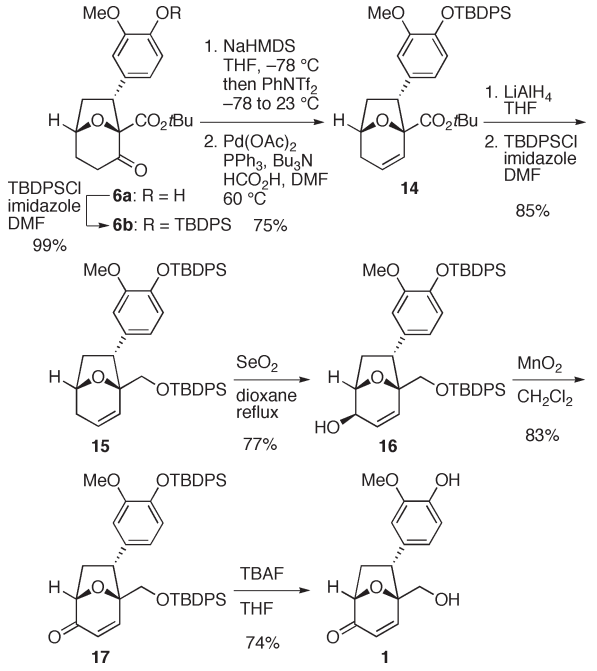
SCHEME 5. Synthesis of Natural Product 1



of two TBDPS protecting groups with TBAF in THF completed the asymmetric synthesis of **1**. The synthetic material **1** exhibited spectroscopic data (^{1}H and ^{13}C NMR, IR, HRMS) consistent with those reported for natural product **1**, except for their circular dichroism (CD) spectra. The absolute maximal molar CD of synthetic **1** ($\Delta\varepsilon$ - 3.81 at 348 nm) displayed a startling difference in magnitude to that of natural **1** ($\Delta\varepsilon$ +0.01 at 355 nm).[1] This observation suggests that natural product **1** might be biosynthesized in near-racemic form like polygalolides A and B.[27,28] Our result provides experimental support for the biogenetic hypothesis by Snider's group.[4b,29]

In summary, we have developed an enantioselective intermolecular 1,3-dipolar cycloaddition of a six-membered cyclic formyl-carbonyl ylide derived from *tert*-butyl 2-diazo-5-formyl-3-oxopentanoate with phenylacetylene dipolarophiles under the influence of Rh_2(*S*-TCPTTL)$_4$ to provide 8-oxabicyclo[3.2.1]oct-6-en-2-one derivatives in up to 97% ee. This is the first example of an enantioselective cycloaddition of a formyl-derived cyclic carbonyl ylide. Using this catalytic methodology, we have achieved the asymmetric synthesis of *endo*-6-aryl-8-oxabicyclo[3.2.1]oct-3-en-2-one natural product **1** in 13 steps and 11% overall yield from γ-butyrolactone (**10**). This represents the first example of a total synthesis of a natural product using a catalytic enantioselective carbonyl ylide cycloaddition strategy. Further application of this methodology to asymmetric synthesis of biologically active natural products containing an 8-oxabicyclo[3.2.1]octane skeleton is currently in progress.[30]

Experimental Section

Representative Procedure for the Tandem Carbonyl Ylide Formation/1,3-Dipolar Cycloaddition (Table 1, Entry 5). A solution of **8** (452 mg, 2.0 mmol) and **9e** (889 mg, 6.0 mmol) in $CF_3C_6H_5$ (10 mL) was added via syringe pump over 1 h to a stirred solution of Rh_2(*S*-TCPTTL)$_4$ (**4**) (39.5 mg, 0.020 mmol, 1 mol %) in $CF_3C_6H_5$ (10 mL) at 23 °C. After the addition was complete, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to give **7e** (505.0 mg, 73%) as a pale yellow amorphous liquid: R_f = 0.45 (1:1 hexane/AcOEt); $[\alpha]^{22}_D$ +147.1 (*c* 1.10, $CHCl_3$) for 95% ee; IR (KBr) ν 3437, 2979, 1743, 1208 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.89 (m, 1H), 2.56−2.68 (m, 2H), 2.85 (m, 1H), 3.87 (s, 3H), 5.14 (br d, J = 4.1 Hz, 1H), 5.67 (br, 1H), 6.33 (d, 1H, J = 1.5 Hz), 6.84−6.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 27.8, 33.7, 55.7, 79.1, 82.8, 93.0, 109.2, 113.8, 119.8, 124.4, 130.0, 143.2, 145.4, 145.6, 163.5, 198.6; HRMS (EI) calcd for $C_{19}H_{22}O_6$ (M^+) 346.1416, found 346.1416. The enantiomeric excess of **7e** was determined to be 95% by HPLC with a Chiralpak IA column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 17.8 min for (1*R*,5*R*)-**7e**; t_R (minor) = 22.9 min for (1*S*,5*S*)-**7e**.

Acknowledgment. This research was supported, in part, by a Grant-in-Aid for Scientific Research on Innovative Areas (Project No. 2105: Organic Synthesis Based on Reaction Integration) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank S. Oka, M. Kiuchi, and T. Hirose of the Center for Instrumental Analysis at Hokkaido University for mass measurements and elemental analysis.

Supporting Information Available: Full experimental and characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, as well as X-ray crystallographic data (CIF) for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) The enantiomeric purity of synthetic **1** was determined to be >99% ee by comparison of HPLC retention time with a racemic sample of **1**, which was prepared according to the literature. See ref 4b.

(28) (a) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532–6535. (b) Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873–874.

(29) Recently, Peterson and co-workers reported that compound **1** could be produced from glucose, glycine, and ferulic acid in 3% yield in a simulated baking model system (10% moisture at 200 °C for 15 min). Jiang, D.; Chiaro, C.; Maddali, P.; Prabhu, K. S.; Peterson, D. G. *J. Agric. Food Chem.* **2009**, *57*, 9932–9943. We thank one of the reviewers for pointing out the reference, which provides further support for the proposed biosynthesis.

(30) After submission of this manuscript, a catalytic asymmetric synthesis of 8-oxabicyclo[3.2.1]octane derivatives via enantio- and diastereoselective [3 + 2]-cycloaddition of platinum-containing carbonyl ylides with vinyl ethers was published by Iwasawa and co-workers. Ishida, K.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *132*, 8842–8843.