

THE TOTAL SYNTHESIS OF (+)-SIKKIMOTOXIN VIA THE BENZO-
PETERSON REACTION

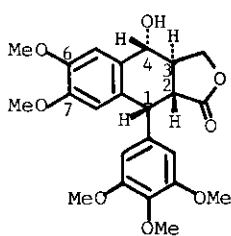
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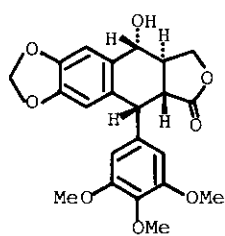
(Dedicated to Professor Gilbert Stork on the occasion of
his sixtyfifth birthday)

Abstract — The total synthesis of a lignan lactone
sikkimotoxin (1) in racemic forms has been completed by
employing the Benzo-Peterson reaction as key step.

Sikkimotoxin was isolated from the root of Himalayan plant, *Podophyllum sikkimensis*, by Chatterjee and co-workers¹ who proposed its structure to be shown as 1.^{2,3} Although the later study carried out by Schreier⁴ casted doubt on the correctness of the original structural assignment, the assigned structure is of particular interest since its 6,7-methylenedioxy analogue podophyllotoxin (2)⁵ and its



(1)

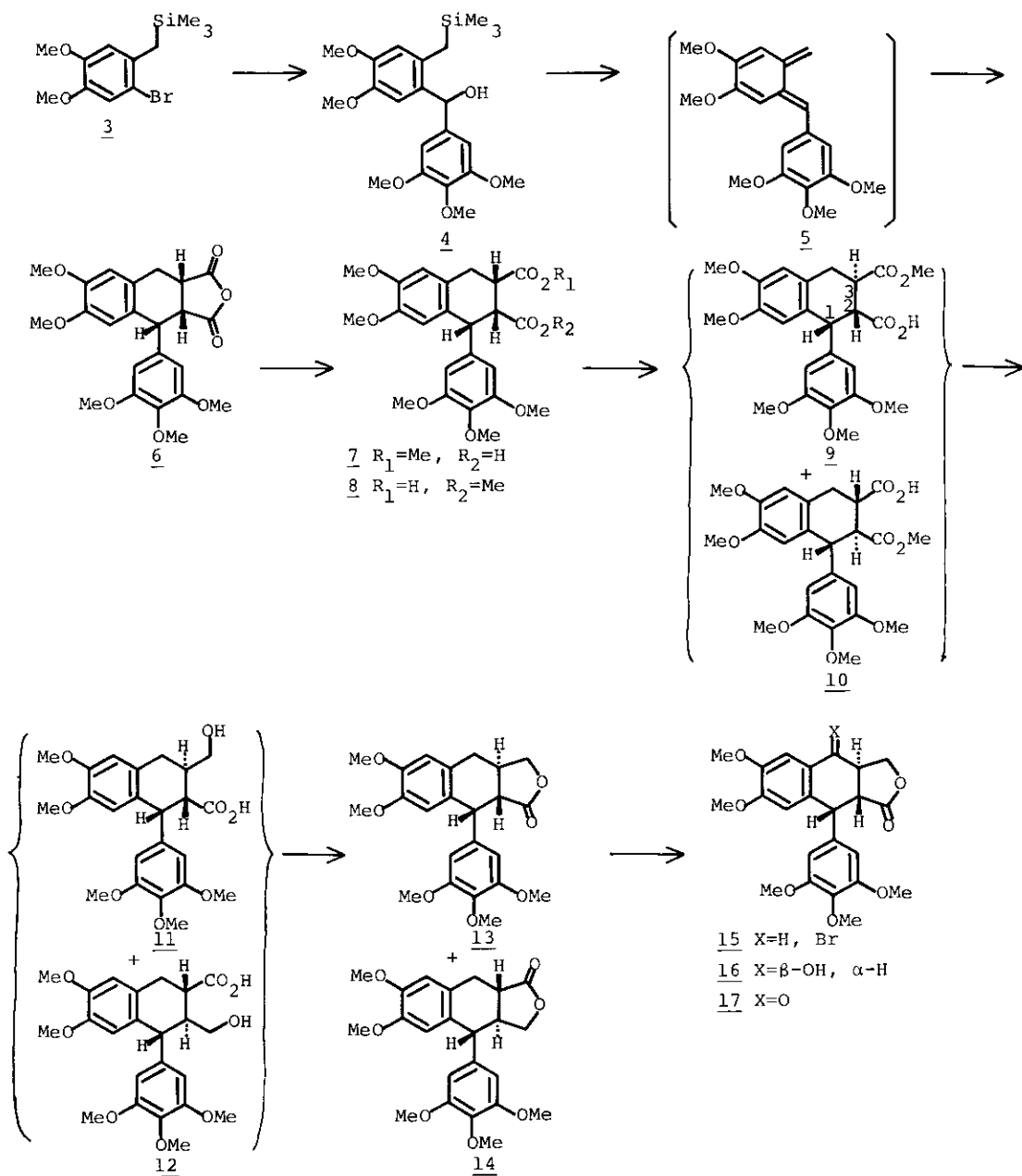


(2)

derivatives have been received considerable attention from both the synthetic and the biological points of view because of their potent antineoplastic activity.⁵ We now report the first synthesis of sikkimotoxin (1) in racemic forms by

employing the Benzo-Peterson reaction which was developed recently by us.^{6,7} On lithiation followed by condensation with 3,4,5-trimethoxybenzaldehyde the benzylsilane (3)⁸ gave the benzhydrol (4) in 89% yield. This compound was refluxed with five equivalents of maleic anhydride in toluene for 12 h. The Peterson type desilyl-dehydroxygenation took place readily to generate the transient o-quinodimethane intermediate (5) which was immediately trapped with maleic anhydride in endo fashion to give the all cis-adduct (6) in 98% yield. In order to elaborate the proper stereochemistry for the construction of sikkimotoxin (1), the all cis-anhydride (6) was refluxed with methanol for 12 h and then treated with 3 equivalents of sodium methoxide in the same solution under refluxing for 8 h. We expected that it would generate the half ester (7) via regioselective methanolysis from the less hindered side which then would be stereoselectively epimerized at the center substituted by the ester group into the sterically less congested 1,2-cis, 2,3-trans-epimer (9) via the sodium enolate to relieve steric compression remaining the center substituted by the carboxy group unchanged.⁶ However, the reaction gave a mixture of two compounds and we later found that the major one to be the desired one (9) and the minor one to be the structurally isomeric 3-methoxycarbonyl compound (10) possessing 1,2-trans, 2,3-trans configuration owing to incomplete selectivity in the methanolysis of the anhydride (6).⁹ Since the mixture was very difficult to separate at this stage, it was reduced with lithium triethylborohydride to give a mixture of the hydroxyacids (11) and (12) which without separation was then refluxed azeotropically in benzene in the presence of p-toluenesulfonic acid to yield the lactone mixture. The mixture, on separation by silica gel column followed by recrystallization, afforded deoxysikkimotoxin (13)¹⁰ and the structural isomer (14)¹¹ in 37 and 16% overall yields from the anhydride (6). The stereochemistry of 13 was evident from the comparison of its n.m.r. spectrum with that of the its 6,7-methylenedioxy analogue deoxypodophyllotoxin (1: OH=H) which has been prepared by employing the Benzo-Peterson method.⁶

Introduction of the oxygen function at 4 position of 13 was accomplished by the method recently developed by Yamaguchi and co-workers¹² who have recently succeeded to convert naturally occurring deoxypodophyllotoxin (1: OH=H) into podophyllotoxin (1) by bromination with N-bromosuccinimide (NBS) followed by hydrolysis in the presence of silica gel. Thus, deoxysikkimotoxin (13) was



treated with NBS in carbon tetrachloride to yield the 4-bromo derivative (15). The 4-bromo derivative (15) was too unstable to isolate and was spontaneously transformed into a mixture of sikkimotoxin (1) and 4-epi-sikkimotoxin (16) during

isolation stage. We, therefore, treated the reaction mixture briefly with silica gel and then chromatographed on silica gel column to obtain the mixture of hydroxygenated products. The reaction was greatly affected by the amount of N-bromosuccinimide used. When one equivalent of NBS was used, 36% yield (66% yield based on consumed starting material) of a 4:3 mixture of 1 and 16 was obtained accompanied by 45% yield of the starting material, while virtually none of the starting material was recovered when more than 1.25 equivalent of NBS was used though yield of the hydroxygenated mixture (7:6) was increased to 41% yield.¹³ The mixture could be separated by preparative silica gel tlc at this stage to give (+)-sikkimotoxin (1) and (+)-episikkimotoxin (16), however, for practical purpose, the mixture was directly oxidized with pyridinium chlorochromate to the single 4-keto derivative (17), in 68% yield. This compound was then reduced with diisobutylaluminum hydride at -90 C to give a 9:1 mixture of (+)-sikkimotoxin (1) and its 4-epimer (16) which was readily separated by silica gel chromatography to give each compound in pure state in 83 and 9% yields, respectively. We concluded that the synthetic sikkimotoxin (1) possessed the assigned stereochemistry since it showed virtually the same proton n.m.r. spectrum (500 MHz in CDCl₃) to that of (±)-podophyllotoxin (2) except the signals of methylenedioxy and methoxy groups.

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 9. 6,7-Methylenedioxy analogue reacted selectively to give the 3-methoxycarbonyl derivative on reflux in methanol; see ref. 6.
 10. Proton n.m.r. spectrum (500 MHz in CDCl_3) well corresponded to that of deoxy-podophyllotoxin except signals of methylenedioxy and methoxy groups.
 11. Proton n.m.r. spectrum (500 MHz in CDCl_3) well corresponded to that of α -conidendrine: see, R. Dhal, Y. Nabi, and E. Brown, Tetrahedron, **42**, 2005 (1986).
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 13. Tetradehydro and its brominated derivatives were obtained as by-products.
 14. All compounds gave satisfactory elemental analyses and high resolution mass spectra. Spectral data are the following: **4**: viscous oil; $\nu_{\text{max}}^{\text{neat}}$ 3500 cm^{-1} ; δ (CDCl_3) 0.0 (s, 9H), 2.05 (d, 1H, J 3.5 Hz, exchangeable), 2.07 (s, 2H), 3.75, 3.78, 3.80 (each s, 15H), 5.83 (d, 1H, J 3.5 Hz), 6.47 (s, 1H), 6.51 (s, 2H), 6.85 (s, 1H); m/z 420 (M^+), 299 (100%). **6**: mp 140-142°C; $\nu_{\text{max}}^{\text{Nujol}}$ 1860, 1780 cm^{-1} ; δ (CDCl_3) 3.03-3.45 (m, 2H), 3.53-3.96 (m, 2H), 3.77, 3.82, 3.86 (each s, 15H), 4.25-4.53 (m, 1H), 6.36 (s, 2H), 6.68 (s, 1H), 6.77 (s, 1H); m/z 428 (M^+ , 100%). **13**: mp 192-193°C; $\nu_{\text{max}}^{\text{Nujol}}$ 1770 cm^{-1} ; δ (CDCl_3) 2.70-2.82 (m, 3H), 3.10 (dd, 15.0, 4.0 Hz), 3.74 (s, 6H), 3.78, 3.82, 3.91 (each s, 9H), 3.89-3.96 (m, 1H), 4.47 (dd, 1H, J 10.0, 6.0 Hz), 4.65 (d, 1H, J 4.5 Hz), 6.35 (s, 2H), 6.55 (s, 1H), 6.70 (s, 1H); m/z 414 (M^+ , 100%). **14**: mp 179-181°C; $\nu_{\text{max}}^{\text{Nujol}}$ 1772 cm^{-1} ; δ (CDCl_3) 2.48-2.63 (m, 2H), 3.01 (dd, 1H, 15.0, 10.0 Hz), 3.23 (dd, 1H, 15.0, 5.0 Hz), 3.63 (s, 3H), 3.82 (s, 6H), 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (d, 1H, 10.0 Hz), 4.06 (dd, 1H, 10.0, 8.0 Hz), 4.26 (dd, 10.0, 6.0 Hz), 6.33 (s, 1H), 6.35 (s, 2H), 6.72 (s, 1H); m/z 414 (M^+ , 100%). **16**: mp 194-195.5°C (lit.⁴ mp 118-120°C); $\nu_{\text{max}}^{\text{Nujol}}$ 3445, 1754 cm^{-1} ; δ (CDCl_3) 1.82 (d, 1H, J 5.0 Hz, exchangeable), 2.78-2.86 (m, 1H), 3.29 (dd, 1H, J 16.0, 8.8 Hz), 3.72 (s, 6H), 3.81 (s, 6H), 3.94 (s, 3H), 4.38 (dd, 1H, 16.0, 8.8 Hz), 4.40 (dd, 1H, 16.0, 8.1 Hz), 4.67 (d, 1H, 5.0 Hz), 4.91 (dd, 1H, 5.0, 5.0 Hz), 6.25 (s, 2H), 6.60 (s, 1H), 6.90 (s, 1H); m/z 430 (M^+ , 100%). **17**: mp 203-204°C; $\nu_{\text{max}}^{\text{Nujol}}$ 1778, 1678 cm^{-1} ; δ (CDCl_3) 3.18-3.55 (m, 2H), 3.63 (s, 6H), 3.72, 3.80, 3.90 (each s, 9H), 4.17-4.62 (m, 2H), 4.78 (d, 1H, J 3.0 Hz), 6.30 (s, 2H), 6.63 (s, 1H), 7.50 (s, 1H); m/z 428 (M^+ , 100%). **1**, mp 207-208°C (lit. 120°C¹; 125-130°C⁴); $\nu_{\text{max}}^{\text{Nujol}}$ 3500, 1720 cm^{-1} ; δ (CDCl_3) 1.66 (d, 1H, J 9.4 Hz, exchangeable), 2.70-2.80 (m, 1H), 2.86 (dd, 1H, 14.0, 5.0 Hz), 3.74 (s, 6H), 3.79 (s, 3H), 3.94 (s, 3H), 4.10 (d, d, 1H, 9.4, 7.5 Hz), 4.61 (d, d, 1H, 9.4, 8.8 Hz), 4.65 (d, 1H, 5 Hz), 4.81 (dd, 1H, 9.4, 9.4 Hz), 6.40 (s, 2H), 6.51 (s, 1H), 7.30 (s, 1H); m/z 430 (M^+ , 100%).

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