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Total Synthesis of Herbertenediol, an Isocuparane Sesquiterpene Isolated from Liverworts

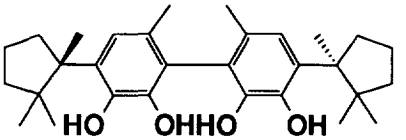
Yoshiyasu Fukuyama,* Yuuko Kiriyama, and Mitsuaki Kodama

Faculty of Pharmaceutical Sciences, Tokushima Bunri University,

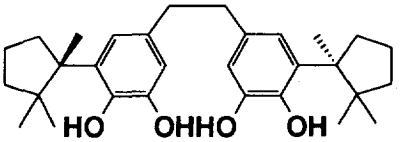
Yamashiro-cho, Tokushima 770, Japan

Abstract: Total synthesis of herbertenediol, an isocuparane-sesquiterpene possessing a potent anti-lipid peroxidation activity isolated from a liverwort, has been achieved via herbertenol using intramolecular Heck reaction as the key step.

From the liverwort, *Mastigophora diclados*, we have recently isolated mastigophorenes [e.g. A (**1**) and D (**2**)],[1] which attracted much our attention since they were found to exhibit interesting neurotrofic properties, i.e. accelaration of neurite sprouting and network formation. Mastigophorenes are considered to be biosynthesized by the oxidative coupling of herbertenediol (**3**) which has also been found in the liverwort, *Herberta adunca*.[2] Quite recently, we have found out that herbertenediol (**3**) exhibits a potent anti-lipid peroxidation activity.[3] From the interests for the biomimetic synthesis of mastigophorenes and the biological activity of **3** itself, we investigated the efficient method for the synthesis of herbertenediol (**3**), an essential unit of **1** and **2**.

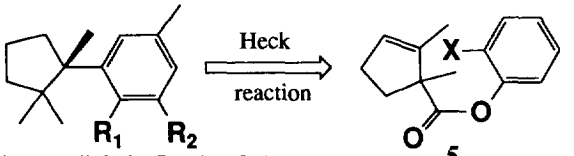


1



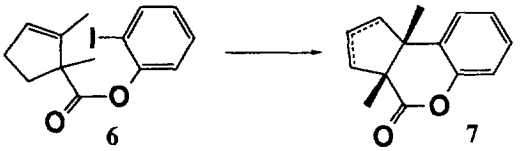
2

While cuparane- and isocuparane (herbertane)-type sesquiterpenes have been synthesized frequently because these substances offer a good model for the construction of quaternary carbon at the benzylic position,[4] we have developed a new method for the synthesis of isocuparane skeleton utilizing intramolecular Heck reaction.[5] In this communication we would like to report the first total synthesis of (±)-herbertenediol (**3**) *via* herbertenol[6] (**4**) according to this methodology.



Herbertenediol (**3**); R_1=R_2=OH
Herbertenol (**4**); R_1=OH, R_2=H

Prior to start the synthesis of natural product, we examined the conditions of intramolecular Heck reaction by using iodo-ester **6** prepared by the same method as **9** (*vide infra*). As can be seen from the table, $Pd(PPh_3)_4$ and $Pd(OAc)_2$ are equally effective for the present reaction and *tert*-amine (especially nBu_3N) is superior as the base. The best results for the formation of lactone **7** was obtained by the combination of $Pd(OAc)_2$-nBu_3N-(*o*-Tol)$_3$P in DMF at 120°C (Entry 9). In the case of entries 7, 8, and 11, substantial amount of hydrolysis was observed. Since the conditions of intramolecular Heck reaction has now been established, we next proceeded to the synthesis of natural products.



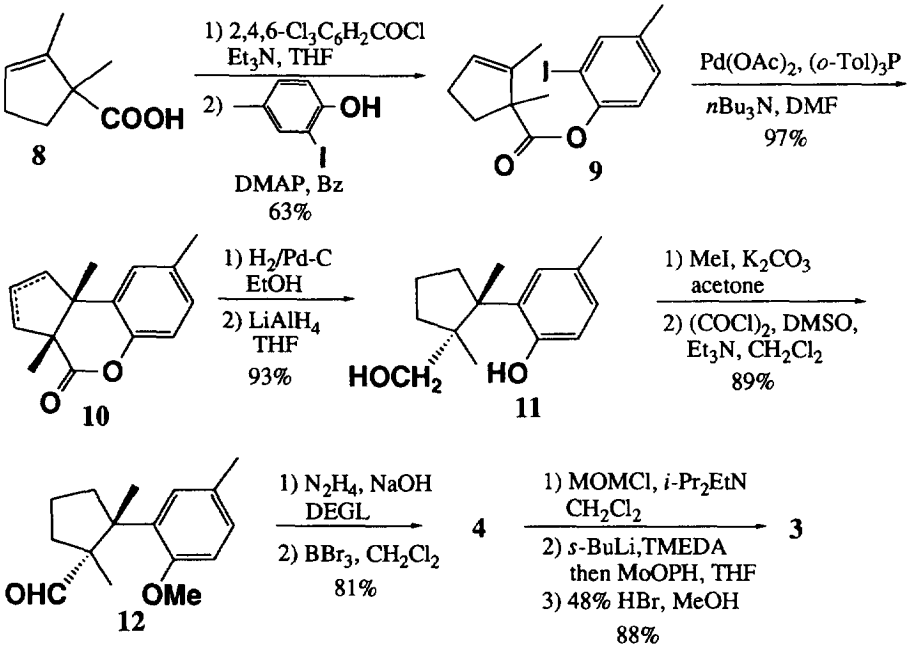
Entry	Catalyst[a]	Base[b]	Additive[c]	Solvent	Temp.	Yield (%)
1	$Pd(PPh_3)_4$	K_2CO_3		CH_3CN	80	NR
2	$Pd(PPh_3)_4$	K_2CO_3		Toluene	110	NR
3	$Pd(PPh_3)_4$	Et_3N		DMF	120	40.3
4	$Pd(PPh_3)_4$	Et_3N		CH_3CN	80	NR
5	$Pd(PPh_3)_4$	Et_3N	(*o*-Tol)$_3$P	DMF	120	51.8
6	$Pd(OAc)_2$	Et_3N	(*o*-Tol)$_3$P	DMF	120	58.2
7	$Pd(OAc)_2$	Ag_2CO_3	(*o*-Tol)$_3$P	DMF	120	12.8
8	$Pd(OAc)_2$	Tl_2CO_3	(*o*-Tol)$_3$P	DMF	120	Hydrol.
9	$Pd(OAc)_2$	nBu_3N	(*o*-Tol)$_3$P	DMF	120	79.1
10	$Pd(OAc)_2$	iPr_2NEt	(*o*-Tol)$_3$P	DMF	120	73.8
11	$Pd(CH_3CN)_2Cl_2$	nBu_3N	(*o*-Tol)$_3$P	DMF	120	43.8
12	$Pd(OAc)_2$	nBu_3N	DPPE	DMF	120	66.2

[a]10 mol%. [b]2 equivalent. [c]20 mol%.

Cyclopentenecarboxylic acid[7] **8** was reacted with 2-iodo-*p*-cresol under the Yamaguchi's condition[8] to give an ester **9** in 63% yield. Intramolecular Heck reaction of **9** under the conditions described above yielded a lactone **10** in 97% yield as a mixture of double bond isomers. After hydrogenation of the double bond in **10**, the lactone moiety was converted into diol with $LiAlH_4$ in THF. The phenolic hydroxyl group in **11** was protected and the primary alcohol was oxidized to afford an aldehyde **12**. Huang-Minlon reduction of **12** yielded (±)-herbertenol (**4**) in 83% yield after deprotection with BBr_3. Although **4** has already been

converted into herbertenediol (3),[6] we attempted to develop more efficient method of hydroxylation by applying Vedejs' method.[9] Thus, 4 was first converted into MOM-ether, which was metalated with *s*-BuLi regio-selectively at *ortho*-position of MOMO-group and then reacted with oxodiperoxymolybdenum (pyridine)(HMPT) (MoOPH) affording a hydroxylation product in high yield. Deprotection with 48% HBr afforded (±)-herbertenediol (3), whose IR, Mass, ^1H and ^{13}C NMR spectra indicated the identity with natural product.

Thus, a highly efficient synthetic method (36% overall yield from 8) of herbertendiol (3) has been developed.[10]



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References and Notes

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2) A. Matsuo, S. Yuki, M. Nakayama, and S. Hayashi, *Chem. Lett.*, 463 (1982).

3) 100% inhibition at the concentration of 1 μg/ml in rat brain homogenates.

4) For the synthesis of herbertene, see S. Chandrasekaran and J. V. Turner, *Tetrahedron Lett.*, **23**, 3799 (1982); S. Takano, M. Moriya, and K. Ogasawara, *Tetrahedron Lett.*, **33**, 329 (1992); A. K. Saha, S. Das, and D. Mukherjee, *Tetrahedron Lett.*, **35**, 3353 (1994).

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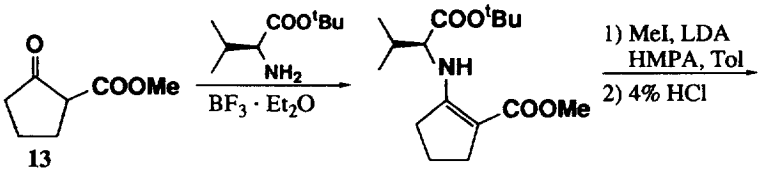
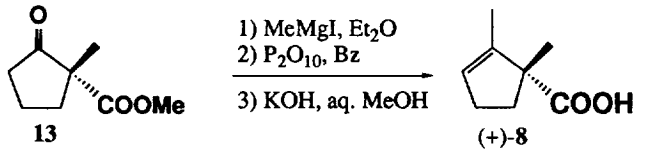
10) Since optically active keto-ester **13**[11] was synthesized according to the Koga's method[12] and was converted into the carboxylic acid (+)-**8**, present work constitutes the formal total synthesis of natural (-)-herbertenediol.



13



13

$[\alpha]_D$ -10.8° (90% ee by G.C.)
(lit.[11] $[\alpha]_D$ -10.6°)

(+)-**8**

$[\alpha]_D$ +128.8°

11) T. Sato, H. Maeno, T. Noro, and T. Fujisawa, *Chem. Lett.*, 1739 (1988).

12) K. Ando, Y. Takemasa, K. Tomioka, and K. Koga, *Tetrahedron*, **49**, 1579 (1994).

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