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Synthesis and Absolute Configuration of (+)-Phrymarolin I, a Lignan

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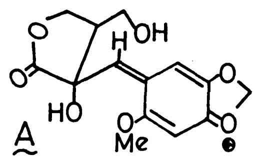
(+)-Phrymarolin I was synthesized from (S)-(+)-β-vinyl-γ-butyrolactone, and the absolute configuration of the natural product was established as (1S,2S,5R,6S).

Phrymarolin I, an insecticidal lignan, was isolated from Phryma leptostacya L. and the 1,2-dioxyganated 3,7-dioxabicyclo[3.3.0]octane structure **1a**, except for the absolute configuration, has been assigned to it on the basis of chemical and spectroscopic informations.[1)] Starting from an optically active material with definite stereochemistry, we have accomplished a total synthesis of **1a**, which also enabled us to establish the absolute configuration of (+)-phrymarolin I. In our preliminary synthesis of racemic **1a**, cadmium carbonate-catalyzed condensation[2)] of the chloride **2** with the phenol **4** only gave the 2α-epimer **1b** in low yield (14%). In the present synthesis, we have applied a new glycosidation method using glycosyl fluoride and tin (II) chloride[3)] to the acetalization of the fluoride **3** with the phenol **4**.

The chiral starting substance, (S)-(+)-β-vinyl-γ-butyrolactone, was prepared from its racemate[4)] by optical resolution in the following manner. The racemate, (±)-**5**, was converted to a mixture of the diastereomeric hydroxy amides, **6a** and **6b**, with (-)-α-phenylethylamine (1.1 equiv., Me_3Al,[5)] CH_2Cl_2, r.t., 56%) and the mixture was separated by medium-pressure liquid chromatography on silica gel (3% ^{i}PrOH in EtOAc as the eluant). Purely isolated **6a**, oil, $[\alpha]_D^{30}$ +92.2° (c 1.54, $CHCl_3$), [**6b**, mp 97-99 °C, $[\alpha]_D^{30}$ +83.1° (c 1.78, $CHCl_3$)], was subjected to alkaline hydrolysis (KOH, ethylene glycol, 170 °C) followed by lactonization with azeotropic removal of water (cat. p-TsOH, benzene) to give (+)-**5**, $[\alpha]_D^{19}$ +4.9° (c 4.3, EtOH), in 63% yield from **6a**. Hydrogenation of (+)-**5**

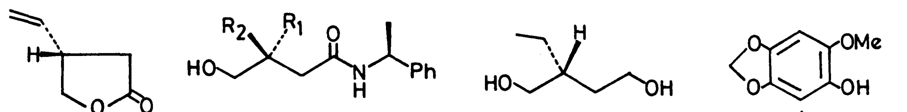
(H_2, Pd/C, EtOH) followed by reduction with $LiAlH_4$ (ether, 0 °C, 1 h) gave (R)-(+)-7, $[\alpha]_D^{19}$ +14.3° (c 3.0, $CHCl_3$), [lit.[6] $[\alpha]_D$ +7.7° (neat) for the 39% e.e. compound]. Therefore, the stereochemistry of (+)-5 was defined as (S)-configuration.

Addition of the lithium enolate of (S)-(+)-5 generated by LDA (1.1 equiv.) to 2-methoxy-4,5-methylenedioxybenzaldehyde (THF, -75 °C, 3 h) afforded a mixture of the aldols 8 (*erythro*/*threo*=65/35) in 98% yield. Without separation, the mixture was silylated[7] (1.5 equiv. $^tBuMe_2SiOTf$, 2.0 equiv. 2,6-lutidine, CH_2Cl_2, -30 °C, 40 min, 92%) and reduced with $LiAlH_4$ [ether-THF (2:1), -10 °C, 30 min, 82%] to give the diol 10. Successive oxidation with osmium tetroxide [1.2 mol%, 4-methylmorpholine *N*-oxide,[8] acetone-^tBuOH-H_2O (4:1:1), r.t., 15 h] and sodium periodate (1.0 equiv., EtOAc-H_2O, r.t., 3 h) gave 11, while ozone cleaved the aromatic ring in preference to the terminal double bond. To facilitate dehydration of the hydroxymethyl group to a methylene function, the lactol 11 was oxidized to the lactone 12 (1.5 equiv. Ag_2CO_3-celite, benzene, reflux, 45 min) in 91% overall yield from 10. After sulfonylation (1.2 equiv. MsCl, Et_3N, benzene, r.t., 4 h) of 12, the mesylate was immediately treated with DBU (1.5 equiv., benzene, r.t., 30 min) to furnish the methylene lactone 13 in 87% yield. Dihydroxylation with catalytic osmium tetroxide[8] [1.5 mol%, 4-methylmorpholine *N*-oxide, acetone-^tBuOH-H_2O (4:1:1), r.t., 12 h] gave the diol 14 quantitatively in a high stereoselectivity, as a result of exclusive attack of the reagent to the less hindered α-face of the molecule.



A

After removal of the $^tBuMe_2Si$ group (1.1 equiv. $^nBu_4NF$, THF, 0 °C, 2 h), the triol 15 was subjected to dehydrative cyclization (cat. 10-camphorsulfonic acid, CH_2Cl_2, r.t., 3 h) to afford the key intermediate 16,[9] $[\alpha]_D^{25}$ +67.3° (c 2.0, $CHCl_3$), in 59% yield along with 10% recovered 14. Both *erythro* and *threo* isomers of 15 gave 6α-16 as the sole product via the thermodynamically preferable common transition state A, while the cyclization under strongly acidic conditions, e.g., $BF_3 \cdot O(Et)_2$ in CH_2Cl_2 or HCl in THF, gave a mixture of the 6α and 6β isomers of 16 due to the isomerization of 6α-16. The optical purity of (+)-16 was determined to be over 95% e.e. on the basis of the 400 MHz ^1HNMR spectrum of its (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester 18.[10] After masking the tertiary hydroxyl group of 16 with $^tBuMe_2SiOTf$[7] (2 equiv., 3 equiv. 2,6-lutidine,

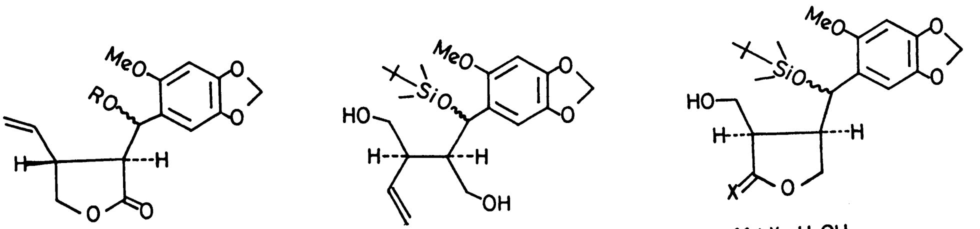


(S)-(+)-5

6a: R_1= -CH=CH$_2$, R_2=H
6b: R_1=H, R_2= -CH=CH$_2$

7

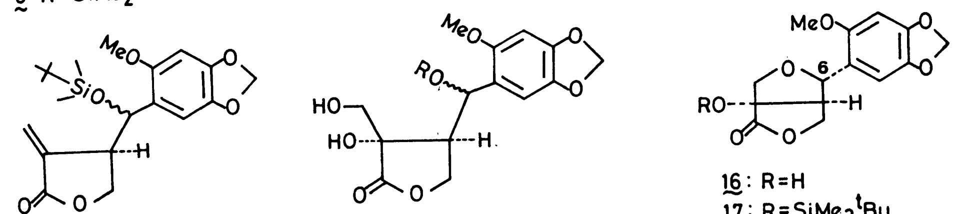
4



8: R=H
9: R=SiMe$_2{}^t$Bu

10

11: X=H,OH
12: X=O



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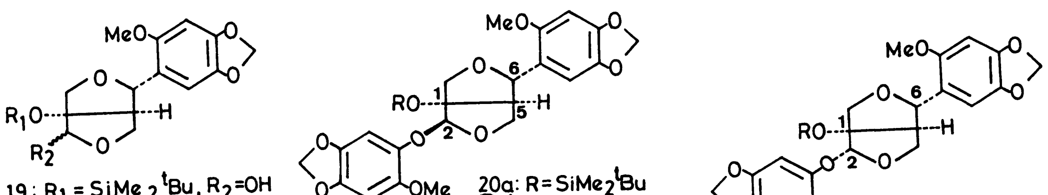
14: R=SiMe$_2{}^t$Bu
15: R=H

16: R=H
17: R=SiMe$_2{}^t$Bu
18: R=MeO---C(CF$_3$)(Ph)---C(=O)-



19: R_1 = SiMe$_2{}^t$Bu, R_2=OH
3: R_1 = SiMe$_2{}^t$Bu, R_2= F
2: R_1 =Ac, R_2=Cl

20a: R=SiMe$_2{}^t$Bu
21a: R=H
1a: R=Ac
22: R=MeO---C(CF$_3$)(Ph)---C(=O)-

20b: R=SiMe$_2{}^t$Bu
21b: R=H
1b: R=Ac

CH_2Cl_2, r.t., 18 h, 85%), the resulting silyl ether 17 was reduced with $^iBu_2AlH$ (1.1 equiv., toluene, -75 °C, 1 h) to give the lactol 19 in 98% yield. The lactol was fluorinated with 2-fluoro-1-methylpyridinium tosylate[3] (1.5 equiv., 2.0 equiv. Et_3N, CH_2Cl_2, r.t., 50 min, 92%) and the unstable fluoride 3 ($2\alpha/2\beta$= 1/1) was immediately subjected to the acetalization[3] with the phenol 4 (1.2 equiv., 3.0 equiv. $SnCl_2$, 1.2 equiv. $TrClO_4$, 4A molecular sieve, ether, 0 °C, 2.5 h). A mixture of 20a and 20b was obtained in 50% combined yield (20a/20b= 33/67, based on NMR). Desilylation of the mixture (2.0 equiv. $^nBu_4NF$, THF, r.t., 3 h) and separation of the products by preparative TLC (silica gel, 10% EtOAc in benzene) furnished 21a[11] (11% yield from 3), $[\alpha]_D^{23}$ +128.6° (c 0.49, $CHCl_3$), [natural 21a, $[\alpha]_D^{24}$ +163.6° (c 1.58, $CHCl_3$)], along with 21b[11] (29% yield from 3), $[\alpha]_D^{24}$ -38.1° (c 1.3, $CHCl_3$). The optical purity of (+)-21a was estimated as 85% e.e. on the basis of the 400MHz ^{1}HNMR spectrum of its (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester 22.[12] The partial racemization (ca. 10%) occurred during the 5 steps from 16 to 21a. Finally, the target molecule 1a,[13] $[\alpha]_D^{25}$ +106.9° (c 0.11, dioxane), [natural 1a, $[\alpha]_D^{25}$ +131.3° (c 0.12, dioxane)], was obtained by acetylation of (+)-21a in acetic anhydride containing a small excess of 4-(dimethylamino)pyridine (r.t., 12 h).

In summary, we have accomplished a total synthesis of (+)-phrymarolin I from (S)-(+)-β-vinyl-γ-butyrolactone through 15 steps in 3% overall yield. The absolute stereochemistry of (+)-phrymarolin I has been established as the (1S, 2S,5R,6S)-configuration. Partial financial support of this work by a Grant-in-Aid of the Ministry of Education, Science and Culture is greatly acknowledged.

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9) 16: mp 136-137 °C, ^{1}HNMR (acetone-d_6) δ, 2.84 (1H, s), 2.93 (1H, dt, J=8, 5 Hz), 3.81 (3H, s), 4.11 (2H, s), 4.38 (1H, dd, J=5, 10 Hz), 4.63 (1H, dd, J= 8, 10 Hz), 5.07 (1H, d, J=5 Hz), 5.92 (2H, s), 6.67 (1H, s), 6.97 (1H, s).
10) The ^{1}HNMR spectrum shows a pair of singlets at δ 6.73 and 6.97 due to the Ar-H of the (1S,S)-ester and the (1R,S)-ester, respectively.
11) 21a: mp 133-134 °C (lit.[1] mp 133-134 °C); ^{1}HNMR ($CDCl_3$) δ, 2.57 (1H, m), 3.72 (1H, d, J=10 Hz), 3.72-3.96 (1H, br.), 3.74 (3H, s), 3.75 (3H, s), 4.06 (1H, dd, J=7, 10 Hz), 4.91 (1H, d, J=6 Hz), 5.16 (1H, s), 5.88 (2H, s), 5.89 (2H, s), 6.48 (1H, s), 6.53 (1H, s), 6.76 (1H, s), 7.12 (1H, s). 21b: viscous oil; ^{1}HNMR ($CDCl_3$) δ, 2.64 (1H, q, J=7 Hz), 2.80-3.24 (1H, br.), 3.74 (3H, s), 3.78 (3H, s), 4.05 (1H, d, J=7 Hz), 5.30 (1H, s), 5.87 (2H, s), 5.89 (2H, s), 6.47 (1H, s), 6.54 (1H, s), 6.74 (1H, s), 7.05 (1H, s).
12) The ^{1}HNMR spectrum shows two pairs of the methyl singlets (δ3.65/3.68 and 3.75/3.73) due to the (1S,S)-/(1R,S)-ester, respectively.
13) 1a: mp 155-157 °C (lit.[1] mp 156-157 °C); ^{1}HNMR ($CDCl_3$) δ,2.14 (3H, s), 2.90 (1H, m), 3.75 (3H, s), 3.77 (3H, s), 3.82 (1H, d, J=11 Hz), 4.05 (1H, dd, J=2, 9 Hz), 4.51 (1H, dd, J=7, 11 Hz), 4.62 (1H, d, J=11 Hz), 4.89 (1H, d, J=7 Hz), 5.68 (1H, s), 5.88 (2H, s), 5.93 (2H, s), 6.53 (2H, s), 6.48 (1H, s), 7.05 (1H, s).

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