A concise synthesis of \((1S^*,3R^*,6R^*)-1\)-hydroxy-7(14),10-bisaboladien-4-one, an antifeedant against the locust \textit{Locusta migratoria}\(^{a}\), was achieved by starting from 4-hydroxy-2-cyclohexenone.

Key words: antifeedant; sesquiterpene; \textit{Locusta migratoria}; \textit{Cryptomeria japonica}

In 2007, Kashiwagi \textit{et al.}\(^1\) isolated two bisabolanoids, \((1S^*,3R^*,6R^*)-1\)-hydroxy-7(14),10-bisabolatrien-4-one \((1)\) and \((1S^*,3R^*,6R^*)-1\)-hydroxy-7(14),10-bisaboladien-4-one \((2)\) (Scheme 1), from the Japanese cedar \textit{Cryptomeria japonica} as antifeedants against the locust \textit{Locusta migratoria}.\(^{2}\) Based on the bioassay results, they reported that \(2\) was essential for the antifeeding activity against \textit{L. migratoria}, while \(1\) played a role in supporting the activity of \(2\).\(^{3}\) Compound \(1\) had originally been reported as a chemical constituent of \textit{C. japonica} by Nagahama \textit{et al.},\(^{4}\) and its absolute stereochemistry was later determined by Kim \textit{et al.}\(^{5}\). Compound \(2\) was also previously isolated from \textit{C. japonica} by Nagahama \textit{et al.},\(^{4}\) and its absolute stereochemistry was unambiguously determined through its first enantioselective synthesis performed by Nakahata \textit{et al.}\(^{6}\) More recently, other enantioselective syntheses of \(1\) and \(2\) have been disclosed by Shimizu and Kuwahara.\(^{7}\) Although these two recent enantioselective syntheses were reasonable and efficient, we decided to develop a new and simpler synthetic route to \(2\). We report here a concise and straightforward synthesis.

Scheme 1 illustrates our synthetic route to \((\pm\)-2\) using \((\pm\)-4-hydroxy-2-cyclohexenone \((3)\)\(^7\) as the starting material. It should be mentioned that this starting material is a common building block in the synthesis of natural products, and that various methods have been disclosed so far for the preparations of optically active \(3\).\(^{8–11}\) According to the reported procedure, \(3\) was converted to corresponding \textit{t}-butyldimethylsilyl (TBS) ether \(4\) \((92\%)\),\(^7\) which was then methylated to give \(5\) \((55\%)\) as a 1:1 mixture of diastereomers at \(C_6\).\(^{12}\) The next step was Michael addition of the side chain to \(5\). After a considerable number of attempts to optimize the reaction conditions, the most preferable outcome was observed by reacting \(5\) with Grignard reagent \(6\) in the presence of \textit{CuBr}·\textit{SMe}_2, trimethylsilyl chloroform (TMSCl), and \(N,N,N',N'\)-tetramethylethlenediamine (TMEDA).\(^{13,14}\) Grignard reagent \(6\) was prepared from the known 2-bromo-6-methyl-1,5-heptadiene.\(^{15}\) It should be noted that the presence of TMSCl and TMEDA was preferable, and that CuCl and Cu were not as effective as \textit{CuBr}·\textit{SMe}_2 as copper catalysts. The resulting silyl enol ether adduct was immediately treated with tetra-\textit{n}-butylammonium fluoride (TBAF) to afford a \(ca\). 2:3 mixture of \((\pm\)-2\) and \((\pm\)-2\). This mixture was separated by silica gel column chromatography to give \((\pm\)-2\) \((17\%)\) and \((\pm\)-2\) \((27\%)\). The various spectral data for synthetic \((\pm\)-2\) are in good agreement with those for the natural product.\(^{1}\)

We observed that the diastereomeric ratio changed from 1:1 in \(5\) to 2:3 in \(5\) \((\pm\)-2\) during the final two steps. As mentioned by Nakahata \textit{et al.},\(^{5}\) this change might have been due to epimerization at the \(C_3\) stereogenic center under basic TBAF treatment conditions. Based on this finding, undesired epimer \((\pm\)-2\) was treated with TBAF to induce intentional epimerization. Our intended epimerization took place, and the mixture came to equilibrium after 8 h of stirring at room temperature, affording a \(ca\). 2:3 mixture of \((\pm\)-2\) and \((\pm\)-2\) \((quant.)\). It should be mentioned that \(K_2CO_3\) was not effective for this epimerization. Thus, we were successful in converting undesired epimer \((\pm\)-2\) to natural and desired \((\pm\)-2\).

In summary, we developed a new and concise route to an antifeeding bisabolanoid \((2)\) isolated from the Japanese cedar. The overall yield was \(14\%\) in five steps, including one recycling step from 4-hydroxy-2-cyclohexenone \((3)\). By comparison, the above-mentioned two enantioselective syntheses took 19 steps (15\% yield)\(^5\) and 11 steps (9\% yield),\(^5\) respectively. It is obvious that the enantiospecific synthesis of \(2\) is possible based on our developed synthetic route, because preparations of optically active \(3\) are well established. Bioassays using our synthetic samples are currently being prepared.

Experimental

\(^1\)H-NMR spectra were recorded at 300 MHz with a Jeol JNM-AL300 spectrometer. The residual solvent peak in CDCl\(_3\) \((\delta_H = 7.26)\) was used as the internal standard. \(^13\)C-NMR spectra were recorded at 75 MHz with the Jeol JNM-AL300 spectrometer, the peak for CDCl\(_3\) \((\delta_C = 77.0)\) being used as the internal standard. Mass spectra were measured with a Jeol JMS-SX102A spectrometer. (\(1S^*,3R^*,6R^*\))-1-hydroxy-7(14),10-bisaboladien-4-one \((\pm\)-2\) and \((1S^*,3S^*,6R^*)\)-1-hydroxy-7(14),10-bisaboladien-4-one \((\pm\)-2\). To a stirred suspension of \textit{CuBr}·\textit{SMe}_2 \((160\text{mg}, 0.75\text{mmol})\) in dry THF...
and concentrated under reduced pressure to give the crude product. (±)-2 (16 mg, 24 mg, quant.); to a solution of (±)-2 (24 mg, 0.10 mmol) in THF (0.5 ml), TBAF (1.0 M in THF; 0.25 ml, 0.25 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was successively washed with water and brine, dried (MgSO4), and concentrated under reduced pressure to give a ca. 2:3 mixture of (±)-2 and 2′ (24 mg, quant.)

References