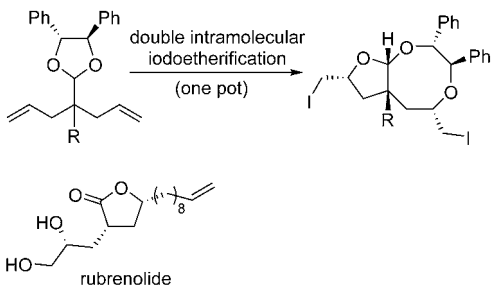
Asymmetric Synthesis

A Double Iodoetherification of σ-Symmetric Diene Acetals for Installing Four Stereogenic Centers in a Single Operation: Short Asymmetric Total Synthesis of Rubrenolide**

Hiromichi Fujioka, Yusuke Ohba, Hideki Hirose, Kenichi Murai, and Yasuyuki Kita**

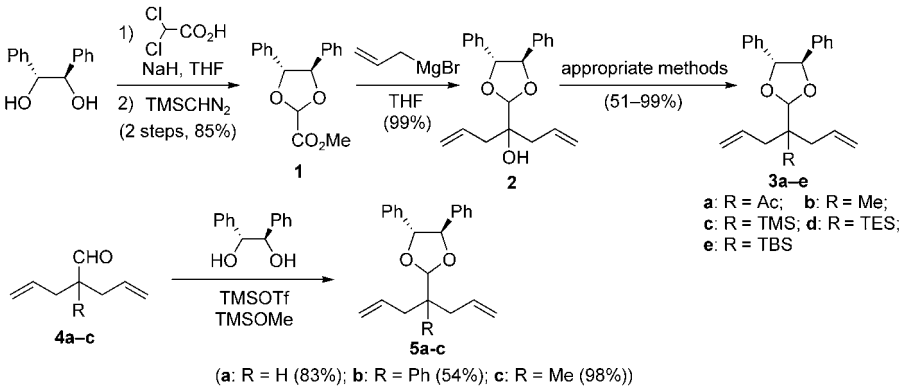
Many biologically active natural products contain multiple chiral centers and occur in their optically active form, and therefore the development of methodologies that can lead to multiple chiral centers is desirable in synthetic organic chemistry. Recently, we developed the intramolecular haloetherification of chiral ene acetals from (*R*,*R*)-hydrobenzoin in which two new chiral centers are formed at remote positions.[1] As an extension of this remote asymmetric induction method we studied the reaction of acyclic σ-symmetric diene acetals, and found an unprecedented double intramolecular haloetherification leading to the formation of four asymmetric centers in a single operation (Scheme 1).



Scheme 1. Double intramolecular haloetherification of acyclic σ-symmetric diene acetals leading to the formation of four asymmetric centers.

Although there are several reports on the discrimination of acyclic σ-symmetric dienes by intramolecular halolactonization,[2] no domino-type reaction has been reported. Furthermore, the reaction was applied to a short asymmetric synthesis of rubrenolide.

The chiral diene acetals (**2** and **3**) with oxygen-containing functional groups, such as hydroxy, ether, and ester groups, were prepared as shown in Scheme 2: 1) reaction of (*R*,*R*)-hydrobenzoin and dichloroacetic acid in the presence of NaH is followed by the formation of the ester to afford **1**; 2) reaction of allylmagnesium bromide with **1** leads to the hydroxy diene acetal **2**; and 3) protection of the *tert*-hydroxy function of **2** by appropriate methods leads to **3**. The chiral

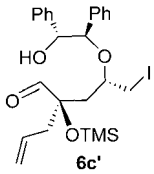


a: R = Ac; **b**: R = Me; **c**: R = TMS; **d**: R = TES; **e**: R = TBS

Scheme 2. Preparation of various acyclic diene acetals. TBS = *tert*-butyldimethyl silyl, TES = triethylsilyl, Tf = trifluoromethanesulfonate, TMS = trimethylsilyl.

diene acetals (**5**) with a hydrogen, phenyl, and methyl substituent were prepared by acetalization of the diallyl aldehyde **4** with (*R*,*R*)-hydrobenzoin.[3]

We first studied the reactivity of substrate **3c** by treatment with *N*-iodosuccinimide (NIS; 2.5 equivalents) and methanol (5.0 equivalents) in acetontrile at −40–0 °C.[1] However, no reaction occurred and the starting material **3c** was recovered. When the reaction was carried out at room temperature, the product obtained resulted from the attack of the methanol on the olefin in an intermolecular fashion. We then changed the nucleophile from methanol to water. The reaction proceeded smoothly to give **6c** (R = OTMS) as the major product in a yield of 73%. Other stereoisomers were obtained as a mixture in an approximate yield of 10% (Scheme 3).



6c'

To our surprise, the hydroxy aldehyde **6c′** was not detected, which we predicted from the occurrence of intermediate II.[4] Even the use of 0.5 equivalents of NIS did not give **6c′** at all, and **3c** and **6c** were obtained. The structure of **6c** was determined as follows: The relationship of the substituents on the five-membered ring was determined by NOE interaction experiments between two protons (H_a and H_b) and the methyl group of the trimethylsilyl (TMS) functional group. The complete structure of the product, including the absolute configuration of all of the asymmetric

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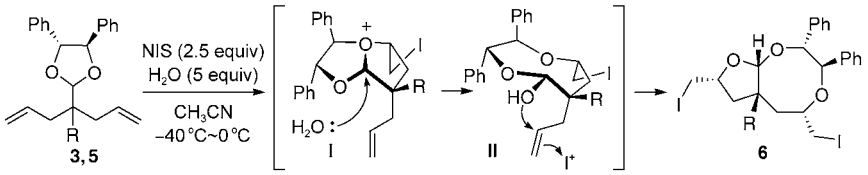
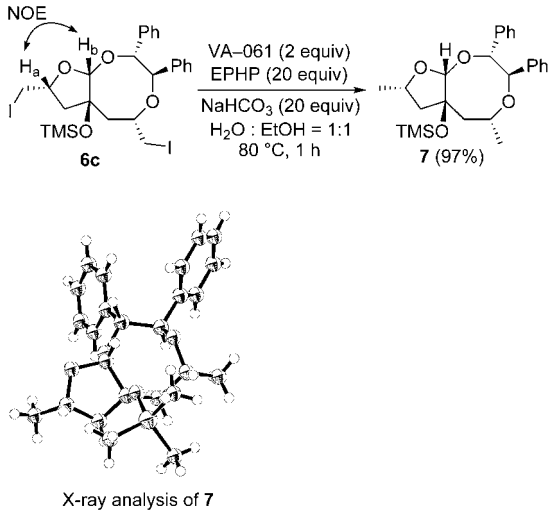


Scheme 3. Domino-type intramolecular iodoetherification of **3c**.

carbon centers, was unambiguously determined by X-ray crystallographic analysis[5] of the dimethyl compound **7** by radical reduction using 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061)[6] of **6c** (Scheme 4).



Scheme 4. Radical reduction of **6c**. VA-061 = 2,2′-azobis[2-(2-imidazolin-2-yl)propane], EPHP = 1-ethylpiperidine hypophosphite.

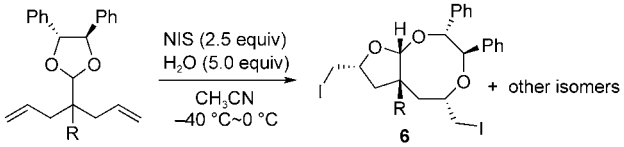
A mechanistic rationale is shown in Scheme 3. The hemiacetal intermediate II was obtained via the oxonium cation intermediate I. The hemiacetal structure of an eight-membered ring usually opens to give the hydroxy aldehyde, such as **6c′**. However, in this case, another olefin unit is present at the proper position. The second intramolecular iodoetherification then occurred faster than the opening of the eight-membered ring to give **6c** in good yield.

This unprecedented double intramolecular iodoetherification proved to be a general reaction. That is, various diene acetals **3b–e**, which have an ether group next to the acetal function, and **5a–c**, which have a hydrogen, methyl, and phenyl substituent next to the acetal function, respectively, afforded the double intramolecular iodoetherification products **6c–h** as major products in fair to good yields (Table 1).

Dreiding models and the X-ray crystal structure of **7** have led to the proposed conformation of the oxocyclic compounds **6c–h**. Their conformations show that the environments of the two iodomethyl functions (a) and (b) are completely different and that the iodomethyl group (b) bearing the eight-membered acetal ring is less hindered, so we expected it to be more reactive. We then examined this observation using compound **6c**. As expected, nucleophiles predominantly attacked at the iodomethyl group (b) bearing the eight-membered acetal ring (Scheme 5).

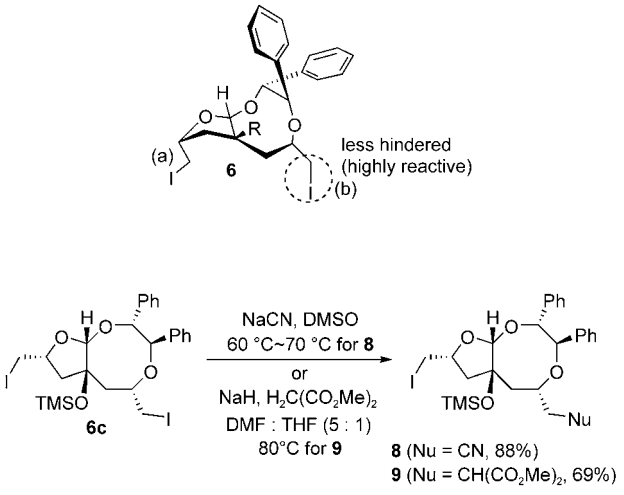
The utility of this domino-type reaction was shown with a short asymmetric synthesis of rubrenolide (Scheme 6). Rubrenolide was isolated from the trunk wood of the Amazonian tree *Nectandra rubra* of the Lauraceae family. It has a remote asymmetric center in addition to a γ-lactone ring with two asymmetric centers.[7] Although one asymmetric synthesis has already been reported,[8] we have developed a shorter asymmetric synthesis. The intramolecular iodoetherification of the diene acetal **5a**, obtained by acetalization of the aldehyde **4a** with (*R*,*R*)-hydrobenzoin, afforded **6f** in 62% yield. Although the mixture contained 18% of other stereoisomers, **6f** was readily purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1). Hydrolysis of **6f** by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [9] followed by oxidation

Table 1: Intramolecular iodoetherification of various diene acetals.

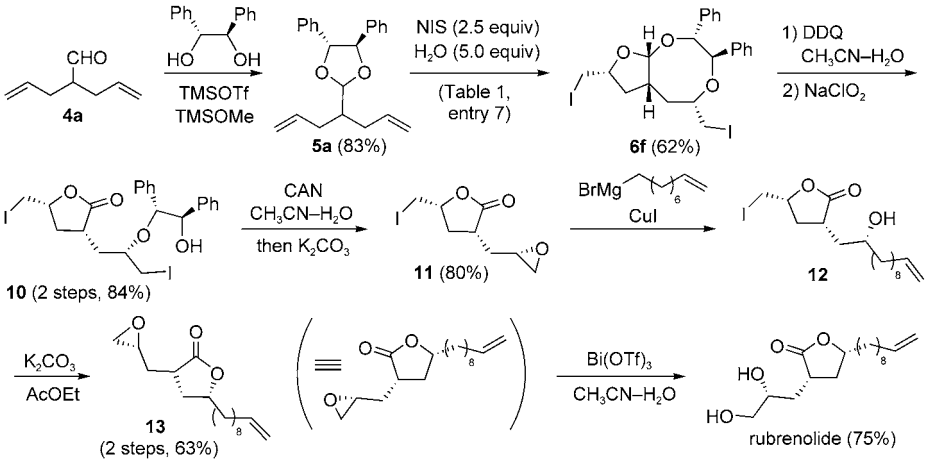


Entry	Diene acetal	*t* [h]	Total yield [%]	d.r.[a]	Major product
1	**2**	–	decomp	–	
2	**3a** (R = OAc)	–	decomp	–	
3	**3b** (R = OMe)	12	38	n.d.[b]	
4	**3c** (R = OTMS)	1.5	82	8/1	**6c**
5	**3d** (R = OTES)	3.5	58	11/1	**6d**
6	**3e** (R = OTBS)	3	84	11/1	**6e**
7	**5a** (R = H)	3	80	3.5/1	**6f**
8	**5b** (R = Ph)	3	72	2/1	**6g**
9	**5c** (R = Me)	13	72	1.5/1	**6h**

[a] Major diastereomer/other diastereomers. [b] Not determined.



Scheme 5. Regioselective nucleophilic addition to **6c**.



Scheme 6. Asymmetric total synthesis of rubrenolide.

with $NaClO_2$ gave the lactone **10**. Cleavage of the carbon–oxygen bond of the hydrobenzoin unit by ammonium cerium nitrate (CAN)[10] followed by treatment with K_2CO_3 afforded the epoxide **11**. The introduction of the alkenyl unit to the epoxide by a copper-assisted Grignard reagent gave the hydroxylactone **12**. To our surprise, treatment of **12** with K_2CO_3 caused recyclization of the lactone ring and epoxide formation to give the epoxide **13**. Opening of the epoxy ring of **13** by $Bi(OTf)_3$[11] smoothly proceeded to give (+)-rubrenolide. Optical rotation studies and ^{1}H NMR, ^{13}C NMR, and IR spectroscopic analysis of the product with an authentic sample of (+)-rubrenolide were in good agreement.[12]

In conclusion, we have found unprecedented double intramolecular haloetherifications of σ-symmetric diene acetals. The reactions proceed in a highly diastereoselective manner to give tetrahydrofuran units with multiple chiral centers in a one-pot operation. Furthermore, a short asymmetric synthesis of (+)-rubrenolide was carried out as an application of the methodology. Since tetrahydrofuran moieties with multiple chiral centers are found in a large number of biologically active natural products, this method could prove to be a highly useful tool.

Experimental Section

Intramolecular iodoetherification reaction of **5a**: *N*-iodosuccinimide (NIS; 351 mg, 1.6 mmol) was added to a solution of **5a** (100 mg, 0.31 mmol) in CH_3CN (0.62 mL) at −40 °C under nitrogen, and the mixture was stirred for 30 min at the same temperature. Water (0.028 mL, 1.6 mmol) was added to the resulting mixture, which was allowed to warm to 0 °C over 40 min. A saturate aqueous $Na_2S_2O_3$ solution was added to the mixture, which was then extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) to give **6f** (114 mg, 0.19 mmol, 62%) and a diastereoiomeric mixture (33 mg, 0.056 mmol, 18%).

6f: $[\alpha]_D^{24}$ +65.4 (c = 1.1, $CHCl_3$); IR (KBr): no OH, no CO; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.98–2.03 (2H, m), 2.10–2.23 (1H, m), 2.40–2.42 (2H, m), 3.00–3.07 (3H, m), 3.28 (1H, dd, J = 9.3, 4.5 Hz), 4.03–4.21 (2H, m), 4.32 (1H, d, J = 8.4 Hz), 4.44 (1H, d, J = 8.4 Hz), 5.89 (1H, d, J = 4.5 Hz), 6.72–6.79 (4H, m), 7.04–7.19 ppm (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 6.3, 32.5, 35.4, 38.2, 65.3, 76.7, 77.4, 87.8, 127.0, 127.1, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.7, 138.7, 139.4, 178.0 ppm; FAB-HRMS: calcd for $C_{22}H_{25}O_3I_2$: m/z 590.9906 (M^++H); found: 590.9875.

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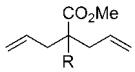
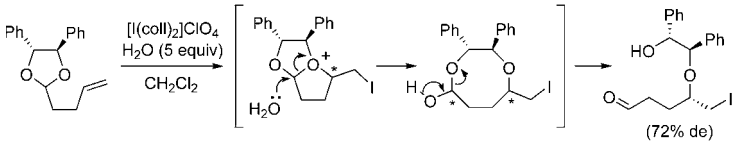
[3] Diallyl aldehyde **4a** (R = H) and phenyl aldehyde **4b** (R = Ph) are known compounds (for **4a**, see: B. B. Snider, B. R. Smith, *Tetrahedron* **2002**, *58*, 25–34; for **4b**, see: W. A. Nugent, J. Feldman, J. C. Calabrese, *J. Am. Chem. Soc.* **1995**, *117*, 8992–8998). Diallylmethyl aldehyde (**4c**, R = Me) was prepared from the known diallyl ester **15b** (obtained by methylation of **15a**; see above reference for **4a**) first by reduction of the ester and then oxidation with pyridinium dichromate.



15a: R=H
15b: R=Me

[4] In our previous work (Ref. [1]), alcohols were used as nucleophiles, whereas here the use of water instead afforded the hydroxyaldehyde by intramolecular haloetherification followed by opening of the eight-membered hemiacetal ring (coll = 2,4,6-collidine, H. Fujioka, H. Kitagawa, Y. Kita, unpublished results).



[5] CCDC-244868 contains the supplementary crystallo-graphic data for this paper. These data can be obtained free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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[12] Authentic rubrenolide was obtained by separation of a mixture donated by Prof. B. Zwanenburg and Dr. L. Thijs, according to Ref. [8b]. The synthetic rubrenolide has a $[\alpha]_D^{25}$ value of $+20.5$ ($c = 0.29$, $CHCl_3$), while the $[\alpha]_D^{20}$ value of the authentic sample (Ref. [7c]) is $+21.2$ ($CHCl_3$).

