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# The first total synthesis of hibarimicinone, a potent v-Src tyrosine kinase inhibitor

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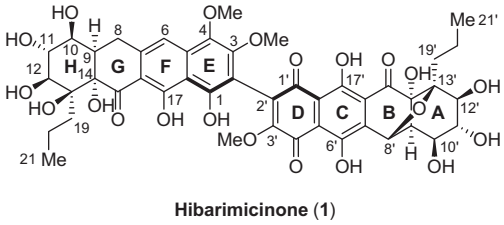
ABSTRACT

The first total synthesis of hibarimicinone has been achieved. The polyhydroxydecalin moieties (**AB** and **GH** rings) have been synthesized from sulfonylenone **4** derived from D-arabinose. The chiral biaryl **20** was coupled with two polyhydroxydecalins **11** by Michael–Dieckmann type condensation to give the eight rings system. Aromatization and oxidation with $Ag^{+}$ gave quinone **24**, and the subsequential transannular etheration gave the hibarimicinone skeleton. Deprotection and tautomerization were performed in one pot to give hibarimicinone (**1**).



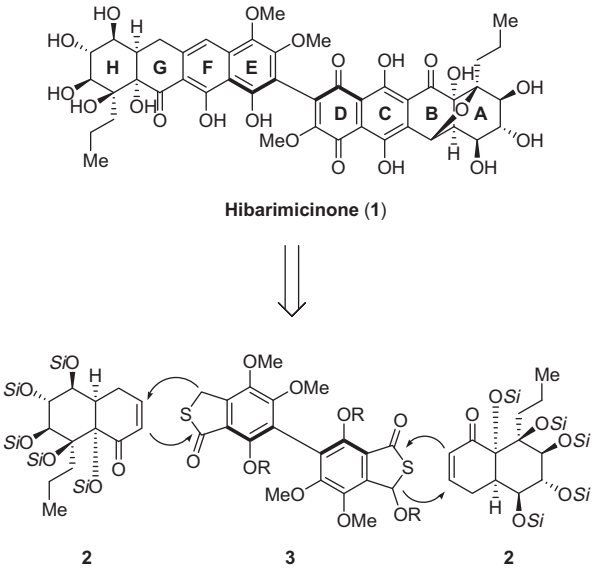
Hibarimicins, isolated from the culture broth of *Microbispora rosea* subsp. *hibaria*, have been known to possess v-Src tyrosine kinase inhibitory activity and differentiation inducing activity of HL-60 cells.[1] Among them, hibarimicinone (**1**) has the most potent activity of v-Src tyrosine kinase inhibition without differentiation inducing activity.[2] The structure of hibarimicinone (**1**) has been disclosed to be pseudo-dimer of tetracyclin, which includes 13 stereogenic centers as well as the axial chirality (Fig. 1). The absolute structure of **1** has been determined by the Mosher method and CD spectra.[2,3] We embarked the synthetic studies of this compound possessing the unique structure and activity. Herein, we present the first total synthesis of hibarimicinone (**1**).




**Hibarimicinone (1)**

**Figure 1.** The structure of hibarimicinone (**1**).

Our synthetic plan toward hibarimicinone is shown in Scheme 1. The eight rings skeleton was decided to be constructed by double Michael–Dieckmann type cyclization[4] using the chiral biaryl thiolactone **3** (**DE** moiety) and the chiral decalin **2** (**AB** and **GH**




**Hibarimicinone (1)**

**Scheme 1.** The synthetic plan of hibarimicinone (**1**).

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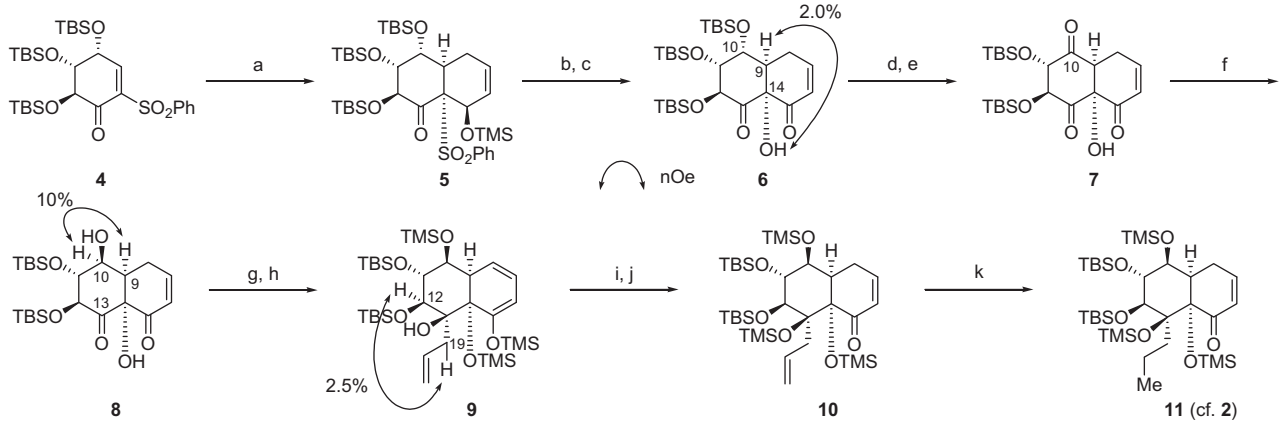


**Scheme 2.** The synthesis of decalin segment **2**. Reagents and conditions: (a) 1-trimethylsiloxy-1,3-butadiene, DTBC, PhMe, 90 °C, 4 d, 90%; (b) Jones reagent, acetone, rt, 6 h, 94%; (c) $SmI_2$, THF, −78 °C, 10 min, then OXONE®, −78 °C to rt, 1 h, satd $NaHCO_3$ aq, rt, 12 h, 89%; (d) $SnCl_4$, $CH_2Cl_2$, −30 °C, 64 h, 83%; (e) IBX, PhMe-DMSO, 50 °C, 4 h, 87%; (f) $NaBH(OAc)_3$, EtOH, 0 °C to rt, 20 min, 96%; (g) TMSOTf, 2,6-lutidine, $ClCH_2CH_2Cl$, 80 °C, 12 h, 88%; (h) $CH_2{=}CHCH_2MgCl$, $Et_2O$, 0 °C, 10 min, 86%; (i) TMSOTf, 2,6-lutidine, $ClCH_2CH_2Cl$, 80 °C, 12 h, 87%; (j) DBU, *i*-PrOH, PhMe, 80 °C, 1.5 h, 90%; (k) $H_2$, 10% Pd–C, PhMe, rt, 8 h, 88%.

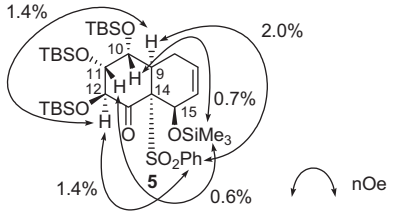
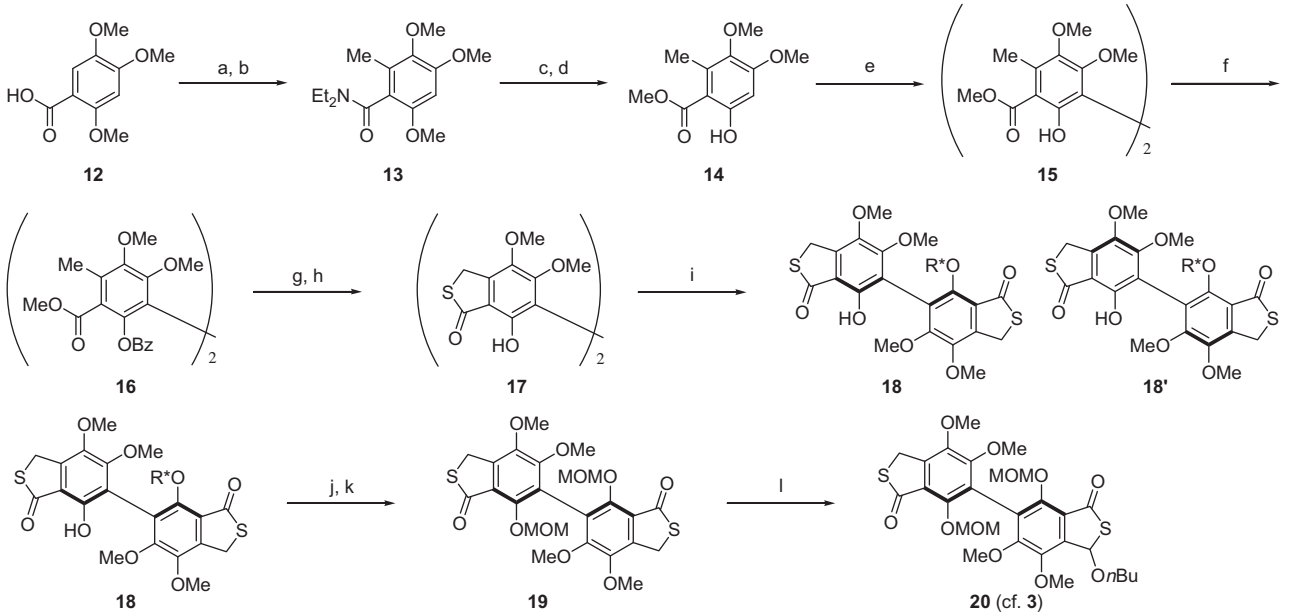


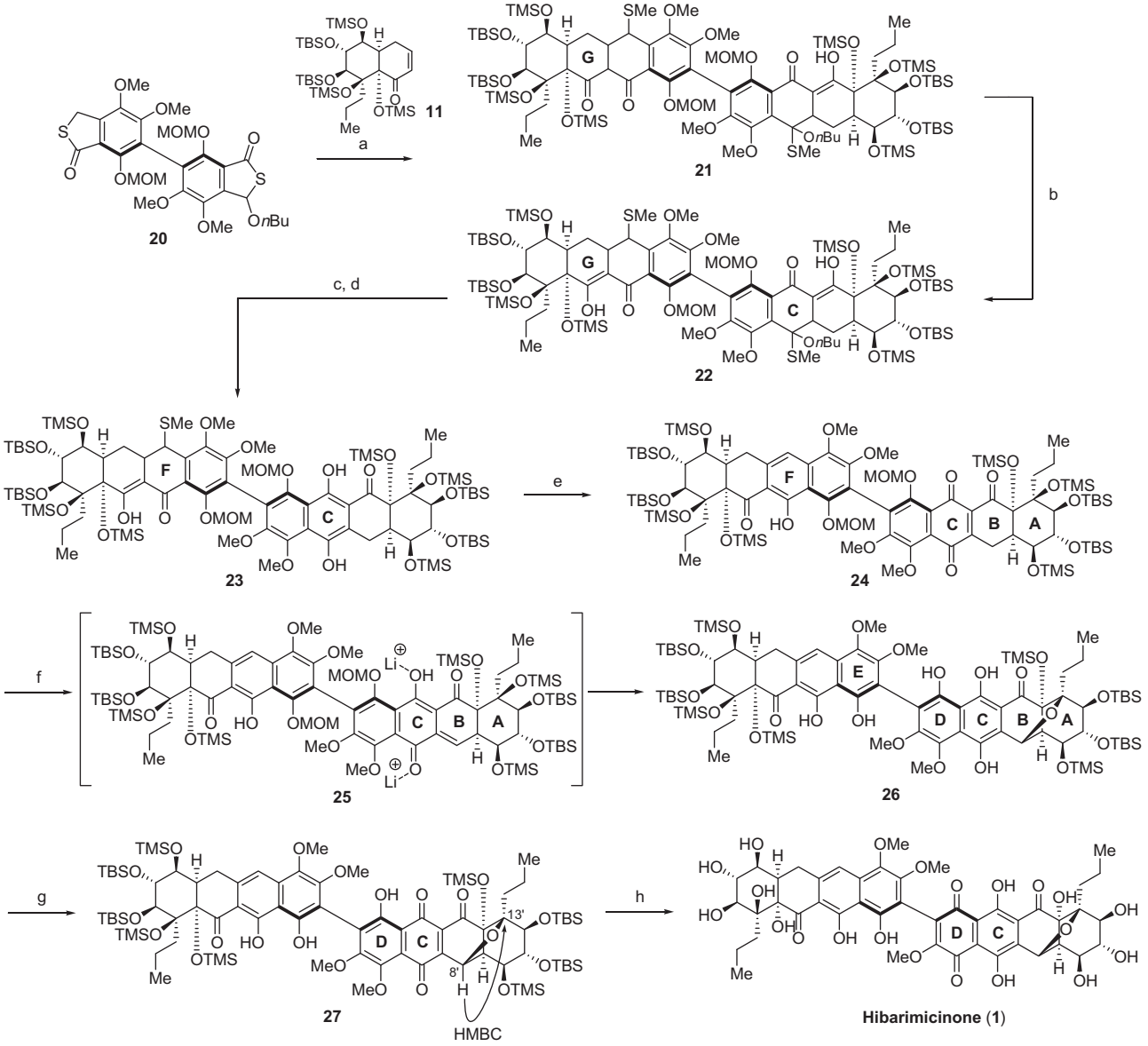
**Figure 2.** The NOE correlations of Diels–Alder adduct **5**.

rings). Difference of the oxidation stage of thiolactones in biaryl **3** should reflect the oxidation stage of **CD** and **EF** rings. At first, we show the synthesis of decalin **2**, the common structure of **AB** and **GH** rings.

The synthesis of decalin **2** started from enone **4**[5] derived from D-arabinose (Scheme 2). Diels–Alder reaction proceeded stereoselectively to give adduct **5**. The stereochemistry of **5** was confirmed by NOE (Fig. 2). Correlations between H9 and H12 as well as the phenyl group and H12 revealed that the **5** possessed the desired 9*R* configuration (hibarimicinone numbering). Correlations between TMS and H10 as well as TMS and H11 indicated that Diels–Alder reaction proceeded via the *endo* transition state from the opposite face to the siloxy group at C10 position. Jones oxidation, converting allyl trimethysilyl ether to enone, and the subsequent reduction with $SmI_2$[6] to remove sulfone gave Sm(III) enolate, which was oxidized to provide tertiary alcohol **6**. The stereochemistry of **6** was determined by NOE between H9 and the hydroxy group. Trisiloxy **6** was subjected to regioselective desilylation at C10 position and the resulting alcohol was oxidized to triketone **7**. The regio- and stereoselective reduction of triketone



**Scheme 3.** The synthesis of the chiral biaryl **3**. Reagents and conditions: (a) PivCl, $Et_3N$, THF, 0 °C, 1 h, then $Et_2NH$, 0 °C to rt, 5 h, 94%; b) *s*-BuLi, TMEDA, THF, −78 °C, 30 min, then MeI, −78 to −20 °C, 2 h, 96%; (c) $BCl_3$, $CH_2Cl_2$, rt, 40 min, 84%; (d) $Me_3OBF_4$, $Na_2HPO_4$, MeCN, rt, 3 h, then aq $NaHCO_3$, overnight, 86%; (e) $AgOCOCF_3$, $Et_3N$, $ClCH_2CH_2Cl$, 60 °C, 20 h, 48% and 23% recovery of SM; (f) BzCl, Py, rt, 30 min, 96 %; (g) 1,3-dibromo-5,5-dimethylhydantoin, AIBN, $CCl_4$, 70 °C, 4 h, 97 %; (h) AcSK, THF, rt, 1 h, then NaOMe, rt, 30 min, 69%; (i) (−)-camphanic chloride, $Et_3N$, $ClCH_2CH_2Cl$, −78 °C, 30 min, then resolution, **18** (43%) and **18′** (43%); (j) NaOMe, MeOH–THF, 0 °C to rt, 95%; (k) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, rt, 30 min, 93%; (l) 1,3-dibromo-5,5-dimethylhydantoin, AIBN, $CCl_4$, 60 °C, 40 min, then *n*-BuOH, $Et_3N$, rt to 50 °C, 12 h, 45%, and recovery of SM 38%.




**Scheme 4.** Connection of segments and completion of the total synthesis of hibarimicinone (**1**). Reagents and conditions: a) NaHMDS, MeI, THF–PhMe–Py, −20 °C, 20 min, 57% (**21**: 39% and **22**: 18%); (b) LiCl, THF, rt, 1 h, 97%; (c) $AgNO_3$, PhMe–acetone–$H_2O$, 40 °C, 1 h; (d) DBU, PhMe, 0 °C, 15 min; (e) $Ag_2CO_3$, PhMe–acetone–$H_2O$, 40 °C, 4 d, then MeI, 20 h, 63% (three steps); (f) LiI, MeCN, $ClCH_2CH_2Cl$, 50 °C, 3 h; (g) DDQ, THF–toluene, 0 °C, 5 min, 70% (two steps); (h) 1 N HCl, MeOH, 40 °C, 10 h, 80%.

**7** was achieved in excellent yield by treatment with $NaBH(OAc)_3$ in EtOH, which gave the alcohol **8** with the desired stereochemistry of the C10 position. The regioselective addition of an alkyl chain at C13 position was accomplished as follows. Protection of the tertiary alcohol of **8** accompanied with the formation of the dienyl silyl ether in the right ring, and the subsequent Grignard reaction introduced allyl group in a stereoselective manner to give tertiary alcohol **9**, in which the NOE between H12 and an allylic hydrogen (H19) was observed. After silylation of the tertiary alcohol, treatment of the dienyl silyl ether with DBU in hot toluene in the presence of *i*-PrOH promoted the regioselective de-silylation to afford enone **10**. Hydrogenation of the *exo* olefin of **10** yielded enone **11**, the decalin segment **2** in Scheme 1.

On the other hand, the chiral biaryl thiolactone **3** was obtained as shown in Scheme 3. The commercially available carboxylic acid **12** was converted into amide, with which *ortho*-lithiation-methylation was performed to give **13**. Regioselective de-O-methylation was followed by the transformation of amide into ester to give phenol **14**. Phenol **14** was subjected to oxidative dimerization by using silver trifluoroacetate, and the resulting bisphenol **15** was protected as benzoate **16**. Two benzylic positions of **16** were brominated and the sequential substitution with thioacetate ion and methanolysis produced thiolactones with free phenols (**17**). The racemic biaryl **17** was derived to the diastereo-mixture of monocamphanate, which was resolved by column chromatography and subsequent crystallization to give optically pure **18** and **18′** in good yield. The desired isomer **18** was converted into symmetrically protected **19**. The absolute structure of **19** was determined by X-ray crystallography.[7] Mono-bromination of **19** and substitution with *n*-butanol were performed in one pot to give **20**, the chiral biaryl **3** in Scheme 1.

With both segments **2** and **3** in hand, we examined to connect these segments to obtain the eight rings skeleton in one pot (Scheme 4). In preliminary studies, we found that Michael-Dieckmann type cyclization using non-substituted benzothiolactone (the left ring type of **20**) proceeded in THF while the cyclization with alkoxybenzothiolactone (the right ring type) was promoted in toluene. Pyridine suppressed generation of polymerized products.

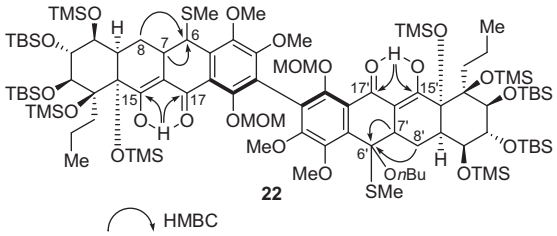



**Figure 3.** HMBC of the octacyclic **22**.

Therefore, bisthiolactone **20** was treated with base in the mixed solvent including THF, toluene, and pyridine to promote double Michael–Dieckmann type cyclization to give eight rings, and the resulting thiolates were methylated to provide compounds **21** and **22**. The labile trione **21**, the keto form in **G** ring, was smoothly converted into the enol form **22** in the presence of LiCl. Formation of the octacycllic skeleton was confirmed by HMBC with **22** (Fig. 3). Hydrolysis of semithioacetal was performed with $AgNO_3$, and the subsequent treatment with DBU gave the hydroquinone at the **C** ring of **23**. Oxidation of the **C** ring and aromatization of **F** ring, including elimination of thioether and tautomerization, were attained with $Ag_2CO_3$ and MeI to afford **24** in one pot. The ether acrossing **AB** rings formed with excess amounts of LiI by enolization at **BC** rings and conjugate addition to the resulting enone **25**. The simultaneous de-O-methoxymethylation gave free phenols (rings **D** and **E**) in **26**. The resulting **26** was immediately oxidized to quinone **27**. The correlation between H8' and C13′ in **27** made sure the transannular ether formation. Finally, de-O-silylation as well as de-O-methylation and tautomerization at **CD** rings were achieved by treatment of **27** under the acidic conditions to give hibarimicinone (**1**). The spectral data of the synthetic **1** including the $^1$H NMR and the CD spectra were identical with those of the natural hibarimicinone.

In conclusion, we have achieved the total synthesis of hibarimicinone (**1**). The synthesis features the chemistry of a chiral biaryl thiolactone including double Michael–Dieckmann type cyclization and aromatization. The ether acrossing **AB** rings in **26** was formed via enolization and conjugate addition in **BC** rings of **24**. Removal of protective groups and tautomerization under the acidic conditions gave hibarimicinone (**1**).

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## Supplementary data

The spectrum data of compounds **5**–**11**, **14**, **15**, **17**, **18**, **18′**, **19**, **20**, **22**, **24**, **27**, and **1**, $^1$H NMR spectrum of synthetic hibarimicinone (400 MHz in $CD_3OD$), $^{13}$C NMR spectrum of synthetic hibarimicinone (150 MHz in $CD_3OD$) and the CD spectrum of synthetic hibarimicinone. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.062.

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7. Crystallographic data (excluding structure factors) for the structures of **19** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 843601 for **19**.