Synthetic Studies on the Ochtodane Type Terpenes II.[1] Synthesis of Pleraplysillin-1

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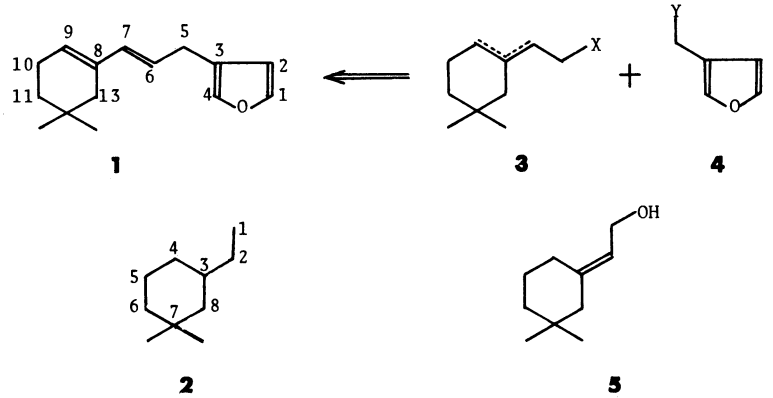
A furyl sesquiterpene pleraplysillin-1 (**1**), which possesses the ochtodane skeleton (**2**) in the molecule, was synthesized regio- and stereoselectively starting from the ochtodane type monoterpene (**5**). Two approaches were investigated: One is the route by way of the benzenesulfenyl chloride addition to a sesquiterpene (**9**) or (**13**) which involve the whole carbon framework of **1** and the exocyclic *E*- or *Z*-double bond, and the other involves the regioselective formation of the endocyclic double bond of the ochtodane synthon (**15**) utilizing the hydroxyl-assisted epoxide opening reaction followed by homologation with the 3-furylmethyl moiety. In both of the routes the geometry of the exocyclic double bond of the ochtodane synthon played an important role in the regioselective formation of the endocyclic double bond in **1**.

The explosive growth of marine natural product chemistry during the last decade has given rise to the discovery of a vast array of compounds which have polyhalogenated and/or oxygenated, and unique carbon frameworks never found in the terrestrial organisms.[2] In 1972, a furyl sesquiterpene pleraplysillin-1 (**1**) was isolated from a marine sponge, *Pleraplysilla spinifera*, by Cimino and coworkers.[3] The terpene (**1**) possesses a unique carbon skeleton which is postulated to arise by enzymic carbocyclization involving a lateral methyl group of the presumed farnesyl precursor and the terminal oxidation forming the furan portion. The structural elucidation of **1** has been done by spectral analyses of itself and the hydrogenated product.[3] Recently, two groups, Moore *et al.*[4a] and Fenical *et al.*,[4b] have isolated variously functionalized monoterpenes with the 3,3-dimethyl-1-ethylcyclohexane carbon skeleton (**2**), which was suggested to name "ochtodane."

The carbon framework of pleraplysillin-1 (**1**) is analyzed retro-synthetically as the assembly of an ochtodane (**3**) and 3-furylmethyl (**4**) derivatives. In the preceding paper, we have introduced a facile method for the stereoselective construction of the ochtodane skeleton (**2**) starting from myrcene.[1] Here we report the first regio- and stereoselective synthesis of the sesquiterpene (**1**).[5] The major synthetic efforts focused on the regio- and stereoselective construction of the conjugated diene system in the molecule (**1**). We have investigated two approaches. One of them involves the benzenesulfenyl chloride addition to the trisubstituted and exocyclic C(7)-olefin in the sesquiterpene (**9**) or (**13**) which contain the whole carbons of **1**, followed by formation of the requisite conjugated diene system. The other involves the regioselective formation of the requisite endocyclic C(3)-olefin of the ochtodane moiety followed by the homologation with 3-furylmethyl synthon and latent formation of the other acyclic C(6)-olefinic portion of the conjugated diene system. By the latter method the successful synthesis of **1** was achieved.

1) Approach by Way of the Benzenesulfenyl Chloride Addition (Scheme 1). In order to obtain the sesquiterpene (**9**), the key compound for the olefinic elaboration aiming at the requisite conjugated diene system, the ochtodane type compound with the sulfur-containing auxiliary activator for C–C bond formation at the C(1)-position was prepared from the (*E*)-alcohol (**5**) which was obtained highly stereoselectively by the reported method.[1] Thus, bromination of **5** with PBr_3 followed by treatment of the bromide (**6**) with *p*-Tol-SO_2Na in DMF afforded the crystaline sulfone (**7**), which was purified by recrystallization to remove the (*Z*)-isomer arising from the (*Z*)-alcohol which existed in the starting alcohol (**5**) as impurity.[1] The carbon–carbon bond formation between the allylic sulfone (**7**) and 3-furylmethyl bromide (**4** Y=Br) was performed smoothly in 76% yield with *n*-BuLi in THF at −78—



1 **3** **4**

2 **5**

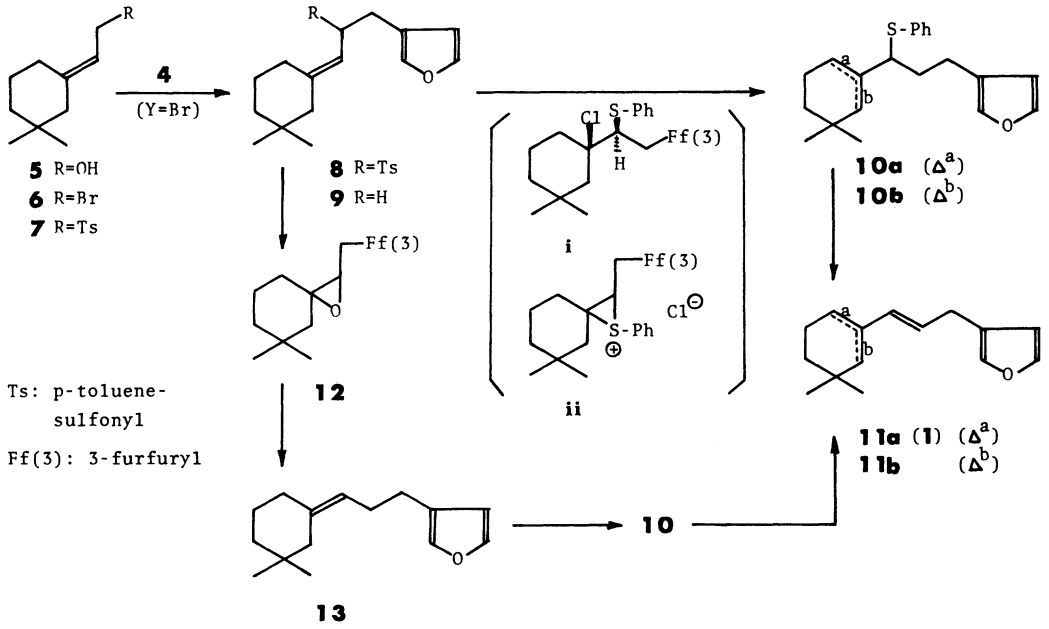
Chart 1.

0°C providing the sesquiterpenoid (**8**). Reductive desulfurization of this compound leading to the sulfur-free compound (**9**) was carried out by the Birch reduction with Li in liq. NH_3 in 74% yield. Treatment of the furyl terpene (**9**), which possesses the pure exocyclic *E*-double bond, with an equimolar amount of PhSCl in CH_2Cl_2 at −78°C for 10 min followed by evaporation of the solvent at room temperature gave the regioisomeric mixture of allylic sulfides (**10**) (79%) instead of the expected adduct (**i**). The structure and regioisomeric proportion were determined by spectral analysis: Mass spectrum showed the M^+ ion at 326, and ^{1}H-NMR exhibited signals for the olefinic protons at δ 4.85 as the major singlet and 5.23 as the minor broad singlet in a ratio 77:23 and those of the geminal dimethyl groups at δ 0.65, 0.86, and at δ 0.80, 0.92 in the same ratio of intensity. The major component was assigned to the undesirable isomer (**10b**) on the basis of the shape of the signal at δ 4.85 for the isolated C(13)-olefinic proton in ^{1}H-NMR. The allylic sulfide (**10**) obtained was converted into the final conjugated diene (**11**) in 83% yield by the sequential treatment of **10** with 30% H_2O_2 in AcOH followed by heating the corresponding sulfoxide in refluxing toluene. Comparison of ^{1}H-NMR of the resultant diene (**11**) with the reported data of natural pleraplysillin-1 (**1**)[3] indicated that the product contains the desired **1** (**11a**) in a minor proportion (*ca.* 23%) and the regioisomer (**11b**) as the major component (*ca.* 77%). Characteristic signals of these regioisomers **1** and **11b** were detected at δ 0.92 (s) and 0.97 (s) assignable respectively to the geminal methyl groups of **1** and **11b**, at δ 1.68 (s) to the C(13)-methylene of **1**, and at δ 5.30 (s) to the C(13)-olefinic proton of **11b**.

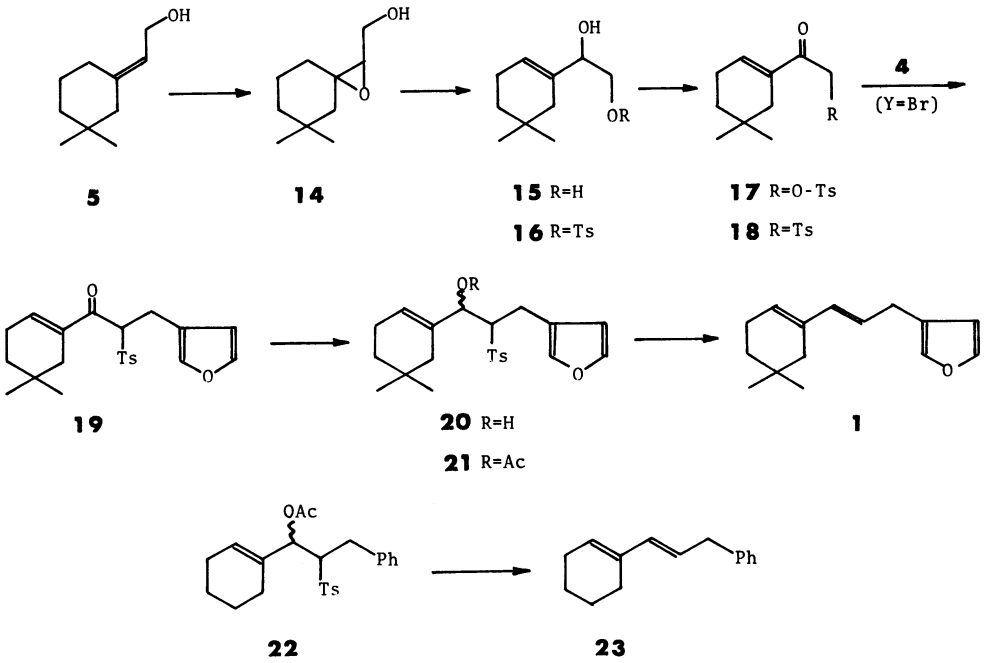
Although the stereo-electronic mechanisms in the dehydrochlorination of the intermediary adduct (**i**) or the episulfonium ion (**ii**) are not clear, the stereochemistry of the exocyclic C(7)-double bond of **9** seemed to affect the regioselectivity in the formation of the allylic sulfide (**10**). Thus, we tried the same procedure on the (*Z*)-olefin (**13**) (*E*:*Z*=20:80), which was prepared from the (*E*)-olefin (**9**) (*E*:*Z*=85:15) *via* the epoxide (**12**) according to the method for geometric inversion of olefins developed by Vedejs.[6] Addition of PhSCl to the (*Z*)-olefin (**13**) gave the anticipated result that the product contained the desired allylic sulfide (**10a**) as the major component (60%) and the undesirable one (**10b**) as the minor (40%). The identical product ratio (**1**:**11b**=60:40) was observed in the final diene (**11**) derived analogously. The above results implied that the desired natural **1** would be obtained in less than *ca.* 77% regioselectivity concerning the C(8)-double bond so far as use of this sequence of procedures even if the pure (*Z*)-olefin (**13**) would be used. Attempted separation of each component of the regioisomers of allylic sulfides (**10**) and the final diene (**11**) was unsuccessful. So, we searched for the more regio- and stereoselective route.

II) Approach by Way of the Regioselective Epoxide-ring Opening (Scheme 2). Considering the above results, we investigated another route in which the endocyclic double bond in the ochtodane moiety of **1** is formed regioselectively in the early stage of the synthesis. Application of the regioselective epoxide-ring opening method developed by Sharpless[7] to the β,γ-epoxy alcohol (**14**) prepared from (*E*)-alcohol (**5**) seemed to be the method of choice for this purpose.

Epoxidation of the alcohol (**5**) with *m*-chloroperbenzoic acid providing the epoxide (**14**) (91%) and subsequent treatment of **14** with 1.2 equiv of $Ti(OPr^i)_4$ in CH_2Cl_2 at 15°C for 20 h afforded regioselectively the enediol (**15**) in 77% yield. ^{1}H-NMR spectrum of the product showed a little contamination of the undesirable regioisomer which would be ascribed to the



Scheme 1.



Scheme 2.

presence of the (*Z*)-isomer (*ca.* 6%) in the starting material (**5**),[1] and to the undesirable olefination which might take place slightly in the epoxide-ring opening reaction (**14**→**15**). Selective tosylation of the primary alcohol in **15** was carried out on treatment of **15** with 1.3 equiv of *p*-TsCl in pyridine to give the mono tosylate (**16**) in 76% yield. Oxidation of the allylic alcohol (**16**) with active MnO_2 gave the keto tosylate (**17**) which was converted to the crystalline keto sulfone (**18**) (70% overall yield from **16**) by treatment with *p*-Tol-SO_2Na in DMF. Purification of the compound **18** by recrystallization removed the undesirable olefinic regioisomer with 3(8)-double bond and furnished the regiochemically homogeneous sulfone (**18**) (mp 111—113 °C). The structure of **18** was characterized by spectral and elemental analyses: Signals for the two allylic methylene at δ 1.96 (bs, C(8)-methylene) and 2.10—2.50 (m, C(5)-methylene) and for the C(4)-olefinic proton at δ 6.95 as broad singlet appeared in ^{1}H-NMR. The carbon-carbon bond formation between **18** and 3-furylmethyl bromide (**4** Y=Br) proceeded smoothly in the presence of 1.2 equiv of NaH DMF-THF (1:1) at 15 °C to give the crystalline sulfone (**19**) (mp 136—140 °C) in high (92%) yield. Attention was focused on the next step for the stereoselective formation of the other C(6)-olefinic bond of the conjugated diene system in **1**. Kocienski reported that treatment either of *erythro*- or *threo*-β-acetoxy sulfones with sodium amalgam (Na-Hg) effected reductive elimination to afford exclusively (*E*)-olefins.[8] We tried to apply this condition to our system. Reduction of the keto sulfone (**19**) with $NaBH_4$ in EtOH at 0 °C afforded the crystalline alcohol (**20**), which was, without further separation of the diastereoisomers, acetylated to give the β-acetoxy sulfone (**21**) in nearly quantitative yield. Unfortunately, application of Kociensky's condition using 5% Na-Hg with MeOH in AcOEt at −20 °C to **21** resulted in the preponderant formation of the methanolysis product (**20**) with a small amount of the conjugated diene (**1**) (7%) which proved to be contaminated with the undesirable (6*Z*)-olefinic isomer to some extent (*ca.* 20%) in high performance liquid chromatography (HPLC) using 5% $AgNO_3$-imprgnated silica gel (see the experimental section) and ^{1}H-NMR analyses. The desired reductive elimination producing **1**, in turn, was accomplished by treatment of **21** with Na and EtOH in THF at −78 °C (modified Bouvault-Blanc conditions)[9] in 65% yield. Analyses by HPLC and ^{1}H-NMR proved the product containing *ca.* 11% of the (6*Z*)-isomer. This stereoselectivity observed in the reductive elimination was constant regardless of the stereochemistry of the β-acetoxy sulfone (**21**) because the stereochemically pure **21** prepared from the recrystallized β-hydroxy sulfone (**20**), although not characterized stereochemically, afforded the diene (**1**) with the identical isomeric ratio (**1**:(6*Z*)-isomer=89:11). The analogous results were obtained in the model compound (**22**). Thus, the compound **22** which possesses the same functionality as **21**, produced the conjugated diene (**23**) of the ratio *E*:*Z*=86:14. The desired diene (**1**) was separated by careful column chromatography on 5% $AgNO_3$-impregnated silica gel and identified with natural pleraplysilin-1 (**1**) by spectral comparison.[3]

Experimental

General. IR spectra were recorded on a JASCO IRA-1 spectrometer in $CHCl_3$ solution and the absorption bands (ν_{max}) are reported in cm^{-1}. Mass spectra (MS) were taken on a

JMS-D300 instrument at an ionizing potential of 70 eV and peaks are given in *m/z* values with relative intensities (%) in parenthesis. ^{1}H-NMR spectra were run on a Hitachi R-20B spectrometer (60 MHz)in CCl_4 solution, unless otherwise noted, with tetramethylsilane (TMS) as an internal standard and chemical shifts are reported in δ (ppm) relative to TMS and coupling constants (J) in hertz (Hz). The numbering of pleraplysillin-1 (**1**) was adopted in the description of the synthetic intermediates with sesquiterpene skeleton in ^{1}H-NMR data. All the solvents used in reactions were freshly distilled to remove moisture. Reactions were carried out under nitrogen unless otherwise noted. Reaction mixtures were usually worked up as follows: A mixture was extracted with Et_2O or CH_2Cl_2, washed with water or saturated brine and saturated $NaHCO_3$, if necessary, dried over anhydrous $MgSO_4$, concentrated *in vacuo* below room temperature to give a crude product which was purified by column chromatography. Silica gel (Wakogel B-5F) and Wokogel C-200 were employed respectively for analytical thin-layer (TLC) and column chromatography using hexane-Et_2O solvent system as eluent. High performance liquid chromatography (HPLC) was carried out by using a column (4.0 mm×25cm) packed with 5% $AgNO_3$-impregnated silica gel, which was prepared by drying the slurry of LiChrosorb Si 60 (MERCK) (10 g) and $AgNO_3$ (0.5 g) in water (40 ml) at 100—110 °C for 20 h, and by elution with hexane.

Materials. The starting material in the present synthesis, (*E*)-2-ochtodene-1-ol (**5**) was prepared in 85—94% of *E*-stereoselectivity from myrcene *via* the benzensulfenyl chloride adduct or the 6,7-epoxide according to the method described in the preceding parer.[1)]

Synthetic Approach to Pleraplysillin-1 (1) by Way of the Benzenesulfenyl Chloride Addition. (E)-1-(p-Tolylsulfonyl) 2-ochtodene (7): PBr_3 (95 μl, 1.0 mmol) was added dropwise into an ice-cold solution of the alcohol (**5**) (376 mg, 2.4 mmol) in Et_2O (4.0 ml) and the mixture was stirred for 30 min at 0 °C and then kept in refrigerator 16 h. The mixture was diluted with Et_2O, washed successively with saturated $NaHCO_3$ and brine, dried, and concentrated to give the crude oily bromide (**6**) (420 mg, 80%): NMR 0.90 (6H, s, $C(CH_3)_2$), 1.20—1.90 (4H, m, $C(5)H_2C(6)H_2$), 1.93 (2H, s, $C(8)H_2$), 2.22 (2H, bt, J=5.5, $C(4)H_2$), 3.98 (2H, d, J=9.0, $=CHC\underline{H}_2Br$), 5.48 (1H, bt. J=9.0, $=CHC\underline{H}_2Br$). To a solution of the bromide in DMF (4.5 ml) was added in portions sodium *p*-toluenesulfinate (*p*-TsNa) (690 mg, 3.8 mmol) at room temperature and the mixture was stirred for 16 h. The reaction mixture was worked up by the usual manner to give a crude product (540 mg), which was purified by column chromatography providing the crystalline sulfone (**7**) (480 mg, 87%). Recrystallization from Et_2O–hexane gave pure (*E*)-sulfone (**7**), mp 65—66 °C. Data for **7** follow: IR 1650, 1595; MS 292 (M^+, 2), 157 (8), 137 (100), 136 (44), 121 (18); NMR $(CDCl)_3$ 0.80 (6H, s, $C(CH_3)_2$), 1.20—1.40 (4H, br, $C(4)H_2$), 1.85 (2H, s, $C(8)H_2$), 2.43 (3H, s, CH_3Ph), 3.82 (2H, d, J=8.5, $=CC\underline{H}_2Ts$), 5.02 (1H, bt, J=8.5, $=C\underline{H}$-$C\underline{H}_2Ts$), 7.27—7.81 (4H, A_2B_2q, J=9.0, arom-H); Found: C, 69.75; H, 8.38%. Calcd for $C_{17}H_{24}O_2S$: C, 69.83; H, 8.27%.

(E)-3-[3-(3-Furyl)-2-(p-tolylsulfonyl)-propylidene]-1,1-dimethylcyclohexane (8): 1.6 M (1M=1 mol dm^{-3}) solution of *n*-BuLi-hexane (0.75 ml) was added dropwise over 5 min into a solution of the sulfone (**7**) (290 mg, 1.0 mmol) and hexamethylphosphoric triamide (HMPA) (250 μl) in THF (2.5 ml) at −78 °C under argon. After stirring the mixture for 20 min at the temperature, a solution of 3-furylmethyl bromide (**4** Y=Br) (170 mg, 1.1 mmol), freshly prepared from 3-furylmethanol, in THF (0.5 ml) was added into the mixture. The mixture was stirred for 1.5 h under gradual warming up to 0 °C and worked up by the usual manner to give a crude product (380 mg). Purification by column chromatography afforded the oily coupled sulfone (**8**) (282 mg, 76%). Data for **8** follow: NMR 0.63, 0.72 (each 3H, s, $C(CH_3)_2$), 1.73 (2H, s, $C(13)H_2$), 2.40 (3H, s, CH_3Ph), 2.59 (1H, dd, J=14.5 and 11.5, one of $C(5)H_2$), 3.28 (1H, dd, J=14.5 and 3.0, the other one of $C(5)H_2$), 3.92 (1H, m, J=11.5, 10.0, and 3.0, CH(Ts)), 4.78 (1H, d, J=10.0, C(7)H), 6.18, 7.15, 7.20 (each 1H, s, C(2)H, C(1)H, and C(4)H), 7.15—7.72 (4H, A_2B_2q, J=8.5, arom-H (Ts)); Found: C, 71.08; H, 7.51%. Calcd for $C_{22}H_{28}O_3S$: C, 70.94; H, 7.58%.

(E)-3-[3-(3-Furyl)propylidene]-1,1-dimethylcyclohexane (9): To a chilled blue solution of Li (70 mg, 10 mg atm) in liq. NH_3 (*ca.* 10 ml) was added dropwise a solution of the sulfone (**8**) (270 mg, 0.7 mmol) in THF (1.0 ml) at −78 °C under argon. Stirring was continued for 40 min at the temperature and then reaction was quenched by introduction of gaseous butadiene followed by addition of MeOH (1.0 ml). After the cold bath was removed to evaporate NH_3, the residue was extracted with Et_2O, washed with water, dried, and concentrated to give a crude oil (135 mg). Purification of the product by column chromatography yielded the sesquiterpene (**9**) (100 mg, 74%) as oil: NMR 0.82 (6H, s, $C(CH_3)_2$), 1.20—1.60 (4H, m, $C(10)H_2C(11)H_2$), 1.79 (2H, s, $C(13)H_2$), 1.85—2.50 (6H, m, $C(5)H_2C(6)H_2$ and $C(9)H_2$), 4.97 (1H, bt, J=6.0, C(7)H), 6.15, 7.08, 7.21 (each 1H, s, C(2)H, C(1)H and C(4)H).

Reaction of the (E)-Furyl Sesquiterpene (9) with Benzenesulfenyl Chloride (PhSCl). A solution of PhSCl (75 mg, 0.5 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise into a cold mixture of the terpene (**9**) (110 mg, 0.5 mmol) in CH_2Cl_2 (3.0 ml) at −78 °C and the mixture was stirred for 10 min at the temperature. Evaporation of the solvent at room temperature gave a crude product (170 mg). Purification by column chromatography afforded the oily sulfide, 1-[3-(3-furyl)-1-(phenylthio)propyl]-5,5-dimethylcyclohexene and -3,3-dimethylcyclohexene (**10**) (130 mg, 79%). Data for **10** follow: IR 1580; MS 326 (M^+, 9), 217 (100), 135 (42); NMR 0.65, 0.86 (major pair of singlets of 77% intensity) and 0.80, 0.92 (minor pair of singlets of 23% intensity) (overall 6H, $C(CH_3)_2$), 3.25—3.65 (1H, m, CH(SPh)), 4.85 (major singlet assignable to C(13)H of **10b**) and 5.23 (minor broad singlet to C(9)H of **10a**) (overall 1H), 6.14 (1H, s, C(2)H), 7.00—7.35 (7H, m, arom-H); Found: C, 77.43; H, 7.89%. Calcd for $C_{21}H_{26}OS$: C, 77.27; H, 8.03%.

Oxidative Elimination of the Thiophenol from the Sulfide (10) Providing the Diene, (E)-1-[3-(3-Furyl)-1-propenyl]-5,5-dimethyl and 3,3-dimethylcyclohexene (11). A mixture of the sulfide (**10**) (100 mg, 0.3 mmol), 30% H_2O_2 (40 μl), and AcOH (2.0 ml stirred for 16 h at room temperature. The mixture was diluted with Et_2O, washed successively with water, saturated $NaHCO_3$, and brine, dried, and concentrated to give the crude sulfoxide (105 mg), which was, without further purification, heated with $NaHCO_3$ (50 mg) in toluene (6.0 ml) under reflux for 3 h. The mixture was worked up by the usual manner and purification of the product by column chromatography gave the oily diene (**11**) (55 mg, 83%). Data for **11** follow: IR 1560, 1500; MS 216 (M^+, 100), 201 (25), 160 (31), 135 (18), 107 (18); NMR 0.92 (minor) and 0.97 (major) (overall 6H, s (23:77), $C(CH_3)_2$), 1.20—2.20 (6H, m, $C(10)H_2C(11)H_2$ and $C(9)H_2$ or $C(13)H_2$), 3.16 (2H, d, J=6.0, $C(5)H_2$), 5.20—5.95 (3H, m, 3 =CH containing C(13)H of **11b** as singlet), 6.15, 7.10, 7.23

(each 1H, s, C(2)H, C(1)H, and C(4)H).

Olefinic Inversion of the (E)-Furyl terpene (9) via the Epoxide (12) Providing the (Z)-Furyl Terpene (13) by the Vedejs' Method.[6] *m*-Chloroperbenzoic acid (MCPBA) (net 80%) (202 mg, 0.9 mmol) was added in portions into a solution of the (*E*)-furyl terpene (**9** *E*:*Z*=85:15) (186 mg, 0.8 mmol), prepared from the alcohol (**5** *E*:*Z*=85:15) by the same procedure described above without recrystallization of the sulfone (**7**), in CH_2Cl_2 (10 ml) at 0 °C. The mixture was diluted with CH_2Cl_2, washed successively with 3% NaOH and water, dried, and concentrated to give a crude product (190 mg). Purification by column chromatography gave the epoxide (**12**) (152 mg, 76%) as oil: NMR 0.86, 0.95 (each 3H, s, $C(CH_3)_2$), 1.51—1.90 (10 H, m), 2.35—2.70 (3H, m, $C(5)H_2$ and C(7)H), 6.18, 7.13, 7.23 (each 1H, s, C(2)H, C(1)H, and C(4)H). To a solution of $LiP(Ph)_2$ in THF, prepared from $ClP(Ph)_2$ (120 mg, 0.5 mmol) and Li (7 mg, 1.0 mg atm) in THF (1.5 ml) under ultrasonic irradiation at 15 °C for 2 h, was added dropwise a solution of the epoxide (**12**) (100 mg, 0.4 mmol) in THF (0.5 ml) at room temperature under argon. After stirring the mixture for 1 h, MeI (50 μl) was added into the mixture at room temperature. Stirring was continued for 45 min and the mixture was worked up by the usual manner. Purification of the product by column chromatography provided the inverted olefin (**13**) (58 mg, 65%) as oil: NMR 0.82 (minor) and 0.86 (major) (overall 6H, s (20:80), $C(CH_3)_2$), 1.20—1.70 (4H, m, $C(10)H_2C(11)H_2$), 1.79 (minor) and 1.87 (major) (overall 2H, s, $C(13)H_2$), 1.80—2.50 (6H, m, $C(5)H_2C(6)H_2$ and $C(9)H_2$), 4.97 (minor) and 5.12 (major) (overall 1H, bt, *J*=6.0, C(7)H), 6.15, 7.08, 7.21 (each 1H, s, C(2)H, C(1)H, and C(4)H).

Synthesis of Pleraplysillin-1 (1) from (Z)-Furyl Sesquiterpene (13). The PhSCl addition of the (*Z*)-olefin (**13** *E*:*Z*=20:80) was carried out by the identical conditions described for the (*E*)-olefin (**9**) to give the allylic sulfide (**10**) in 77% yield. ^{1}H-NMR analysis indicated the isomeric ratio of **10** to be **10a**:**10b**=60:40 as follows: NMR 0.65, 0.86 (minor pair of singlets 40% intensity) and 0.80, 0.92 (major pair of singlets of 60% intensity) (overall 6H, $C(CH_3)_2$), 4.85 (minor singlet assignable to C(13)H of **10b**) and 5.23 (major broad singlet assignable to C(9)H of **10a**) (overall 1H, 40:60). Oxidative elimination of thiophenol from the sulfide (**10**) obtained was achieved analogously by oxidation with H_2O_2 in AcOH followed by heating in toluene as described above for **10** (**10a**:**10b**=23:77). The diene, thus obtained in 80% yield, contained desired pleraplysillin-1 (**1**) as the major component: IR 1560, 1500; MS 216 (M^+, 100), 201 (20), 160 (32), 135 (21), 107 (28); NMR 0.92 (major) and 0.97 (minor) (overall 6H, s (60:40), $C(CH_3)_2$), 1.34 (major triplet assignable to $C(11)H_2$ of **1**), 1.85 (major singlet assignable to $C(13)H_2$), 3.15 (2H, d, *J*=6.0, $C(5)H_2$), 5.20—6.10 (3H, m, 3 =CH), 6.15, 7.10, 7.23 (each 1H, s, C(2)H, C(1)H, and C(4)H). The major signals in ^{1}H-NMR were identical with those observed for the pure **1** synthesized by the alternative route, *vide infra*. The diene obtained showed a single peak in HPLC analysis and all the efforts for separation of each regioisomer were unsuccessful.

Synthetic Approach to Pleraplysillin-1 (1) by Way of Regioselective Epoxide-Ring Opening of the β,γ-Epoxy Alcohol (14). *2,3-Epoxyochtodane-1-ol (14)*: A solution of MCPBA net 80%) (920 mg, 4.3 mmol) in CH_2Cl_2 (10 ml) was added dropwise into an ice-cold solution of the alcohol (**5**) (600 mg, 3.9 mmol) in CH_2Cl_2 (20 ml) and the mixture was stirred for 45 min at 0 °C. The mixture was worked up analogously as described for **12** gave the epoxide (**14**) (605 mg, 91%): NMR 0.93, 0.98 (each 3H, s, $C(CH_3)_2$), 1.15—1.90 (8H, br), 2.77 (1H, t, *J*=6.0, $C(O)\underline{H}CH_2OH$), 3.64 (2H, d, *J*=6.0, $C(O)HC\underline{H}_2OH$), 3.92 (1H, bs, OH).

3-Ochtodene-1,2-diol (15): The epoxide-ring opening was achieved according to the procedure developed by Sharpless.[7] To a solution of the epoxy alcohol (**14**) (650 mg, 3.8 mmol) in CH_2Cl_2 (20 ml) was added dropwise a solution of $Ti(OPr^i)_4$ (1.3 g, 4.5 mmol) in CH_2Cl_2 (5.0 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 15 h at room temperature. After evaporation of the solvent *in vacuo*, Et_2O (20 ml) and 5% H_2SO_4 (15 ml) was added to the residue and the mixture was stirred for 30 min at room temperature. The reaction mixture was worked up by the usual manner to give a crude product (630 mg), which was purified by column chromatography to afford the diol (**15**) (500 mg, 77%) as oil: IR 3520, 3380; NMR 0.88 (major) and 0.97 (minor) (overall 6H, s (94:6), $C(CH_3)_2$), 1.31 (2H, t, *J*=6.5, $C(6)H_2$), 1.73 (2H, s, $C(8)H_2$), 1.85—2.20 (2H, m, $C(5)H_2$), 3.35—4.10 (2H, m, $C(OH)HC\underline{H}_2OH$), 3.85—4.13 (1H, m, $C(OH)\underline{H}CH_2OH$), 4.46 (2H, bs, 2×OH), 5.40 (minor) and 5.65 (major) (overall 1H, bs (94:6), =CH).

2-Hydroxy-3-ochtodene-1-yl Tosylate (16): A mixture of the diol (**15**) (430 mg, 2.5 mmol) and *p*-TsCl (570 mg, 3.0 mmol) in pyridine (8.0 ml) was stirred for 16 h at room temperature. The reaction mixture was extracted with Et_2O, washed successively with 3% HCl, 5% $NaHCO_3$, and brine, dried, and concentrated to give a crude product (770 mg). Purification of the product by column chromatography afforded the mono tosylate (**16**) (620 mg, 76%) as oil: NMR 0.82 (major) and 0.91 (minor) (overall 6H, s, $C(CH_3)_2$), 1.23 (2H, t, *J*=7.0, $C(6)H_2$), 1.62 (2H, bs, $C(8)H_2$), 1.77—2.20 (2H, m, $C(5)H_2$), 2.39 (3H, s, CH_3Ph), 3.07 (1H, s, OH), 3.75—4.25 (3H, m, $C(OH)HCH_2OTs$), 5.38 (minor) and 5.60 (major) (overall 1H, bs, =CH), 7.20—7.80 (4H, A_2B_2q, *J*=8.5, arom-H).

2-Oxo-3-ochtodene-1-yl Tosylate (17): Active MnO_2 (2.5 g) was added into a solution of the alcohol (**16**) (440 mg, 1.3 mmol) in CH_2Cl_2 (20 ml) at room temperature and the mixture was stirred for 3.5 h. The reaction mixture was filtered and the filtrate was purified by column chromatography to give the keto tosylate (**17**) (390 mg, 89%) as oil: IR 1650, 1620, 1590; NMR 0.85 (major) and 1.02 (minor) (overall 6H, s, $C(CH_3)_2$), 1.30 (2H, t, *J*=6.5, $C(6)H_2$), 1.90 (2H, bs, $C(8)H_2$), 2.00—2.40 (2H, m, $C(5)H_2$), 2.40 (3H, s, CH_3Ph), 4.88 (2H, $C(O)CH_2OTs$), 6.46 (minor) and 6.77 (major) (overall 1H, bs, =CH), 7.20—7.83 (4H, A_2B_2q, *J*=8.5, arom-H).

1-Tosyl-3-ochtodene-2-one (18): A mixture of the keto tosylate (**17**) (370 mg, 1.15 mmol) and *p*-TsNa (574 mg, 2.2 mmol) in DMF (8.0 ml) was stirred for 16 h at room temperature. The reaction mixture was worked up by the usual manner to give a crude product (345 mg). Purification by column chromatography gave the crystalline keto sulfone (**18**) (286 mg, 82%). Recrystallization from Et_2O–hexane yielded the pure regio isomer (**18**), mp 110—113 °C. Data for **18** follow: IR 1650, 1625, 1595; NMR ($CDCl_3$) 0.89 (6H, s, $C(CH_3)_2$), 1.34 (2H, t, *J*=6.5, $C(6)H_2$), 1.96 (2H, bs, $C(8)H_2$), 2.10—2.50 (2H, m, $C(5)H_2$), 2.45 (3H, s, CH_3Ph), 4.44 (2H, s, $C(O)CH_2Ts$), 6.95 (1H, bs, =CH), 7.25—7.83 (4H, A_2B_2q, *J*=8.5, arom-H); Found: C, 66.53; H, 7.29%. Calcd for $C_{17}H_{22}O_3S$: C, 66.64; H, 7.24%.

1-[3-(3-Furyl)-2-tosylpropionyl]-5,5-dimethylcyclohexene (19): A solution of the keto sulfone (**18**) (140 mg, 0.45 mmol) in THF (0.5 ml) was added into an ice-cold mixture of NaH (13 mg, 0.55 mmol), THF (1.5 ml), and DMF (2.0 ml) and stirring was continued for 10 min at 0 °C. Then, a solution of 3-

furylmethyl bromide (**4** Y=Br) (82 mg, 0.5 mmol) in THF (0.5 ml) was added into the mixture at room temperature. The mixture was stirred for 16 h at room temperature and worked up by the usual manner. Purification of the crude product (172 mg) by column chromatography afforded the crystalline coupled keto sulfone (**19**) (164 mg, 92%), mp 136—140 °C (Et_2O-hexane). Data for **19** follow: IR 1650, 1630, 1600; NMR ($CDCl_3$) 0.77, 0.82 (each 3H, s, $C(CH_3)_2$), 1.25 (2H, t, J=6.5, $C(11)H_2$), 1.88 (2H, bs, $C(13)H_2$), 2.00—2.30 (2H, m, $C(10)H_2$), 2.42 (3H, s, CH_3Ph), 3.11, 3.12 (each 1H, d, J=8.5 and 6.0, C(Ts)HC$\underline{H}_2$-furyl), 4.93 (1H, dd, J=8.5 and 6.0, C(Ts)$\underline{H}CH_2$-furyl), 6.08 (1H, s, C(2)H), 6.73 (1H), bs, C(9)H), 7.07, 7.22 (each 1H, s, C(1)H and C(4)H), 7.20—7.72 (4H, A_2B_2q, J=8.5, arom-H); Found: C, 68.30; H, 6.86%. Calcd for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78%.

*3-(3-Furyl)-1-(5,5-dimethyl-1-hexenyl)-2-tosyl-1-propanol (**20**)*: $NaBH_4$ (24 mg, 0.63 mmol) was added in portions into a solution of the keto sulfone (**19**) (124 mg, 0.32 mmol) in EtOH (5.0 ml) at 0 °C and stirring was continued for 30 min at 0 °C. Extraction of the mixture with Et_2O followed by the usual work-up gave the crystalline hydroxy sulfone (**20**) (125 mg, 100%), mp 130—135 °C (Et_2O-hexane). Data for 20 follow: IR 3440, 1590; MS 388 (M^+, 2), 307 (19), 233 (85), 215 (100), 165 (47); NMR 0.79, 0.82 (each 3H, s, $C(CH_3)_2$), 1.15 (2H, t, J=6.5, $C(11)H_2$), 1.69 (1H, bs, $C(13)H_2$), 1.90—2.20 (2H, m, $C(10)H_2$), 2.42 (3H, s, CH_3Ph), 2.78, 2.85 (each 1H, d, J=6.0 and 5.0, C(Ts)HC$\underline{H}_2$-furyl), 3.15—3.57 (1H, m, C(OH)HC(Ts)$\underline{H}CH_2$-furyl), 4.00 (1H, d, J=4.0, OH), 4.32 (1H, dd, J=7.5 and 4.0, C(OH)$\underline{H}$C(Ts)H), 5.70 (1H, bs, C(9)H), 6.07, 7.06, 7.20 (each 1H, s, C(2)H, C(1)H, and C(4)H), 7.15—7.75 (4H, A_2B_2q, J=8.5, arom-H); Found: C, 68.04; H, 7.24%. Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26%.

*1-[1-Acetoxy-3-(3-furyl)-2-tosylpropyl]-5,5-dimethylcyclohexene (**21**)*: A mixture of the alcohol (**20**) (100 mg, 0.26 mmol), Ac_2O (0.5 ml), and pyridine (0.5 ml) was stirred for 16 h at room temperature. The reaction mixture was worked up by the usual manner to give the acetoxy sulfone (**21**) (105 mg, 95%) as oil. Data for **21** follow: IR 1740, 1595; MS 370 [$(M-60)^+$, 2], 275 (7), 232 (12), 215 (100); NMR 0.79, 0.83 (each 3H, s, $C(CH_3)_2$), 1.25 (2H, t, J=6.5, $C(11)H_2$), 1.55 (2H, bs, $C(13)H_2$), 1.67 (3H, s, CH_3CO_2), 1.83—2.20 (2H, m, $C(10)H_2$), 2.42 (3H, s, CH_3Ph), 2.76, 2.90 (each 1H, d, J=6.0 and 5.5, C(Ts)HC$\underline{H}_2$-furyl), 3.10—3.60 (1H, m, C(OAc)HC(Ts)$\underline{H}CH_2$-furyl), 5.36 (1H, d, J=8.0, C(OAc)$\underline{H}$C(Ts)H), 5.65 (1H, bs, C(9)H), 6.24, 7.17, 7.23 (each 1H, s, C(2)H, C(1)H, and C(4)H), 7.20—7.72 (4H, A_2B_2q, J=8.5, arom-H).

*Synthesis of Pleraplysillin-1 (**1**) by Reductive Elimination of the Acetoxy Sulfone (**21**). Method A Using Sodium Amalgam.*[8] 5% Na-Hg (2.0 g) was added at once into a cold solution of the acetoxy sulfone (**21**) (150 mg, 0.35 mmol) in a mixed solvent of MeOH (1.5 ml) and AcOEt (0.7 ml) at −20 °C and stirred was continued for 2.5 h at the temperature. The mixture was worked up by the usual manner. Purification of the product by column chromatography gave mainly the hydroxy sulfone (**20**) (96 mg, 71%) and a small amount of the sulfur-free diene (**1**) (5 mg, 7%), which appeared homogeneous in the ordinary TLC but proved to contain two compounds in a ratio *ca.* 80:20 by HPLC analysis using 5% $AgNO_3$-impregnated silica gel. The major less polar component was identified with pleraplysillin-1 (**1**) by coinjection of pure **1** prepared by the alternative conditions (Method B), *vide infra*. Spectral data for the diene were almost identical with those of pure **1** obtained by the modified Bouvault-Blanc conditions (Method B) except for the ratio (*ca.* 80:20) of intensity of the doublet signals at δ 3.15 and 3.26 (J=6.5 Hz) respectively assignable to the $C(5)H_2$ of **1** and the corresponding (6*Z*)-isomer in ^{1}H-NMR.

Method B Utilizing the Modified Bouvalut-Blanc Conditions.[9] Pieces of Na (70 mg, 3.0 mgatm) were added into a cold solution of the acetoxy sulfone (**21**) (150 mg, 0.35 mmol) and EtOH (0.3 ml) in THF (2.0 ml) at −78 °C and the mixture was stirred for 1 h at the temperature. The mixture was extracted with hexane, washed with water, dried, and concentrated. Purification of the product by column chromatography gave the diene (**1**) (49 mg, 65%) as oil. Spectral properties of the diene were consistent with those of the isolated pure **1**, described below, except for the appearance of minor doublet (*ca.* 11%) at 3.26 assignable to the $C(5)H_2$ of the corresponding (6*Z*)-isomer of **1** in ^{1}H-NMR. HPLC analysis also showed that the product contains a minor amount (*ca.* 11%) of the isomer as the more polar component. Careful column chromatography of the diene on 5% $AgNO_3$-impregnated silica gel by elution with hexane gave pure pleraplysillin-1 (**1**). Spectral data for the synthetic compound were consistent with those reported for the natural **1**:[3] IR 1560, 1500, 1445, 1425, 1380, 1360, 1050, 1010, 960, 865; MS 216 (M^+, 100), 201 (25), 160 (40), 145 (30), 135 (27), 131 (37), 118 (29), 107 (37), 91 (50), 81 (49); NMR 0.92 (6H, s, $C(CH_3)_2$), 1.34 (2H, t, J=6.0, $C(11)H_2$), 1.85 (2H, s, $C(13)H_2$), 2.00—2.25 (2H, m, $C(10)H_2$), 3.15 (2H, d, J=6.5, $C(5)H_2$), 5.20—5.70 (2H, m C(6)H and C(9)H), 6.03 (1H, d, J=15.0, C(7)H), 6.15, 7.10, 7.23 (each 1H, s, C(2)H, C(1)H, and C(4)H).

*Synthesis of the Model Compound, 1-(1-Acetoxy-3-phenyl-2-tosylpropyl)cyclohexene (**22**).* 1.6 M solution of *n*-BuLi-hexane (3.1 ml) was added dropwise into a solution of phenethyl *p*-tolyl sulfone (1.17 g, 4.5 mmol), prepared from phenethyl bromide, in THF (8.0 ml) at −78 °C under argon. After stirring of the mixture for 30 min at −78 °C, a solution of 1-cyclohexenecarbaldehyde (550 mg, 5.0 mmol), prepared from cyclohexanone *p*-tosylhydrazone,[10] in THF (1.0 ml) was added into the mixture. The mixture was stirred for 30 min at the temperature and worked up by the usual manner. Product isolation gave 1-(1-cyclohexenyl)-3-phenyl-2-tosyl-1-propanol (1.42 g, 85%) as a diasteroisomeric mixture: NMR 0.85—1.50 (6H, br, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$=), 1.65—2.10 (2H, br, $C\underline{H}_2CH$=), 2.41 (3H, s, CH_3Ph), 2.40—3.60 (3H, m, C(OH)HC(Ts)$\underline{H}C\underline{H}_2Ph$), 4.03 (1H, s, OH), 3.92 (major doublet (J=15.0)) and 4.30 (minor doublet (J=12.0)) (overall 1H, C(OH)$\underline{H}$C(Ts)H), 5.62 (major) and 5.86 (minor) (overall 1H, bs, =C$\underline{H}CH_2$), 6.80—7.87 (9H, m, arom-H). Careful column chromatography of the diasteroisomeric mixture gave one of the stereoisomer as a TLC-homogeneous oil: IR 3450, 1595; MS 370 (M^+, 3), 352 (4), 260 (31), 214 (81), 197 (98), 196 (100); NMR showed almost identical spectrum with that of the stereoisomeic mixture except for absence of the minor doublet at δ 4.30 and of the minor broad singlet at δ 5.86. The hydroxy sulfone (diastereoisomeric mixture) was acetylated analogously as described for **20** to give the crystalline acetoxy sulfone (**22**) in 88% yield as a diastereoisomeric mixture. Data for **22** follow: IR 1740, 1590; NMR 1.10—1.55 (6H, br, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$=), 1.66 (major) and 1.92 (minor) (overall 3H, s, CH_3CO_2), 1.70—2.05 (2H, br, $C\underline{H}_2CH$=), 2.38 (3H, s, CH_3Ph), 2.40—3.80 (3H, m, C(OAc)HC(Ts)$\underline{H}C\underline{H}_2$-Ph), 5.33 (1H, d, J=8.0, C(OAc)$\underline{H}$C(Ts)H), 5.40 (minor) and 5.60 (major) (overall 1H, bs, C$\underline{H}CH_2$), 7.09 (5H, s, arom-H (Ph)), 7.15—7.73 (4H, A_2B_2q, J=8.5, arom-H (Ts)). From the

purified stereoisomer of hydroxysulfone was obtained the stereochemically pure one of acetoxy sulfone (**22**); mp 81—83 °C (Et_2O–hexane). Spectral properties were identical with the corresponding diastereoisomeric mixture except for absence of the minor singlet at δ 1.92 and broad singlet at δ 5.40 in ^{1}H-NMR. Found: C, 69.72; H, 6.93%. Calcd for $C_{24}H_{28}O_4S$: C, 69.88; H, 6.84%.

*Reductive Elimination of the Acetoxy Sulfone (**22**) Providing the Diene, 1-(3-Phenyl-1-propenyl)cyclohexene (**23**).* Treatment of the acetoxy sulfone (**22**) with Na and EtOH in THF by the same procedure (Method B) as described for **21** gave the diene (**23**) in 76% yield as oil. HPLC analysis of the diene (**23**) obtained either from the diastereoisomeric mixture of **22** or from the stereochemically pure **22** showed the identical chromatogram of a mixture of the geometric isomers (86:14) concerning the disubstituted olefinic bond. Data for **23** follow: IR 1600, 1490, 1445, 1430; MS 198 (M^+, 100), 169 (24), 155 (34), 141 (34), 129 (45), 117 (33), 107 (63), 91 (90), 97 (84); NMR 1.40—1.77 (4H, br, CH_2CH_2), 1.88—2.27 (4H, br, 2×=CHC$\underline{H}_2$), 3.35 (major) and 3.54 (minor) (overall 2H, d (*E*:*Z*=86:14) *J*=6.0, CHC$\underline{H}_2$Ph), 5.21—5.70 (2H, m, 2×=C$\underline{H}$ CH_2), 5.94 (1H, d, *J*=15.0, =CC$\underline{H}$=CHCH$_2$Ph).

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