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Synthesis of the CD ring in taxol from (*S*)-(+)-carvone

Tony K. M. Shing,* Chi M. Lee and Ho Y. Lo

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong, China

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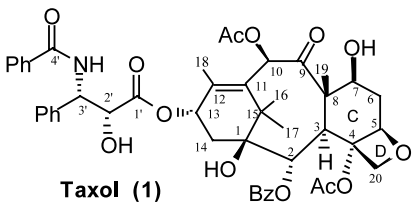
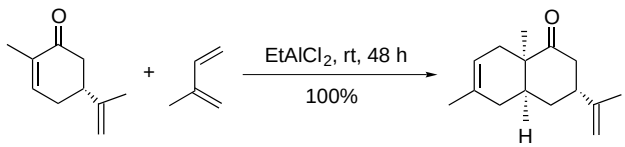
Abstract—The tricycle **16** containing a functionalized CD ring is constructed from (*S*)-(+)-carvone in 21 steps involving a Baeyer–Villiger oxidation, an Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction, a stereospecific Grignard addition, and an intramolecular S_N2 reaction as the key steps.

Paclitaxel (Taxol)[1] (**1**) is a tetracyclic diterpenoid anticancer drug routinely used for the treatment of breast, lung, and ovarian carcinomas.[2] The outstanding cytotoxic activity of taxol is believed to arise from its unique propensity to hinder cell replication by preventing microtubules from depolymerization.[3] To date, six total syntheses of taxol have been published.[4] The shortest route was reported by Wender et al.,[4d] starting from (1*R*)-(+)-verbenone and involving 37 steps in an overall yield of about 0.37%.



Taxol (1)

In our quest for the discovery of a structurally simplified, synthetically accessible taxol analogue which possesses a comparable biological profile, we started a project to investigate a facile and flexible construction of the CD rings of the taxol carbon skeleton. Our preliminary experiments have shown that the Diels–Alder reaction between (*R*)-(−)-carvone and isoprene occurred preponderantly in an *anti* orientation with respect to the isopropylene group in (*R*)-(−)-carvone to give the decalin **2**.[5] Such a decalin system **2**, containing a stereo-defined angular methyl group, could be a valuable synthetic precursor for the taxol C ring system.



***R*-(–)-Carvone** **Isoprene** **2**

These experiments have also indicated that in order to obtain the correct absolute configuration at the angular methyl group in taxol, (*S*)-(+)-carvone has to be employed in our synthesis. Thus, the intermolecular Diels–Alder reaction of (*S*)-(+)-carvone with isoprene using $EtAlCl_2$ as the catalyst followed by protection[6] of the carbonyl group with ethylene glycol gave acetal **3** in an overall yield of 82%. Dihydroxylation of the two double bonds in acetal **3** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO)[7] furnished the corresponding tetraol which was subjected to a selective glycol cleavage oxidation[8] at the terminal diol unit, giving ketone **4**, mp 171.5–172°C; $[\alpha]_D^{20}$+3.0 (*c* 0.3, $CHCl_3$), in a 74% overall yield. Baeyer–Villiger oxidation[9] of ketone **4** using *m*-chloroperbenzoic acid (*m*CPBA) afforded acetate **5**, mp 175.5–176°C; $[\alpha]_D^{20}$−15.1 (*c* 0.37, $CHCl_3$), in 90% yield. Protection of the vicinal diol unit in **5** with 2,2-dimethoxypropane (DMP) followed by deacetylation and pyridinium chlorochromate (PCC) oxidation of the resultant hydroxy group afforded ketone **6**, mp 89.5–90.5°C; $[\alpha]_D^{20}$+40.6 (*c* 0.4, $CHCl_3$). After considerable experimentation, direct introduction of a 1-carbon unit to C-4 (taxol numbering) was unsuccessful and an alternative route was adopted. Thus, selective enolisation[10] of ketone **6** with Et_3N occurred at C-4 and subsequent treatment with *tert*-butyldimethylsilyltriflate (TBSOTf) at −78°C gave the corresponding silyl enol ether which was oxidized with Oxone[11] to give the α-hydroxy ketone **7** in 65% overall yield. The inter-

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* Corresponding author. E-mail: tonyshing@cuhk.edu.hk

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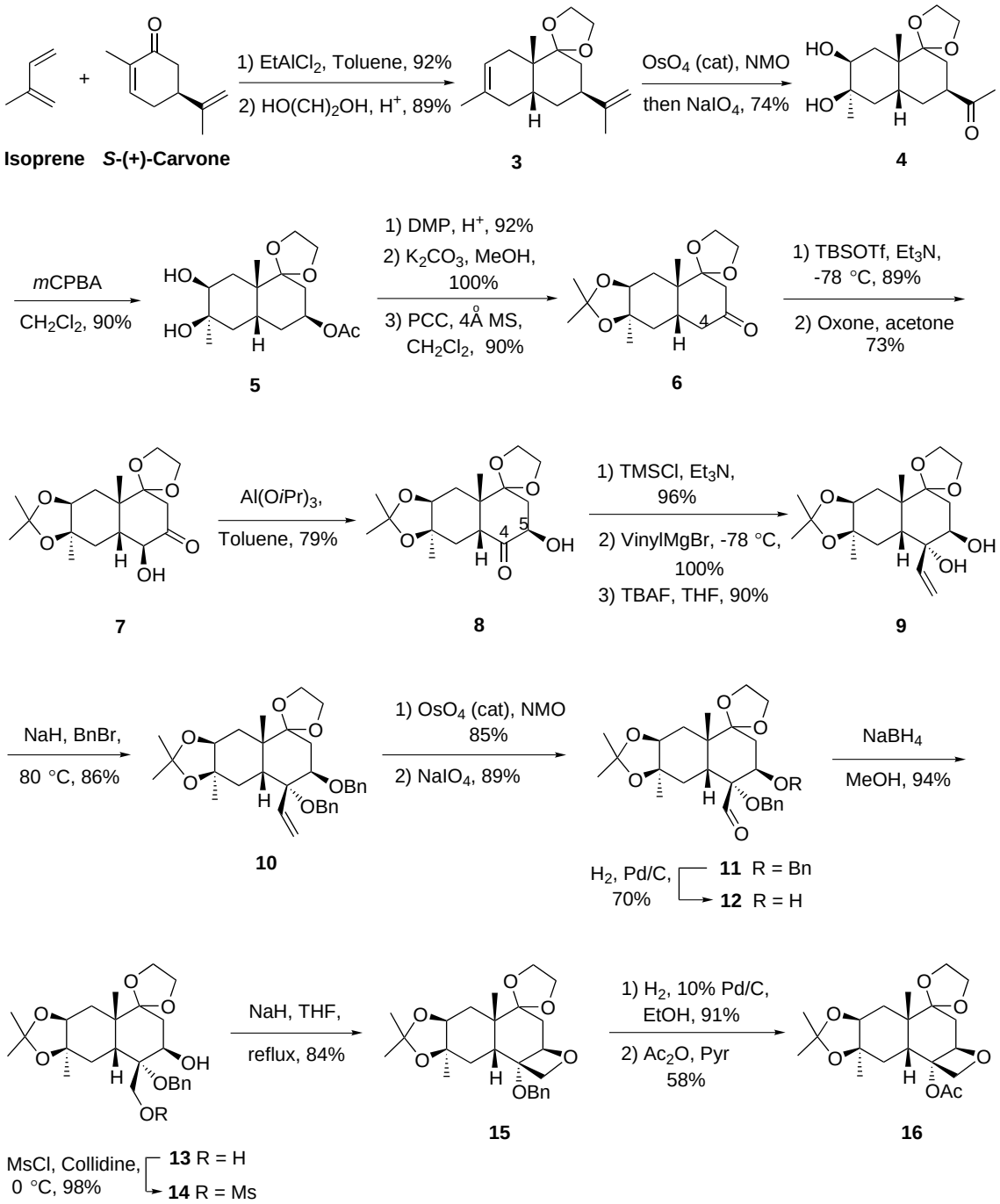

molecular redox reaction i.e. Oppenaurer oxidation and Meerwein–Ponndorf–Verley reduction,[12] of α-hydroxy ketone **7** using $Al(OiPr)_3$ as the catalyst gave the thermodynamically more stable 5-hydroxy-4-one **8** in 79% yield. Transient protection of the free alcohol in **8** as a trimethylsilyl (TMS) ether was followed by the addition of vinyl magnesium bromide and subsequent deprotection with tetrabutylammonium fluoride (TBAF), affording the diol **9**, mp 150–151°C; $[\alpha]_D^{20}$+24.1 (*c* 0.3, $CHCl_3$), in 86% overall yield. It is noteworthy that the Grignard addition was stereoselective and only one stereoisomer was isolated in a quantitative yield. The constitution and especially the stereochemistry of the tertiary alcohol in **9** was confirmed by X-ray crystallographic analysis.[13] Benzylation of the diol **9** gave the dibenzyl ether **10** without incident, $[\alpha]_D^{20}$+6.5 (*c* 1.0, $CHCl_3$). The double bond in **10** was dihydroxylated[7] and then oxidatively cleaved[8] to form a rather stable aldehyde **11**, $[\alpha]_D^{20}$+11.4 (*c* 0.4, $CHCl_3$), in an overall yield of 76%. Selective hydrogenolysis of the secondary benzyl ether in **11** gave the hydroxy aldehyde **12** which was reduced with sodium borohydride to give diol **13**, $[\alpha]_D^{20}$+10.6 (*c* 0.5, $CHCl_3$). Selective mesylation[14] of the less hindered primary alcohol in **13** gave the mesylate **14** that was treated with sodium hydride to cause an intramolecular S_N2 reaction,[15] furnishing the oxetane **15**, $[\alpha]_D^{20}$+16.4. (*c* 0.7, $CHCl_3$), in 82% overall yield. The benzyl ether protecting group in **15** was transformed into the desired acetyl group of **16**, mp 131–131.5°C; $[\alpha]_D^{20}$+26.1 (*c* 0.25, $CHCl_3$), by hydrogenolysis and

acetylation. Thus, the tricycle **16** was constructed from (*S*)-(+)-carvone in 21 steps with an overall yield of 4%.

In summary, we have presented a facile, efficient, and stereocontrolled synthetic route for the construction of the functionalized CD ring in taxol. The transformation of tricycles **15** and **16** into taxol analogues is under active investigation.

Acknowledgements

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