Total Synthesis of (+)-Phyllanthocin

D. R. Williams*[1] and Sing-Yuen Sit

Contribution from Indiana University, Department of Chemistry, Bloomington, Indiana 47405.
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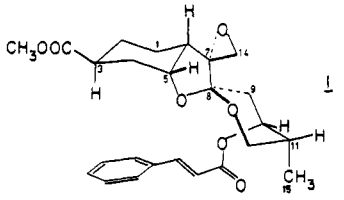
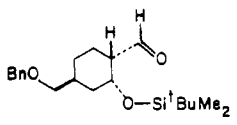
Abstract: Investigations culminating in the total synthesis of (+)-phyllanthocin via a highly convergent route beginning with natural tartaric acid are reported. The stereochemical consequences of internal spiroketalization with protic acid and Lewis acid chelation conditions are presented.

In 1977 Kupchan and co-workers reported isolation and characterization of (+)-phyllanthocin (**1**), the aglycon of an an-



1

tileukemic glycoside, (+)-phyllanthoside.[2] The structure and relative stereochemistry of **1** were determined by X-ray crystallographic analysis. Recently characterizations of several antineoplastic glycosides, termed phyllanthostatins **1**, **2**, and **3**, were



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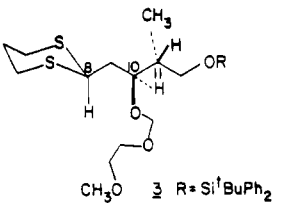


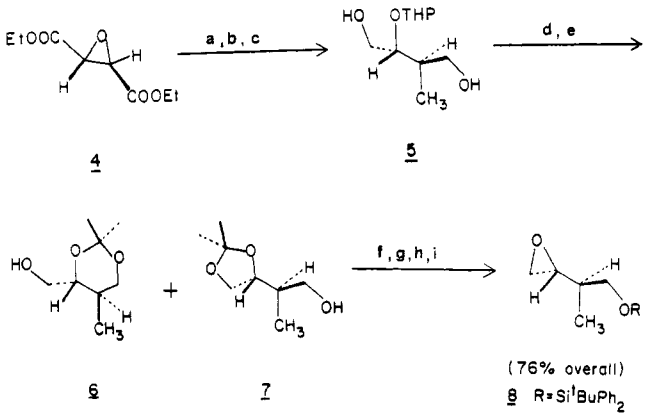
3 R = Si^tBuPh_2

reported along with structural elucidation of (+)-phyllanthoside,[3] and a total synthesis of (+)-phyllanthocin was achieved, establishing the absolute configuration of these natural products.[4] Considerable interest in phyllanthoside continues with advanced preclinical development by the National Cancer Institute. Herein we communicate our efforts for a highly convergent total synthesis of optically active (+)-phyllanthocin from natural tartaric acid.[5]

Our approach has utilized preparation of the cyclohexane carboxaldehyde **2** and the substituted dithiane **3** with convergency by C-7–C-8 carbon bond formation. Thus, the dithioacetal **3** is suitably masked for effective conversion to an acyl anion equivalent.

Formation of the optically active 1,3-dithiane component **3** proceeded as illustrated in Scheme I. Beginning with natural diethyl tartarate, conversion to the chiral epoxide **4** was achieved as recently reported by Mori and co-workers.[6] Reaction with lithium dimethylcuprate[6] afforded a single optically active alcohol, which was protected as its tetrahydropyranyl (THP) ether. Reduction with lithium aluminum hydride provided diol **5**, thus establishing the required absolute configurations of C-10 and C-11 for phyllanthocin. The utilization of the THP ether allowed for convenient isolation of diol **5** from the crude reduction mixture, and subsequent treatment with catalytic *p*-toluenesulfonic acid

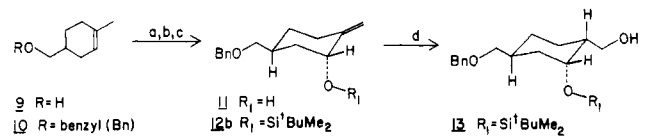
Scheme I



4 **5** **6** **7** **8** R = Si^tBuPh_2 (76% overall)

[a] $LiMe_2Cu$, ether, −78 °C. [b] Dihydropyran, ether, catalytic *p*-TsOH. [c] $LiAlH_4$, ether, 22 °C, 18 h. [d] *p*-$TsOH_2$, CH_3OH, 22 °C (70% overall). [e] Acetone, *p*-TsOH (80%). [f] *t*-$BuPh_2SiCl$, DMAP, CH_2Cl_2, 22 °C, 2 h (98%). [g] Ethanedithiol (7 equiv), $CHCl_3$, *p*-TsOH (0.05 equiv), reflux (92%). [h] TsCl, Et_3N, CH_2Cl_2, 36 h. [i] NaH, THF, 0 °C → room temperature (76% overall from 7).

Scheme II



9 R = H; **10** R = benzyl (Bn); **11** R_1 = H; **12b** R_1 = Si^tBuMe_2; **13** R_1 = Si^tBuMe_2

[a] MCPBA, CH_2Cl_2, 10 °C → room temperature (89%). [b] Lithio-2,6-dimethylpiperidide (1.2 equiv), ether, 50 °C, 2 h, Carius tube (90% exocyclic olefins). [c] *t*-$BuMe_2SiCl$, DMF, DMAP, 22 °C, 18 h (100%). [d] Borane, THF, 22 °C, then H_2O_2, ^-OH.

in methanol afforded a water-soluble triol **5a** (75% yield). Ketalization proceeded with a mild exotherm to provide an 80% yield of a mixture (1:5 ratio) of acetonides **6** and **7**, bp 85–88 °C (4.5 mmHg). However, protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether was uneventful, and flash chromatography (silica gel) at this stage readily provided separation of the desired dioxolane **7a**, as the silyl ether, from its corresponding silyl isomer, dioxane **6a**.

Selective hydrolysis of the acetonide without concomitant removal of the silyl ether proved troublesome. This difficulty was solved by ketal exchange using ethanedithiol (6 equiv) in chloroform (reflux, 1 h) with *p*-toluenesulfonic acid (0.20 equiv) affording a 92% yield of diol, which was readily transformed into the terminal epoxide **8** in 76% overall yield from dioxolane **7**.

Rigorous structural assignments of dioxolane **7** and subsequent intermediates toward epoxide **8** vs. comparable isomers stemming from dioxane **6** were uncertain based upon spectral information. However, the analogous reaction sequence as described above, led to a facile cyclization in the case of **6** providing the four-membered

(1) Alfred P. Sloan Foundation Fellow (1983–1985).
(2) Kupchan, S. M.; LaVoie, E. J.; Braufman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.
(3) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544.
(4) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496.
(5) An account of this work was presented: Williams, D. R.; Sit, S. Y. *Abstr. Pap.–Am. Chem. Soc.* **1983**, *186th*, ORGN 12.
(6) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87.

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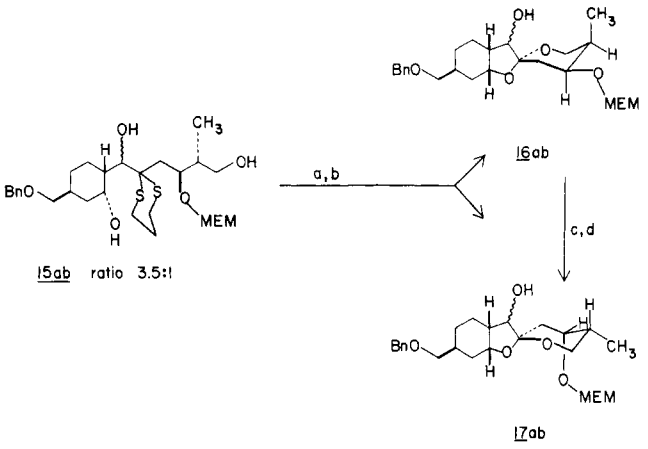
Scheme III

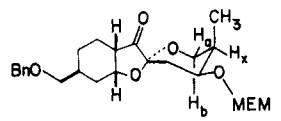


trans-3-methyl-2-[(*tert*-butyldiphenylsiloxy)methyl]oxetane.[7] Subsequent nucleophilic addition of 2-lithio-1,3-dithiane to the reactive epoxide **8** (THF, −25 °C, 95% yield), and protection of the resulting secondary alcohol as its (β-methoxyethoxy)methyl ether (MEM-Cl, 10 equiv, DMAP in diisopropylethylamine, 40 h, 95% yield) afforded the chiral component **3**.

Preparation of cyclohexane **2** was accomplished as shown in Scheme II, starting with the known cyclohexenyl alcohol **9**.[8] Benzylation and oxidation gave a 1:1 mixture of α/β-epoxides,[9] which was for basic isomerization with lithio-2,6-dimethylpiperidide to an equal proportion of exocyclic allylic alcohols.[10] Only 6% of endocyclic allylic alcohols were obtained; however, other strong bases gave inferior results. After formation of the corresponding *tert*-butyldimethylsilyl ethers, the desired axial isomer **12b** and its unwanted equatorial silyl ether **12a** were readily separable by column chromatography.[11] Hydroboration of **12b** produced 65% yield of alcohol **13** as the product of axial attack, combined with its corresponding β-isomer in a 70:30 ratio, respectively.[12] Oxidation (PCC, CH_2Cl_2, 22 °C) gave cyclohexane carboxaldehyde **2** in 90% yield. Generally this sensitive isomer was utilized immediately following flash chromatography.

Convergency of our synthetic route was realized upon deprotonation of dithiane **3** using *tert*-butyllithium (1.5 equiv, THF, HMPA (4 equiv), −78 °C, 20 min). Metallation was not complete without subsequent warming to −20 °C for 2.5 h and then cooling to −78 °C for addition of aldehyde **2** (1.0 equiv, THF). Although some elimination of the β-siloxy substituent of **2** was apparent with formation of the corresponding α,β-unsaturated aldehyde, the major reaction course provided nucleophilic addition to the carbonyl affording four separable diastereomeric adducts in 80% yield (based on starting **2**). Thus, optically active dithiane **3** could perform the necessary resolution of synthetic intermediates when utilizing racemic **2**. However, resolution of the primary alcohol **13** was achieved by esterification with (−)-camphanic acid (Aldrich) followed by chromatography and hydrolysis (KOH, aqueous CH_3OH). Subsequent condensation of **3** with the (−) antipode of **2** afforded two diastereoisomers as a 3.5:1 ratio of α/β secondary alcohols **14** which were cleanly separated. A complete characterization, following removal of the silyl protecting units (n-$Bu_4N^+F^-$, THF, 22 °C), identified the triols **15a,b**.

Each triol **15a,b** was individually treated as illustrated in Scheme III. Hydrolysis of the dithiane moiety ($HgCl_2$, HgO, aqueous CH_3CN) gave a 3:1 mixture of the spiro ethers **16** and **17**, and predominantly the unmasked, stable keto triol, which was separated by silica gel chromatography. These keto triols rapidly formed spiro ketals upon introduction of protic acids. Thus, either triol **15a** or **15b** resulted in a mixture of **16** and **17** in approximately a 6:1 ratio, respectively, demonstrating that protic acid conditions had favored formation of **16** bearing the unnatural configuration of the critical spiro center (C-8). Although further equilibration of this mixture with protic acids was extremely slow, it was concluded that these ring-forming processes afforded kinetic product development.[13] Fortunately, the major products **16a,b** could be treated with certain Lewis acids to promote isomerization to the desired spiro ketals **17a,b**.[14] Treatment of **16a,b** with magnesium trifluoroacetate (Scheme III) gave a stable chelation complex, which was then freed of the cation by exchange with buffered aqueous EDTA solution, yielding spiro ketals **17a,b** with only traces of the unnatural ketal isomers.[15] Oxidation of **16a** or **16b** (H_2CrO_4, aqueous acetone, 22 °C) gave a single ketone **18**, and likewise alcohols **17a,b** yielded ketone **19**. Structural



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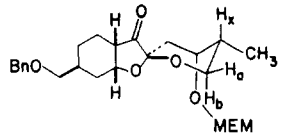
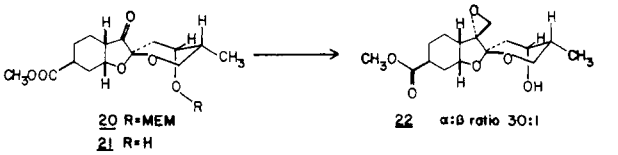


19

assignments of the unnatural and natural series were aided by the observed proton coupling constants at C-12. For example, ketone **18** displayed geminal coupling J_{a-b} of 11.6 Hz, and vicinal coupling constants of J_{a-x} = 2.2 and J_{b-x} = 1.4 Hz, whereas ketone **19** demonstrated vicinal coupling of J_{a-x} = 6.5 and J_{b-x} = 10.8 Hz in addition to the large geminal coupling (J_{a-b} = 10.8 Hz) for H_a (δ 3.90, which also displayed long range w-coupling), and H_b (δ 3.79), respectively.

Finally, catalytic debenzylation (H_2, 5% Pd–C, CH_3OH), Jones' oxidation (22 °C, 30 min), and esterification (ethereal CH_2N_2) led to an 80% overall yield of keto ester **20** from **19**. Removal of the MEM ether was quantitatively achieved using anhydrous zinc bromide (CH_2Cl_2, 22 °C, 8 h), giving the unmasked secondary alcohol **21**. Excess methyleneoxysulfurane, generated as a 0.5 M stock solution in dimethyl sulfoxide, afforded the anticipated epoxide **22** in 98% yield (THF, 22 °C) with selective attack at



20 R=MEM
21 R=H

22 α:β ratio 30:1

the less hindered carbonyl face (α/β epoxides in 30:1 ratio).

(7) Oxetanes are readily distinguished from isomeric epoxides by the relative downfield chemical shift of protons at the C-2 and C-4 positions. *trans*-2-[(*tert*-Butyldiphenylsiloxy)methyl]-3-methyloxetane gave ^1H NMR ($CDCl_3$) δ 7.64 (m, 4 H), 7.38 (m, 6 H), 4.30 (dt, 1 H, J = 2.9, 4.7 Hz), 3.90 (t, 1 H, J = 7.6 Hz), 3.63 (dd, 1 H, J = 4.0, 9.4 Hz), 3.59 (dd, 1 H, J = 2.9, 9.4 Hz), 3.58 (dd, 1 H, J = 7.6, 9.0 Hz), 2.11 (m, 1 H), 1.08 (s, 9 H), 1.06 (d, 3 H, J = 6.86 Hz).

(8) Inukai, T.; Kasai, M. *J. Org. Chem.* **1965**, *30*, 3567. Monti, S.; White, G. L. *Ibid.* **1975**, *40*, 216.

(9) These epoxides appeared as a single, homogeneous substance by TLC and spectral data until the mixture was examined at higher field (360 MHz) ^1H NMR and (90.8 MHz) ^{13}C NMR.

(10) For a review: Crandall, J. K.; Apparu, M. *Org. React.* **1984**, *30*, 345–443. Williams, D. R.; Grote, J. *J. Org. Chem.* **1983**, *48*, 134.

(11) The secondary alcohols **12** were transformed into their corresponding *tert*-butyldiphenylsilyl ethers in only modest yields.

(12) Higher yields (80%) were achieved in small-scale experiments (100 mg or less). More sterically demanding thexyl- and diisoamylborane reagents gave less favorable proportions of **13** and its β isomer.

(13) Factors controlling the configuration of the spiro ketal center may be quite subtle. In a closely related case, breynogenin has been isomerized to isobreynogenin establishing a 1:1 thermodynamic equilibrium under protic acid conditions (Sakai, F.; Ohkuma, H.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *Chem. Pharm. Bull.* **1976**, *24*, 114). Pure **17** did not produce a mixture of **16** and **17** after resubmission to protic acid (TFA, CH_2Cl_2), and prolonged reaction times and elevated temperatures led exclusively to MEM ether cleavage.

(14) Lewis acids, such as zinc bromide, titanium tetrachloride, and stannic chloride, all provide facile isomerization to the natural spiro ether **17**, however, these also remove the MEM ether protection (see also ref 4). Perhaps Lewis acid site complexation favors the spiro ketal configurational isomer, which provides a more stabilized coordination.

(15) Our evidence of the magnesium chelate is limited. However, the complex is stable to silica gel chromatography, exhibiting slightly greater polarity than the free alcohols **17a,b**. Additionally, ^1H NMR spectra of the complex displayed all of the appropriate signals for **17a,b** but with line broadening. Use of EDTA for the sequestering of coordinated magnesium cations has been reported: Evans, D. A.; Bryan, C. A.; Wahl, G. M. *J. Org. Chem.* **1970**, *35*, 4122.

Esterification with cinnamoyl chloride (CH_2Cl_2, DMAP, 40 °C, 2 h) resulted in completion of the total synthesis of (+)-phyllanthocin, which was identical in all respects with a sample of authentic natural product.[16]

Experimental Section[17]

2-[4-(*tert*-Butyldiphenylsiloxy)-3(*R*)-methyl-2(*S*)-hydroxybutyl]-1,3-dithiane (8a). *n*-Butyllithium (2.4 M, 3.9 mL, 9.4 mmol in hexane) was added dropwise to a solution of 1,3-dithiane (1.15 g, 9.6 mmol, sublimed and dried over P_2O_5 at 24 °C for 8 h) in 8 mL of dry tetrahydrofuran cooled to −78 °C under argon. The pale yellow solution was stirred at −78 °C for 15 min, then allowed to warm to −30 °C, and maintained between −30 and −40 °C for 3 h. A solution of (2*R*,3*R*)-4-(*tert*-butyldiphenylsilyloxy)-1,2-epoxy-3-methylbutane (2.35 g, 6.9 mmol) in 10 mL of dry tetrahydrofuran was added slowly via a syringe with continued stirring at −30 °C for 10 min then at 0 °C for 3 h. Analytical TLC (20% ethyl acetate in hexanes) showed a single product at R_f 6.30 along with excess of dithiane at 0.81. The reaction was quenched by pouring into a mixture of 20 mL saturated NH_4Cl and 40 mL ether followed by extraction and separation. The aqueous phase was back-extracted twice with ether (2 × 20 mL). Organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 3.39 g of crude product **8a**, which generally was used for the next preparation without further purification: $[\alpha]^{24}_D$ −30.9° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.42 (m, 6 H), 4.40 (dd, *J* = 5.42, 9.13 Hz, 1 H), 3.92 (m, 1 H), 3.75 (dd, *J* = 3.97, 10.47 Hz, 1 H), 3.64 (dd, *J* = 7.58, 10.11 Hz, 1 H), 1.05 (s, 9 H), 0.83 (d, *J* = 7.22 Hz, 3 H); IR (film) 3467, 3083, 2923, 2889, 2845, 1577, 1468, 1459, 1425, 1359, 1275, 1243, 1110, 908, 822, 742 (s), 710 (s), 701 (s), 613 cm^{-1}. Anal. Calcd for $C_{25}H_{36}O_2S_2Si$: C, 65.17; H, 7.87. Found: C, 65.12; H, 8.06.

2-[1-(*tert*-Butyldiphenylsiloxy)-2(*R*)-methyl-3(*S*)-((β-methoxyethoxy)methoxy)butyl]-1,3-dithiane (3). To a stirred solution of **8a** (3.39 g, 6.9 mmol) in 10 mL of dry dichloromethane and 14.5 mL (83 mmol) of diisopropylethylamine was added 4-(dimethylamino)pyridine (100 mg) and (β-methoxyethoxy)methyl chloride (6.3 mL, 56 mmol) at 0 °C under argon. A white precipitate was formed almost instantaneously as (β-methoxyethoxy)methyl chloride entered the solution with a slight exotherm. Stirring was continued at 0 °C for 2 h then at room temperature for 20 h. Analytical TLC (10% ethyl acetate in hexanes, three elutions) showed only one product at R_f 0.16, and the brownish suspension was poured into 40 mL of water and 40 mL of ether followed by extraction and separation. The aqueous phase was extracted with 20 mL ether, and organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a reddish oil (4.58 g). The crude product was further purified by column chromatography (40 g of silica gel) using a gradient elution with 2% ethyl acetate in hexanes, 0.5 L, 5%, 0.5 L, and 10%, 1 L, to give 3.58 g (94.6%) of pure product. Overall yield in two steps was 95%. The dithane **3** was characterized as follows: $[\alpha]^{25}_D$ −10.81° (*c* 0.805, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.40 (m, 6 H), 4.77 (s, 2 H), 4.20 (dd, *J* = 6.50, 7.22 Hz, 1 H), 4.04 (dt, *J* = 6.14, 5.42 Hz, 1 H), 3.72 (m, 1 H), 3.66 (m, 1 H), 3.54 (m, 4 H), 3.38 (s, 3 H), 2.85 (m, 4 H), 2.10 (m, 2 H), 1.90 (dd, *J* = 6.50, 7.22 Hz, 2 H), 1.88 (m, 1 H), 1.05 (s, 9 H), 0.88 (d, *J* = 6.86 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.58, 133.58, 129.49, 127.46, 95.62, 76.34, 71.73, 67.34, 65.57, 58.94, 43.84, 39.04, 36.75, 30.30, 29.71, 26.86, 25.99, 19.19, 11.81; IR (film) 3060, 3040, 2921, 1587, 1468, 1459, 1425, 1388, 1360, 1275, 1240, 1185, 1110, 1039, 825, 705, 605 cm^{-1}; MS (70 eV), *m/e* (no M^+), 199.10 (100), 355.20 (3), 269 (56), 257 (26), 239 (16), 213 (28), 191 (53), 183 (45), 135 (41), 119 (37), 105 (26). Anal. Calcd for $C_{29}H_{44}O_4S_2Si$: C, 63.61; H, 8.08. Found: C, 63.46; H, 8.13.

***cis*- and *trans*-4-[(Benzyloxy)methyl]-2-hydroxyl-1-methylenecyclohexane (11a,b).** *n*-Butyllithium (2.4 M, 25.3 mL, 61 mmol) was added to a solution of freshly distilled 2,6-dimethylpiperidine (8.2 mL, 61 mmol) in 20 mL of dry ether cooled to 0 °C under argon. The mixture was stirred for 15 min at 0 °C and epoxide **10a,b** (as a mixture of cis and trans isomers, 11.8 g, 51 mmol) was added dropwise. The solution was stirred in a resealable pressure bottle, and the temperature was increased to 45–50 °C for 1 h giving a medium yellow color. Upon cooling, analytical TLC of the mixture showed no trace of starting material while two major spots were formed (at R_f 0.17 and 0.11 (20% v/v ethyl acetate in hexanes, two elutions)). After addition of 2 M HCl (70 mL, 140 mmol), the aqueous phase was partitioned and washed twice with two 50-mL portions of ether. Organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to give a medium-yellow oil. The crude material was separated on a Waters Prep 500 using a single Prep Pak/500 silica gel column, eluting with 25% ethyl acetate in hexanes. Fractions were combined to give a 10.62 g (90.3%) mixture of **11a** and **11b** and a minor product 0.72-g (6.1%) mixture of endocyclic alcohols. Spectral data indicated a 1:1 mixture of exocyclic alcohols: ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 4.93 (t, *J* = 1.08 Hz, cis-exo olefin, 1 H), 4.84 (m, 1, trans-exo olefinic H), 4.78 (d, *J* = 1.44 Hz, cis-exo olefinic H), 4.76 (t, *J* = 1.81 Hz, trans-exo olefinic H), 4.50 (s, benzylic, 4 H), 4.32 (t, *J* = 3.43 Hz, methine at C_2 of trans), 4.08 (ddd, *J* = 5.05, 11.55 Hz, methine at C_2 of cis), 3.33 (m, 4 H), 2.44 (m, 2 H), 2.1–2.3 (m, 3 H), 2.05 (br dd, 1 H, *J* = 4, 11 Hz), 1.8–2.0 (m, 4 H), 1.42 (m, 2 H), 1.62 (m, 1 H), 1.80 (m, 1 H), 1.0–1.2 (m, 2 H); IR (film) 3400, 2920, 2850, 1450, 1095, 730; MS (70 eV), *m/e* 232.145 (M^+, 0.85), 91.054 (100); ^{13}C NMR ($CDCl_3$) δ 151.24, 150.02, 138.50, 138.33, 128.21, 127.38, 109.21, 103.92, 74.85, 72.92, 72.77, 71.63, 71.57, 60.32, 40.27, 37.39, 37.15, 33.15, 31.61, 30.79, 30.63, 29.33, 20.95, 14.09. Anal. Calcd for $C_{15}H_{20}O_2$:C, 77.55; H, 8.68. Found: C, 77.37; H, 8.77.

***cis*- and *trans*-2-(*tert*-Butyldimethylsiloxy)-4-[(benzyloxy)methyl]-1-methylenecyclohexane (12a,b).** Imidazole (6.2 g, 91 mmol) was added to a stirred solution of exocyclic allylic alcohols **11a,b** (10.5 g, 45 mmol) in 20 mL of dry DMF under argon at room temperature. One portion of *tert*-butyldimethylsilyl chloride (18.9 g, 59 mmol) was added and the mixture was stirred at room temperature with observation of a slight exotherm and white precipitate. The resulting suspension was stirred overnight (9 h) at 22 °C. Analytical TLC showed a quantitative conversion into products at R_f 0.30 and 0.20 (5% v/v ethyl acetate in hexanes, two elutions). The contents were poured into 50 mL of ether and 50 mL of water, and the layers were partitioned. The organic layer was washed twice with water (2 × 50 mL) and the aqueous layers were back-extracted with hexanes (2 × 50 mL). Organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The crude material was filtered through a bed of silica gel to give 14.5 g (92.8%) of a mixture of two products. The individual isomers were separated by silica gel column chromatography (300 g), eluting with hexanes (2 L) followed by 1% ethyl acetate in hexanes to afford 5.38 g (34%) of pure trans isomer **12b**, 7.13 g (45%), cis isomer **12a**, and 0.18 g of mixed fractions. The desired silyl ether **12b** was characterized as follows: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 4.71 (br s, 1 H), 4.65 (t, 1 H, *J* = 1.62 Hz), 4.49 (s, 2 H), 4.25 (t, 1 H, *J* = 3.25 Hz), 3.34 (dd, 1 H, *J* = 5.78, 9.03 Hz), 3.27 (dd, 1 H, *J* = 7.22, 9.03 Hz), 2.42 (dt, 1 H, *J* = 5.4, 12 Hz), 2.3 (m, 1 H), 2.08 (dt, 1 H, J = 4.1, 13 Hz), 1.8–1.9 (m, 2 H), 1.28 (ddd, 1 H, *J* = 2.7, 9.5, 13.5 Hz), 1.12 (dq, 1 H, J = 4, 12 Hz), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H); IR (film) 2930, 2850, 1255, 1090, 1053, 832 cm^{-1}; MS (70 eV), *m/e* 346.235 (M^+, 0.76), 91.055 (100), 289 (21); ^{13}C NMR ($CDCl_3$) δ 151.00, 138.71, 128.20, 127.35, 127.30, 107.55, 75.28, 72.82, 72.37, 39.16, 31.73, 31.14, 29.63, 25.80, 18.10, −4.73, −5.02. Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.78; H, 9.89. Found: C, 72.67; H, 10.02.

The cis isomer **12a** gave the following spectral data: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5H), 4.97 (br s, 1 H), 4.72 (br s, 1 H), 4.48 (s, 2 H), 4.03 (dd, 1 H, *J* = 5.2, 11.7 Hz), 3.29 (d, 2 H, *J* = 6.14 Hz), 2.40 (dt, 1 H, *J* = 3, 13 Hz), 1.8–2.1 (m, 4 H), 1.10 (q, 1 H, *J* = 11 Hz), 1.01 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); IR (film) 2940, 2920, 1470, 1465, 1252, 885; MS (70 eV), *m/e* 346.232 (M^+, 0.18), 91.053 (100), 289 (6); ^{13}C NMR ($CDCl_3$) δ 150.72, 138.49, 128.18, 127.44, 105.05, 75.03, 72.93, 72.43, 40.93, 37.25, 33.16, 30.99, 25.85, 18.26, −4.92. Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.0; H, 9.89. Found: C, 72.80; H, 10.08.

1α-(Hydroxymethyl)-2α-[(*tert*-butyldimethylsilyl)oxy]-4β-[(benzyloxy)methyl]cyclohexane (13). To a neat sample of **12b** (1.305 g, 3.8 mmol) at 0 °C under argon was added borane–tetrahydrofuran complex (1.0 M, 5.7 mL, 5.7 mmol) dropwise via syringe. The reaction mixture was stirred at 0 °C for 1 h followed by warming to ambient temperature and continued stirring for 30 min. Analytical TLC (20% ethyl acetate in hexanes) showed no remaining starting material and several more polar spots. Aqueous sodium hydroxide solution (30%, 1 mL) was slowly added at 0 °C followed by addition of H_2O_2 solution (30%, 0.5 mL). This two-phase mixture was stirred at room temperature for 30 min and was then diluted with 25 mL of ether followed by washing with brine. The aqueous phase was separated and back-extracted with 25 mL of ether. Organic layers were combined, dried over $MgSO_4$, and concentrated at reduced pressure to give a viscous oil. Column chromatography (silica gel, 20 g, 28 mm × 90 mm, elution with 1 L of 8% ethyl acetate in hexanes) gave 0.87 g (65%) of product. NMR spectra of this material indicated a 70:30 mixture of **13a** and **13b**. The minor unwanted isomer was more conveniently removed in the subsequent oxidation. A purified sample of **13a** gave the following spectral data: ^1H NMR ($CDCl_3$) δ 7.3

(16) We gratefully thank Professor George Pettit, Arizona State University, for generously providing an authentic sample of (+)-phyllanthocin for comparison.

(17) Proton magnetic resonance spectra were recorded on a Nicolet NT-360 instrument in $CDCl_3$ (0.1% Me_4Si), and carbon-13 spectra were determined at 90.8 MHz with proton decoupling. All coupling constants are reported in hertz. Silica gel 60 from E. Merck (0.063–0.2 mm), silica gel-H for flash chromatography, and precoated glass plates (60F-254) were employed throughout.

(m, 5 H), 4.49 (s, 2 H), 4.16 (m, 1 H), 3.56 (m, 2 H), 3.29 (br dd, 2 H, J = 1.81, 6.14 Hz), 2.09 (m, 1 H), 1.3–1.6 (m, 6 H), 1.0–1.2 (m, 2 H), 0.87 (s, 9 H), 0.08 (s, 6 H); IR (film) 3400, 2940, 2920, 1460, 1450, 1110, 775 cm^{-1}; MS (70 eV), m/e (no M^+), 91.053 (100), 307 (2); ^{13}C NMR ($CDCl_3$) δ 138.59, 128.02, 127.24, 75.66, 72.56, 67.96, 65.14, 44.45, 37.04, 31.51, 29.06, 25.71, 22.37, 17.90, −4.41, −5.26.

4β-[(Benzyloxy)methyl]-2α-[(*tert*-butyldimethylsilyl)oxy]-1β-cyclohexanecarboxaldehyde (2). One portion of pyridinium chlorochromate (1.6 g, 8.8 mmol) was added to a vigorously stirred solution of **13** (1.432 g, 3.9 mmol) in 200 mL of dry dichloromethane at room temperature under argon. The orange solution rapidly changed to a deep brown suspension over 2 h. Analytical TLC of the crude reaction mixture showed a minor spot at R_f 0.33 and a major spot at R_f 0.27 (20% v/v ethyl acetate in hexanes). Filtration of the suspension through a bed of silica gel with the aid of small amounts of dichloromethane gave crude product after removal of solvent. The products were separated on a silica gel column (85 g, 27 mm × 350 mm eluted with 1.5 L of 4% v/v ethyl acetate in hexanes) affording 0.393 g (28%) of unwanted 1β isomer and 0.892 g (63%) of desired aldehyde **2**: ^1H NMR ($CDCl_3$) δ 9.64 (s, 1 H), 7.30 (m, 5 H), 4.57 (br d, 1 H, J = 2.53 Hz), 4.49 (s, 2 H), 3.32 (dd, 1 H, J = 6.14, 9.03 Hz), 3.29 (dd, 1 H, J = 6.14, 9.50 Hz), 2.05–2.15 (m, 2 H), 1.85–1.95 (m, 3 H), 1.80 (m, 1 H), 1.23 (dt, 1 H, J = 2.17, 11.9 Hz), 1.03 (dq, 1 H, J = 3, 13 Hz), 0.852 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); IR (film) 2950, 2880, 2710, 1725, 1260, 1105, 1050, 780 cm^{-1}; MS (70 eV), m/e (no M^+), 75 (100), 91 (27), 105 (86), 179 (33), 213 (28), 335 (11); ^{13}C NMR ($CDCl_3$) δ 204.59, 138.66, 128.24, 127.36, 127.28, 75.42, 72.83, 66.80, 54.71, 36.82, 31.43, 28.10, 25.69, 19.69, 17.97, −4.22, −5.19. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.36; H, 9.34.

The minor isomeric aldehyde **2a** was characterized as follows: ^1H NMR ($CDCl_3$) δ 9.70 (s, 1 H), 7.30 (m, 5 H), 4.48 (s, 2 H), 4.31 (dd, 1 H, J = 2.89, 4.87 Hz), 3.30 (dd, 1 H, J = 6.50, 9.03 Hz), 3.25 (dd, 1 H, J = 7.22, 9.03 Hz), 2.43 (q, 1 H, J = 4.69 Hz), 2.16 (m, 1 H), 1.89 (m, 2 H), 1.6–1.7 (m, 2 H), 1.39 (ddd, 1 H, J = 2.89, 2.89, 10.1 Hz), 1.05–1.2 (m, 1 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); IR (film) 2940, 2850, 2700, 1723, 1260, 1095, 780 cm^{-1}; MS (70 eV), m/e (no M^+), 91.057 (100), 105 (43), 179 (28), 213 (18), 231 (12), 321 (5), 335 (4); ^{13}C NMR ($CDCl_3$) δ 204.08, 138.55, 128.26, 127.39, 74.57, 72.91, 66.23, 55.42, 34.90, 31.87, 26.16, 25.73, 20.29, 17.94, −4.53, −5.03. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.32; H, 9.45.

Preparation of Intermediate 14. To a stirred solution of dithiane **3** (dried over P_2O_5 at room temperature for 8 h at 0.1 mmHg, 1.2 g, 2.2 mmol) in 8 mL of freshly distilled dry tetrahydrofuran in a flame-dried flask under argon at −40 °C was added, via syringe, hexamethylphosphoramide (1.0 mL, 5.7 mmol) followed by *tert*-butyllithium (12.0 M, 1.4 mL, 2.8 mmol) dropwise forming a deep reddish solution. The bath temperature was gradually increased and maintained between −18 and −24 °C for 2 h. A solution of (−)-cyclohexanecarboxaldehyde **2** (0.892 g, 2.5 mmol), $[\alpha]^{26}_D$ −21.1° (c 1.40, $CHCl_3$),[18] in 6.0 mL of dry tetrahydrofuran was added rapidly via syringe into this deep red solution after cooling to −78 °C. The characteristic color was immediately discharged forming a pale yellow solution. Analytical TLC (20% ethyl acetate in hexanes, two elutions) showed a pair of products at R_f 0.24 and 0.22, starting material (dithiane) at R_f 0.18, and an additional product at R_f 0.06. The reaction was poured into a mixture of 20 mL of saturated NH_4Cl solution and 20 mL of ether followed by extraction and separation. The aqueous phase was extracted twice with ether (2 × 20 mL). Organic layers were combined, washed twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 2.44 g of crude product. The material was preabsorbed onto 6 g of silica gel-H followed by chromatographic separation (35 g of silica gel-H) using a gradient elution with 7.5% ethyl acetate in hexanes, 1 L, 10%, 1.5 L, and 20%, 0.6 L, to give 81% of condensation adducts, 17% of elimination product (4-[(benzyloxy)methyl]-1-cyclohexenecarboxaldehyde), and 15% of unreacted dithiane. Products at R_f 0.24 and 0.06 were identified in accord with the following spectral data.

Less polar component **14a**: ^1H NMR ($CDCl_3$) δ 7.65–7.70 (m, 4 H), 7.25–7.45 (m, 11 H), 4.93 (d, 1 H, J = 6.86 Hz), 4.78 (d, 1 H, J = 6.86 Hz), 4.49 (s, 2 H), 4.15 (m, 1 H), 3.97 (br s, 1 H), 3.76 (dt, 1 H, J = 4.3, 11.2 Hz), 3.64 (m, 3 H), 3.51 (m, 4 H), 3.37 (s, 3 H), 3.26 (d, 2 H, J = 6.1 Hz), 2.85–2.90 (m, 2 H), 2.7 (br s, 1 H), 2.6–2.7 (m, 2 H), 2.22 (m, 1 H), 1.95–2.15 (m, 4 H), 1.75–1.90 (m, 6 H), 1.3–1.4 (m, 1 H), 1.05 (s, 9 H), 0.92 (s, 9 H), 0.90 (d, 3 H, J = 6.86 Hz), 0.09 (s, 3 H), 0.10 (s, 3 H); IR (film) 3462, 3060, 2900, 1460, 1200, 1100, 835, 707 cm^{-1}.

The more polar dithiane adduct **14b**: ^1H NMR ($CDCl_3$) δ 7.68 (br d, 4 H, J = 7.58 Hz), 7.25–7.45 (m, 11 H), 4.98 (d, 1 H, J = 6.86 Hz), 4.80 (d, 1 H, J = 6.86 Hz), 4.49 (s, 2 H), 4.28 (d, 1 H, J = 3.61 Hz), 4.20 (br d, 1 H, J = 4.7 Hz), 3.98 (br m, 1 H), 3.77 (dt, 1 H, J = 4, 10.8 Hz), 3.65 (m, 2 H), 3.51 (t, 2 H, J = 4.7 Hz), 3.37 (s, 3 H), 3.37 (m, 1 H), 3.27 (d, 2 H, J = 6.14 Hz), 2.87 (br q, 2 H, J = 11.2 Hz), 2.52 (br t, 2 H, J = 13.7 Hz), 2.1–2.3 (m, 2 H), 1.7–2.0 (m, 8 H), 1.4–1.55 (m, 2 H), 1.2–1.4 (m, 2 H), 1.05 (s, 9 H), 0.84 (s, 9 H), 0.89 (d, 3 H, J = 6.86 Hz), 0.14 (s, 6 H).

Formation of Triols 15a and 15b. To a stirred solution of dithiane adduct **14a** (0.253 g, 0.277 mmol) in 5.0 mL of dry tetrahydrofuran at room temperature was added *n*-Bu_4NF (1.0 M solution in tetrahydrofuran, 1.1 mL, 1.1 mmol). The resulting brownish solution was stirred for 2 h at room temperature. After concentration of solvent under reduced pressure, the oily residue was separated by preparative TLC (four 20 cm × 20 cm × 0.5 mm thick plates) eluted 4 times with 35% ethyl acetate in hexanes to give 94.3 mg of the triol adduct **15a** (61%): $[\alpha]^{25}_D$ +26.9° (c 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.04 (d, 1 H, J = 6.86 Hz), 4.80 (d, 1 H, J = 6.86 Hz), 4.49 (s, 2 H), 4.12 (br s, 1 H), 4.08 (m, 2 H), 3.85 (dt, 1 H, J = 4.33, 11.2 Hz), 3.75–3.65 (m, 3 H), 3.57 (t, 2 H, J = 4.69 Hz), 3.49 (m, 1 H), 3.39 (s, 3 H), 3.30 (dd, 2 H, J = 0.72, 5.78 Hz), 2.9–3.0 (m, 2 H), 2.65–2.80 (m, 4 H), 2.40 (br m, 1 H), 2.2 (br m, 1 H), 2.00–2.10 (m, 2 H), 1.7–2.0 (m, 7 H), 1.29 (m, 1 H), 1.09 (m, 1 H), 0.98 (d, 3 H, J = 6.86 Hz); IR (film) 3420, 2920, 2880, 1450, 1200, 1110, 752 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 138.61, 128.14, 127.33, 127.25, 96.44, 78.50, 75.61, 75.31, 72.76, 72.25, 71.64, 67.57, 64.51, 58.67, 58.87, 41.99, 40.20, 36.96, 36.68, 31.24, 29.11, 25.90, 25.76, 24.42, 20.89, 11.77.

Similarly 159.6 mg (0.175 mmol) of dithiane adduct **14b** was subjected to the same reaction in 3.0 mL of tetrahydrofuran and 0.44 mL of 1 M *n*-Bu_4NF. The single polar product was purified by preparative TLC (two 20 cm × 20 cm, 0.5 mm thick plates with 35% ethyl acetate in hexanes, four elutions) to give 49.5 mg (50.6%) of a single pure triol **15b**: $[\alpha]^{25}_D$ +29.5° (c 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.04 (d, 1 H, J = 6.86 Hz), 4.44 (d, 1 H, J = 6.86 Hz), 4.50 (s, 2 H), 4.11 (br s, 1 H), 4.07 (m, 2 H), 3.85 (dt, 1 H, J = 4.69, 10.8 Hz), 3.63–3.76 (m, 2 H), 3.57 (t, 2 H, J = 4.69 Hz), 3.50 (m, 1 H), 3.39 (s, 3 H), 3.33 (br s, 1 H), 3.30 (dd, 2 H, J = 0.72, 5.78 Hz), 2.9–3.0 (m, 2 H), 2.6–2.8 (m, 4 H), 2.35 (br m, 1 H), 2.15–2.25 (m, 2 H), 2.0–2.1 (m, 4 H), 1.7–2.0 (m, 4 H), 1.29 (dt, 1 H, J = 2.17, 13.4 Hz), 1.09 (dq, 1 H, J = 5.78, 12.3 Hz), 0.98 (d, 3 H, J = 6.86 Hz); IR (film) 3410, 2910, 2880, 1450, 1203, 1100, 752 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 138.70, 128.22, 127.41, 127.33, 96.59, 78.67, 75.66, 75.28, 72.84, 72.39, 71.72, 67.71, 64.62, 59.03, 58.98, 41.99, 40.36, 37.24, 36.74, 31.32, 29.19, 25.99, 25.83, 24.42, 20.96, 12.01.

Spiroketalization to 16 and 17. To a vigorously stirred suspension of **15a** (100.0 mg, 0.18 mmol) and red mercuric oxide (150 mg, excess) in aqueous acetonitrile (14 mL, 10% H_2O in CH_3CN) at room temperature was added a solution of mercuric chloride (4.5 mL, 0.1 M $HgCl_2$ in CH_3CN). The creamy orange suspension was stirred for 30 min. Analytical TLC (50% ethyl acetate in hexanes) showed spots at R_f 0.32 (UV active, $HgCl_2$ residue), 0.15 (mixture of cyclized products), and 0.02 (keto triol). The reaction mixture was diluted by adding 20 mL of absolute ethyl ether followed by drying over anhydrous $MgSO_4$. After filtration through a bed of celite and concentration under reduced pressure, the oily concentrated solution was applied onto two (20 cm × 20 cm × 0.5 mm) preparative TLC plates eluted (three elutions) with 35% ethyl acetate in hexanes. Recovery from silica gel followed by evaporation yielded 30.9 mg (38.1%) of the mixture of 1,6-dioxaspiro[4.5]-decanes **17** and **16** in the ratio of 1:3 along with 35.0 mg (41.5%) of the uncyclized keto triol **15c**. Total yield was 80%.

The uncyclized keto triol **15c** was dissolved in 10 mL of methylene chloride at 0 °C followed by adding trifluoroacetic acid (3 μL). TLC after 1 min showed only cyclized products. Most of the solvent was evaporated at room temperature under reduced pressure and the product was isolated as before yielding 32.3 mg (96.0%) of isomeric 1,6-dioxaspiro[4.5]decanes **17** and **16** in the ratio of 1:6, respectively.

Similarly the minor product **15b** from desilylation (51.7 mg, 0.092 mmol) was subjected to identical procedures. The desulfurized products were purified as described above leading to similar results and ratios of isomeric products. These ketals are fully characterized by their spectroscopic data as described in subsequent experiments below.

Isomerization to Ketals 17a and 17b. To a stirred solution of the major isomeric ketal product **16a** (61.1 mg, 0.136 mmol) in 6.0 mL of methylene chloride at 0 °C (ice bath) under argon were added trifluoroacetic acid (100 μL, 1.3 mmol) and methyl magnesium chloride (2 M in tetrahydrofuran, 50 μL). The resulting suspension was stirred for 6 h. Analytical TLC (30% ethyl acetate in hexanes) showed a major product at R_f 0.08 along with the starting ketal at R_f 0.05. Addition of a saturated aqueous solution of Na_2H_2 EDTA (2.0 mL) gave a white voluminous precipitate almost instantaneously. The suspension was stirred an additional 30 min and then diluted with 20 mL of water followed by extraction with 20 mL of ethyl acetate. The aqueous phase was separated

(18) Specific rotation of the (−)-enantiomer of **13**.

and was back-extracted with a 20-mL portion of ethyl acetate. Organic layers were combined and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure at room temperature furnished a crude product, which was further purified by preparative TLC using two (20 cm × 20 cm × 0.25 mm) plates and two elutions with 30% ethyl acetate in hexanes yielding 38.2 mg (62.5%) of pure **17a** having the natural geometry at the spiro carbon: $[\alpha]^{22}_D$ +97.2° (*c* 0.955, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.90 (d, 1 H, *J* = 7.22 Hz), 4.72 (d, 1 H, *J* = 7.22 Hz), 4.47 (s, 2 H), 4.31 (dt, 1 H, *J* = 3.61, 5.05 Hz), 3.89 (t, 1 H, *J* = 11.6 Hz), 3.85 (m, 1 H), 3.82 (br d, 1 H, *J* = 2.89 Hz), 3.70 (ddd, 1 H, *J* = 3.61, 5.05, 11.5 Hz), 3.5–3.6 (m, 4 H), 3.36 (s, 3 H), 3.29 (dd, 1 H, *J* = 5.42, 8.66 Hz), 3.24 (dd, 1 H, *J* = 6.50, 8.66 Hz), 3.12 (br d, 1 H, *J* = 4.7 Hz, D_2O exch.), 2.14 (dd, 1 H, *J* = 2.89, 14.4 Hz), 1.98 (br dt, 1 H, *J* = 1.4, 14.1 Hz), 1.6–1.9 (m, 4 H), 1.88 (dd, 1 H, *J* = 3.25, 14.4 Hz), 1.2–1.4 (m, 3 H), 1.0–1.1 (m, 1 H), 0.90 (d, 3 H, *J* = 6.86 Hz); IR (film) 3510, 2930, 2870, 1235, 1160, 1100, 735 cm^{-1}; high-resolution MS (70 eV), *m/e* (no M^+), 91.055 (100), 374.210 (1), 314.188 (1), 279.160 (4), 254.094 (3), 232.147 (1), 219.124 (6), 167.034 (24), 148.988 (96), 113.133 (9); ^{13}C NMR ($CDCl_3$) δ 138.64, 128.24, 127.37, 101.10, 94.28, 83.20, 75.19, 74.58, 72.94, 72.60, 71.68, 66.78, 63.09, 58.98, 44.72, 37.08, 34.04, 31.40, 30.44, 26.54, 24.23, 12.75.

Additionally, the C-7 diastereomeric hydroxy ketal **16b** was treated in identical fashion affording the C-7 isomeric alcohol **17b**: $[\alpha]^{22}_D$ +92.4° (*c* 0.805, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.90 (d, 1 H, *J* = 7.22 Hz), 4.72 (d, 1 H, *J* = 7.22 Hz), 4.47 (s, 2 H), 4.31 (dt, 1 H, *J* = 3.97, 4.69 Hz), 3.89 (t, 1 H, *J* = 11.2 Hz), 3.85 (m, 2 H), 3.71 (ddd, 1 H, *J* = 3.97, 5.05, 10.5 Hz), 3.5–3.6 (m, 4 H), 3.37 (s, 3 H), 3.29 (dd, 1 H, *J* = 5.78, 8.66 Hz), 3.24 (dd, 1 H, *J* = 6.86, 9.03 Hz), 3.11 (br s, 1 H, D_2O exchange), 2.14 (dd, 1 H, *J* = 2.89, 14.4 Hz), 1.88 (dd, 1 H, *J* = 3.25, 14.4 Hz), 1.6–2.0 (m, 5 H), 1.2–1.4 (m, 3 H), 1.0–1.1 (m, 1 H), 0.90 (d, 3 H, *J* = 6.86 Hz); IR (film) 3510, 2920, 2870, 1235, 1110, 1100, 740 cm^{-1}; high-resolution MS (70 eV), *m/e* (no M^+), 410.318 (9), 91 (100), 149 (96); ^{13}C NMR ($CDCl_3$) δ 138.66, 128.26, 127.40, 101.12, 94.30, 83.24, 75.22, 74.61, 72.97, 72.61, 71.71, 66.81, 63.12, 59.01, 44.76, 37.11, 34.07, 31.44, 30.47, 26.58, 24.27, 12.77.

Jones' Oxidations of Alcohols 16 and 17. A diastereomeric mixture of alcohols **17a** and **17b** (51.1 mg, 0.114 mmol) was added to 8.0 mL of reagent grade acetone at room temperature. To this vigorously stirred solution was added 80 μL of 3.0 M Jones' reagent. Stirring was continued for 45 min. Analytical TLC (30% ethyl acetate in hexanes) showed complete disappearance of starting materials while a less polar spot at R_f 0.20 was formed as the sole product. Excess of Jones' reagent was destroyed by adding 3–5 drops of isopropyl alcohol. After addition of 8.0 mL of reagent grade acetone, the reaction mixture was filtered through a bed of celite. Evaporation under reduced pressure furnished a pale yellow oil, which was purified by prep TLC using two (20 cm × 20 cm × 0.25 mm) plates with 20% ethyl acetate in hexanes (two elutions) yielding 38.8 mg of pure ketone **19**: $[\alpha]^{22}_D$ +64.9° (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 4.87 (d, 1 H, *J* = 7.2 Hz), 4.75 (d, 1 H, *J* = 7.2 Hz), 4.49 (s, 2 H), 3.95 (q, 1 H, *J* = 3.61 Hz), 3.90 (ddd, 1 H, *J* = 3.61, 6.50, 10.83 Hz), 3.79 (t, 1 H, *J* = 10.8 Hz), 3.70 (ddd, 1 H, *J* = 3.61, 5.42, 10.83 Hz), 3.48–3.55 (m, 3 H), 3.35 (s, 3 H), 3.34 (dd, 1 H, *J* = 3.61, 7.58 Hz), 3.27 (dd, 1 H, *J* = 6.50, 9.03 Hz), 2.37 (m, 1 H), 2.2 (br d, 1 H, *J* = 14.8 Hz), 2.01 (dd, 1 H, *J* = 3.25, 14.1 Hz), 1.95 (dd, 1 H, *J* = 3.97, 14.4 Hz), 1.8–1.9 (m, 5 H), 1.40 (m, 1 H), 1.28 (m, 1 H), 1.07 (m, 1 H), 0.93 (d, 3 H, *J* = 7.22 Hz); IR (film) 2922, 2860, 1762, 1450, 1200, 1100, 940, 700 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 211.76, 138.46, 128.24, 127.41, 127.36, 98.77, 94.58, 75.10, 72.96, 72.30, 71.66, 66.86, 63.05, 58.96, 43.38, 33.65, 33.25, 31.54, 30.15, 27.09, 23.31, 12.50.

Alcohols **16a,b** bearing the unnatural configuration at C-8, were treated with Jones' reagent as described above affording 82% of ketone **18**: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 4.78 (d, 1 H, *J* = 6.86 Hz), 4.75 (d, 1 H, *J* = 6.86 Hz), 4.51 (s, 2 H), 4.28 (dd, 1 H, *J* = 4.33, 4.69 Hz), 4.16 (dt, 1 H, *J* = 5.05, 11.9 Hz), 4.07 (dd, 1 H, *J* = 2.2, 11.6 Hz), 3.7 (m, 2 H), 3.59 (dd, 1 H, *J* = 1.4, 11.6 Hz), 3.55 (m, 2 H), 3.39 (s, 3 H), 3.35 (m, 2 H), 2.4 (m, 1 H), 2.0–2.1 (m, 4 H), 1.90 (t, 1 H, *J* = 12.3 Hz), 1.70–1.80 (m, 3 H), 1.50–1.65 (m, 2 H), 1.10 (d, 3 H, *J* = 6.86 Hz); IR (film) 2925, 2860, 1760, 1450, 1100, 940, 700 cm^{-1}.

Hydrogenolysis of Benzyl Ether 19. Benzyl ether **19** (50.9 mg, 0.113 mmol) was dissolved in 12 mL of distilled ethyl acetate in a 35-mL single-neck round-bottom flask fitted with a T-shape three-way stopcock. To this stirred solution was added 10% palladium–charcoal (75 mg) followed by cooling in a dry ice–acetone bath. The flask was then evacuated followed by purging with hydrogen gas. Hydrogenolysis preceeded at room temperature for 45 min. Analytical TLC (50% ethyl acetate in hexanes) showed complete disappearance of starting material while a single polar product was formed at R_f 0.06. The suspension was diluted with an equal volume of ethyl acetate followed by filtration through a bed of celite. The filtrate was concentrated under reduced pressure to give 33.3 mg (82.2%) of **19a**: $[\alpha]^{23}_D$ +59.1° (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.88 (d, 1 H, *J* = 7.22 Hz), 4.75 (d, 1 H, *J* = 7.22 Hz), 4.57 (dt, 1 H, *J* = 2.53, 3.97 Hz), 3.93 (m, 2 H), 3.80 (t, 1 H, MS = 11.2 Hz), 3.71 (ddd, 1 H, *J* = 3.97, 5.05, 10.5 Hz), 3.51 (m, 5 H), 3.38 (s, 3 H), 2.39 (ddd, 1 H, *J* = 4.33, 6.86, 11.2 Hz), 2.23 (br d, 1 H, *J* = 14 Hz), 2.03 (dd, 1 H, *J* = 3.61, 14.4 Hz), 1.96 (dd, 1 H, *J* = 3.97, 14.4 Hz), 1.75–1.85 (m, 4 H), 1.53 (t, 1 H, *J* = 5.42 Hz, D_2O exchange), 1.34 (m, 2 H), 1.03 (m, 1 H), 0.93 (d, 3 H, *J* = 6.86 Hz); IR (film) 3500, 2920, 2880, 1765, 1445, 1175, 1100, 730 cm^{-1}; MS (70 eV), *m/e* (no M^+), 89.05 (100), 113.15 (19), 131.15 (3), 219 (10); ^{13}C NMR ($CDCl_3$) δ 211.68, 98.76, 94.84, 72.63, 72.27, 71.57, 67.66, 66.68, 63.00, 58.99, 43.31, 33.75, 33.64, 33.44, 29.86, 26.54, 23.29, 12.50.

Preparation of Methyl Ester 20. A stirred solution of alcohol **19a** (31.2 mg, 0.087 mmol) in 8.0 mL of reagent acetone was combined with Jones' reagent (3.0 M, 100 μL) forming a deep brown solution, which was stirred at room temperature for 30 min. TLC analysis (75% ethyl acetate in hexanes) showed a very polar spot at R_f 0.15 as a sole product. After dilution with an equal volume of reagent acetone followed by filtration through a bed of celite, the filtrate was concentrated under reduced pressure to give a crude oil, which was further purified by preparative TLC (two 10 cm × 20 cm × 0.25 mm plates) eluted 3 times with 50% ethyl acetate in hexanes. Recovery from silica gel followed by evaporation gave 31.0 mg (95%) of carboxylic acid. Esterification upon addition of ethereal diazomethane was nearly instantaneous (TLC analysis in 75% ethyl acetate in hexanes showed the less polar methyl ester, R_f 0.50).

Evaporation of solvent afforded the methyl ester **20**: $[\alpha]^{21}_D$ +59.8° (*c* 1.265, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.88 (d, 1 H, *J* = 7.22 Hz), 4.77 (d, 1 H, *J* = 7.22 Hz), 4.58 (dt, 1 H, *J* = 2.89, 3.61 Hz), 3.92–3.98 (m, 2 H), 3.80 (t, 1 H, *J* = 10.8 Hz), 3.69 (s, 3 H), 3.69 (m, 1 H), 3.56 (m, 2 H), 3.50 (dd, 1 H, *J* = 4.33, 11.2 Hz), 3.37 (s, 3 H), 2.57 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.40 (br d, 1 H, *J* = 10 Hz), 1.7–2.1 (m, 6 H), 1.25–1.50 (m, 3 H), 0.93 (d, 3 H, *J* = 6.86 Hz); IR (film) 2950, 2880, 1755, 1735, 1435, 1255, 1100, 775 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 210.90, 175.55, 98.71, 94.82, 72.55, 71.61, 71.49, 66.84, 62.97, 58.91, 51.66, 42.35, 36.55, 33.58, 33.23, 29.13, 26.08, 22.57, 12.45; MS (70 eV), *m/e* (no M^+), 113.15 (100), 281.20 (1), 108.05 (34), 219.15 (62), 311 (1).

Conversion to Alcohol 21. Excess $ZnBr_2$ (25 mg, free-flowing powder) was added to a vigorously stirred solution of **20** (25.1 mg, 0.065 mmol) in dry methylene chloride (6.0 mL) under argon at room temperature. The suspension turned from colorless to a very pale orange after stirring for about 2 h. TLC (20% ethyl acetate in hexanes, two elutions) showed a single spot at the same R_f 0.14 as the starting material. The reaction was quenched by adding a saturated aqueous solution of Na_2H_2 EDTA (4.0 mL) and ethyl acetate (10 mL). After the white suspension was stirred for 30 min, the aqueous layer (with undissolved white suspension) was separated and back-extracted with 4.0 mL of ethyl acetate. Organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrated crude oil was purified on one (10 cm × 20 cm × 0.5 mm) silica plate eluted 3 times with 30% ethyl acetate in hexanes yielding 18.3 mg (100%) of pure **21**: $[\alpha]^{21}_D$ +60.4° (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.61 (dt, 1 H, *J* = 2.89, 3.97 Hz), 3.91 (dq, 1 H, *J* = 2.8, 10.1 Hz), 3.73 (t, 1 H, *J* = 11.6 Hz), 3.70 (s, 3 H), 3.52 (dd, 1 H, *J* = 5.05, 11.9 Hz), 2.80 (d, 1 H, *J* = 9.75 Hz, D_2O exchange), 2.62 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.43 (ddd, 1 H, *J* = 4.33, 7.22, 11.6 Hz), 2.36 (ddd, 1 H, *J* = 2.53, 4.33, 15.2 Hz), 2.18 (dd, 1 H, *J* = 3.25, 14.4 Hz), 1.83–2.05 (m, 4 H), 1.78 (dd, 1 H, *J* = 3.25, 14.1 Hz), 1.25–1.50 (m, 2 H), 0.93 (d, 3 H, *J* = 6.86 Hz); IR (film) 3552, 2950, 1765, 1733, 1245, 1050, 775 cm^{-1}; MS (70 eV), *m/e* (no M^+), 131.05 (100), 43.05 (25), 71.05 (62), 80.05 (33), 113.05 (36); ^{13}C NMR ($CDCl_3$) δ 209.50, 175.36, 99.38, 72.45, 67.28, 61.91, 51.84, 42.32, 36.60, 36.03, 34.24, 29.21, 26.08, 22.85, 13.03.

Formation of Epoxide 22. Sodium hydride (210 mg, 56.8% in mineral oil, 5 mmol) was added to a flame-dried two-neck 25-mL round-bottom flask and washed with anhydrous ether under argon at room temperature. Dry dimethyl sulfoxide (10 mL) was added via syringe followed by addition of vacuum dried (0.5 mmHg at 56 °C, 14 h) trimethylsulfoxonium iodide (1.10 g, 5 mmol) in a single portion. An exotherm subsided after the mixture was stirred at ambient temperature for 20 min forming a clear solution. This reagent was found to be stable and remained active after storing in the frozen state at −20 °C for over 6 months.

To a stirred solution of **21** (19.1 mg, 0.064 mmol) in 1.0 mL of dry tetrahydrofuran at room temperature under argon was added 500 μL of the stock solution of dimethylsulfoxonium methylide (0.5 M in Me_2SO) forming a yellowish suspension. After 10 min at room temperature, TLC (20% ethyl acetate in hexanes, eluted twice) indicated complete absence of starting ketone with a single new product at R_f 0.08. Reaction was quenched by adding 1 mL of water and 1 mL of NH_4Cl(aq) saturated solution and 5 mL of ethyl acetate. The aqueous layer was separated

followed by back-extraction with 5 mL of ethyl acetate. Organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude oil, which solidified on standing at room temperature. Further purification by preparative TLC using one (10 cm × 20 cm × 0.5 mm) plate with two elutions of 30% ethyl acetate in hexanes yielded 18.3 mg (91.6%) of pure epoxide **22**: mp 104 °C (sealed capillary); $[\alpha]^{26}_D$ +143.9° (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.44 (q, 1 H, *J* = 3.61 Hz), 3.81 (dq, 1 H, *J* = 2.53, 10.1 Hz), 3.73 (t, 1 H, *J* = 11.6 Hz), 3.69 (s, 3 H), 3.38 (dd, 1 H, *J* = 4.69, 11.6 Hz), 3.16 (d, 1 H, *J* = 10.1 Hz, D_2O exchange), 2.93 (s, 2 H), 2.63 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.30 (ddd, 1 H, *J* = 2.53, 4.33, 14.8 Hz), 1.96–2.06 (m, 2 H), 1.854 (dd, 1 H, *J* = 2.89, 14.4 Hz), 1.60 (dd, 1 H, *J* = 3.25, 14.4 Hz), 1.6–1.4 (m, 3 H), 1.24–1.50 (m, 2 H), 0.89 (d, 3 H, *J* = 6.86 Hz); IR (KBr pellet) 3510, 2950, 1734, 1440, 1165, 1110, 1055, 950, 855 cm^{-1}; MS (70 eV), *m/e* (no M^+), 71.10 (100), 191.10 (9.3), 182.20 (71.1), 164.20 (33), 140.10 (38), 131.10 (86), 113.10 (49), 81.1 (47); ^{13}C NMR ($CDCl_3$) δ 175.95, 103.52, 73.81, 70.43, 68.01, 62.35, 51.68, 49.83, 38.14, 37.13, 36.69, 34.48, 29.60, 26.31, 22.03, 13.02.

(+)-Synthetic Phyllanthocin (1). To a solution of epoxide **22** (17.7 mg, 0.058 mmol) in 2.0 mL of dry methylene chloride under argon in a 10-mL round-bottom flask fitted with a condenser was added excess anhydrous 4-(dimethylamino)pyridine (25 mg) followed by 20 mg of freshly distilled cinnamoyl chloride. This yellow solution was stirred at room temperature for 10 min then warmed to reflux under argon. A white precipitate was formed with refluxing for 8 h. TLC analysis showed a new product at R_f 0.41. After it was quenched with aqueous saturated NH_4Cl solution (2 mL) and ethyl acetate (10 mL), the aqueous phase was separated and back-extracted twice with 5.0 mL of ethyl acetate. Organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude brown product, which was further purified on two (20 cm × 20 cm × 0.25 mm) TLC plates eluted 3 times with 30% ethyl acetate in hexanes. Recovery from silica gel followed by evaporation furnished a crystalline (+)-phyllanthocin **1**, 18.6 mg (72.6%): mp 118–120 °C uncorrected (pentane); $[\alpha]^{24}_D$ +24.9° (*c* 1.86, $CHCl_3$); ^1H NMR 360 MHz ($CDCl_3$) δ 7.76 (d, 1 H, J = 15.9 Hz), 7.53 (m, 2 H), 7.38 (m, 3 H), 6.48 (d, 1 H, *J* = 15.9 Hz), 5.09 (br q, 1 H, *J* = 2.89 Hz), 4.39 (q, 1 H, *J* = 3.43 Hz), 4.02 (t, 1 H, *J* = 11.2 Hz), 3.45 (dd, 1 H, *J* = 4.33, 10.8 Hz), 3.28 (s, 3 H), 2.97 (d, 1 H, *J* = 5.42 Hz), 2.92 (d, 1 H, *J* = 5.42 Hz), 2.42 (tt, 1 H, *J* = 3.61, 11.9 Hz), 2.23 (br d, 1 H, *J* = 14.4 Hz), 2.04 (dd, 1 H, *J* = 2.89, 15.2 Hz), 1.84–2.00 (m, 3 H), 1.72 (ddd, 1 H, *J* = 3.61, 12.3, 14.8 Hz), 1.63 (dd, 1 H, *J* = 3.25, 15.2 Hz), 1.60 (m, 1 H), 1.35 (dq, 1 H, *J* = 3.61, 13.7 Hz), 1.22 (dq, 1 H, *J* = 3.25, 14.8 Hz), 0.88 (d, 3 H, *J* = 6.86 Hz); IR (KBr pellet) 2950, 1720, 1700, 1635, 1625, 1445, 1434, 1357, 1292, 1287, 1248, 1200, 1167, 1120, 1050, 1020, 988, 978, 945, 898, 763, 705, 678, 618; UV λ_{max} (ε) 202 (15 100), 214 (15 400), 220 (13 000), 274 (20 100); ^{13}C NMR 90 mHz ($CDCl_3$) δ 176.08, 166.64, 144.43, 134.64, 129.97, 128.73, 127.98, 118.91, 101.98, 72.65, 71.12, 69.83, 63.00, 51.21, 50.23, 38.63, 36.86, 34.37, 33.11, 29.94, 26.54, 22.22, 12.79.

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Supplementary Material Available: A complete listing of experimental procedures, proton and carbon NMR, infrared, mass spectral data, rotations, and combustion analyses for remaining compounds of Schemes I and II (5 pages). Ordering information is given on any current masthead page.

Total Synthesis of a Macrocyclic Pyrrolizidine Alkaloid, (±)-Integerrimine, Utilizing an Activable Protecting Group

Koichi Narasaka,* Toshiyasu Sakakura, Tadafumi Uchimaru, and Denis Guédin-Vuong

Contribution from the Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan. *Received October 11, 1983*

Abstract: A new esterification reaction has been developed utilizing a (methylthio)methyl (MTM) group as an activable protecting group of carboxylic acid. A total synthesis of a 12-membered pyrrolizidine alkaloid, (±)-integerrimine (**1**), has been achieved by applying the above method to formation of the macrocyclic bislactone skeleton. The acid anhydride (**16b**) of the integerrinecic acid derivative was coupled with lithium alkoxide of retronecine silyl ether (**5b**) in the presence of DMAP to afford the α,β-unsaturated ester. Oxidation of the MTM group afforded an active (methylsulfonyl)methyl ester (**28b**), which cyclized to give the macrocyclic bislactone **29**.

Large-ring bislactonic pyrrolizidine alkaloids, which display diverse biological activities, have attracted much interest as synthetic targets due to their characteristic tricyclic bislactonic structures.[1,2] These macrocyclic pyrrolizidine alkaloids generally consist of necine base (pyrrolizidine diol) and necic acid (long-chain diacid) components, combined through ester linkages. Although syntheses of the pyrrolizidine moiety of these alkaloids have been widely studied, a successful total synthesis of a macrocyclic pyrrolizidine alkaloid had not been reported when we first commenced this work in spite of the recent rapid progress made in macrolide synthesis. We therefore sought to develop a strategy for the synthesis of macrocyclic pyrrolizidine alkaloids.

During the course of our studies, a few examples have been reported concerning the formation of 11-membered bislactonic skeletons.[3] As a model study, Robins demonstrated that the formation of a large-ring bislactone proceeds efficiently utilizing the Corey–Mukaiyama method.[3a] And they successfully applied

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