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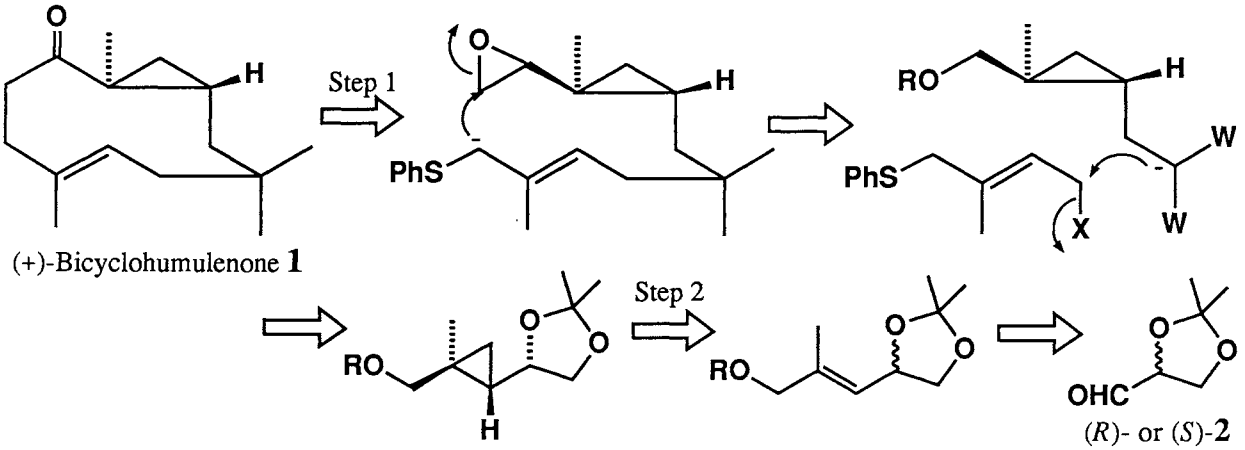
Total Synthesis of (+)-Bicyclohumulenone

Yoshiyasu FUKUYAMA, Motoko HIRONO, and Mitsuaki KODAMA*
Faculty of Pharmaceutical Sciences, Tokushima Bunri University,
Yamashiro-cho, Tokushima 770

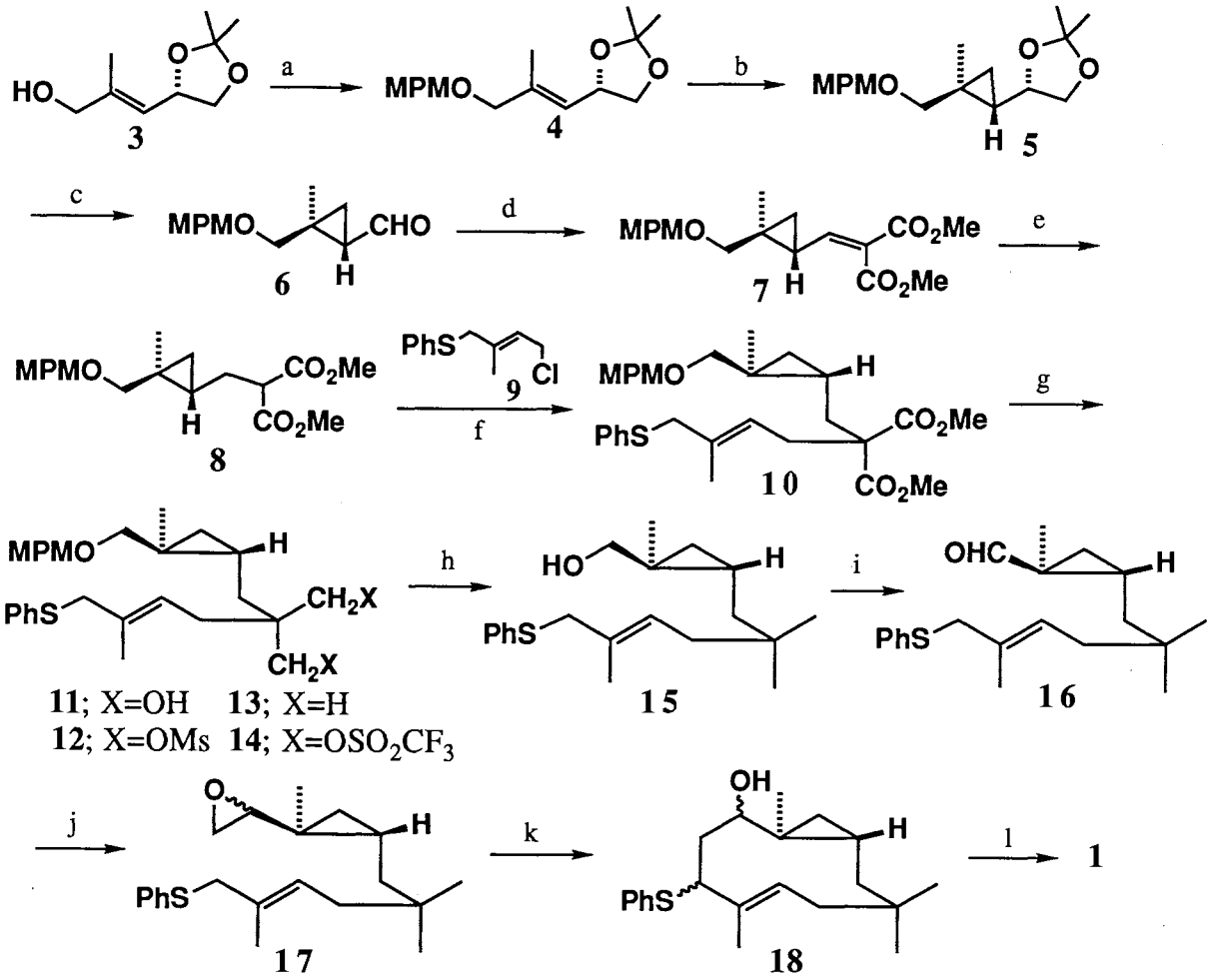
(+)-Bicyclohumulenone, a bicyclic sesquiterpene isolated from liverworts, was synthesized using stereoselective Simmons-Smith cyclopropanation and intramolecular alkylation of α-sulfenyl carbanion as key steps.

(+)-Bicyclohumulenone (**1**) is a novel humulane-type sesquiterpene isolated from the liverwort, *Plagiochila siophila*.[1] The structure including absolute configuration has been determined by X-ray analysis of mono-*p*-bromobenzoate of its triol derivative.[1] The novel framework having a cyclodecenone ring fused with cyclopropane ring attracted much attention of synthetic chemists and thus racemic bicyclohumulenone has been synthesized by two groups by means of biomimetic cyclization of epoxyhumulene[2] or cyclopropanation of cyclodecadienone.[3] Herein, we report the first total synthesis of (+)-bicyclohumulenone (**1**).



Our synthetic strategy was briefly illustrated in the above scheme. The key step in this synthesis is stereoselective introduction of cyclopropane

ring (Step 2) for which Simmons-Smith reaction seems to be most suitable, and ten-membered ring formation (Step 1) which could be achieved by the intramoleculer alkylation of α-sulfenyl carbanion with epoxide.[4] 1,2-*O*-Isopropylidene glyceraldehyde (**2**) was chosen as starting material since both enantiomers are available[5] and therefore it is possible to synthesize both enantiomers of **1**, if desired. The synthesis was started from the allylic alcohol[6] **3** readily available from (*R*)-**2**. Thus, the hydroxyl group of **3** was



a. *p*-$MeOC_6H_4CH_2Cl$/NaH, DMF. b. CH_2I_2/Zn-Cu, ether, rt. c. 1) 2 M HCl, MeOH; 2) $NaIO_4$, THF-H_2O (3:1). d. $(MeO_2C)_2CH_2$/pyridinium acetate, CH_2Cl_2. e. L-Selectride, THF, -78 °C. f. NaH, DMF. g. 1) $LiAlH_4$,THF; 2) MsCl/Et_3N, CH_2Cl_2; 3) $LiBHEt_3$, THF, 60 °C or 1) $LiAlH_4$, THF; 2) $(CF_3SO_2)_2O$, py; 3) $LiBHEt_3$, THF, rt. h. DDQ, CH_2Cl_2-H_2O (18:1). i. PCC, CH_2Cl_2. j. Me_3S^+=OI^-/NaH, DMSO. k. *n*-BuLi, HMPA-THF, -78 - 0 °C. l. 1) Na, *t*-BuOH, rt; 2) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2.

first protected as *p*-methoxybenzyl (MPM) ether[7] to give **4** (96%). Simmons-Smith reaction on **4** took place in high yield (88.8%) and in high diastereoselectivity. HPLC analysis of the product displayed that diastereomeric cyclopropane derivatives were formed in a ratio of 90.7:9.3. The stereochemical relationship of these products was not able to clarify at this stage, but the major product was shown to have the desired (2*S*,3*S*)-configuration after converting to natural **1**. Interestingly, same cyclopropanation carried out on the diol derived by acid-hydrolysis of **4** yielded again (2*S*, 3*S*)-product in high selectivity (more than 98%) but in slightly decreased yield though the substrate in this case is an allylic alcohol.[8] The major product **5** was treated with acid and the resulting diol was cleaved to aldehyde **6** (91%). This aldehyde **6** was then condenced with malonic ester to the unsaturated ester **7** (95.6%). Since the attempted reductive alkylation[9] (L-Selectride then chloride **9**[10]) was unsuccessful, the olefinic bond of **7** was first reduced with L-Selectride, and then the saturated diester **8** was alkylated with the chloride **9** in the presence of sodium hydride to afford **10** (86%). The next task is the reduction of the diester group in **10**. For this purpose, **10** was first reduced to the corresponding diol **11** which was then converted to dimesylate **12** (81%). Reduction of the dimesylate using Super-Hydride was very slow and after 2 days at 60°C, the desired *gem*-dimethyl product **13** was obtained in only 43% yield. However, the reduction of corresponding ditrifrate **14** took place smoothly at room temperature to give **12** in 81% yield. Oxidative deprotection of the MPM group[7] to **15** followed by oxidation of the resulting prim. alcohol afforded an aldehyde **16** (64% in two steps) which was converted to the epoxide **17** by treatment with dimethyl sulfoxonium methylide. The epoxide **17** was a mixture of diastereomers, but was subjected to the next cyclization reaction without separation because of its instability. In contrast to the similar reactions so far reported,[4,12] cyclization of **17**, in general, did not proceed cleanly. We have examined various conditions using *n*-butyllitium or *tert*-butyllitium in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) or HMPA, but the yield of **17** (a diastereomeric mixture) was limited up to 17%. **18** was desulfurized and then oxidized under Swern's condition. The TLC behavior, ^{1}H NMR spectrum, and optical rotation ($[\alpha]_D$ +43.8°, *lit.*[1] +60.0°) as well as the sign of CD spectrum of the product were identical with those of natural (+)-bicyclohumulenone (**1**).

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