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Total Synthesis of Monocyclofarnesane Norsesquiterpenoids Isolated from Mushroom Ingested by Beetle: Efficiency of Solid State Baeyer-Villiger Reaction

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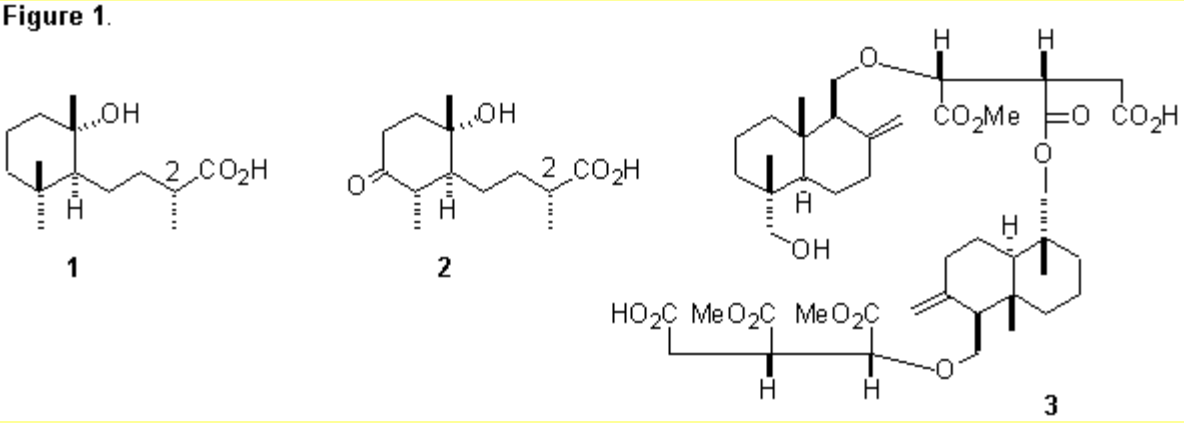
Abstracts: Nor- and bisnorsesquiterpenoids **1** and **2** have been synthesized starting from (*S*)-(+)-Wieland-Miescher ketone analogue **4** *via* solid state Baeyer-Villiger reaction as a key step.

Introduction

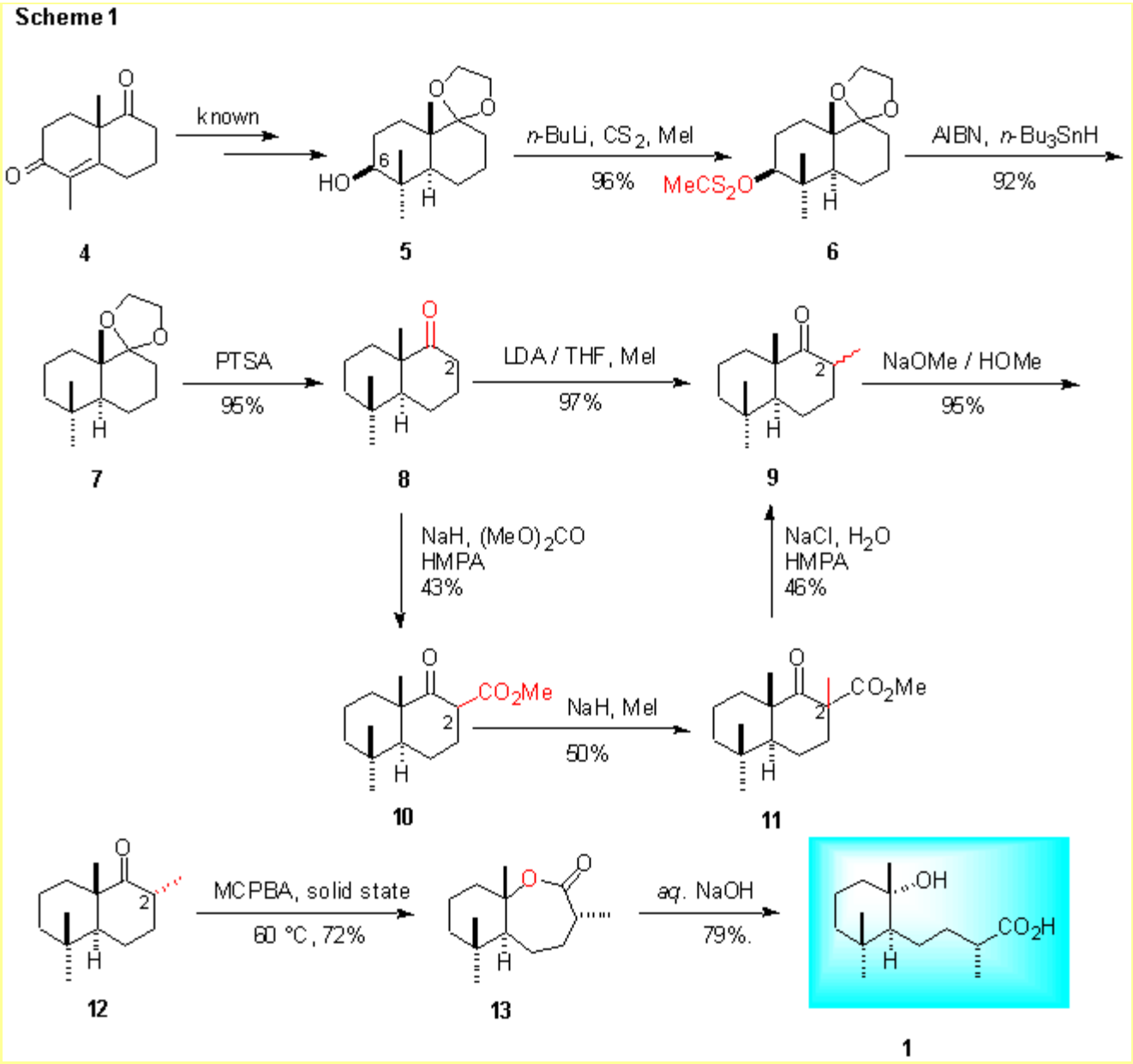
Cryptoporic acid **3**, isolated from basidiomycetes fungi (*Cryptoporus volvatus*) by Hashimoto and Asakawa,[1] has strong inhibitory activity on the release of superoxide anion radical from guinea pig peritonel macrophages (Figure 1). From the dry powders of the mushroom ingested by the beetle *Tibolium castaneum,* several novel metabolites were isolated whose relative stereostructures were determined by combination with extensive 2D NMR studies. Among them, a norsesquiterpene hydroxy-acid **1** and a bisnorsesquiterpene keto-acid **2** are unique monocyclofarnesane derivatives and anticipated to be metabolites of cryptoporic acid **3** *via* bio-Baeyer-Villiger transformation by the insects.[1] Their absolute stereostructures at C-2 were determined to be *R* as depicted in Figure 1, structures **1** and **2**, by employing Kusumi's PGME (phenylglycine methyl ester) method.[2] This paper deals with the first total syntheses of **1** and **2** demonstrating efficiency of solid state Baeyer-Villiger reaction.

Figure 1.



Total synthesis of norsesquiterpenoid 1 [3]

According to the plausible biogenetic pathway[1] of **1** and **2** *via* bio-Baeyer-Villiger reaction of bio-degradation products of **3**, decalone **12** (Scheme 1) was chosen as a key intermediate for the total synthesis of **1**. Though optically active decalone **8** is known in literature,[4] we took an alternative route from alcohol **5** derived from optically active (*S*)-(+)-Wieland-Miescher ketone analogue **4**[5] (>95% e.e.). By employing Barton's radical protocol,[6] the hydroxyl group at C-6 of the alcohol **5** was removed to give ketal **7** in 88% overall yield followed by deprotection of the ketal to give the decalone **8** {[a]$_D^{21}$ - 42.2 (*c* 2.2, $CHCl_3$)} in 95% yield. In order to ensure mono-methylation at C-2 of the decalone **8**, methoxycarbonyl group was introduced at first to give **10**, which was followed by methylation to afford **11** and finally demethoxycarbonylation to give decalone **9** as an diastereomeric mixture. However, overall yield of the reactions from decalones **8** to **9** was unsatisfactory. Fortunately, mono-methylation of **8** with excess LDA and methyl iodide furnished **9** as a 1 : 1 diastereomeric mixture in 97% yield. No dimethylation occurred under the reaction conditions employed. The methyl group at C-2 of the decalone **9** was isomerized in 95% yield by treatment with base into the thermodynamically more stable a-isomer **12** in which the orientation of methyl group was apparent from coupling patterns of the proton at C-2 (d 2.68, ddq, *J*=12.8, 6.4, 6.4 Hz). Under normal circumstances, the sterically congested and less strained carbonyl groups resist to Baeyer-Villiger reaction. In fact, attempted Baeyer-Villiger reactions of the decalone **12** with various peracids[7,8] in solvent were not successful resulting in recovery of **12**. Hence, we turned our attention to solid state Baeyer-Villiger reaction[9] whose advantages have been underestimated in natural product synthesis. Solid state reaction of the decalone **8** provided lactone **26** in 90% yield at room temperature overnight (Figure 2). Encouraged by this success, the solid state Baeyer-Villiger reaction of **12** was then investigated. While monitoring the progress of the solid state reaction by tlc, we observed the formation of a new reaction product which was supposed to be an adduct of the decalone **12** with MCPBA, since it disappeared gradually with increasing amount of lactone **13**. In order to enhance rearrangement, the reaction mixture was heated to 60°C to give the lactone **13** in 72% yield. Finally, alkaline hydrolysis of the lactone **13** furnished hydroxy acid **1** in 79% yield as a crystalline compound (m.p. 102 ~ 104°C, natural 103 ~ 104°C). The spectral data including optical rotation {[a]$_D^{21}$ - 7.9 (*c* 0.5, $CHCl_3$), lit.,[1] [a]$_D^{21}$ - 6.8 (*c* 0.6, $CHCl_3$)} completely agreed with those of the natural product **1** which indicates no epimerisation at C-2 during alkaline hydrolysis of the lactone **13**.



Total synthesis of bisnorsesquiterpenoid 2

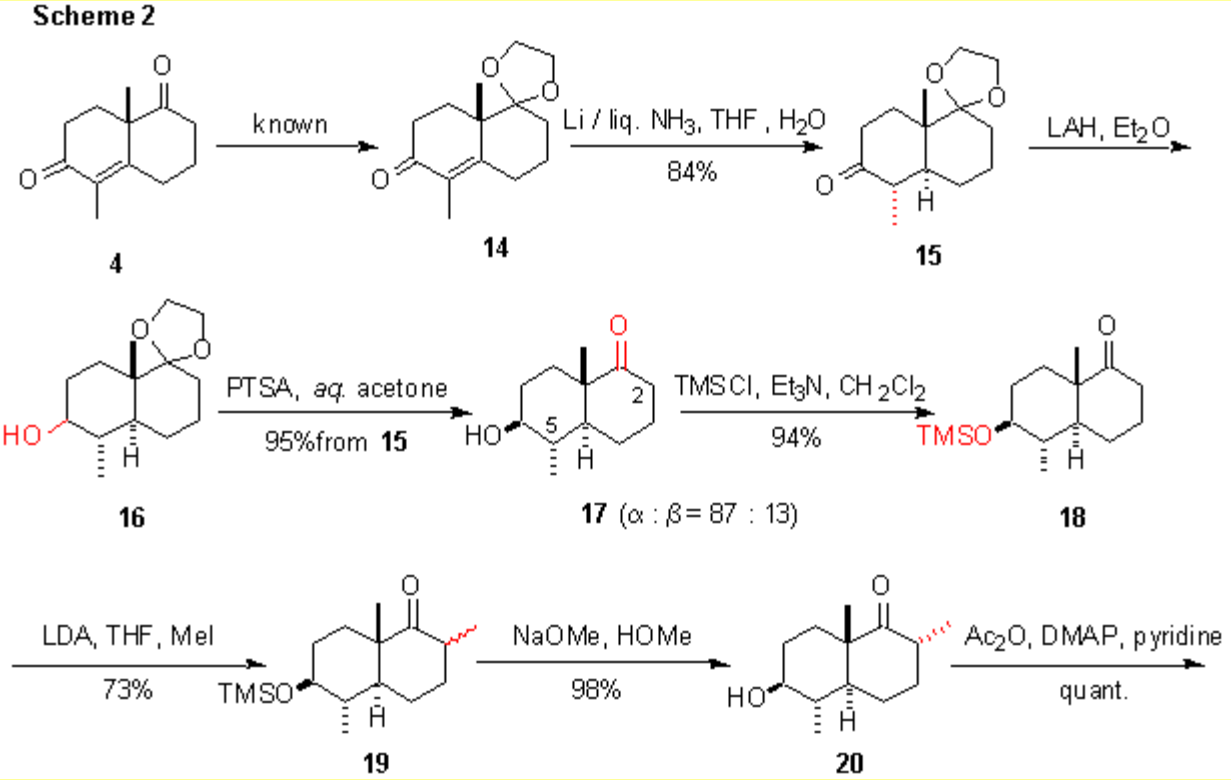
The same strategy was employed to the synthesis of **2** starting from optically active (*S*)-(+)-Wieland-Miescher ketone analogue **4**[5] (>95% e.e.) to target decalone **20** as a key intermediate with all requisite stereocenters for **2** (Scheme 2). Reduction of a ,b -unsaturated moiety of enone **14** with lithium in liquid ammonia provided in 84% yield ketone **15** which was reduced with lithium aluminum hydride to give a mixture of two inseparable isomeric alcohols **16**. Deprotection of the acetal provided b - and a -alcohol **17** in 83 and 12% yields respectively in two steps. Coupling constants of the proton at C-5 of the major isomer **17** (d 2.64, ddq, *J* 14.0, 13.8 and 7.0 Hz) revealed equatorial orientation of the methyl group at C-5 and *trans* ring junction of the decalin framework. In order to introduce methyl group at C-2, the b -alcohol **17** was protected with TMSCl to give TMS ether **18** in 94% yield. Treatment of the ketone **18** with LDA at -20°C followed by addition of MeI provided an inseparable 1 : 1 diastereomeric mixture of monomethylated products **19** in 73% yield. When hydroxy group at C-6 of **17** was protected as TBDMS ether, all similar attempts have failed. By treatment with sodium methoxide, the decalones **19** equilibrated into 98% yield with concomitant deprotection of TMS group to thermodynamically stable a -isomer **20** in which the orientation of methyl

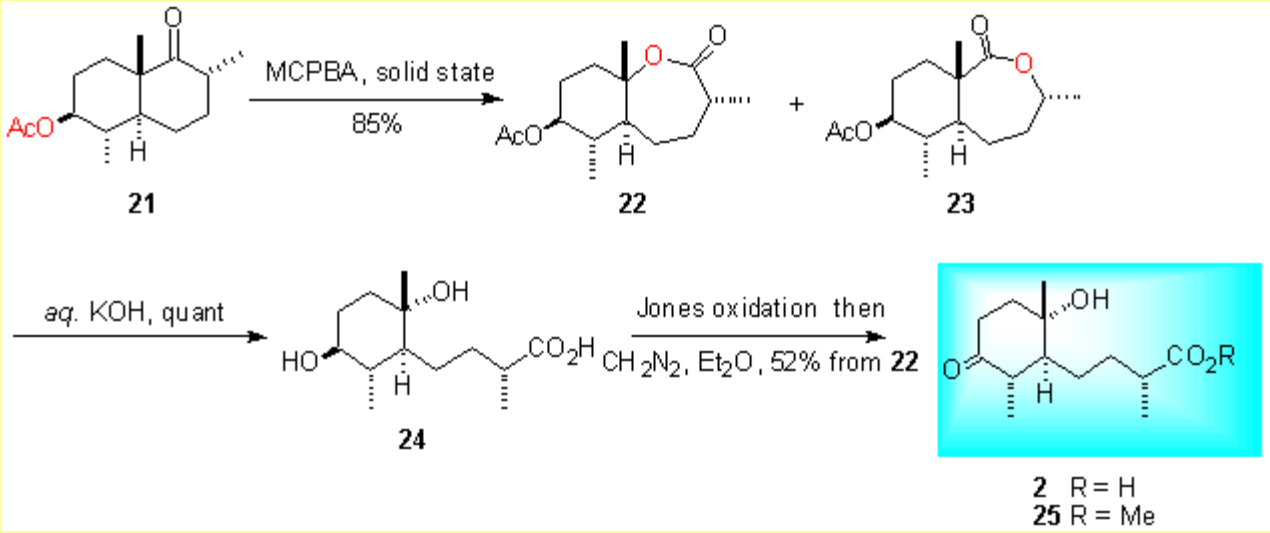
group was apparent from coupling patterns of the proton at C-2 (d 2.68, ddq, *J* 12.8, 6.4 and 6.4 Hz). All the requisite stereocenters for the target compound **2** were furnished at this stage.

Solid state Baeyer-Villiger reaction of **20** with MCPBA gave a small amount of lactonic compounds. Then, the hydroxy group of **20** was quantitatively acetylated as an acetate to provide **21**. Though conventional Baeyer-Villiger reaction of **21** in solvent with MCPBA or trifluoroperacetic acid[8] with or without $Yb(OTf)_3$[7] was very sluggish and resulted again in recovery of **21**, solid state reaction[9] of the acetate **21** with MCPBA furnished desired lactonic compound **22** and its regio-isomer **23** in 58 and 27% yields respectively.

Hydrolysis of the lactone **22** with aqueous potassium hydroxide followed by Jones oxidation provided very unstable acid **2** which was soon esterified with diazomethane to give methyl ester **25** in 52% overall yield in three steps. Spectral data of the synthetic **25** were completely identical with the data of the natural **25** including optical rotation [a $]_D^{23}$ - 13.1 (*c* 0.26, $CHCl_3$) {lit.,[1] [a $]_D^{23}$ - 14.3 (*c* 0.28, $CHCl_3$)}.

Scheme 2





Selectivity in solid state Baeye-Villiger reaction

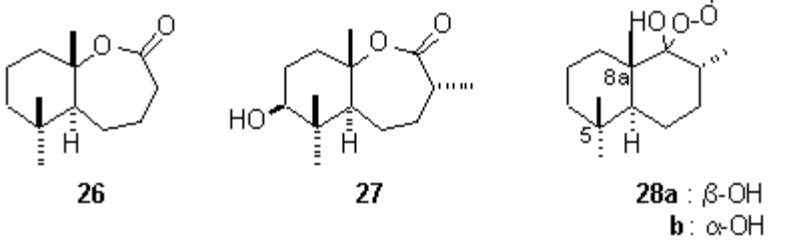
Some of our results on the solid state Baeyer-Villiger reactions are compiled in Table 1.

Table 1. Solid state Baeyer-Villiger oxidation of the decalones.

Entry	Decalone	Reagent	Reaction Condition	Product : Yield (%)
1	**19**	MCPBA	r. t., 144 hr	**27** : 0 (73)[a]
2	**20**	MMPA[b]	50 °C, 7 hr	**27** : 22 (54)[a]
3	**20**	MCPBA	r. t., 112 hr	**27** : 15 (52)[a]
4	**21**	MCPBA	r. t., 72 hr	**22** : 58 **23** : 27
5	**8**	MCPBA	r. t., 16 hr	**26** : 90
6	**12**	MCPBA	60 °C, 16 hr	**13** : 72

[a]The decalones **19** ~ **21** were recovered.
[b]Monoperoxyphthalic acid magnesiun salt

Figure 2



Smooth reactions and perfect regioselectivities of the decalones **8** and **12** in entries 5 and 6 rather than the decalone **21** in entry 4 might be result of 1,3-steric repulsions between two axial methyl groups at C-5 and C-8a in **8** and **12** (Figure 2). The rate determining step of Baeyer-Villiger reaction is migration from Crieege's intermediate *via* early transition state.[10,11] To this end, semiempirical molecular orbital calculations (PM3)[12] on Crieege's intermediates **28a** and **b** derived from the decalone **12** were performed by using Gaussian 98.[13] Though the difference of heat of formation of both intermediates **28a** and **b** were subtle (0.07 Kcal), C-1-C-8a bond in the more stable intermediate **28a** was longer (1.61 Å)[14] than C-1- C-2 bond (1.56 Å) and anti periplaner (dihedral angle 173°) to O-O bond. These

results explain regioselectivity of the present Baeyer-Villiger reactions. Substrates **19** ~ **21**, **8** and **12** in the Table 1 were all unreactive in Baeye-Villiger reactions in solvent. However, exact reasoning of great enhancement in the present solid state Baeye-Villiger reaction is yet to be clarified.

In conclusion, we have completed the total synthesis of norsesquiterpenoid **1** and bisnorsesquiterpenoid **2**, demonstrating effectiveness of solid state Baeyer-Villiger reaction in natural product synthesis.

Acknowledgement

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