Synthetic Studies on Spirovetivane Phytoalexins. III. \(^1\) A Total Synthesis of (±)-Lubiminol\(^{2}\)

Chuzo IWATA, Yoshiji TAKEMOTO, Hitoshi KUBOTA, Minoru YAMADA, Shuji UCHIDA, Tetsuaki TANAKA, and Takeshi IMANISHI

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan. Received August 18, 1988

A total synthesis of (±)-lubiminol (2) from the allylic alcohol (3) was achieved through the introduction of a bis(ethoxy)carbonylmethyl group with inversion at C\(_2\) followed by hydrogenation of the C\(_6\)-C\(_7\) double bond and transformation of the bis(ethoxy)carbonylmethyl group into isopropenyl. On the other hand, the alcohol (1) was an inefficient starting material for the synthesis.

Keywords spirotetivane sesquiterpene; phytoalexin; lubiminol; total synthesis; Sn2 reaction; sodio diethyl malonate; bis(ethoxy)carbonylmethyl group; allylic alcohol; hydride reduction; isopropenyl group

In the preliminary paper,\(^1\) we reported the stereoselective synthesis of a potential intermediate, (2RS,5RS,6RS,8RS, 10SR)-6-hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4,5]decane (1), for highly oxygenated spirovetivane phytoalexins. Herein we wish to describe a total synthesis of (±)-lubiminol (2), one of the highly oxygenated phytoalexins, using this potential synthon (1) or another key compound (3).

Lubiminol (2) was isolated from Solanum genus infected with Glomerella cingulata\(^{3}\) or with Phytophthora infestans\(^{4}\) in 1976—1977. This natural product has two more asymmetric carbon centers than solavetivone (4)\(^{5}\) and has been considered to be a biosynthetic intermediate to other highly oxygenated phytoalexins\(^{5}\) (i.e. lubim (5) and oxylubim (6)). Though solavetivone (4) has been synthesized by several groups,\(^{6}\) little is known concerning the successful synthesis of lubimin-type phytoalexins.\(^7\)

To transform 1 into (±)-lubiminol (2), it is necessary to introduce an isopropenyl group with inversion at C\(_2\). For this purpose we adapted the Sn2 reaction with the enolate anion of diethyl malonate by reference to the synthesis of (±)-solavetivone (4).\(^{6}\) The alcohol (1) was transformed into the methoxymethyl (MOM) ether (7), which was converted into the alcohol (8) by treatment with methylolithium. The mesylate (9) was subjected to the reaction with the enolate anion of diethyl malonate to give 10 in only 14% yield from 8 along with a moderate amount of unidentified products. Considering that compound 11 (R\(^1\) = MOM, R\(^2\) = H), the C\(_6\) epimer of 8, was converted into 12 under the same conditions with ease (67% yield) via the mesylate (11: R\(^1\) = MOM, R\(^2\) = Ms), the low yield of 10 should be attributable to steric hindrance of the equatorial bond.
protected hydroxymethyl group at C9 in 9 (Fig. 1). From this point of view, it is expected that compound 15 having an \textit{sp}^3 carbon at C9 would undergo the \textit{Sn}2 reaction more easily than 9.

Compound 15 was obtained from the unsaturated alcohol (3)\textsuperscript{1} via 13 and 14 in the same manner as described above. As expected, the reaction of 15 with sodio diethyl malonate proceeded smoothly to afford 16 in 57% yield. Furthermore, hydrogenation of the unsaturated compound (16) on Raney Ni (W2) resulted in exclusive formation of a single diastereoisomer (10) in 97% yield. This compound was identical with 10 prepared from 1 on the basis of spectral comparisons.

Next, transformation of the bis(ethoxycarbonyl)methyl group into an isopropenyl group was investigated. In the previous synthesis of (\textpm)-solvatine (4),\textsuperscript{6a} the same group was converted into an \textalpha,\textbeta-unsaturated ester in 2 steps,\textsuperscript{8} and subsequent reduction of the ester group to a methyl group in 3 additional steps gave the isopropenyl derivative in 32% overall yield. For the present purpose, we planned to synthesize (\textpm)-lubiminol (2) from 10 through another route (Chart 4).

After several attempts, we found that reduction with sodium bis(2-methoxoyethyl)aluminum hydride (Red-Al) in dimethoxyethane (DME) afforded mainly the allylic alcohol, with suppression of the formation of the saturated alcohol and others. Namely, the sodium salt of 10 was reduced with a large excess of Red-Al in refluxing DME to give 17 in 50% yield. Successive treatment with methane-sulfonyl chloride and lithium aluminum hydride furnished (\textpm)-lubiminol bis(methoxymethyl ether) (18) in 72% yield. Transformation of 18 into lubiminol (2) was tried under various conditions, but unfortunately, was unsuccessful. It is assumed that the double bond of the isopropenyl group is labile under the conditions employed. So, we examined an alternative route which consisted of the final introduction of the C-C double bond after deprotection of methoxymethyl groups. Hydrogenation of 17 on Raney Ni (W2) at room temperature gave the saturated alcohol (19), which was converted to the mesylate (20) in the usual manner. Hydrolysis of 20 with 3 N hydrochloric acid in tetrahydrofuran (THF) gave the corresponding diol (21), which was treated with 1,8-diazabicyclo[5.4.0]undecene (DBU) and sodium iodide in dimethoxyethane to afford the target molecule, (\textpm)-lubiminol (2), in 76% yield. This compound and its diacetate were identified with lubiminol and lubiminol diacetate, respectively, by comparison of their spectral data.

**Experimental**

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (H-NMR) spectra were recorded on a Hitachi R-22 (90 MHz) or JEOL FX-90Q (90 MHz) with tetramethylsilane as an internal standard. The following abbreviations for the signal patterns are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer. For column chromatography and preparative thin layer chromatography (PLC), Merck Kieselgel 60 (70—
230 mesh) and Merck Kieselgel 60 PF254 were used, respectively. Extracts were dried over MgSO4 before evaporation.

(2RS,5R,6RS,8RS,10(S),12R)-8-Methoxyhexano-6-methoxyhexanoyl-16-methyl-2-pivaloyloxyspiro[4,5]decane-17 (17) 

After addition of saturated NaHCO3 solution to the mixture at 0°C, the mixture was extracted with ether. The extract was washed with saturated NaHCO3 solution, H2O, and then dried. After removal of the ether, the residue was chromatographed by column chromatography on silica gel (10 g, 230 mesh) (12) to give the MOM ether (13) as a colorless oil (32 mg, 87%).

(2RS,5R,6RS,8RS,10(S,R)-8-Methoxyhexano-6-methoxyhexanoyl-16-methyl-2-pivaloyloxyspiro[4,5]decane-17 (17) 

The extract was washed with saturated NaHCO3 solution and extracted with ether. The extract was washed with saturated NaHCO3 solution, H2O, and then dried. After removal of the ether, the residue was chromatographed by column chromatography on silica gel (10 g, 230 mesh) (12) to give the MOM ether (13) as a colorless oil (32 mg, 87%).

(2RS,5R,6RS,8RS,10(S,R)-8-Methoxyhexano-6-methoxyhexanoyl-16-methyl-2-pivaloyloxyspiro[4,5]decane-17 (17) 

The extract was washed with saturated NaHCO3 solution and extracted with ether. The extract was washed with saturated NaHCO3 solution, H2O, and then dried. After removal of the ether, the residue was chromatographed by column chromatography on silica gel (10 g, 230 mesh) (12) to give the MOM ether (13) as a colorless oil (32 mg, 87%).

(2RS,5R,6RS,8RS,10(S,R)-8-Methoxyhexano-6-methoxyhexanoyl-16-methyl-2-pivaloyloxyspiro[4,5]decane-17 (17) 

The extract was washed with saturated NaHCO3 solution and extracted with ether. The extract was washed with saturated NaHCO3 solution, H2O, and then dried. After removal of the ether, the residue was chromatographed by column chromatography on silica gel (10 g, 230 mesh) (12) to give the MOM ether (13) as a colorless oil (32 mg, 87%).
(et)-Lubiminol (2) DBU (2 drops) and NaI (large excess) were added to a solution of the diol (21) (3.5 mg, 0.010 mmol) in dry DME (2 ml), and the mixture was refluxed for 3 h. The reaction mixture was diluted with CH₂Cl₂ under cooling, and the solution was washed with H₂O and brine, and then dried. Removal of the solvent under reduced pressure gave the residue, which was purified by PLC with ethyl acetate-isopropanol (9:1) to give (et)-lubiminol (2) (1.9 mg, 76%), colorless needles, mp 114–116 °C (ether-hexane). IR ν(C=O) cm⁻¹: 3590, 3400, 1640. ¹H-NMR (CDCl₃) δ: 0.93 (3H, d, J = 6.5 Hz, C₃H₃Me), 1.73 (3H, s, C(CH₃)₂), 3.33 (1H, dd, J = 8.6 and 10.4 Hz, C₃H₃O), 3.66 (1H, m, C₃H₃), 3.94 (1H, dd, J = 3.2 and 10.4 Hz, C₃H₃O), 4.67 (2H, br s, C(CH₃)₂). MS m/z (%): 238 (M⁺, 5), 220 (13), 202 (25), 107 (100). HRMS Caled for C₆H₁₂O₃: 238.1933. Found: 238.1951.

Acknowledgement We are grateful to Professors A. Stoesz, Agriculture Canada Research Centre, and A. Murali, Hokkaido University, for generous gifts of natural dihydroxylubiminol, lubiminol diacetate, and the copies of their spectra. Thanks are also due to the Fujisawa Foundation for financial support.

References