CHEMICAL MODIFICATIONS OF THE MACROCYCLIC TRICHOTHECENES, BACCHARINOID B4 AND MYROTOXIN B

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A series of chemical modifications have been made to the Brazilian plant-derived macrocyclic trichothecene, baccharinoid B4 (1) and the fungal-produced macrocyclic trichothecene, myrotoxin B (12). The C8-thionocarbonate of 1 upon thermolysis gave a novel A-ring modified trichothec-8-ene 6 and the trichothec-7,9-diene 4a. The enol ether double bond in 12 underwent electrophilic addition reactions with a variety of electrophiles (H_3O^+, BrOH, IN_3, and INCO), and when treated with base (DBU), the iodo azide adduct 21 gave diene 24. Cytotoxicity data are given for these new compounds.

INTRODUCTION

Much of what is known today in the area of phytochemical diversity and function in Brazilian plants can be traced to the work of Otto Gottlieb and his associates[1]. One of the axioms in this discipline is that the secondary metabolites found in plants are a reflection of the plants' evolutionary relationships, particularly in the case of unusual structure types that are found localized in species within a specific plant genera. The task of sorting out chemosystematic relationships is daunting since many secondary metabolites are produced only under specific environmental conditions and then often only in very small amounts. On the other hand, natural products chemists have isolated enough structure types from plants and cultures of microorganisms to give them a general idea of the type of compounds to expect (and not to expect) from a given source. When compounds well known from one source, turn up in a totally unrelated source (e.g. giberellins first found in fungi but later found to be plant metabolites and prostaglandins first isolated from mammalian systems then later found in sea corals), the community is somewhat surprised. Nonetheless, certain structure types appear to be the province of microorganisms and are not produced by the higher plants, e.g. penicillins. It therefore came as a surprise in 1976, when Kupchan et al.[2] reported that a Brazilian plant, *Baccharis megapotamica* contained a series of highly toxic antibiotics belonging to a well known class of mycotoxins called the trichothecenes. Heretofore, trichothecenes had been isolated only from fungal cultures. In addition, these toxins are notoriously phytotoxic,[3] and yet, *B. megapotamica* was neither visibly contaminated by fungi nor was the plant in any way suffering any apparent distress. Several years later, other workers found that a related Brazilian plant, *B. Coridifolia* containded trichothecenes of similar structure[4]. This latter species is known locally as "mio-mio" and is considered one of the most agriculturally important toxic plants in Brazil and Argentina[5]. Its toxicity can clearly be traced to the presence of these potent toxins,[6] particularly in the flowering female plants[7].

In recent years, we have published a good deal about the phytochemistry of Brazilian *Baccharis* as it is related to the presence of trichothecenes[7-12], but have found no other examples (from over 20 additional *Baccharis* species examined) of additional trichothecene-containing *Baccharis* species[11].

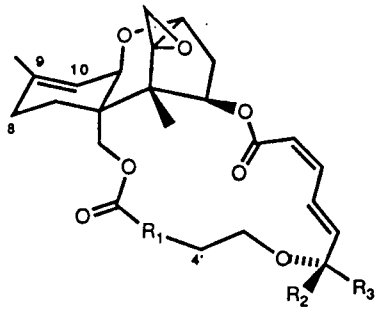
As part of a program to develop clinically useful anticancer agents from plant sources, we performed a large scale extract of *B. megapotamica* in order to isolate large quantities of the trichothecenes (called baccharinoids) found in this plant[13]. The original aim was to reisolate baccharinoid B5 which had exhibited high *in vivo* antileukemic activity, but in the process, we also isolated large amounts of baccharinoid B4 (1). Since one of the targets in this laboratory has been to develop anticancer agents through chemical modifications of the macrocyclic trichothecenes[14-16] we have used baccharinoid B4 (1) as a starting material for this modification work. Also available to us are the myrotoxins[17] which are particularly potent toxic macrocyclic trichothecene metabolites[18] of a plant pathogenic fungus, *Myrothecium roridum*. Herein, we report some of the novel reactions of 1 and myrotoxins A and B.

RESULTS AND DISCUSSION

The baccharinoids are closely related in structure to the roridins and verrucarins which are metabolites of the fungus *Myrothecium*[19]. The most striking feature of the baccharinoids *cf.* the roridins and the verrucarins (Fig. 1) is that many of the baccharinoids exhibit excellent *in vivo* activity against murine P-388 leukemia; whereas, at best, the roridins and verrucarins exhibit only marginal activity[16]. This difference in anticancer activity can be traced to the presence of either an 8β-hydroxyl group or a 9β,10β-epoxide in the baccharinoids; introduction of these functionalities into the roridins and verrucarins transforms these compounds into highly active *in vivo* P-388 agents[14,15].

Since the introduction of these oxygen functionalities into the corresponding C8α and C9α,C10α positions of the roridins and verrucarins did not effect the *in vivo* P-388 activity[14,15] it is clear that subtle changes in the substitution pattern of the A-ring can bring about marked changes in *in vivo* anticancer activity. We therefore sought to alter the position of the 9,10-double bond (and the corresponding epoxide) to the 8,9-position. A seemingly simple type of reaction to this end would appear to be the treatment of 1 with an electrophile (e.g. Br^+) to generate the C9 cation, which, under suitable conditions should react with the C8-OH to give the 8β,9β-epoxide. However, all attempts to carry out this con-

version (NBS, CH_3CN, pyridine; PhSeCl, *n*-BuLi, THF) gave only the corresponding C8 ketone[20]. Treatment of the C8 *t*-butyldimethylsilyl ether with NBS and silver fluoride in THF gave recovered baccharinoid B4 (**1**). Treatment of the triacetate of baccharinoid B4 with $Pd(AcO)_2$, *n*-BuLi, and Ph_3P, with[21] or without[22] added diethylamine also gave no sign of formation of the C8,C9 double bond regioisomer.

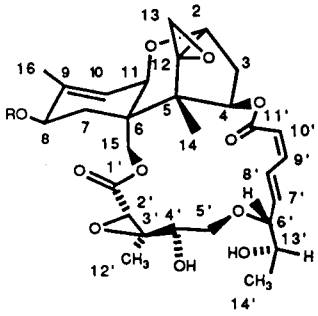


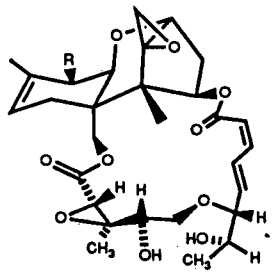
Roridin A: R_1 = CHOHCHCH$_3$; R_2 = H; R_3 = CHOHCH$_3$
Baccharinoid B4: R_1 = CH-CCH$_3$; R_2 = H; R_3 = CHOHCH$_3$; 4',8-OH's
Roridin D: R_1 = CH-CCH$_3$; R_2 = H; R_3 = CHOHCH$_3$
Roridin E: R_1 = CH=CCH$_3$; R_2 = H; R_3 = CHOHCH$_3$
Verrucarin A: R_1 = CHOHCHCH$_3$; R_2, R_3 = O
Verrucarin J: R_1 = CH=CCH$_3$; R_2, R_3 = O

Figure 1. *Structures of macrocyclic trichothecenes.*

We next turned to [3,3]-sigmatropic rearrangement reactions as a possible entry. The idea was to append an appropriate group to the C8-hydroxyl which upon heating would rearrange to the C10 position with concomminant formation of a double bond at the C8,C9 position. Allylic trichloroimidates are reported to undergo such a rearrangement under thermal conditions[23], and to this end, the trichloroimidate **2** was prepared by the selective reaction at the C8-OH of **1** with trichloroacetonitrile and sodium hydride at low temperature. Thermolysis of **2** in refluxing toluene led principally to the slow decomposition of **2**, with only trace amounts of the rearranged trichloroacetamide **3** and diene **4a** formed. More successful was the rearrangement of the thionocarbonate **5**, prepared by the reaction of 1 with phenychlorothionoformate [PhOC(S)Cl]at O°C; again, selectivity for reaction at the C8-OH was observed. Allylic thionocarbonates normally rearrange at lower temperatures (e.g. 10°C[24] *cf.* 100°C for thionoesters[25]), but thionocarbonate **5** was thermally stable at temperatures below 100°C. In refluxing toluene, **5** rearranged to give **6** and diene **4a**, in 30% and 9% iso-lated yield, respectively.

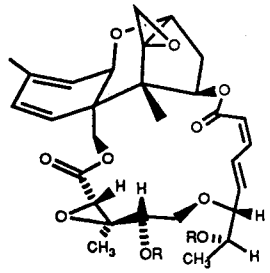
Attempts to hydrolyze the C10-thiocarbonate group in **6** were unsuccessful. When treated at room temperature for 1 hr with concentrated ammonium hydroxide[26] **6** was recovered unchanged. Prolonged reaction times or increasing the reaction temperature led to significant cleavage of the macrolide ring. Interestingly, the C8-phenyl carbonate of **1** (where R = OC(O)OPh) readily reacts with concentrated ammonium hydroxide at room temperture to give the corresponding urethan (**1**, where R = $OC(O)NH_2$). Use of normal hydrolysis conditions (e.g. 0.1-1 M perchloric acid and 0.1-1 M sodium





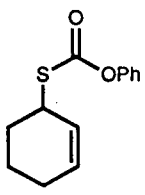
1: R = H
2: R = C(NH)CCl$_3$
5: R = C(S)OPh

3: R = NHC(O)CCl$_3$
6: R = SC(O)OPh



4a: R = H
4b: R = Ac

hydroxide at room temperature) or soft acid catalyzed conditions (e.g. Ag^+ and Hg^+)[27] led only to extensive cleavage of the macrolide ring system. An attempt to remove the thiol group by treating **6** with *meta*-chloroperoxybenzoic acid (MCPBA) gave extensive decomposition, and the only isolable product (10% yeld) was the corresponding 8,9-epoxide, whose stereochemistry was not determined due to a lack of material. The thiolcarbonates **7** and **8** when treated with MCPBA gave only phenol in the organic extract of the aqueous sodium bicarbonate layer, presumably due to the oxidation of remainder of the molecules to water soluble sulfonic acids[28]. The thiolcarbonates **7** and **8** were prepared by treating 2-cyclohexen-1-ol and 1-phenyl-2-propen-1-ol, respectively, with phenylchlorothionoformate at room temperature; the intermediate thionocarbonates rearrante to **7**and **8** under the conditions of the reactions.



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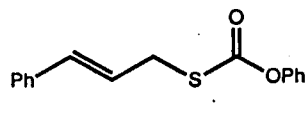

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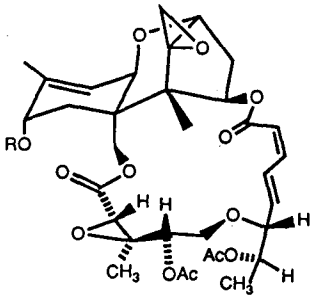
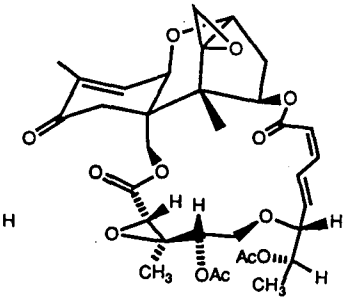
From a stereoelectronic perspective, it would appear that the [3,3]-sigmatropic rearrangement of a C8α-thionocarbonate might bemore efficacious since orbital overlap in the transition state of this axial substituent would be more sub-stantial with the π-orbital of the 9,10-double bond. The C8α-thionocarbonate **10** was prepared (PhOC(S)Cl, 25°C) from the corresponding alcohol **9** available from the reduction of the keto-

ne diacetate **11** with sodium borohydride in methanol at room temperature. Minor amounts of the C8b-OH isomer and the corresponding 9,10-dihydro C8β-alcohol also were formed. The hydroxyls at C4' and C13' were first ace-tylated in the C8 ketone of baccharinoid B4 (**1**)[29] since the 8α-OH is the least reactive of the hydroxyl groups in **1**. Interestingly, when heated in refluxing toluene, **10** gave only diene **4b**, and none of the 8,9-rearranged isomer was observed. It would appear that the macrolide ring sterically inhibits an axial 8α-thionocarbonate group from attaining a proper orientation with respect to the 9,10-π bond in order to undergo the [3,3]-sigmatropic rearrangement. Large substituents at the the C8α and C15 positions tend to force (because of 1,3-diaxial interactions) the A-ring into a half boat conformation which would favor a syn-elimination leading to **4b**.



9: R = H
10: R = C(S)OPh



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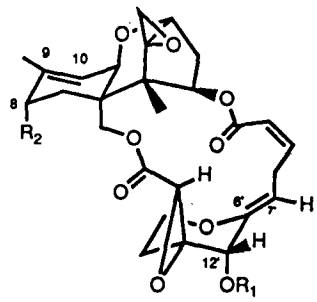
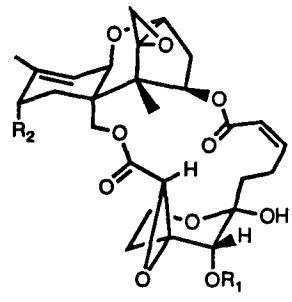
The myrotoxins[17] are among the most toxic of the trichothecenes, with $LD_{50's}$ (in mice) well below 1 mg/kg[18]. Like the satratoxins[30] and the roritoxins[31] the macrolide ring in the myrotoxins is modified through a linkage between C6' and C12' resulting in the formation of a tetrahydropyran ring. However, the myrotoxins have the novel feature of being enol ethers as well, and the C6',C7'-enol ether is an obvious target for modification due to the expected reactivity of such functionality.

The C6',C7'-double bond is reactive toward various electrophilic additions including: hydration, epoxidation, and addition of "BrOH", "IN_3", and "INCO". Myrotoxin B (**12**) reacted with dilute HCl in aqueous THF at 50°C to give myrotoxin B hydrate (**15**), but myrotoxin B diacetate (**14**) was recovered unchanged under these conditions; diacetate **17** was produced by the acetylation (Py/Ac_2O) of **15**. Treatment of **12** with MCPBA in the presence or absence of sodium bicarbonate led only to the formation of the *m*-chlorobenzoate **18**, presumably formed from the ready opening of the intermediate 6',7'-epoxide under the conditions of the reaction. Neither of the remaining double bonds in **18** underwent further reaction with MCPBA. Although the 9,10-double bond in **18** is no doubt deactivated by the C8-OAc group, this double bond in myrotoxin A hydrate (**16**), synthesized by hydration of myrotoxin A (**13**) proved surprisingly unreactive toward epoxidation. Under conditions where both verrucarin A and baccharinoid B4 are completely epoxidized (MCPBA, CH_2Cl_2, 24 hr), **16** gave only about a 10% yield of epoxide **19**.

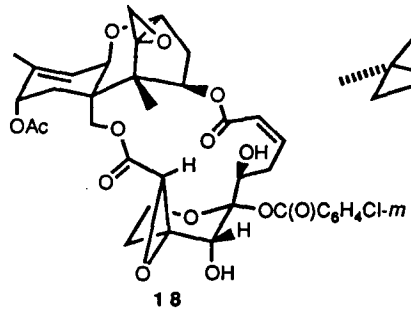
Myrotoxin B (**12**) formed the iodo isocyanate **20**, following the procedure of Hassner (I_2 + AgNCO in CH_2Cl_2)[32], but only in low yield. We employed similar methodology (ICl + NaN_3 in CH_3CN)[33] to synthesize the iodo azides **21** (major product) and **22** (minor product) in good



12: R_1 = H; R_2 = OAc
13: R_1 = R_2 = H
14: R_1 = Ac; R_2 = OAc



15: R_1 = H; R_2 = OAc
16: R_1 = R_2 = H
17: R_1 = Ac; R_2 = OAc



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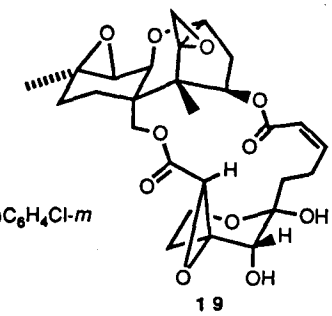

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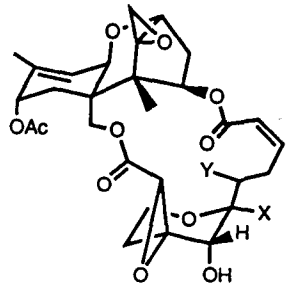
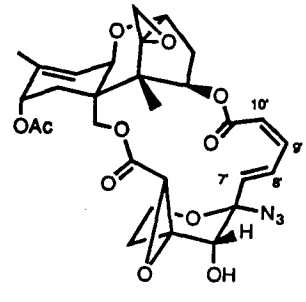
yield. When treated with N-bromosuccinimide (NBS) in aqueous DMSO, **12** gave the bromohydrin **23** in 65% yield. The stereochemical assign-ments for **20-23** are based on assumption that the attacking electrophile ("I^+" or Br+") will approach from the less hindred bottom-face of the enol double bond. When treated with DBU in THF at 50°C, azide **21** gave diene **24**. The large $J_{7',8'}$ (15 Hz) value in the ^{1}H-NMR spectrum of **24** confirms the *trans*-stereochemistry of this new double bond. However, the low coupling constant for the 8',9'-protons ($J_{8',9'}$ = 6.7 Hz in **24** *cf.* 11 Hz in typical macrocyclic trichothecenes) indicates that the diene system has



20: X = NCO; Y = β-I
21: X = N_3; Y = β-I
22: X = N_3; Y = α-I
23: X = OH; Y = β-Br



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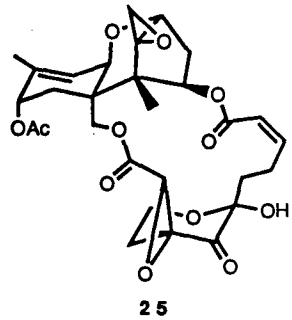

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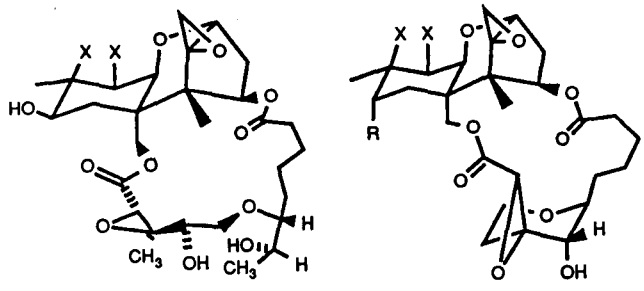
an appreciable twist. Consistent with this twist is the observed λmax at 250 nm for **24**; whereas, this absorption is normally found at 260 nm is the macrocyclic trichothecenes. The strain introduced into this diene system helps to explain our inability to isomerize the 6',7'-double bond, in myrotoxin B, to the 7',8'-position where it would be conjugated to the α,β-unsaturated lactone group. Treatment of myrotoxin B (**12**) with a variety of reagents (strong bases and various transition metal catalysts) all failed to give any indication of the formation of an 7',8'-double bond isomer of **12**. When treated with DBU under the same conditions, bromohydrin **23** unexpectedly underwent a novel rearrangement to give ketone **25**[34].

Baccharinoid B4 (**1**) and myrotoxin B (**12**) were hydrogenated to give their tetrahydro and hexahydro derivatives (**26-29**). Under conditions sufficient to hydrogenate the 9,10-double bond of myrotoxin B, the C8 -acetoxy group is hydrogenolyzed to give **29**. Cytotoxicities (ED_{100}'s in baby hamster kidney cells)[35] of these and a number of the other derivatives reported in this paper are presented in Table 1. In general, hydrogenation and epoxidation gave less cytotoxic derivatives; whereas, the B4 diene derivative **4a** and the rearranged thio carbonate **6** exhibit cytotoxicities close to that of baccharinoid B4. It is clear from these data as well as those of Jeker and Tamm[36] that significant changes can take place in the structures of macrocyclic trichothecenes without a marked loss in biological activity.



26: X = –
27: X = H

28: R = OAc; X = –
29: R = X = H

Table 1. ED_{100} in Baby Hamster Kidney Cells of Macrocyclic Trichothecene Derivatives.

Compound	$ED_{100(ng/ml)}$
Verrucarin A	14
3'-Hydroxy T-2 Toxin	4.6
1	120
9β,10β-Epoxy B4	1100
4a	41
6	120
12	1.5
15	4.6
19	3300
24	14
26	3300
27	1100
28	120
29	4.6
Triacetate of **27**	370
Baccharinoid B5	41

EXPERIMENTAL

General

Melting points (uncorrected) were determined on a Fisher-Johns apparatus. Infrared (IR) spectra were recorded in chloroform on a Perkin-Elmer 281 or 298, using polystyrene (1601.8 cm^{-1}) as a reference; FTIR spectra were registered on a Nicolet 5DXC spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ on either a Bruker AM-200 using either δ 0.00 signal of tetramethylsilane or the δ 7.24 signal of chloroform as an internal standard. 2D-COSY spectra were obtained on a Bruker AM-400 spectrometer, ^1H-NMR chemical shift were assigned by homonuclear (^1H-^1H) COSY 45, (^1H-^1H) COSY 90 and/or by decoupling techniques. ^{13}C-NMR signals were assigned by using INEPT and by comparison of chemical shifts data with those in the literature. The δ 77.0 signal of deuteriochloroform was used as an internal standard. Mass espectra data were collected on a VG 7070E mass spectrometer using direct chemical ionization (DCI) probe in the chemical ionization mode.

Filtration and flash chromatographies were done with flash grade silica gel (230-400 mesh, E. Merck) in a sintered glass funnel or glass columns. Thin-layer chromatography (TLC) was performed on precoated TLC plates of either silica gel 60F-254 (0.2 mm), aluminum oxide 150F-254 (0.2 mm), or amino F-254S (0.2 mm). Visualization was done by viewing the developed plates under short wavelength UV light or by spraying with vanillin spray [40 g/L vanillin in ethanol-sulfuric acid (1:4)]. Preparative TLC was achieved on the Model 7942 Chromatotron (Harrison Research Laboratories) and preparative HPLC was done employing an Altex Model 332 high performance liquid chromatograph. The Chromatotron plates of 1-, 2-, or 4-mm thickness were prepared according to the instructions in the manual using E. Merck silica gel.

The general procedure for acetylation consisted of dissolving the alcohol in excess amounts of acetic anhydride and pyridine. Typically, 10 mg of trichothecene was dissolved in 50 μL each of acetic anhydride and pyridine. A catalytic amount of 4-dimethylaminopyridine (DMAP) was added, and reaction carried out for 24 h. The reaction mixture was diluted with dichloromethane and excess base was removed by washing with 2 M HCl. Dichloromethane extracts provided acetylated products which were further purified by centrifugal preparative TLC (Chromatotron). The yields were invariably high (>90%).

Attempted Bromination of Baccharinoid B4 (1). To a solution of 10 mg (0.0178 mmol) of **1** in 1 mL acetonitrile (CH_3CN) was added 3 mg (1 equiv) of N-bromosuccinimide (NBS) and 2 μL (1.5 equiv) of pyridine. The solution was heated in an oil bath (50-60°C) with stirring for 2 h, cooled and poured in 2 mL of 5% hydrochloric acid followed by extraction with 3 x 2 mL dichloromethane. The organic layer was washed with 2 mL of 5% Na_2SO_3, 5 mL of distilled water, dried (Na_2SO_4) and evaporated *in vacuo*. TLC analysis (5% methanol in dichloromethane, silica plate) showed two spots corresponding to product (high R_f) and starting material. Separation on the Chromatotron (1 mm silica plate, 3-6% methanol in dichloromethane as eluent) afforded 2 mg (20%) of the high R_f product and 5 mg (50%) of recovered starting material. The high R_f product was shown to be 8-oxobaccha-

rinoid B4[29] by comparison with the spectroscopic data of the authentic sample and by the characteristic color (green) of the spot after heating the plate following spraying the plate with vanillin spray. In a similar manner, when a solution of 1 and phenylselenyl chloride (Aldrich) was treated with butyllithium at room temperature in THF 8-ketobaccharinoid B4 was isolated in 30% yield along with recovered starting material.

8β-Trichloroimidate of Baccharinoid B4 (2). To 100 mg (0.177 mmol) of baccharinoid B4 (**1**) dissolved in 8 mL of THF was added 8 mg (0.283 mmol) of sodium hydride (NaH) previously washed with hexane. To this, at - 15°C was added 30 μL (0.265 mmol) of trichloroacetonitrile (Aldrich), and the reaction mixture allowed to warm to 0°C. The mixture was stirred for 1.5 h, evaporated *in vacuo* and subjected to flash chromatography on 5 g silica gel (2 x 30 cm column) with 40% ethyl acetate in hexane as eluent to yield 64 mg (51%) of **2** (a glass) and 10 mg (10%) of recovered starting material. 8β-Trichloroimidate of baccharinoid B4 (**2**): IR 3613, 3380, 3012, 2988, 1755, 1730, 1667 cm^{-1}; ^{1}H-NMR δ 0.75 (s, 3 H, H 14), 1.11 (d, J = 5.6 Hz, 3 H, H-14'), 1.73 (s, 3 H, H-12'), 1.76 (s, 3 H, H-16), 1.79-2.18 (m, 3 H, H-3β, H-7), 2.37 (dd, J = 8.1 Hz, 15.6 Hz, 1 H, H-3α), 2.78, 3.07 (AB, J = 3.9 Hz, 1 H each, H-13), 3.39 (s, 1 H, H-2'), 3.52-3.95 (m, 6 H, H-4', H 5', H 6', H-11, H-13'), 3.80 (d, J = 4.8 Hz, 1 H, H-2), 4.21, 4.39 (AB, J = 12.4 Hz, 1 H each, H-15), 4.56 (m, 1 H, H-8), 5.41 (d, J = 5.0 Hz, 1 H, H-10), 5.67 (dd, J = 8.1 Hz, 4.4 Hz, 1 H, H-4), 5.75 (d, J = 11.4 Hz, 1 H, H-10'), 5.91 (dd, J = 3.4 Hz, 15.6 Hz, 1 H, H-7'), 6.54 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.4 Hz, 1 H, H-9'), 7.44 (dd, J = 11.4 Hz, 15.6 Hz, 1 H, H 8'), 8.43 (s, 1 H, CCl_3CNH). ^{13}C-NMR δ 79.0 (C2), 34.7 (C3), 71.2 (C4), 45.1 (C5), 47.6 (C6), 30.1 (C7), 86.8 (C8), 142.8 (C9), 120.5 (C10), 67.7 (C11), 64.8 (C12), 49.4 (C13), 7.0 (C14), 65.1 (C15), 18.7 (C16), 166.6 (C1'), 65.0 (C2'), 63.7 (C3'), 73.8 (C4'), 66.8 (C5'), 81.9 (C6'), 137.8 (C7'), 126.0 (C8'), 143.1 (C'9), 118.1 (C10'), 166.5 (C11'), 12.9 (C12'), 6.90 (C13'), 17.8 (C14'), 90.9 ($\underline{C}Cl_3$), and 161.9 ($\underline{C}$=N); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{31}H_{38}Cl_3NO_{11}$ + H m/z 708.0156, found 708.0187.

4',13'-Diacetate of 2: IR 3380, 3012, 2980, 1755, 1730, 1667 cm^{-1}; ^{1}H-NMR δ 0.69 (s, 3 H, H-14), 1.09 (d, J = 6.4 Hz, 3 H, H-14'), 1.62 (s, 3 H, H-12'), 1.67 (s, 3 H, H-16), 1.91, 1.97 (s, 6 H, CH_3COO), 2.05-2.19 (m, 3 H, H 3β, H-7), 2.34 (dd, J = 8.0 Hz, 15.4 Hz, 1 H,H 3α), 2.70, 3.02 (AB, J = 3.9 Hz, 1 H each, H-13), 3.44 (s, 1 H, H 2'), 3.50 (d, J = 5.0 Hz, 1 H, H-11), 3.67-3.87 (m, 4 H, H-4', H-5', H-6'), 3.78 (d, J = 4.8 Hz, 1 H, H-2), 4.19, 4.46 (AB, J = 12.4 Hz, 1 H each, H-15), 5.01 (dq, J = 4.7 Hz, 6.4 Hz, 1 H, H-13'), 5.46 (d, J = 5.0 Hz, 1 H, H-10), 5.61 (dd, J = 4.2 Hz, 8.0 Hz, 1 H, H-4), 5.71 (d, J = 11.3 Hz, 1 H, H-10'), 5.85 (dd, J = 3.0 Hz, 15.6 Hz, 1 H, H-7'), 6.50 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.3 Hz, 1 H, H 9'), 7.28 (dd, J = 11.3 Hz, 15.6 Hz, 1 H, H-8'), 8.34 (s, 1 H, CCl_3CNH).

Synthesis of 8β-Phenylthionocarbonate of Baccharinoid B4 (5). To a solution of 10 mg (0.018 mmol) of **1** in 2 mL of dry dichloromethane containing 5.7 μL (4 equiv) of pyridine was added 3.7 μL (0.027 mmol) of freshly distilled phenylchlorothionoformate (Aldrich) at 0°C. The reaction was maintained at this temperature for 4 h, diluted to 10 mL with dichloromethane, washed with 2 x 3 mL of 2 M hydrochloric acid, followed by 2 mL of saturated sodium chloride solution. The organic layer was dried over Na_2SO_4, evaporated *in vacuo* and subjected to centrifugal chromatography (Chromatotron, 1 mm silica plate, 1-3% methanol in dichloromethane as eluent) to afford 7 mg (54%) of **5**. Recrystallization from dichloromethane/hexane gave colorless crystalline plates: mp 160-163°C; IR 3600, 3051, 2980, 1756, 1716, 1599 cm^{-1}; ^{1}H-NMR δ 0.75 (s, 3 H, H-14), 1.15 (d, J = 5.4 Hz, 3 H, H-14'), 1.50 (s, 3 H, H-12'), 1.76 (s, 3 H, H-16), 1.97-2.19 (m, 3 H, H-3β, H-7), 2.44 (dd, J = 8,2 Hz, 15.6 Hz, 1 H, H-3α), 2.77, 3.09 (AB, J = 3.9 Hz, 1 H each, H-13), 3.36 (s, 1 H, H-2'), 3.41-3.84 (m, 6 H, H-4', H-5', H-6', H-11, H-13'), 4.32, 4.42 (AB, J = 12.6 Hz, 1 H each, H-15), 5.57 (d, J = 5.1 Hz, 1 H, H-10), 5.63 (m, 1 H, H-8), 5.65 (dd, J = 8.2 Hz, 3.9 Hz, 1 H, H-4), 5.75 (d, J = 11.3 Hz, 1 H, H-10'), 6.50 (dd, J = 3.3 Hz, 16.4 Hz, 1 H, H-7'), 6.53 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.3 Hz, 1 H, H-9'), 7.02-7.39 (m, 6 H, H-8' and aromatic H's); ^{13}C-NMR δ 79.3 (C2), 34.9 (C3), 74.3 (C4), 49.7 (C5), 45.5 (C6), 25.7 (C7), 87.5 (C8), 138.5 (C9), 122.9 (C10), 66.4 (C11), 65.0 (C12), 47.6 (C13), 7.0 (C14), 64.0 (C15), 18.6 (C16), 167.1 (C1'), 56.6 (C2'), 64.7 (C3'), 75.9 (C4'), 71.8 (C5'), 80.9 (C6'), 137.8 (C7'), 126 (C8'), 142.1 (C9'), 118.6 (C10'), 166.6 (C11'), 12.5 (C12'), 72.7 (C13'), 18.4 (C14'), 153.5, 121.8, 129.6 and 126.7 (aromatics), and 195.3 (OC(S)O); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{36}H_{42}O_{12}S$ + H m/z 699.7969, found 699.79153.

[3,3]-Sigmatropic Rearrangement of 5. A solution of 12 mg (0.017 mmol) of **5** in 5 mL of freshly distilled toluene was purged with nitrogen employing a firestone valve (>70 cycles). A slow stream of nitrogen was allowed to pass through the reaction pot as heating to reflux was carried out. Thin layer chromatography (TLC) analysis of aliquots drawn at intervals (30 min) revealed two products gradually increasing in quantity. The reaction solution was cooled to room temperature after 3.5 h, evaporated *in vacuo* and the mixture of products subjected to preparative TLC (Chromatotron, 1 mm silica plate, 1-4% methanol in dichloromethane as eluent). Further purification was achieved by using HPLC (semiprep., 25 cm x 10 mm, 5 μm silica, flow rate 4 mL/Min) with 5% 2-propanol in dichloromethane as eluent to afford 4 mg (33%) of the thiolcarbonate **6**, mp 112-114°C, 1 mg (9%) of the 8-deoxy-7,8-dehydrobaccharinoid B4 (**4a**), mp 180-182°C, and 2 mg (17%) of starting material. Under these same conditions, the trichloroimidate **2** gave only trace quantities (by TLC analysis) of **4a** and **6**.

10β-Phenylthiolcarbonate of B4 (6): IR 3600, 3058, 2950, 1750, 1724, 1716, 1584 cm^{-1}; ^{1}H-NMR δ 0.78 (s, 3 H, H 14), 1.15 (d, J = 5.9 Hz, 3 H, H-14'), 1.28 (s, 3 H, H-12'), 1.81 (s, 3 H, H-16), 1.81, 2.63 (AB, J = 11.9 Hz, 1 H each, H-7), 2.04 (dd, J = 4.8 Hz, 15.6 Hz, 1 H, H-3β), 2.76 (dd, J = 7.6 Hz, 15.6 Hz, 1 H, H-3α), 2.84, 3.19 (AB, J = 3.9 Hz, 1 H each, H-13), 3.62-3.90 (m, 5 H, H-2', H-5', H=6', H-13'), 3.97 (d, J = 4.8 Hz, 1 H, H-2), 3.99, 4.37 (AB, J = 12.7 Hz, 1 H each, H-15), 4.12-4.32 (m, 2 H, H-10 and H-4'), 5.48 (m, 1 H-8), 5.85 (d, J = 11.4 Hz, 1 H, H-10'), 5.91 (dd, J = 4.8 Hz, 7.6 Hz, 1 H, H-4), 6.05 (dd, J = 3.7 Hz, 15.6 Hz, 1 H, H-7'), 6.59 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.4 Hz, 1 H, H-9'), 7.15-7.40 (m 5 H, aromatic H's), 7.55 (dd, J = 11.4 Hz, 15.6 Hz, 1 H, H-8'); ^{13}C-NMR δ 80.1 (C2), 37.2 (C3), 71.6 (C4), 48.9 (C5), 44.5 (C6), 25.8 (C7), 121.4 (C8), 129.4

(C9), 49.1 (C10), 69.8 (C11), 63.4 (C12), 48.4 (C13), 6.7 (C14), 65.9 (C15), 20.9 (C16), 168.1 (C1'), 54.9 (C2'), 65.9 (C3'), 75.4 (C4'), 70.4 (C5'), 84.9 (C6'), 136.1 (C7'), 128.1 (C8'), 141.3 (C9'), 119.6 (C10'), 166.3 (C11'), 14.0 (C12'), 71.5 (C13'), 18.2 (C14'), 151.4, 121.3, 129.5 and 126.1 (aromatics), and 176.5 (OC(O)S); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{36}H_{42}O_{12}S$ + H m/z 699.7969, found 699.7929.

8-Deoxy-7,8-dehydrobaccharinoid B4 (4a): IR 3615, 3011, 1754, 1716 cm^{-1}; ^{1}H-NMR δ 0.89 (s, 3 H, H-14), 1.12 (d, J = 5.9 Hz, 3H, H-14'), 1.33 (s, 3 H, H-12'), 1.79 (s, 3 H, H-16), 2.02 (dd, J = 4.4 Hz, 15.5 Hz, 1 H, H-3β), 2.64 (dd, 7.8 Hz, 15.5 Hz, 1 H, H-3α, 2.82, 2.95 (AB, J = 3.8 Hz, 1 H each, H-13) 3.42 (s, 1 H, H-2'), 3.51-3.76 (m, 5 H, H-4', H-5', H-6', H-11), 3.92 (m, 1 H, H-2), 3.96, 4.03 (AB, J = 12.1 Hz, 1 H each, H-15), 5.59 (d, J = 6.3 Hz, 1 H, H-10), 5.62 (d, J = 10.0 Hz, 1 H, H-7), 5.81 (d, J - 11.3 Hz, 1 vH, H-10'), 5.91 (dd, J = 4.1 Hz, 7.8 Hz, 1 H, H-4), 5.95 (d, J = 10.0 Hz, 1 H, H-8), 5.98 (d, J = 3.5 Hz, 15.6 Hz, 1 H, H-7'), 6.56 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.3 Hz, 1 H, H-9'), 7.48 (dd, J = 11.3 Hz, 15.6 Hz, 1 H, H-8'); ^{13}C-NMR δ 78.0 (C2), 36.7 (C3), 72.8 (C4), 47.1 (C5), 46.5 (C6), 127.1 (C7), 127.7 (C8), 135.6 (C9), 119.4 (C10), 66.4 (C11), 66.0 (C12), 48.0 (C13), 6.6 (C14), 63.9 (C15), 21.1 (C16), 167.4 (C1'), 55.4 (C2'), 64.9 (C3'), 75.4 (C4'), 71.5 (C5'), 85.5 (C6'), 136.9 (C7'), 129.4 (C8'), 141.7 (C9'), 118.2 (C10'), 166.3 (C11'), 13.6 (C12'), 70.3 (C13') and 18.3 (C14'); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{29}H_{36}O_{10}$ + H 545.6122, found 545.6130.

Synthesis of 8-Keto-4',13'-diacetate of B4 (11). A mixture of 280 mg (0.5 mmol) of 8-oxobaccharinoid B4[29] in 800 μL pyridine and 800 μL acetic anhydride containing a catalytic amount of 4-dimethylaminopyridine (DMAP) was allowed to stand at room temperature for 24 h. The reaction solution was diluted with 10 mL of dichloromethane and washed with 2 x 10 mL of 2 M HC1. Evaporation of the organic layer *in vacuo* yielded 93% of the title compound as a crystalline product: mp 155-157° C; IR 1750, 1700, 1690 cm^{-1}; ^{1}H-NMR δ 0.75 (s, 3 H, H-14), 1.17 (d, J = 6.5 Hz, 3 H, H-14'), 1.65 (s, 3 H, H-12'), 1.79 (s, 3 H, H-16), 2.01, 210 (s, 6 H, CH_3COO), 2.15-2.29 (m, 1 H, H-3β), 2.52 (dd, J = 8.1 Hz, 15.6 Hz, 1 H, H-3α), 2.74 (AB, J = 10.7 Hz, 1 H each, H-7), 2.81, 3.10 (AB, J = 3.9 Hz, 1 H each, H-13), 3.37 (s, 1 H, H-2'), 3.50-4.32 (m, 5 H, H-2, H-4', H-5', H-6', H-11), 4.21, 4.50 (AB, J = 12.5 Hz, 1 H each, H-15), 4.99 (dq, J = 4.6 Hz, 6.5 Hz, 1 H, H-13'), 5.72 (dd, J = 8.1 Hz, 4.3 Hz, 1 H, H-4), 5.76 (d, J = 11.3 Hz, 1 H, H-10'), 5.90 (dd, J = 15.6 Hz, 3.3 Hz, 1 H, H-7'), 6.48 (d, J = 5.6 Hz, 1 H, H-10), 6.58 (dd, $J_{8'-9'}$ = $J_{9',10'}$ = 11.3 Hz, 1 H, H-9'), 7.41 (dd, J = 15.6 Hz, 11.3 Hz, 1 H, H-8'); ^{13}C-NMR δ 79.2 (C2), 37.2 (C3), 73.4 (C4), 46.3 (C5), 47.4 (C6), 35.0 (C7), 196.3 (C8), 126.9 (C9), 138.7 (C10), 69.6 (C11), 65.5 (C12), 49.5 (C13), 6.9 (C14), 65.2 (C15), 15.3 (C16), 166.6 (C1'), 56.4 (C2'), 63.4 (C3'), 77.6 (C4'), 66.6 (C5'), 81.6 (C6'), 136.8 (C7'), 137.5 (C8'), 143.0 (C9'), 117.9 (C10'), 166.4 (C11'), 15.3 (C12'), 70.7 (C13'), 13.2 (C14'), 20.8 and 20.9 (acetate CH_3's), 170.0 and 170.1 (acetate CO's); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{33}H_{40}O_{13}$+H m/z 645.6869, found 645.6864.

Reduction of Ketone 11. To a solution of 50 mg (0.078 mmol) of **11** in 4 mL methyl alcohol, was added 4 mg (0.0936 mmol) of sodium borohydride. The mixture was stirred at room temperature for 0.5 h, then the reaction quenched by addition of a drop of water. Evaporation *in vacuo* followed by flash chromatography (5 g of silica gel, column 2 x 30 cm) with methanol:dichloromethane as eluent (1:49) gave two fractions. One fraction upon evaporation *in vacuo* yielded 5 mg (10% of the 1,4-reduction product which was recrystallized from dichloromethane/hexane to give white needle-like crystals (mp >280° C). The other fraction was subjected to centrifugal chromatography (Chromatotron, 1 mm silica plate, 1-3% MeOH in CH_2CH_2 as eluent) to afford 25 mg (50%) of 8α-hydroxy epimer of 4',13'-di-O-acetyl B4 (**9**) (a glass) and 7.5 mg (15%) of its β-epimer (a glass): for **9**, IR 3600, 3010, 2980, 1740, 1716 cm^{-1}; ^{1}H-NMR δ 0.82 (s, 3 H, H-14), 1.20 (d, J = 6.5 Hz, 3 H, H-14'), 1.67 (s, 3 H, H-12'), 1.83 (s, 3 H, H-16), 2.01, 2.12 (s, 6 H, CH_3COO), 2.04-2.24 (m, 3 H, H-3β, H-7), 2.47 (dd, J = 8.1 Hz, 15.4 Hz, 1 H, H-3α), 2.80, 3.09 (AB, J = 4.0 Hz, 1 H each, H-13), 3.38 (s, 1 H, H-2'), 3.49-3.82 (m, 4 H, H-2, H-5', H-6', H-11), 3.88 (d, J = 4.8 Hz, 1 H, H-8), 4.32 (m, 1 H, H-4'), 4.36, 4.57 (AB, J = 12.0 Hz, 1 H each, H-15), 5.02 (dq, J = 6.5 Hz, 4.6 Hz, 1 H, H-13'), 5.52 (d, J = 5.4 Hz, 1 H, H-10), 5.75 (dd, J = 8.1 Hz, 4.3 Hz, 1 H, H-4), 5.78 (d, J - 11.5 Hz, 1 H, H-10'), 5.91 (dd, J = 15.6 Hz, 3.4 Hz, 1 H, H-7'), 6.58 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.5 Hz, 1 H, H-9'), 7.47(dd, J = 15.6 Hz, 11.5 Hz, 1 H, H-8'); ^{13}C-NMR δ 78.9 (C2), 34.9 (C3), 74.0 (C4), 42.5 (C5), 47.8 (C6), 28.7 (C7, 70.7 (C8), 139.6 (C9) 121.0 (C10), 67.0 (C11), 65.8 (C12), 49.4 (C13), 7.1 (C14), 65.2 (C15), 20.6 (C16), 166.4 (C1'), 56.7 (C2'), 63.2 (C3'), 77.3 (C4'), 66.6 (C5'), 81.8 (C6'), 137.2 (C7'), 127.0 (C8'), 142.6 (C9'), 118.3 (C10'), 166.3 (C11'), 15.4 (C12'), 69.8 (C13'), 13.1 (C14'), 20.9 and 21.0 (acetate $\underline{C}H_3$'s), 170.1 and 170.2 (acetate $\underline{C}O$'s);

4',13'-Diacetate of Baccharinoid B4 (β-epimer of 9): IR 3600, 3015, 2950, 1745, 1716 cm^{-1}; ^{1}H-NMR δ 0.75 (s, 3 H, H-14), 1.16 (d, J = 6.5 Hz, 3 H, H-14'); 1.64 (s, 3 H, H-12'), 1.76 (s, 3 H, H-16), 1.96, 2.09 (s 6 H, CH_3COO), 1.85-2.79 (m, 3 H, H-3β, H-7), 2.39 (dd, J - 15.6 Hz, 8.1 Hz, 1 H, H-3α), 2.78, 3.06 (AB, J = 3.9 Hz, 1 H each, H-13), 3.34 (s, 1 H, H-2'), 3.35-3.89 (m, 5 H, H-2, H-5', H-6', H-8, H-11), 4.19, 4.30 (AB, J = 12.3 Hz, 1 H each, H-15), 4.26 (m, 1 H, H-4'), 4.98 (dq, J = 6.4 Hz, 4.7 Hz, 1 H, H-13'), 5.41 (d. 5.1 Hz, 1 H, H-10), 5.65 (dd, J = 8.1 Hz, 4.3 Hz, 1 H, H-4), 5.73 (d, J = 11.4 Hz, 1 H, H-10), 6.53 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.4 Hz, 1 H, H-9'), 7.36 (dd, J = 11.4 Hz, 15.6 Hz, 1 H, H-8').

9,10-Dihydro-4',13'-diacetate of B4: IR 3613, 2874, 1738, 1666, 1665 cm^{-1}; ^{1}H-NMR δ 0.69 (s, 3 H, H-14), 0.85 (d, J = 6.0 Hz, 3 H, H 16), 1.15 (d, J -= 6.5 Hz, 3 H, H-14'), 1.48 (m, 2 H, H-10), 1.64 (s, 3 H, H-12'), 1.71-2.12 (m, 3 H, H-3β, H-7), 1.96, 2.08 (s, 6 H, CH_3COO), 2.35 (dd, J = 15.2 Hz, 7.9 Hz, 1 H, H-3α), 2.76, 3.05 (AB, J - 4.0 Hz, 1 H each, H-13), 3.45-4.28 (m, 7 H, H-2, H-4', H-5', H-6', H-8, H-11), 3.35 (s, 1 H, H-2'), 4.35, 4.81 (AB, J = 11.6 Hz, 1 H each, H-15), 4.97 (dq, 4.7 Hz, 6.5 Hz, 1 H, H-13'), 5.65 (dd, J = 7.9 Hz, 4.0 Hz, 1 H, H-4), 5.73 (d, J = 11.9 Hz, 1 H, H-10'), 5.85 (dd, J = 3.2 Hz, 15.3 Hz, 1 H, H-7'), 6.51 (dd, $J_{8',9'}$ = $J_{9',10'}$ = 11.9 Hz, 1 H, H-9'), 7.37 (dd, J = 11.9 Hz,

15.3 Hz, 1 H, H-8'); ^{13}C-NMR δ 79.0 (C2), 35.1 (C3), 73.9 (C4), 43.1 (C5), 48.3 (C6), 30.1 (C7), 70.7 (C8), 29.9 (C9), 29.5 (C10), 69.7 (C11), 67.3 (C12), 49.9 (C13), 7.0 (C14), 65.5 (C15), 17.4 (C16), 166.4 (C1'), 56.8 (C2'), 63.2 (C3'), 77.3 (C4'), 69.4 (C5'), 81.7 (C6'), 136.9 (C7'), 127.0 (C8'), 142.4 (C9'), 118.4 (C10'), 166.4 (C11'), 15.4 (C12'), 70.0 (C13'), 13.1 (C14'), 20.9 and 21.0 (acetate $\underline{C}H_3$'s), 170.1 and 170.2 (acetate $\underline{C}O$'s); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{33}H_{42}O_{13}$ + H m/z 649.7188, found 649.7200.

Preparation of 8α-Phenylthionocarbonate 10. The procedure employed was similar to that used in the preparation of **5** (*vide supra*). To 50 mg (0.078 mmol) of **9** dissolved in 4 mL dry dichloromethane at room temperature, was added 26 μL (0.312 mmol) of pyridine and a catalytic amount of DMAP, and 22 μL (0.156 mmol) of freshly distilled phenylchlorothionoformate. After 9 h, the solution was diluted to 10 mL with dichloromethane, washed twice with 5 mL of 2 M HCl, and with 3 mL of saturated sodium chloride solution. The organic layer was then dried over Na_2SO_4, evaporated *in vacuo* and subjected to flash chromatography on 5 g silica gel with 50% ethyl acetate in hexane as eluent to yield 37 mg (61%) of the title compound **10** (a glass): IR 3051, 2980, 1745, 1710 cm^{-1}; ^{1}H-NMR δ 0.79 (s, 3 H, H-14), 1.19 (d, J = 6.5 Hz, 3 H, H-14'), 1.72-2.33 (m, 3 H, H-3β, H-7), 2.48 (dd, J = 8.0 Hz, 15.5 Hz, 1 H, H-3α), 2.81, 3.09 (AB, J - 3.9 Hz, 1 H each, H-13), 3.34 (s, 1 H, H-2'), 3.41-4.28 (m, 5 H, H-2, H-4', H-5', H-6'), 3.69 (d, J = 5.5 Hz, 1 H, H-11), 4.49 (s, 2 H, H-15), 5.01 (dq, J = 4.5 Hz, 6.5 Hz, 1 H, H-13'), 5.75-5.83 (m, 4 H, H-4, H-8, H-10, H-10'), 5.85 (dd, J = 3.3 Hz, 15.1 Hz, 1 H, H-7'), 6.58 (dd, $J_{8',9'} = J_{9',10'}$ - 11.4 Hz, 1 H, H-9'), 7.15 7.48 (m, 6 H, H-8', aromatic H's); ^{13}C-NMR δ 78.6 (C2), 34.8 (C3), 74.0 (C4), 49.4 (C5), 42.3 (C6), 25.4 (C7), 78.9 (C8), 137.4 (C9), 124.8 (C10), 66.7 (C11), 65.3 (C12), 47.6 (C13), 7.2 (C14), 63.6 (C15), 20.3 (C16), 166.4 (C1'), 56.4 (C2'), 65.0 (C3'), 77.3 (C4'), 69.9 (C5'), 81.8 (C6') 135.5 (C7'), 126.5 (C8'), 142.8 (C9'), 118.1 (C10'), 165.9 (C11'), 13.0 (C12'), 70.7 (C13'), 15.3 (C14'), 20.9 and 21.0 (acetate $\underline{C}H_3$'s), 170.0 and 170.1 (acetate $\underline{C}O$'s), mass spectrum (HRMS, DCI, ammonia reagent gas), calcd for $C_{40}H_{46}O_{14}S$ + H m/z 783.8722, found 783.8775.

Thermolysis of 10. A solution of 20 mg (0.026 mmol) of **10** in 5 mL of freshly distilled toluene was heated at reflux for 1.5 h under conditions similar to those employed with **5** (*vide supra*). The reaction solution was cooled, concentrated *in vacuo*, and the concentrate subjected to centrifugal chromatography (1 mm silica plate, 1-2% methanol in dichloromethane as eluent) to yield 7 mg (44%) of 8-deoxy-7,8-dehydro-4',13'-di-O-acetyl B4 (**4b**) (a glass): IR 3011, 1754, 1716 cm^{-1}; ^{1}H-NMR δ 0.89 (s, 3 H, H 14), 1.14 (d, J = 6.4 Hz, 3 H, H-14'), 1.60 (s, 3 H, H-12'), 1.79 (s, 3 H, H-16), 1.96, 2.08 (s, 6 H, CH_3COO), 2.09-2.17 (m, 1 H, H-3β), 2.46 (dd, J - 8.3 Hz, 15.4 Hz, 1 H, H-3α), 2.79, 2,92 (AB, J = 3.8 Hz, 1 H each, H-13), 3.28 (s, 1 H, H-2'), 3.51 (dd, J = 4.0 Hz, 11.1 Hz, 1 H, H-5'A), 3.65 (d, J = 5.9 Hz, 1 H, H-11), 3.71 (d, J = 5.1 Hz, 1 H, H-2), 3.75-3.83 (m, 2 H, H-5'B, H-6'), 4.18, 4,24 (AB, J = 11.5 Hz, 1 H each, H-15), 4.34 (m, 1 H, H-4'), 4.97 (dq, J = 4.7 Hz, 6.4 Hz, 1 H, H-13'), 5.54 (d, J = 5.9 Hz, 1 H, H=10), 5.72 (dd, J = 3.6 Hz, 8.3 Hz, 1 H, H=4), 5.75 (d, J = 11.2 Hz, 1 H, H-10'), 5.77 (d, J = 9.8 Hz, 1 H, H-8), 6.54 (dd, $J_{8',9'} = J_{9',10'}$ = 11.2 Hz, 1 H, H=9'), 7.40 (dd, J = 11.2 Hz, 15.5 Hz, 1 H, H 8'); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{33}H_{40}O_{12}$ + H m/z 629.6875, found 629.6824.

Preparation of 8β-Phenylcarbonate of B4. To 50 mg (0.088 mmol) of **1** in 5 mL of dichloromethane at –78° C was added 20 μL (0.264 mmol) of pyridine and 19 μL (0.088 mmol) of phenylchloroformate (Aldrich), and the reaction allowed to proceed for 1 h. The solution was washed with 1 M HCl, brine and then dried over Na_2SO_4. Concentration *in vacuo* followed by separation on the Chromatotron (1 mm silica plate, 1-3% methanol in dichloromethane as eluent) gave 36 mg (60%) of of the 8β-phenylcarbonate of baccharinoid B4. Recrystallization from dichloromethane/hexane afforded colorless needle-like crystals: mp 167-169 °C; IR 3600, 2900, 1760, 1720 cm^{-1}; ^{1}H-NMR δ 0.73 (s, 3 H, H-14), 1.13 (d, J = 5.6 Hz, 3 H, H-14'), 1.51 (s, 3 H, H-12'), 1.78 (s, 3 H, H-16), 2.01-2.36 (m, 3 H, H-3β, H-7), 2.45 (dd, J = 8.3 Hz, 15.4 Hz, 1 H, H-3α), 2.76, 3.09 (AB, J = 3.9 Hz, 1 H each, H-13), 3.33 (s, 1 H, H-2'), 3.39-3.70 (m, 6 H, H-4', H-5', H-6', H-11, H-13'), 3.82 (d, J = 4.7 Hz, 1 H, H-2), 4.24, 4.40 (AB, J = 12.5 Hz, 1 H each, H-15), 4.96 (m, 1 H, H-8), 5.56 (d, J = 5.2 Hz, 1 H, H-10), 5.68 (dd, J = 3.9 Hz, 8.3 Hz, 1 H, H-4), 5.76 (d, J = 11.4 Hz, 1 H, H-10'), 5.96 (dd, J = 2.5 Hz, 15.5 Hz, 1 H, H-7'), 6.52 (dd, $J_{8',9'} = J_{9',10'}$ = 11.4 Hz, 1 H, H-9'), 7.09-7.41 (m, 6 H, H-8' and aromatic H's); ^{13}C-NMR δ 79.2 (C2), 35.0 (C3), 75.5 (C4), 45.2 (C5), 49.5 (C6), 26.7 (C7), 74.3 (C8), 138.3 (C9), 123.0 (C10), 66.3 (C11), 64.3 (C12), 47.6 (C13), 6.9 (C14), 65.0 (C15), 18.5 (C16), 167.4 (C'), 56.4 (C2'), 56.2 (C3'), 75.3 (C4'), 72.5 (C5'), 81.7 (C6'), 137 (C7'), 126.1 (C8'), 142,1 (C9'), 118.5 (C10'), 166.5 (C11'), 12.6 (C12'), 71.6 (C13'), 17.0 (C14'), 151.1, 120.9, 129.5 and 126.0 (aromatics); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{36}H_{42}O_{13}$ + NH_4+ m/z 700.7669, found 700.7689.

Ammonolysis Reactions. To a solution of 10 mg (0.015 mmol) of the above carbonate in 1 mL of THF was added 2 mL of concentrated NH_4OH solution (~ 30% NH_3), and the reaction allowed to stand room temperature for 1 h with stirring. The reaction solution was then extracted with 3 x 10 mL of ether, dried over Na_2SO_4 and evaporated under reduced pressure to afford 6 mg (67%) of the urethan (**1**, where R = $NH_2C(O)O$) which was recrystallized from methanol: mp 153-155 °C; IR 3601, 3434, 1702, 1681, 1676 cm^{-1}; ^{1}H-NMR δ 0.78 (s, 3 H, H-14), 1.18 (d, J = 6.4 Hz, 3 H, H-14'), 1.67 (s, 3 H, H-12') 1.73 (s, 3 H, H-16), 2.01-2.36 (m, 3 H, H-3β, H-7), 2.45 (dd, J = 8.3 Hz, 15.4 Hz, 1 H, H-3α), 2.80, 3.09 (AB, J = 3.8 Hz, 1 H each, H-13), 3.47 (s, 1 H, H-2'), 3.53-3.85 (m, 6 H, H-4', H-5, H-6', H-11, H-13'), 4.23, 4.45 (AB, J = 12.0 Hz, 1 H each, H-15), 4.99 (m, 1 H, H-8), 5.54 (d, J = 5.2 Hz, 1 H, H-10), 5.68 (dd, J = 3.9 Hz, 8.3 Hz, 1 H, H-4), 5.75 (d, J = 11.3 Hz, 1 H, H-10'), 5.91 (dd, J = 3.2 Hz, 15.6 Hz, 1 H, H-7'), 6.56 (dd, $J_{8',9'} = J_{9',10'}$ = 11.3 Hz, 1 H, H-9'), 7.35 (dd, J = 11.3 Hz, 15.6 Hz, 1 H, H-8'); ^{13}C-NMR δ 79.2 (C2), 35.0 (C3), 71.0 (C4), 49.2 (C5), 45.1 (C6), 27.4 (C7), 77.8 (C8), 139.4 (C9), 122.0 (C10), 66.5 (C11), 63.2 (C12), 47.8 (C13), 7.0 (C14), 65.0 (C15), 18.6 (C16), 166.9 (C1'), 56.7 (C2'), 65.9 (C3'), 68.7 (C4'), 69.9 (C5'), 81.2 (C6'), 137.4 (C7'), 126.6 (C8'), 143.0 (C9'), 118.2 (C10'), 166.0 (C11'), 13.2 (C12'), 69.5 (C13'), 18.3 (C14'),

and 156 (H_2NCOO); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{30}H_{39}NO_{12} + NH_4$+ m/z 623.6834, found 623.6890. Under these conditions, thiolcarbonate **6** was recovered unchanged. More forcing conditions (longer reaction times, heating, etc.) led to extensive decomposition.

Epoxidation of 10β-Thiolcarbonate of B4 (6). To a solution of 20 mg (0.028 mmol) of **6** in 2 mL of dichloromethane was added 4.9 mg (1 equiv) of MCPBA and reaction stirred at room temperature for 48 h. The mixture was diluted with 2 mL of dichloromethane, washed with 10 mL of $NaHCO_3$ solution, followed by 10 mL of distilled water and the organic portion dried with Na_2SO_4. Concentration of the solution under reduced pressure followed by preparative TLC on the Chromatotron (1 mm silica plate, 1-3% methanol in dichloromethane as eluent) gave 2 mg (10%) of the 8,9-epoxy derivative (a glass); ^{1}H-NMR δ 0.78 (s, 3 H, H-14), 1.15 (d, J = 6.0 Hz, 3 H, H-14'), 1.28 (s, 3 H, H-12'), 1.49 (s, 3 H, H-6), 1,51-1.73 (m, 2 H, H-7), 2.04 (m, 1 H, H-3β), 2.76 (dd, J = 7.6 Hz, 15.6 Hz, 1 H, H-3α), 2.84, 3.19 (AB, J = 4.0 Hz, 1 H each, H-13), 3.09 m, 1 H, H-8), 3.62-4.00 (m, 6 H, H-2, H-2', H-5', H-6', H-13'), 3.99, 4.37 (AB, J = 12.3 Hz, 1 H each, H-15), 4.12-4.32 (m, 2 H, H-4', H-10), 5.85 (d, J = 11.3 Hz, 1 H, H-10'), 5.91 (dd, J = 4.8 Hz, 7.6 Hz, 1 H, H-4), 6.05 (dd, J = 3.7 Hz, 15.6 Hz, 1 H, H-7'), 6.59 (dd, $J_{8',9'} = J_{9',10'}$ = 11.4 Hz, 1 H, H-9'), 7.15-7.40 (m, 5 H, aromatic H's), 7.55 (dd, J = 11.4 Hz, 15.6 Hz, 1 H, H-8'); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{36}H_{42}O_{13}S$ + H m/z 715.7963, found 715.7900.

Preparation of Phenylthiolcarbonate of 2-Cyclohexene-1-ol (7). To a solution of 100 mg (1.018 mmol) of 2-cyclohexene-1-ol in 4 mL of dichloromethane at room temperature was added 223 μL (2.036 mmol) of phenylchlorothionoformate and 240 μL (3.054 mmol) of pyridine. After one hour, TLC analysis (silica gel plate, 10% ethyl acetate in hexane) showed complete consumption of starting material and formation of one major product. The solution was washed with 1 M HCl, brine and dried (Na_2SO_4). Concentration under reduced pressure followed by preparative TLC on the Chromatotron (2 mm silica plate, 4% ethyl acetate in hexane as eluent) gave 200 mg (84%) of the oily compound **7**: IR 3100, 2910, 1720, 1590, 1485 cm^{-1}; ^{1}H-NMR δ 1.81-2.05 (m, 6 H, CH_2), 4.03 (m, 1 H, SCH), 5.60-5.89 (m, 2 H, CH=CH), 7.15-7.54 (m, 5 H, aromatic H's); ^{13}C-NMR δ 19.0 (CH_2), 25.5 (CH_2, homoallylic), 29.5 (CH_2, allylic), 42.6 (CH, allylic), 121, 126, 129.8, 151 (6 aromatic carbons), 127, 133 (CH = CH); mass spectrum (HRMS, DCI, ammonia reagent gas) calcd for $C_{13}H_{14}O_2S$ + H m/z 235.0715, found 235.0797.

Preparation of Phenylthiolcarbonate of 3-Phenyl-2-propene-1-ol (8). A similar procedure to the preparation of **7** was employed. To 200 mg (1.5 mmol) of 1-phenyl-2-propene-1-ol[37] in 10 mL of dichloromethane at room temperature was added 440 μL (3 mmol), of phenylchlorothionoformate followed by 370 μL (4.5 mmol) of pyridine. After 2 h, the solution was washed with 2 M HCl, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification on the Chromatotron (4 mm silica plate, 6% ethyl acetate in hexane as eluent) yielded 400 mg (99%) of **8** (recrystallized from dichloromethane): mp 55-57° C; IR 3040, 2925, 1724, 1600 cm^{-1}; ^{1}H-NMR δ 3.75 (d, J = 7.3 Hz, 2 H), 6.20 (td, J = 15.7 and = 7.3 Hz, 1 H), 6.60 (d, J = 15.7 Hz, 1 H), 7.04-7.30 (m, 10 H, aromatic H's); ^{13}C-NMR δ 33.9 (CH_2), 120,9 (=CH), 121.3, 126.6, 127,0, 128,5, 129.8, 133.8, 136.5, 154.2 (aromatic carbons), 151.3 (PhCH=), 169.6 (SCOO); mass spectrum (HRMS, DCI, ammonia reagent gas), calcd for $C_{16}H_{14}O_2S$ m/z 270.0608, found 270.0715.

Oxidation of 7 and 8 with m-Chloroperbenzoic Acid (MCPBA). To a solution of 200 mg (0.854 mmol) of **7** dissolved in 5 mL dichloromethane was added 177 mg (1.2 equiv) of MCPBA and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was diluted with 5 mL dichloromethane, extracted with 10 mL of saturated $NaHCO_3$ solution, washed with 10 mL of distilled water and the organic portion dried (Na_2SO_4). Concentration of the dry solution gave 50 mg (64%) of phenol, (with ^{1}H-NMR, IR spectra and mp identical to an authentic sample). By the same procedure as that described above, 200 mg of **8** gave 43 mg (62%) of phenol.

Myrotoxin B Hidrate (15). To a solution of 100 mg (0.18 mmole) of myrotoxin B (**12**)[17] in 15 mL of 1% aqueous THF was added dropwise 0.5 ml of 1 N HCl. The mixture was warmed to 50° C and stirred fo 24 h. The solution was neutralized with saturated $NaHCO_3$ and extracted with 3 x 10 mL of methylene chloride. The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was subjected to PTLC to the Chromatotron and eluted with 30%-80% EtOAc/hexane to give a 73% yield of **15** which was recrystallized from EtOAc/hexane, mp 217-219 ° C; IR 3600, 3000, 1760, 1740, 1720, 1405, 1210, 1180 cm^{-1}; ^{1}H-NMR δ 6.60 (ddd, J = 11.3 9.5, 5.6 Hz, 1 H H-9'), 5.88 (dd, J = 11.3, 1.8 Hz, 1 H, H-10'), 5.87 (dd, J = 8.0, 3.9 Hz, 1 H, H-4), 5.65 (d, J = 5.4 Hz, 1 H, H-10), 5.25 (d, J = 4.8 Hz, 1 H, H-8), 4.81 and 4.12 (AB, J = 12.1 Hz, 1 H each, H-15), 4.00 (m, 1 H, H-5'A), 3.86 (m, 1 H, H-5'B), 3.84 (d, J = 5.0 Hz, 1 H, H-2), 3.65 (d, J = 5.4 Hz, 1 H, H-11), 3.52 (s, 1 H, H-2'), 3.11 and 2.81 (AB, J = 4.0 Hz, 1 H each, H-13), 3.01 [br s, 1 H, H-12' (s, after D_2O exchange)], 2.89 (m, 1 H. H-8'A), 2.44 (dd, J = 15.2, 8.0 Hz, 1 H, H-3α), 2.34 (m, 2 H, H-4'A and H-8'B), 2.21 (m, 1 H, H-3β), 2.18 (m, 2 H, H-7), 2.0 (m, 1 H, H-4'B), 1,90 (s, 3 H, CH_3CO), 1.37 (m, 2 H, H-7'); ^{13}C-NMR δ 79.1 (C2), 35.1 (C3), 75.7 (C4), 49.7 (C5), 42.1 (C6), 21.5 C7), 64.6 (C8), 136.8 (C9), 123.8 (C10), 66.9 (C11), 65.1 (C12), 47.6 (C13), 7.9 (C14), 68.3 (C15), 20.8 (C16), 166.3 (C1'), 57.6 (C2'), 60.1 (C3'), 26.4 (C4'), 66.3 (C5'), 97.6 (C6'), 20.4 (C7'), 29.0 (C8"), 150.9 (C9'), 120.1 (C10'), 166.5 (C11'), 72.5 (C12'), 20.5 (acetate CH_3), and 170.1 (acetate CO); mass spectrum (HRMS, DCI, methane gas reagent) m/z calc for $C_{29}H_{36}O_{12}$ + H m/z 577.6110, found 577.6131.

Myrotoxin B Acetate (17): mp > 200 (decomp.); ^{1}H NMR δ 6.59 (ddd, J = 11.2, 9.4, 5.3 Hz, 1 H, H-9'), 5.87 (dd, J = 11.2, 1.9 Hz, 1 H, H-10'), 5.87 (dd, J = 8.1, 4.0 Hz, 1 H, H-4), 5.64 (d, J = 5.2 Hz, 1 H, H-10), 5.24 (d, J = 4.9 Hz, 1 H, H-8), 4.84 and 4.10 (AB, J = 12.3 Hz, 1 H each, H-15), 4.47 (s, 1 H, H-12'), 3.98 (m, 1 H, H-5'A), 3.86 (m, 1 H, H-5'B), 3.84 (d, J = 5.1 Hz, H-2), 3.64 (d, J = 5.2 Hz, 1 H, H-11), 3.51 (s, 1 H, H-2'), 3.12 and 2.82 (AB, J = 4.0 Hz, 1 H each, H-13), 2.90 (m, 1 H, H-8'A), 2.47 (dd, J = 15.1, 8.1 Hz, 1 H, H-3α), 2.40 (m, 1 H, H-4'A), 2.36 (m, 1 H, H-8'B), 2.20 (m, 1 H, H-3β), 2.17 (s, 3 H, 12'-CH_3CO), 2.15 (m, 2 H,

H-7), 1.95 (m, 1 H, H-4'B), 1.90 (s, 3 H, CH_3CO), 1.35 (m, 2 H, H-7'); ^{13}C-NMR δ 79.0 (C2), 34.5 (C3), 75.7 (C4), 49.7 (C5), 42.0 (C6), 22.4 (C7), 68.1 (C8), 136.8 (C9), 123.6 (C10), 66.9 (C11), 65.1 (C12), 47.7 (C13), 7.9 (C14), 66.4 (C15), 20.5 (C16), 166.6 (C1'), 57.7 (C2'), 60.4 (C3'), 26.4 (c4'), 62.9 (C5'), 97.2 (C6'), 20.8 (C7'), 28.9 (C8'), 150.7 (C9'), 121.1 (C10'), 166.6 (C11'), 72.5 (C12'), 20.6 and 20.7 (acetate $\underline{C}H_3$'s), 169.5 and 170.5 (acetate $\underline{C}O$'s).

Reaction of Myrotoxin B (12) with MCPBA. A mixture of myrotoxin B (25 mg, 0.045 mmol) and 11.5 mg of MCPBA (80%, 0.054 mmol) in 5 ML dichloromethane was stirred at room temperature. Sodium bicarbonate was added to the solution under different conditions: i) the solid $NAHCO_3$ was added at the same time with the addition of MCPBA; ii) the solid $NaHCO_3$ was added 5 min after the start of the reaction; iii) saturated $NaHCO_3$ solution was added to form a biphasic solution. After 20 min period, the mixture was diluted with 5 mL of CH_2Cl_2 and washed with 10% HCl, water, and dried (Na_2SO_4). Evaporation followed by PTLC on the Chromatotron (1 mm SiO_2: 1-5% MeOH/CH_2Cl_2) gave 20 mg of compound **18**: mp > 190° C (dec); IR (CH_2Cl_2) 3565, 2925, 2860, 1760, 1740, 1715,1220, 1200, 1185, 1170, 1080, 995, 975 cm^{-1}. ^{1}H-NMR δ 0.90 (s, 3 H, H-14), 1.76 (s, 3 H, H-16), 1.80-2.30 (m, 5 H, H-13β H-7, H-4'), 1.91 (s, 3 H, CH_3CO), 2.40-2.70 (m, 2 H, H-3α, H-8'B, 2.85 and 3.13 (AB, J = 4.0, Hz, 2 H, H-13), 3.20 (m, 1 H, H-8'A), 3.68 (d, J = 5.5 Hz, 1 H, H-11), 3.73 (s, 1 H, H-2'), 3.87 (d, J = 5.1 Hz, 1 H, H-2), 3.95-4.05 (m, 3 H, H-5', H-12'), 4.14 and 4.86 (AB, J = 12.1 Hz, 1 H each, H-15), 4.50 (dd, J = 6.8, 3.0 Hz, 1 H, H-7'), 5.29 (d, J = 5.2, 1 H, H-8), 5.68 (d, J - 5.1 Hz, 1 H, H-10), 5.92 (dd, J - 8.2, 4.2 Hz, 1 H, H-4, 6.08 (dd, J - 11.5, 2.0 Hz, 1 H, H-10'), 6.54 (ddd, J = 11.5 Hz, 9.2, 6.8, 1 H, H-9'), 7.35-8.10 (m, 4-H, aromatic protons); ^{13}C-NMR δ 7.9 (C14), 20.5 (CH_3CO), 20.8 (C16), 22.6 (C4'), 26.5 (C7), 28.2 (C8'), 34.5 (C3), 42.0 (C6), 47.7 (C13), 49.7 (C5), 57.0 (C2'), 60.6 (C7'), 62.4 (C5'), 65.0 (C12), 66.5 (C3'), 66.9 (C11), 68.1 (C8 and C15), 72.8 (C12'), 73.8 (C4), 79.1 (C2), 98.1 (C6'), 121.8 (C10'), 123.7 (C10), 128.1 (aromatic C), 130.0 (aromatic C, 2C's), 131.0 (aromatic C), 133.7 (aromatic C), 134.8 (aromatic C), 136.8 (C9), 148.3 (C9'), 164.4 (C1'), 166.3 (C=O, aryl), 166.8 (C11'), 170.5 (C=O, acetate).

Myrotoxin A Hidrate (16). Myrotoxin A hidrate was prepared in 80% yield from myrotoxin A (**13**) under the same conditions as those used for the conversion of myrotoxin B to myrotoxin B hidrate. Hidrate **16** was recrystallized from EtOAc/hexane, mp 198-203° C; IR 3500, 2850, 1750, 1700, 1350, 1200 cm^{-1}; ^{1}H-NMR δ 6.59 (dt, J - 11.4, 8.3 Hz, 1 H, H-9'), 5.90 (dd, J = 11.4, 2.0 Hz, 1 H, H-10'), 5.87 (m, 1 H, H-4), 5.40 (d, J = 5.1 Hz, 1 H, H-10), 4.51 and 4.15 (AB, J = 12.1 Hz, 1 H each, H-15), 3.91-3.81 (m, 2 H, H-5'), 3.53 (d, J = 5.2 Hz, 1 H, H-2), 3.61 (d, J = 5.1 Hz, 1 H, H-11), 3.42 (s, 1 H, H-2'), 3.17 and 2.74 (AB, J = 3.9 Hz, I H each, H-13), 3.04 (br s, 1 H, H-12'), 3.01 (m, 1 H, H-8'A), 2.46 (m, 1 H, H-3α), 2.38 (m, 1 H, H-8'B), 2.33 (m, 1 H, H-4'A), 2.19 (m, 1 H, H-3β), 2.15 (m, 2 H, H-8), 1.93 (m, 2 H, H-7), 1.69 (m, 3 H, H-7', H-4'B), 1.35 (s, 3 H, H-16), 0.73 (s, 3 H, H 14); ^{13}C-NMR δ 79.1 (C2), 35.0 (C3), 75.3 (C4), 49.0 (C5), 43.2 (C6), 19.7 (C7), 27.4 (C8), 140.2 (C9), 118.6 (C10), 67.4 (C11), 65.4 (C12), 47.6 (C13), 7.9 (C14), 62.3 (C15), 23.3 (C16), 166.1 (C1'), 57.2 (C2'), 65.3 (C3'), 23.4 (C4'), 65.8 (C5'), 97.5 (C6'), 20.4 (C7'), 27.0 (C8'), 149,7 (C9'), 121.9 (C10'), 167.1 (C11'), and 72.3 (C12'); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{27}H_{34}O_{10}$ + H m/z 519.5740, found 519.5722.

9β, 10β-Epoxymyrotoxin A Hidrate (19). To a solution of 43 mg (0.08 mmol) of myrotoxin A hidrate (**16**) in 5 mL dichloromethane was added 28.5 mg (80%, 016 mmol) of MCPBA and the mixture was stirred for 24 h at room temperature. The solvent was evaporated and the crude mixture was separated on the Chromatotron (1 mm SiO_2 plate, 30% EtOAc/hexane) to give 8.7 mg (19%) of epoxide **19** along with *ca.* 10 mg of recovered starting material. Compound **19** was recrystallized from dichloromethane, mp >190°C (dec); IR 3500, 3020, 1760, 1720, 1200, 1100 cm^{-1}; ^{1}H-NMR δ 6.61 (dt, J = 11.4, 7.6 Hz, 1 H, H-9'), 5.87 (dd, J = 11.4, 2.1 Hz, 1 H, H-10'), 5.86 (m, 1 H, H-4), 4.49 and 4.12 (AB, J = 12.1 Hz, 1 H each, H-15), 3.95 (m, 1 H, H-5'A), 3.78 (m, 1 H, H-5'B), 3.53 (d, J = 5.2 Hz, 1 H, H-2), 3.51 (d, J = 5.3 Hz, 1 H, H-11), 3.43 (s, 1 H, H-2'), 3.16 and 2.74 (AB, J = 3.9 Hz, 1 H each, H-13), 3.06 (d, J = 5.3 Hz, 1 H, H-10), 3.04 (br s, 1 H, H-12'), 3.00 (m, 1 H, H-8'A), 2.46 to 2.34 (m, 3 H, H-3α, H'8'B and H 4'A), 2.19 (dt, J = 14.6 Hz, 1 H, H-3'β), 1.40 (s, 3 H, H-16), 0.75 (S, 3 H, H-14); ^{13}C-NMR δ 78.7 (C2), 34.3 (C3), 75.5 (C4), 49.3 (C5), 42.9 (C6), 17.1 (C7), 28.9 (C8), 57.7 (C9), 58.3 (C10), 67.7 (C11), 64.6 (C12), 47.8 (C13), 8.0 (C14), 60.0 (C15), 22.2 (C16), 166.7 (C1'), 57.3 (C2'), 64.7 (C3'), 21.9 (C4'), 63.8 (C5'), 97.6 (C6'), 20.8 (C7'), 26.2 (C8'), 151.1 (C9'), 120.8 (C10'), 166.8 (C11'), and 72.9 (C12'), mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{27}H_{34}O_{11}$ + H m/z 535.5734, found 535.5748.

Preparation of Myrotoxin B Bromohydrin (23) To a solution of 100 mg (0.18 mmol) of myrotoxin B (**12**) in 2 mL of DMSO was added 64 mg (0.32 mmol) of NBS and 20 μL of H_2O, and the reaction mixture was stirred for 2 h at room temperature. Saturated $NaHCO_3$ was added and the yellow color was discharged, and the mixture was extracted with 3 x 10 mL of dichloromethane. The organic layer was washed twice with water and then dried (Na_2SO_4). Evaporation of solvent followed by PTLC on the Chromatotron (2 mm SiO_2, 30%-100% EtOAc/hexane) gave 63.8 mg (54%) of **23**, mp>200°C (dec); IR 3600, 2900, 1750, 1400, 1180 cm^{-1}; ^{1}H-NMR δ 6.44 (ddd, J = 11.6, 9.4, 5.4 Hz, 1 H, H-9'), 6.07 (dd, J = 11.6, 2.1 Hz, 1 H, H-10'), 5.86 (dd, J = 8.2, 4.1 Hz, 1 H, H-4), 5.66 (d, J = 5.3 Hz, 1 H, H-10), 5.24 (d, J = 4.3 Hz, 1 H, H-8), 5.0 (ddd, J = 11.2, 3.9, 1.6 Hz, 1 H, H-7'), 4.83 and 4.10 (AB, J = 12.2 Hz, 1 H each, H-15), 4.18 [d, $J_{7'6'\text{-OH}}$ = 1.6 Hz, 1 H, 6'-OH (disappears after D_2O exchange)], 3.90 (m, 2 H, H-5'), 3.84 (d, J = 5.0 Hz, 1 H, H-2), 3.65 (d, J = 5.3 Hz, 1 H, H-11), 3.55 (s, 1 H, H-2'), 3.50 (ddd, J = 14.4, 5.4, 2.1 Hz, 1 H, H-8'A), 3.11 and 2.82 (AB, J = 4.0 Hz, 1 H each, H-13), 2.90 (ddd, J = 14.4, 11.2, 9.4 Hz, 1 H, H-8'B), 2.59 [d, J = 3.9 Hz, 1 H, H-12' (s, after D_2O exchange)], 2.47 (m, 2 H, H-3α, H-4'H), 2.25 (m, 3 H, H-3β, H-7), 1.93 (s, 3 H, CH_3CO_2), 1.82 (m, 1 H, H-4'B), 1.75 (s, 3 H, H-16), 0.87 (s, 3 H, H-14); ^{13}C-NMR δ 78.9 (C2), 34.5 (C3), 73.1 (C4), 49.6 (C5), 41.9 (C6), 20.9 (C7), 68.2 (C8), 136.7 (C9), 123.7 (C10), 66.8 (C11), 65.1 (C12), 47.7 (C13), 8.1 (C14), 66.3 (C15), 21.0 (C16), 166.4 (C1'), 56.1 (C2'), 63.7 (C3'), 21.3 (C4'), 64.7 (C5'), 98.0 (C6'), 47.6 (C7'), 28.1 (C8'), 147.6 (C9'), 122.3 (C10'), 166.9 (C11'), 72.6 (C12'), 20.5 (acetate CH_3), and 170.6 (acetate $\underline{C}O$);

mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{29}H_{35}BrO_{12}$ + H m/z 655.4991, found 655.5017.

Preparation of 6'-Azido-7'-iodo-6',7'-dihydromyrotoxin B (21 and 22). To a stirred slurry of 5.8 mg (0.09 mmol) of sodium azide in 1 mL of dry acetonitrile in a methanol-ice bath (-15° C) was added slowly 6.7 mg (0.04 mmol) of iodine monochloride (Aldrich). The reaction mixture was stirred for 30 min and, after 20 mg (0.036 mmol) of myrotoxin B was added, allowed to warm to room temperature and stirred for 6 h. The red-brown slurry was poured into 5 mL of water, and the mixture was extracted with 3 x 5 mL of dichloromethane. The organic layer was washed with 5% sodium thiosulfate leaving a colorless solution. This solution was washed with water and dried over Na_2SO_4. Removal of CH_2Cl_2 *in vacuo* at room temperature produced the iodo azide adduct. Further purification by PTLC on the Chromototron (1 mm, 30-70% EtOAc/hexane) gave 51% of (R)-6'-azido-(S)-7'-iodo-myrotoxin B (**21**), mp > 200° C (dec); IR 3600, 2900, 2250, 1740, 1720, 1240, 1190, 1110 cm^{-1}; ^{1}H-NMR δ 6.30 (ddd, J = 11.4, 9.5, 5.4 Hz, 1 H, H-9'), 6.09 (dd, J = 11.4, 2.0 Hz, 1 H, H-10'), 5.82 (dd, J = 8.2, 4.1 Hz, 1 H, H-4), 5.64 (d, J = 5.4 Hz, 1 H, H-10), 5.24 (d, J = 5.1 Hz, 1 H, H-8), 5.01 (dd, J = 12.1, 4.3, Hz, 1 H, H-7'), 4.80 and 4.11 (AB, J = 12.3 Hz, 1 H each, H-15), 4.06 (m, 1 H, H-5'A), 4.01 (m, 1 H, H-5'B), 3.83 (d, J = 5.1 Hz, 1 H, H-2), 3.63 (d, J = 5.4 Hz, 1 H, H-11), 3.54 (s, 1 H, H-2'), 3.38 (ddd, J = 14.2, 4.3, 2.0 Hz, 1 H, H-8'A), 3.10 and 2.82 (AB, J = 3.8 Hz, 1 H each, H-13), 2.74 (m, 1 H, H-8'B), 2.65 (m, 1 H, H'4'A), 2.61 [d, J = 3.2 Hz, 1 H, H-12' (s, after D_2O exchange)], 2.46 (dd, J = 15.5, 8.2 Hz, 1 H, H-3'α), 2.21 (m, 1 H, H3'β), 2.08 (m, 3 H, H-7 and H-4'B), 1.92 (s, 3 H, CH_3CO_2), 1.75 (s, 3 H, H,16), 0.87 (s, 3 H, H-14); ^{13}C-NMR δ 78.8 (C2), 34.6 (C3), 75.9 (C4), 48.4 (C5), 42.0 (C6), 21.5 (C7), 68.2 (C8), 136.4 (C9), 123.7 (C10), 66.8 (C11), 65.1 (C12), 48.0 (C13), 5.9 (C14), 66.4 (C15), 20.1 (C16), 165.3 (C1'), 53.3 (C2'), 63.3 (C3'), 21.5 (C4'), 65.5 (C5'), 82.9 (C6'), 43.7 (C7'), 29.8 (C8'), 144,8 (C9'), 124.0 (C10'), 167.0 (C11'), 75.5 (C12'), 21.1 (acetate $\underline{C}H_3$), and 170.3 (acetate $\underline{C}O$); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{29}H_{34}IN_3O_{11}$ + H m/z 728.5203, found 728.5244.

The same reaction also afforded 5% of a lower R_f compound (R)-6'-azido-(R)-7'-iodo-6',7'-dihydromyrotoxin B (**22**), mp 180°C (decomp.); IR 3600, 3000, 2800, 2250, 1750, 1710, 1150, cm^{-1}; ^{1}H-NMR δ 6.35 (ddd, J = 11.4, 9.6, 5.3 Hz, 1 H, H-9'), 6.00 (d, J = 11.4, Hz, 1 H, H-10'), 5.81 (d, J = 5.6 Hz, 1 H, H-10), 5.55 (dd, J = 8.3, 4.1 Hz, 1 H, H-4), 5.29 (d, J = 5.4 Hz, 1 H, H-8), 4.78 and 3.69 (AB, J = 12.1 Hz, 1 H each, H-15), 4.49 (dd, J = 12.1, 8.3 Hz, 1 H, H-7'), 4.12 (m, 1 H, H-5'A), 4.05 (m, 1 H, H-5'B), 3.82 (d, J = 5.1 Hz, 1 H, H-2), 3.62 (d, J = 5.6 Hz, 1 H, H-11), 3.35 (s, 1 H, H-2') 3.18 and 2.89 (AB, J = 3.9 Hz, 1 H each, H-13), 2.81 (m, 1 H, H-4'A), 2.62 (dd, J = 15.5, 8.3 Hz, 1 H, H-3α), 2.46 (dd, J = 14.9, 8.3 Hz, 1 H, H'8'A), 2.20 (m, 3 H, H-3β, H-4'B, H-8'B), 2.06 (s, 3 H CH_3CO_2), 1.98 (m, 2 H-7), 1.75 (s, 3 H, H-16), 0.87 (s, 3 H, H-14); ^{13}C-NMR δ 78.7 (C2), 34.5 (C3), 75.9 (C4), 48.2 (C5), 43.0 (C6), 21.2 (C7), 68.4 (C8), 136.5 (C9), 124.0 (C10), 67.3 (C11), 65.1 (C12), 48.1 (C13), 5.8 (C14), 66.3 (C15), 20.2 (C16), 165.2 (C1'), 55.3 (C2'), 62.8 (C3'), 21.2 (C4'), 65.5 (C5'), 83.5 (C6'), 45.9 (C7'), 30.8 (C8'), 151,0 (C9'), 124.5 (C10'), 167.1 (C11'), 75.0 (C12'), 21.0 (acetate $\underline{C}H_3$), and 170.3 (acetate $\underline{C}O$).

Preparation of Diene Azide 24. To a solution of 10 mg (0.014 mmol) iodo azide **21** in 5 mL of dry THF was added 6.2 μL (0.042 mmol) of DBU, and the reaction was warmed at 50°C under a nitrogen atmosphere for a 30 min period. The mixture was cooled and poured onto a solution of ice in 1N HCl. The aqueous mixture was extracted with dichloromethane, and the extract was washed with aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated, and the crude product was subjected to PTLC on the Chromatotron (1 mm, 30-70% EtOAc/hexane) to yield 4.1 mg (50%) of compound **24** which was recrystallized from EtOAc/hexane, mp 209°C (dec): IR 3600, 2980, 2850, 2250, 1720, 1180, cm^{-1}; ^{1}H-NMR δ 7.10 (dd, J = 16.2, 6.7 Hz, 1 H, H-8'), 6.68 (dd, J = 11.3, 6.7 Hz, 1 H, H-9'), 5.95 (d, J = 11.3 Hz, 1 H, H-10'), 5.88 (dd, J = 8.2, 4.8 Hz, 1 H, H-4), 5.66 (d, J = 5.5 Hz, 1 H, H-10), 5.60 (d, J = 16.2 Hz, 1 H, H-7'), 5.21 (br s, 1 H, H-8), 4.65 and 4.22 (AB, J = 12.3 Hz, 1 H each, H-15), 4.18 (m, 1 H, H-5'A), 4.02 (m, 1 H, H-5'A), 4.02 (m, 1 H, H-5'B), 3.82 (d, J = 4.9 Hz, 1 H, H-2), 3.65 (d, J = 5.5 Hz, 1 H, H-11), 3.19 (s, 1 H, H-2') 3.11 and 2.80 (AB, J = 4.0 Hz, 1 H each, H-13), 2.78 (m, 1 H, H-4'A), 2.45 (dd, J = 15.6, 8.2 Hz, 1 H, H-3α), 2.24 (m, 1 H, H-3β), 2.13 (m, 2 H, H-7), 1.95 (m, 1 H, H-4'B), 1.91 (s, 3 H, CH_3CO_2), 1.75 (s, 3 H-16), 0.76 (s, 3 H, H-14); ^{13}C-NMR δ 79.1 (C2), 34.4 (C3), 74.9 (C4), 49.6 (C5), 42.0 (C6), 26.4 (C7), 68.4 (C8), 136.7 (C9), 121.7 (C10), 67.3 (C11), 65.1 (C12), 47.9 (C13), 8.1 (C14), 66.7 (C15), 20.5 (C16), 166.2 (C1'), 57.3 (C2'), 62.1 (C3'), 22.3 (C4'), 62.9 (C5'), 92.9 (C6'), 142.1 (C7'), 131.1 (C8'), 149.7 (C9'), 123.8 (C10'), 166.5 (C11'), 73.4 (C12'), 20.8 (acetate CH_3), and 170.7 (acetate $\underline{C}O$); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{29}H_{33}N_3O_{11}$ + H m/z 600.6078, found 600.6059. UV spectrum, λ_{max} (EtOH) = 250 nm.

Preparation of 6'-Isocyano-7'-iodo-6',7'-dihydromyrotoxin B (20). To 2 mL of anhydrous dichloromethane was added 13.5 mg (0.053 mmol) of I_2 and 10.5 mg (0.07 mmol) of freshly prepared silver cyanate.[32] The slurry was stirred at room temperature for 30 min, after which 30 mg (0.054 mmol) of myrotoxin B was added. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 h. The inorganic salts (AgI and AgNCO) were filtered through Celite, and the solution was evaporated. The crude reaction mixture was subjected to PTLC on the Chromatotron (1 mm SiO_2 plate, 20%-70% EtOAc/hexane) to give 4.9 mg (16% yield) of iodoisocyanate **20**, mp>190°C (dec); IR 3500, 2850, 2850, 2240, 1750, 1720, 1190, 1050 cm^{-1}; ^{1}H-NMR δ 6.49 (ddd, J = 11.4, 9.3, 5.6 Hz, 1 H, H-9'), 6.12 (d, J = 11.4 Hz, 1 H, H-10'), 5.80 (dd, J = 8.1, 4.0 Hz, 1 H, H-4), 5.65 (d, J = 5.2 Hz, 1 H, H-10), 5.28 (d, J = 4.3 Hz, 1 H, H-8), 4.85 and 4.13 (AB, J = 12.1 Hz, 1 H each, H-15), 4.62 (dd, J = 12.0, 4.5 Hz, 1 H, H-7'), 4.18 [br 2, 1 H, H-12' (s, after D_2O exchange)], 4.00 (m, 2 H, H-5'), 3.82 (d, J = 4.9 Hz, 1 H, H-2), 3.69 (m, 1 H, H-2), 3.69 (m, 1 H, H-8'A), 3.60 (d, J = 5.2 Hz, 1 H, H-11), 3.36 (s, 1 H, H-2'), 3.13 and 2.80 (AB, J = 4.0 Hz, 1 H each, H-13), 2.78 (m, 1 H, H-8'B), 2.48 (dd, J = 15.3, 8.1 Hz, 1 H, H-3'α), 2.20 (m, 3 H, H-3'β, H-4'), 2.18 (s, 3 H, CH_3CO_2), 2.11 (m, 2 H, H-7), 1.98 (s, 3 H, H-16), 0.80 (s, 3 H, H-14); ^{13}C-NMR δ 79.0 (C2), 35.5 (C3), 75.5 (C4), 48.2 (C5), 43.7 (C6),

20.6 (C7), 68.9 (C8), 136.7 (C9), 123.0 (C10), 66.9 (C11), 65.7 (C12), 48.1 (C13), 7.5 (C14), 65.5 (C15), 21.0 (C16), 165.7 (C1'), 53.5 (C2'), 63.2 (C3'), 21.2 (C4'), 67.7 (C5'), 82.9 (C6'), 44.7 (C7'), 30.8 (C8'), 144.3 (C9'), 124.0 (C10'), 167.1 (C11'), 75.4 (C12'), 20.0 (acetate $\underline{C}H_3$), and 170.7 (acetate $\underline{C}O$); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{30}H_{34}INO_{12}$ + H m/z 728.5175, found 728.5160.

Preparation of 6',7',9',10'-Tetrahydromyrotoxin B (28). To a solution of 6.0 mg of 10% Pd/C in 10 mL of ethanol saturated with H_2, was added 30 mg (0.054 mmol) of myrotoxin B (**12**). The slurry was stirred until 6.8 mL (0.11 mmol) of H_2 was consumed (35 min). The solid was removed by filtration and the solvent was concentrated. Purification on the Chromatotron (1 mm SiO_2 plate, 33% EtOAc/hexane) gave 23 mg (75% yield) of tetrahydro **28**, mp >210°C (dec); IR 3600, 3010, 1760, 1740, 1400, 1210, 1020 cm^{-1}; ^{1}H-NMR δ 5.78 (dd, J = 8.3, 4.4 Hz, 1 H, H-4), 5.64 (d, J = 5.2 Hz, 1 H, H-10), 5.21 (d, J = 5.0 Hz, 1 H, H-8), 4.64 and 4.23 (AB, J = 12.1 Hz, 1 H each, H-15), 4.04 and 3.79 (m, 1 H each, H5'), 3.80 (d, J = 4.8 Hz, 1 H, H-2), 3.64 (d, J = 5.2 Hz, 1 H, H-11), 3.29 (s, 1 H, H-2'), 3.11 and 2.82 (AB, J = 3.9 Hz, 1 H each, H-13), 3.02 (s, after D_2O exchange, 1H, H-12'), 2.54 to 2.39 (m, 3 H, H-4'A, H-6', H-3α), 2.24 to 2.16 (m, 2 H, H-4'B, H-3β), 2.08 (m, 4 H, H-7, H-7'), 1.92 (s, 3 H, CH_3CO_2), 1.74 (s, 3 H, H-16), 1.78 to 1.02 (m, 6 H, H-10', H-9', H-8'), 0.88 (s, 3 H, H-14); ^{13}C-NMR δ 80.3 (C2), 35.1 (C3), 74.9 (C4), 48.8 (C5), 42.3 (C6), 23.8 (C7), 68.4 (C8), 136.6 (C9), 123.7 (C10), 66.8 (C11), 65.2 (C12), 47.8 (C13), 8.1 (C14), 65.9 (C15), 20.9 (C16), 166.5 (C1'), 57.6 (C2'), 63.3 (C3'), 22.7 (C4'), 58.6 (C5'), 78.8 (C6'), 27.7 (C7'), 26.2 (C8'), 26.7 (C9'), 35.9 (C10'), 174.9 (C11'), 72.6 (C12'), 20.5 (acetate $\underline{C}H_3$), and 170.7 (acetate $\underline{C}O$); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{29}H_{38}O_{11}$ + H m/z 563.6276, found 563.6251.

Preparation of Hexahydromyrotoxin A (29). A solution of 30 mg of myrotoxin B (**12**) (0.11 mmol) and 6 mg of Pd/C in 10 mL of ethanol was stirred at room temperature while a stream of hydrogen gas was bubbled through the mixture for 1 h. The mixture was worked up as above to give 21 mg (79%) of **29** which was recrystallized from CH_2Cl_2, mp 210°C (dec): IR 3500, 2950, 1760, 1740, 1220, 1040 cm^{-1}; ^{1}H-NMR δ 5.71 (dd, J = 8.1, 4.4 Hz, 1 H, H-4), 4.60 and 4.14 (AB, J = 12.2 Hz, 1 H each, H-15), 4.04 and 3.85 (m, 1 H each, H5'A and H-5'B), 3.82 (d, J = 3.8 Hz, 1 H, H-2'), 3.79 (d, J = 5.4 Hz, 1 H, H-11), 3.33 (s, 1 H, H-2'), 3.16 and 2.84 (AB, J = 4.0 Hz, 1 H each, H-13), 3.03 (br s, 1 H, H-12'), 2.54 (br s, 1 H, H-6'), 2.50 (m, 3 H, H-4'A, H-8), 2.47 (dd, J = 15.5, 8.3 Hz, 1 H, Hα), 2.20 (m, 2 H, H-7), 2.08 (m, 2 H, H-4'B, H-3β, 1.95 (m, 2 H, H-7'), 1.77 (m, 2 H, H-10'), 1.75 (m, 1 H, H-9), 1.65 (m, 2 H, H-8'), 1.35 (m, 2 H, H-10), 1.08 (m, 2 H, H-9'), 0.87 (d, J = 6.4 Hz, 3 H, H-16), 0.85 (s, 3 H, H-14); ^{13}C-NMR δ 80.2 (C2), 35.8 (C3), 74.9 (C4), 49.2 (C5), 43.7 (C6), 23.0 (C7), 23.4 (C8), 26.5 (C9), 23.4 (C10), 64.5 (C11), 65.1 (C12), 48.7 (C13), 8.0 (C14), 69.8 (C15), 21.8 (C16), 166.9 (C1'), 58.1 (C2'), 63.2 (C3'), 23.8 (C4'), 58.6 (C5'), 79.2 (C6'), 27.8 (C7'), 26.5 (C8'), 29.6 (C9'), 36.4 (C10'), 174.8 (C11'), and 72.9 (C12'); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{27}H_{38}O_9$ + H m/z 507.6065, found 507.6094.

Hexahydrobaccharinoid B4 (27). By the same procedure as that described above, 25 mg of tetrahydrobaccharinoid B4 (**26**)[29] in 10 mL of absolute ethanol was hydrogenated at atmospheric pressure using 10% palladium on charcoal (9 mg) as catalyst. After 1 equivalent of hydrogen was taken up (~30 min), the catalyst was removed by filtration and the solvent evaporated to afford 15 mg (60%) of the hexahydro derivative **27**. Recrystallization from dichloromethane/hexane gave **27**, mp 118-120°C; IR 3610, 1745, 1680 cm^{-1}; ^{1}H-NMR δ 0.74 (s, 3 H, H-14), 0.96 (d, J = 6.4 Hz, 3 H, H-16), 1.09 (d, J = 6.3 Hz, 3 H, H-14') (s, 3 H, H-12'), 2.85, 3.16 (AB, J = 3.9 Hz, 1 H each, H-13), 3.45 (s, 1 H, H-2'), 4.25, 4.33 (AB, J = 12.3 Hz, 1 H each, H-15), 5.65 (dd, J = 3.8 Hz, 1 H, H-4); ^{13}C-NMR δ 79.3 (C2), 35.0 (C3), 75.8 (C4), 49.2 (C5), 46.7 (C6), 24.5 (C7), 73.2 (C8), 32.6 (C9), 33.8 (C10), 68.2 (C11), 64.6 (C12), 48.4 (C13), 7.3 (C14), 65.3 (C15), 19.1 (C16), 167.2 (C1'), 56.4 (C2'), 64.9 (C3'), 77.2 (C4'), 70.9 (C5'), 86.7 (C6'), 24.9 (C7'), 31.7 (C8'), 34.4 (C9'), 35.9 (C10'), 173.2 (C11'), 17.5 (C12'), 72.0 (C13'), and 12.5 (C14'); mass spectrum (HRMS, DCI, methane gas reagent) calc for $C_{29}H_{44}O_{11}$ + H m/z 569.6754, found 569.6730.

4',8,13'-Triacetate of 27: ^{1}H-NMR δ 0.70 (s, 3 H, H-14), 0.88 (d, J = 6.2 Hz, 3 H, H-16), 1.06 (d, J = 10.2 Hz, 3 H, H-14'), 1.50 (s, 3 H, H-12'), 1.99, 2.01, 2.09 (s, 3 H each, CH_3COO), 2.82, 3.17 (AB, J = 3.9 Hz, 1 H each, H-13), 3.56 (s, 3 H, H-2'), 4.86 (dq, J = 4.8 Hz, 6.5 Hz, 1 H, H-13'), 5.67 (dd, 4.8 Hz, 7.8 Hz, 1 H-4).

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