Total Synthesis of (-)-Laurequinone

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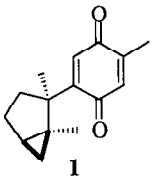
The first synthesis of (-)-laurequinone, cyclolaurane-type sesquiterpenoid isolated from the red alga *Laurencia nidifica*, has been achieved by using an intramolecular Heck reaction and an insertion of carbene as the key steps for the construction of quaternary carbon at the benzylic position and cyclopropane ring, respectively.

Red algae of the genus *Laurencia* (Rhodomelaceae) are rich in haloganated or nonhaloganated laurane and cyclolaurane-type sesquiterpenes.[1] Shizuri *et al.* isolated (-)-laurequinone (**1**) and debromolaurinterol (**2**) from *Laurencia nidifica*.[2] They are representatives of the cyclolaurane-type sesquiterpenes having two consecutive quaternary carbons which are substituted with benzene and cyclopropane rings. Although cuparane- and isocuparane-type sesquiterpenes have been synthesized frequently as good models for the construction of quaternary carbon at the benzylic position,[3] laurequinone (**1**) has remained an attractive natural product to be synthesized due to not only exercises in the construction of successive quaternary carbons but also anticipation of 5-lipoxygenases inhibitory activity.[4] Recently, we reported a new method for the synthesis of cuparane skeleton utilizing an intramolecular Heck reaction,[5] which was successfully applied to an effective synthesis of isocuparane-type sesquiterpene herbertendiol (**3**)[6b] isolated from the liverwort *Herberta adunca*[7] and *Mastigophora diclados*.[6a] In this communication, we wish to report the first synthesis of **1** by a combination of intramolecular Heck reaction and carbene insertion.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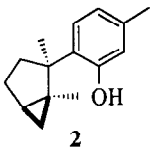
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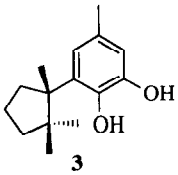
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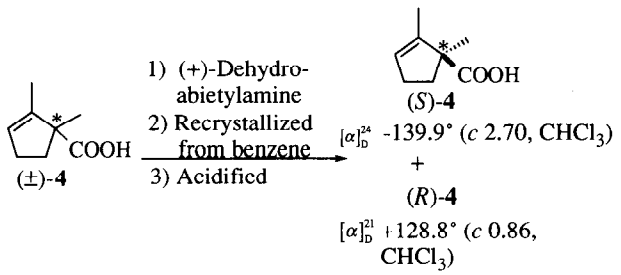
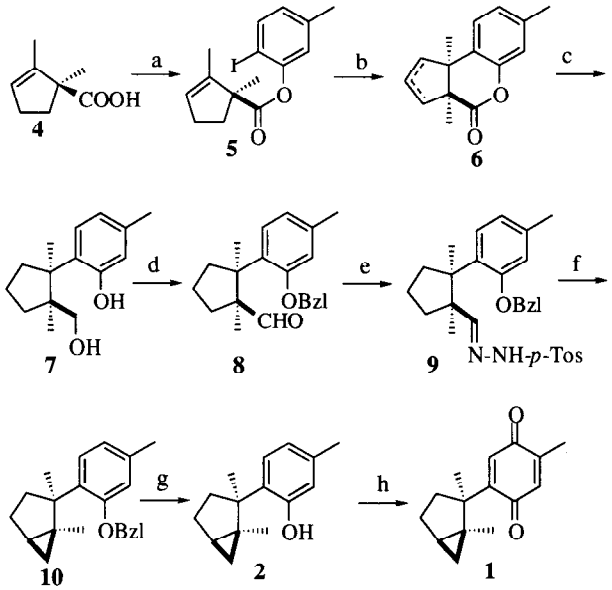
The synthesis of (-)-laurequinone (**1**) was started with optically active cyclopenetencarboxylic acid **4** which was readily prepared by optical resolution of cyclopentencarboxylic acid[8] as shown in scheme 1.



Scheme 1.

(-)-Cyclopentenecarboxylic acid **4** was reacted with 2-iodo-*m*-cresol under the Yamaguchi's condition[9] to give ester **5** in 69% yield. Intramolecular Heck reaction of **5** under the same condition as used for **3**[6b] yielded lactone **6** in 93% yield as a mixture of double bond isomers. After hydrogenation of the double bond in **6**, the lactone moiety was reduced into the diol **7** with $LiAlH_4$ in THF. Methoxy group was not used for the protection of phenolic hydroxyl group in **7**, because demethylation of the phenolic hydroxyl group in **7** was known to be troublesome in later stage.[10] Therefore, the phenolic hydroxyl group was protected with benzyl group and then the primary alcohol was oxidized to afford aldehyde **8**.

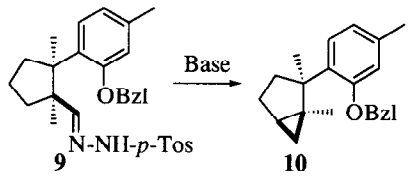


a. 1) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, rt, 15 min; 2) 2-Iodo-*m*-cresol, DMAP, Bz, rt, 4h (69%); b. 10 mol% $Pd(OAc)_2$, 20 mol% (*o*-Tol)$_3P$, 2 eq. *n*-Bu_3N, DMF, 120°C, 12h (93%); c. 1) H_2/Pd-C, EtOH, rt, 12h (quant); 2) $LiAlH_4$, THF, 0°C, 3h (92%); d. 1) Bzl-Cl, K_2CO_3, acetone, reflux, 8h (86%); 2) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, 1h; Et_3N, 78°C → 0°C 20 min (90%); e. *p*-Tos-$NHNH_2$, MeOH, reflux, 4h (57%); f. *t*-BuOK, *t*-BuOH, reflux; g. H_2/Pd-C, EtOH, rt, 12h, 34% from **9**; h. Fremy's salt, acetone, rt, 7h (60%).

Scheme 2.

For the stereoselective construction of cyclopropane ring, carbene insertion reaction was attempted, because we encountered the formation of cyclopropane ring as a side reaction in case of the reduction of the tosylhydrazone **9** during studies on the synthesis of **3**. So, we examined the condition of carbene insertion for synthesis of cyclopropane ring. As can be seen from the table, the best result for the formation of cyclopropane was obtained by *t*-BuOK in *t*-BuOH under reflux (entry 1). Heating

the aldehyde **8** and *p*-toluenesufonic hydrazine in methanol gave tosylhydrazone **9** which was subjected to this condition to give the cyclopropane derivative **10** in 40 % yield.



9 **10**

Table Carbene insertion of **9**

Entry	Base	Solvent	Temp. (°C)	Time (min)	**10** (%)
1	*t*-BuOK	*t*-BuOH	reflux	15	40
2	NaH	*t*-BuOH	reflux	30	34
3	*n*-BuLi	*t*-BuOH	rt	15	25
4	*t*-BuOK	Benzene	reflux	30	13
5	*t*-BuOK	DMF	120	30	32
6	*t*-BuOK	DMSO	120	30	0

Removal of the benzyl group by catalytic reduction afforded debromolaurinterol (**2**),[11, 12] whose spectral data were identical to those cited in the literature.[1a] Finally, **2** was oxidized with Fremy's salt to give quinone **1**, whose spectral data (^{1}H NMR, IR, MS and UV) were superimposable with those of natural one.[2] Enantiomeric excess of synthetic **1** was 90% ee.[13]

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11 Compound **2**: $[\alpha]_D$ -12.4° (*c* 0.24, $CHCl_3$). Natural $[\alpha]_D$ -12.2° ($CHCl_3$).[1a]

12 A small amount of six member ring compound as by-product was obtained.

13 The ee was determined by GC analysis with chiral column; α-DEX™ 120; film thickness: 0.25 μ; column dimensions: 30 m x 0.25 mm; carrier: helium, 30 cm/sec; temp.: 160 °C; retention time: 31.4 min (-)-**1** and 32.4 min (+)-**1**; detection: FID.