Characterization of an *abeo*-Taxane: Brevifoliol and Derivatives

Steve Tremblay,[†] Chantal Soucy,[‡] Neil Towers,[§] Philip J. Gunning,[§] and Livain Breau*[,†]

Département de Chimie, Université du Québec à Montréal, C.P. 8888 Succ. Centre-Ville, Montréal (PQ), Canada, H3C 3P8, and Department of Botany, University of British Columbia, 6270 University Boulevard, Vancouver B.C., Canada, V6T 1Z4

Received October 16, 2003

Brevifoliol is a natural diterpene isolated from *Taxus baccata* Nutt. A series of brevifoliol **1** derivatives, **2**−**8** and **10**, were prepared for characterization and semisynthesis purposes and included the introduction of acetyl, Troc, and TES groups at C-5 and C-13. Derivatives **16**−**20** of 5-acetylbrevifoliol **2** were obtained via esterification with cinnamic acid, with both 2*S*-(−)- and 2*R*-(+)-3-phenyllactic acid, and with *N*-benzoyl-(2′*R*,3′*S*)-3′-phenylisoserine at C-13. Brevifoliol compounds **12**, **13**, and **15** with either 2*S*-(−)-phenyllactate moieties at C-5 and C-13 or an *N*-benzoyl-(2′*R*,3′*S*)-3′-phenylisoserinyl at C-13 were also prepared. An *abeo*-taxane structure for **1** was clearly defined from the ^{13}C NMR analysis of the 5-acetyl-13-oxo derivative **8** and from the conversion of **1** into **10**, a conformationally restrained compound having a C-13, C-15 oxygen bridge. The biological activity of each of these derivatives is being studied.

The diterpenoid paclitaxel (Taxol), originally isolated from the bark of *Taxus brevifolia*,[1] has stimulated intense research efforts in recent years because of its remarkable anticancer activity.[2,3] Recently, a lot of attention has been focused on the search for other members of the taxane group[4] that may be directly active or may serve as precursors for the semisynthesis of other active analogues.[5−7] The following work describes a detailed characterization of brevifoliol **1**, a relatively abundant metabolite isolated from *Taxus brevifolia* needles (up to 0.30%). We have also been interested in the synthesis of brevifoliol derivatives for their biological activity, that is, microtubule disassembly and P-glycoprotein (P-gp) inhibition.

Brevifoliol had originally been proposed to have a taxa-4(20),11-diene system, **A**, similar to that of taxol[8] (Figure 1). Lewis[9] then proposed a taxane structure, **B**, for brevifoliol, while, later, Georg[10] and Appendino[11] both revised the structure to an 11(15→1)-*abeo*-taxa-4(20),11-diene skeleton, **1**. These assignments were based solely on 1D and 2D NMR spectral data, and three key quaternary signals (i.e., C-1, C-8, and C-15) were missassigned.[9,10] 11-(15→1)-*abeo*-Taxanes are, in general, difficult to characterize by NMR spectroscopy since they shift between different conformational isomers in solution.[12] In fact, most of the *abeo*-taxane structures reported in the literature needed to be confirmed by X-ray crystallography.[11−13]

An X-ray crystal structure of **2** was obtained by one of the present coauthors (C.S.).[14] It showed an 11(15→1)-*abeo*-taxane structure, but unfortunately, the crystals were unstable and its structure was obtained only after replacing the reflections measured during the first 30 h by a set of data taken at the end. Thus, the possibility of a skeletal rearrangement of brevifoliol to the 11(15→1)-*abeo*-taxane structure during the isolation and/or acetylation or during X-ray irradiation could not be ruled out. Indeed, there are examples of such chemical rearrangements in the literature.[15,16]

Results and Discussion

An extract of the needles and twigs of *T. brevifolia* was obtained as previously described.[8] We optimized the isolation of brevifoliol from such extracts. An updated spectral characterization of brevifoliol, **1**, is given in Tables S1 and S2 (Supporting Information).

We began our investigation with the preparation of various derivatives with substituents at C-5 and C-13 (Figure 1). These included the mono- and bisacetyl, mono- and bis-2,2,2-trichloroethoxycarbonyl (Troc), and bis-triethylsilyl (TES) groups. Although 5-, 13-acetyl, and 5,13-bisacetylbrevifoliol, **2**, **3**, and **4**,[8,14] are known in the literature, they have not been adequately characterized. The Troc protecting group was introduced at C-5 with high selectivity by treatment of brevifoliol with Troc-Cl at −25 °C. Reactions at higher temperatures (i.e., 22 and 43 °C) afforded **5**, along with up to 27% of 5,13-bisTroc-brevifoliol **6**. In these reactions, the corresponding 13-Troc derivative could not be isolated. To our surprise, all attempts to prepare the 5-TES derivative gave only low yields of a single product, 5,13-TES-brevifoliol, **7**. However, **7** was obtained in good yield when 3.5 equiv of TESCl was used. Attempts to prepare the corresponding 5- and 13-FMOC (fluorenylmethyloxycarbonyl) derivatives by treating **1** with an excess of FMOC-Cl in pyridine resulted in the recovery of unreacted brevifoliol, even when the reaction mixture was heated to 50 °C. Similarly, the introduction of a benzyl group at C-13 of **5**, via the use of an excess of benzyl bromide in the presence of a catalytic amount of n-Bu_4NI and using dimethylamino pyridine (DMAP) as the base in pyridine, met with failure even when heated to 80 °C. All of these transformations illustrate unprecedented chemical behavior for **1**.

None of these derivatives afforded crystals suitable for X-ray analysis. Nonetheless, we were able to fully characterize all compounds synthesized. As mentioned above, 11-(15→1)-*abeo*-taxoids generally undergo a slow equilibration between two or more conformational isomers in solution, a characteristic of this type of diterpenoid structure.[12] Thus, the typical ^{1}H spectrum of an *abeo*-taxane usually displays a broadening of most of the signals and includes the appearance of many minor additional peaks.[13] However, the room-temperature ^{1}H and ^{13}C NMR spectra of **2**, **3**, and **5** were very similar to that of brevifoliol, **1**, being characterized by the same sharp, well-resolved first-order spectra with chemical shifts, multiplicities, and NOE effects as those of the taxanes. Also, a broad doublet for H-9 was observed in all derivatives, and in the cases of 5,13-disubstituted derivatives **4**, **6**, and **7**, additional broad peaks were noted for the protons assigned to H-5, -10, and

* To whom all correspondence should be sent. E-mail: breau.livain@uqam.ca. Tel: (514) 987-3000, ext 8788#. Fax: (514) 987-4054.
[†] Université du Québec à Montréal.
[‡] ConjuChem, 225 President-Kennedy, Suite 3950, Montréal (PQ), H2X 3Y8.
[§] University of British Columbia.

10.1021/np0304565 CCC: $27.50
Published on Web 04/27/2004

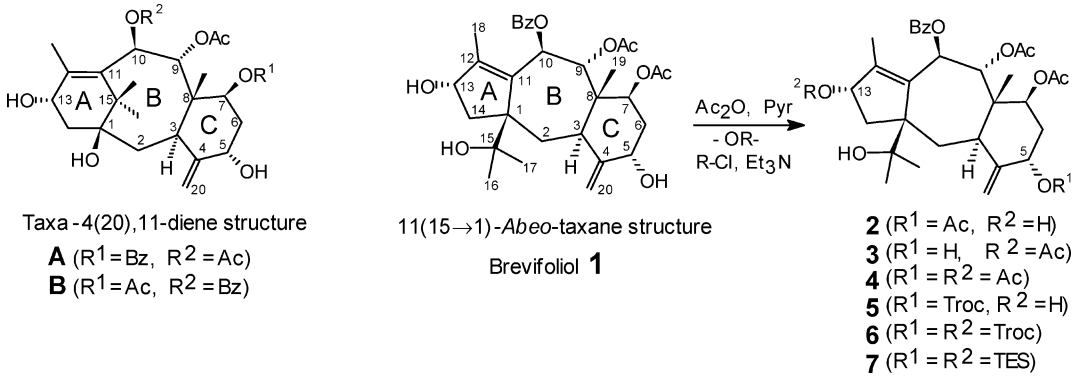

Figure 1. Proposed structures for brevifoliol and syntheses of C-5, C-13 derivatives **2**−**7**.

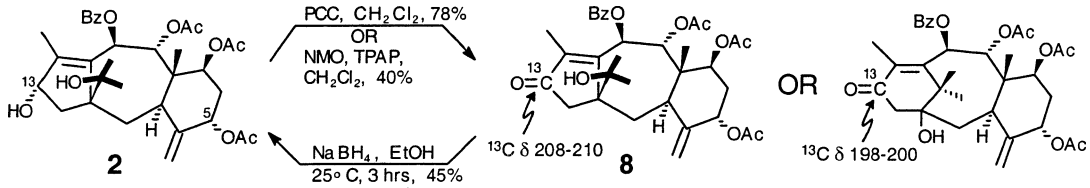

Figure 2. Oxidation of **2** to the conjugated ketone **8** and reduction back to **2**.

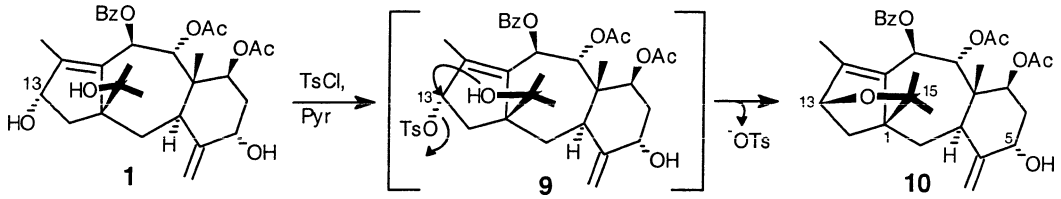

Figure 3. Conversion of brevifoliol **1** to the C-13, C-15 bridge ether compound **10**.

-13. The line broadening of these signals is consistent with an *abeo*-taxane structure for these derivatives.

In the HMBC spectrum of **2**, the signals at δ 5.34 (s, H-5), 5.58 (dd, H-7), and 6.01 (d, H-9) were correlated to three acetyl carbonyl signals at δ 169.8, 170.9, and 170.1, which indicates that these acetyl groups are located at C-5, -7, and -9. Unfortunately, in all cases, the HMBC spectra, acquired at various evolution delays, did not show any key correlations between H-10 and C-15 nor between H-10 and C-1. Also, while a correlation between the signals for the protons of Me-16 and Me-17 with the peak assigned to C-15 was observed, key correlations of these protons with the resonances for the carbons at C-1 and C-11, usually observed in taxane structures, were either absent or buried within the background noise. Confronted with the persistent uncertainty surrounding the analyses of the various 2D NMR data of compounds **1**−**7**, we envisaged other simple chemical transformations that would enable us to establish a more clear-cut distinction between the 11-(15→1)-*abeo*-taxane structure and that of the taxanes, that is, between a five- and six-membered A ring, respectively. To this end, we reasoned that oxidation of the hydroxyl function at C-13 would convert the A ring into either a five- or six-membered enone, which should be easy to differentiate by ^{13}C NMR spectroscopy. Pyridinium chlorochromate (PCC) oxidation of 5-acetylbrevifoliol, **2**, yielded ketone **8** (Figure 2), for which the room-temperature ^{1}H and ^{13}C NMR spectra displayed many broad signals. The ^{13}C NMR spectrum was, nonetheless, quite informative. It is known that the carbonyl of the five-membered A ring enone typically resonates further downfield (δ 208−210)[17,18] than that of the corresponding six-membered A ring enone in taxinines (δ 198−200).[19] The ^{13}C NMR spectrum of enone **8** showed a single peak at δ 207, which suggests a five-membered enone and, thus, an 11(15→1)-*abeo*-taxane structure. To verify that there had not been any skeletal rearrangement of **2** induced by PCC, which is an acidic reagent, another oxidation of **2** was carried out under neutral conditions[20] with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as catalyst and co-oxidant, respectively. This reaction provided the same enone. Indeed, the reduction of enone **8** with $NaBH_4$ in EtOH produced **2** once again, thus ruling out the possibility of rearrangement of the A ring.

Although quite useful, this method is limited to substrates having only one free secondary hydroxyl (i.e., C-13). Another transformation would place a leaving group at C-13. In an *abeo*-taxane structure such as **9**, the angular tertiary C-15 hydroxyl group is well positioned to undergo an intramolecular nucleophilic substitution to form a bridge ether (Figure 3). Such a substitution reaction cannot take place with a taxane-type structure, but it should be possible to isolate derivatives substituted at C-5 and C-13. To our delight, treatment of brevifoliol with tosyl chloride provided a single new product, **10** (Figure 3). Both the ^{1}H and ^{13}C NMR spectra displayed sharp, well-resolved lines at room temperature, consistent with a conformationally fixed structure. A FABMS showed a parent peak at 538 amu for the $[M]^+$ ion, which corresponds to a dehydrated brevifoliol. The peak usually observed at δ 2.7 (OH at C-15) in **1** was also absent in **10**. The unusual shielding of the resonance for H-9 (0.85 ppm) is indicative of a change of conformation relative to **1**.[12] Furthermore, the ^{13}C resonances of all the carbons in ring A and those surrounding this ring were either shielded by an average of 3.5 ppm (C-2, -9, -10, and -12) or deshielded by 4.5 ppm on average (C-11, -13, -14, and -15) relative to those of **1** (Table S2). Thus, the conformational changes observed essentially affect ring A and the connecting parts of ring B. Together, these results are consistent with a substitution product having the

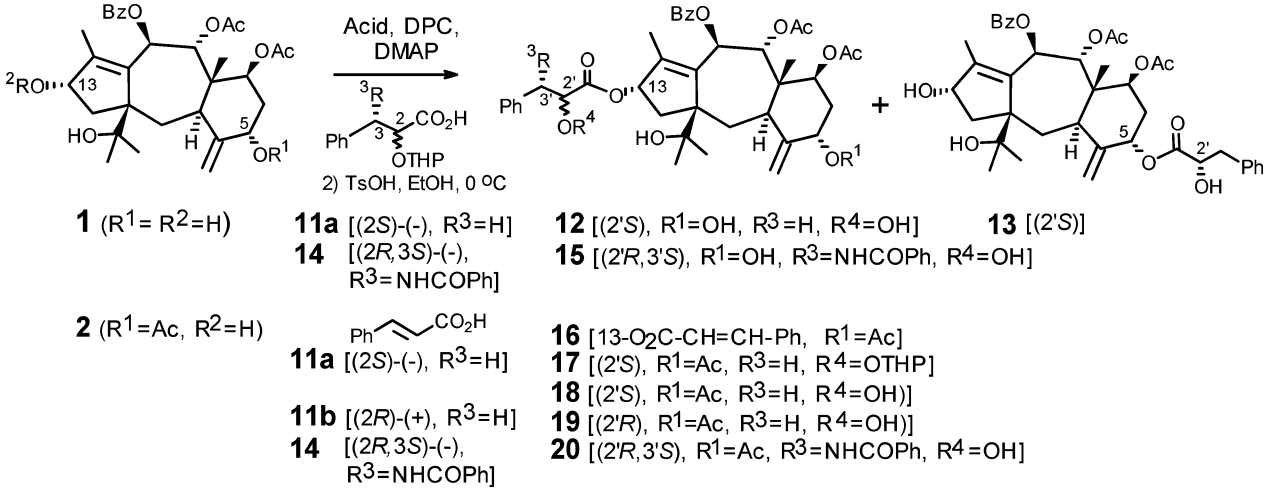

Figure 4. Synthesis of brevifoliol derivatives **12**, **13**, and **15**−**20**.

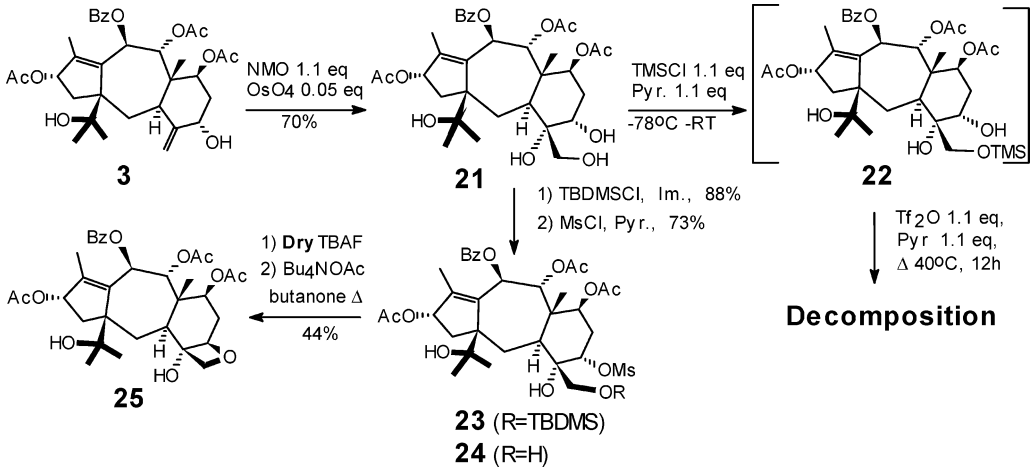

Figure 5. Construction of an oxetane D ring on derivative **3**.

bridge ether depicted for **10**. This structure was unambiguously confirmed by the detection of long-range correlations between H-13 and C-1, C-11, in the HMBC spectrum. Such correlations are not feasible for a taxane structure; therefore, brevifoliol has an 11(15→1)*abeo*-taxane structure. A consideration of the optical rotations provides an interesting side note since all known 13-α-hydroxylated 11(15→1)-*abeo*-taxane structures reported[12,15,21] had negative rotations, while those derivatives having a C13−C15 oxygen bridge (i.e., 13-*β* oxygenated derivatives such as **10**) have positive ones.[12] The above findings agree with that reported for an *abeo*-taxane product having also a C13−C15 bridge ether which was isolated from *Taxus x media* Rehd. Cv Hicksii.[12]

Having firmly established a five-membered A ring for brevifoliol, **1**, we set out to further modify its structure in an attempt to enhance its biological activity profile. Over the past 10 years structure−activity relationship studies[5−7,15,22] have revealed some structural elements that seem to be essential for the antitumor activity of the taxanes. More specifically, these elements include a C-13 phenylisoserine side chain, an oxetane D ring, a C-4 alkoxy group, and a C-2 aromatic ester or cyclohexanoate moiety. As for the inhibition of the drug transport activity of P-gp, the most active taxoids have in common a C-5 cinnamoyl moiety. The A ring could be five- or six-membered, and the C-13 was either substituted with an acetyl group or was a ketone.[23]

Our initial objective was the introduction of a lateral side chain such as cinnamoyl, (*R*)- and (*S*)-phenyl lactate (which may be considered to be deaminated derivatives of phenylisoserine or hydrated derivatives of the cinnamate moiety) and the phenylisoserinate at the C-13 and C-5 positions. A subsequent objective was the construction of an oxetane D ring.

Our first structural modification of brevifoliol, **1**, was to couple it to the propanoic acid (2*S*)-**11a** to give a mixture of isomers **12** and **13** having a C-13 side chain and a free C-5 hydroxyl group and vice versa (Figure 4). These esterifications were carried out using the coupling agent dipyridyl carbonate (2-DPC).[24] An *N*-benzoyl-(2′*R*,3′*S*)-phenylisoserine moiety was introduced at C-13 of **1** via esterification of the corresponding *O*-tetrahydropyranyl (THP)-protected acid **14**, [25] and subsequent hydrolysis of the THP ether afforded the ester **15**.[26] 5-Acetylbrevifoliol, **2**, was coupled with cinnamic acid to provide ester **16**. Both phenyl lactate antipodal moieties were introduced at C-13 of **2**, via esterification of the corresponding O-THP-protected acids, (2*S*)-(−)-**11a** or (2*R*)-(+)-**11b**, and subsequent hydrolysis of the THP ether intermediate **17** produced the hydroxy ester derivatives **18** and **19**. Only the S-intermediate was isolated. An *N*-benzoyl-(2′*R*,3′*S*)-phenylisoserine moiety was also introduced via esterification of the corresponding acid, **14**, with the hydroxyl at the C-13 of **2** to provide **20**.

Our next goal was to place an oxetane D ring on the brevifoliol skeleton. Several methods to accomplish this transformation have been reported.[7,27] A method developed by Danishefsky's group[27c] was applied to compound **3**, but this led to complete decomposition of the starting material

(Figure 5). To close the oxetane ring, we adapted Potier's protocol.[7] Thus, osmylation of **3** was carried out with *N*-methylmorpholine-*N*-oxide (NMO) and OsO_4 to produce the triol **21**. We protected the primary alcohol function as the *tert*-butyldimethylsilyl ether and then mesylated the secondary alcohol. This gave **23**, while subsequent removal of the silane function with dry TBAF gave the free primary alcohol **24**. Further treatment of **24** with tetrabutylammonium acetate produced the oxetane **25** (Figure 5).

We have prepared and characterized the C-5- and C-13-acetyl, **1**−**4**, Troc **5** and **6**, and TES, **7**, derivatives of brevifoliol, **1**. Two simple transformations (oxidation of the C-13 allylic alcohol to give **8** and formation of a C13−C15 ether bridge to give **10**) were used to unambiguously differentiate the *abeo*-taxane-type substrate from that of taxane. Spectroscopic data collected from 5-acetyl-13-oxobrevifoliol, **8**, and its ether, **10**, clearly and definitively established the structure of brevifoliol to be 9α,7*β*-diacetoxy-10*β*-benzoxy-11(15→1)-*abeo*-taxane-4(20),11-dien-5α,13α,15-triol (**1**), in which ring A is five-membered. Derivatives **12** and **13**, having an *S*-(−)-3-phenyllactate at C-5 and C-13 of brevifoliol, as well as brevifoliol-13-[*N*-benzoyl-2′*R*, 3′*S*)-3′-phenylisoserinate], **15**, were prepared. Derivatives with a cinnamoyl (**16**), both *S*-(−)- and *R*-(+)-3-phenyllactate (**18**, **19**), and a [*N*-benzoyl-2′*R*,3′*S*)-3′-phenylisoserinate] (**20**) esterified at the C-13 of 5-acetylbrevifoliol were also synthesized. We are currently evaluating these brevifoliol derivatives for microtubule assembly activity and for P-gp inhibition, and the results will be reported elsewhere.[28]

Experimental Section

General Experimental Procedures. ^{1}H NMR spectra were recorded using a 500, 300BB, or 200 MHz spectrometer with either CD_2Cl_2 or $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (δ) and are downfield from $(CH_3)_4Si$. ^{13}C spectra were recorded at 75 or 125 MHz. Optical rotation data were recorded at 589 nm on a digital polarimeter. Melting points are uncorrected. Mass spectra were obtained using a VG Auto-SpecQ FAB$^+$ Magnet BpI or a GC-MS (GCD plus gas chromatography-electron ionization detector) equipped with a 5% cross-linked PhMe silicone HP 19091 J-433 column, and the mass data are reported as *m*/*z*, with the intensity indicated in parentheses as a percent of the base peak. Silica gel 60 (230−400 mesh) was used for all column chromatography. Some separations were carried out on a centrifugally accelerated, radial, thin-layer chromatograph (Chromatotron) using silica gel PF-254 with $CaSO_4 \cdot {}^1/_2H_2O$ type 60 as adsorbent.

S-(−)- and *R*-(+)-3-phenyllactic acid, chlorotriethylsilane (TESCl), 2,2,2-trichloroethyl chloroformate (TrocCl), TsCl, DMAP, 4-methylmorpholine-*N*-oxide (NMO), tetrapropylammonium perruthenate(VII) (TPAP), imidazole, and *S*-(+)-phenylglycine as well as all other inorganic reagents were used without further purification. The isolation of brevifoliol, **1**, from *T. brevifolia* needles[8] and the syntheses of compounds **2**−**4, 11a**, and **11b** are described in the Supporting Information section. (2*R*,3*S*)-(−)-2-(Tetrahydropyran-2-yloxy)-3-phenylmethanamido)propanoic acid, **14**, was prepared from *S*-(+)-phenylglycine as previously described[25] with the exception that tetrahydropyranyl was used as a protecting group instead of an ethoxyethyl group. Di-2-pyridyl carbonate (2-DPC) was prepared as previously described.[24] Pyridine and triethylamine were freshly distilled over calcium hydride prior to use. Celite was used as a filtering agent. THF and diethyl ether were dried over sodium/benzophenone and distilled under a nitrogen atmosphere immediately prior to use. All reactions were carried out under nitrogen unless otherwise noted. Molecular sieves (4 Å-ms) were crushed and flame dried prior to use.

5-Trocbrevifoliol (5). 2,2,2-Trichloroethoxycarbonyl TrocCl (6.2 μL, 0.045 mmol) was added to a brevifoliol (**1**, 50 mg, 0.090 mmol) solution in pyridine (1 mL) at −30 °C, containing 4 Å-ms (400 mg). The reaction mixture was stirred at −30 °C for 2 h. More Troc-Cl (6.2 μL, 0.045 mmol) was added and stirred for an additional hour at −30 °C. The same quantity of Troc-Cl was added, and the mixture was kept at −20 °C for a 15 h period. One last portion of Troc-Cl was added and stirred at −20 °C for another 2 h. MeOH (50 μL) was then added, and the reaction mixture was allowed to warm to room temperature. The salts that formed were filtered through Celite and washed with CH_2Cl_2 (4 mL) and EtOAc (4 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by radial chromatography (2−5% EtOAc−CH_2Cl_2), giving 0.1 mg (0.1%) of 5,13-bis(Troc)brevifoliol **6** and 44.4 mg (68%) of **5** followed by 21 mg of impure **1**. The derivative **5** was obtained as a white powder: mp 110−112 °C; $[\alpha]^{23}_D$ −35.0° (*c* 1.03, CH_2Cl_2); IR (KBr) ν_{max} 3567, 2970, 1746, 1653, 1602, 1450, 1376, 1244, 1090, 1069, 1033, 904, 819, 784, 759, 712, 602, 572 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (3H, s, H-19), 1.02 (3H, s, H-16), 1.08 (1H, dd, J = 14.3, 6.7 Hz, H-14α), 1.33 (3H, s, H-17), 1.40 [1H, s, OH (C-13)], 1.45 (1H, d, J = 13.9 Hz, H-2α), 1.77 [3H, s, O_2CCH_3, (C-9 or C-7)], 1.93 (1H, td, J = 13.5, 3.9 Hz, H-6*β*), 2.07 [3H, s, O_2CCH_3 (C-9 or C-7)], 2.15 (3H, s, H-18), 2.18 (1H, dd, J = 15.3, 5.2 Hz, H-6α), 2.44 (1H, dd, J = 13.9, 8.9 Hz, H-2*β*), 2.52 (1H, dd, J = 14.3, 7.4 Hz, H-14*β*), 2.76 (1H, d, J = 8.9 Hz, H-3α), 2.84 [1H, br s, OH (C-15)], 4.42 (1H, dd, J = 7.4, 6.7 Hz, H-13*β*), 4.67, 4.86 (each 1H, d, J = 11.7 Hz, CCl_3CH_2O), 4.99 (1H, s, H-20a), 5.30 (1H, t, J = 3.9 Hz, H-5*β*), 5.35 (1H, s, H-20b), 5.60 (1H, dd, J = 11.0, 5.2 Hz, H-7α), 6.02 (1H, br d, J = 10.3 Hz, H-9*β*), 6.62 (1H, d, J = 10.3 Hz, H-10α), 7.43 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.55 (1H, t, J = 7.5 Hz, H_{p-Ph}), 7.87 (2H, d, J = 7.5 Hz, H_{o-Ph}); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.8 (CH_3, C-18), 12.8 (CH_3, C-19), 20.7 [CH_3, O_2CCH_3 (C-9 or C-7)], 21.3 [CH_3, O_2CCH_3 (C-7 or C-9)], 24.8 (CH_3, C-17), 27.0 (CH_3, C-16), 29.0 (CH_2, C-2), 33.5 (CH_2, C-6), 38.9 (CH, C-3), 44.7 (C, C-8), 48.1 (CH_2, C-14), 63.2 (C, C-1), 69.2 (CH, C-7), 70.7 (CH, C-10), 75.4 (C, C-15), 76.7 (CH_2, CH, CCl_3CH_2O and C-9), 77.6 (CH, C-13), 80.0 (CH, C-5), 94.2 (C, CCl_3C), 115.2 (CH_2, C-20), 128.8 (CH, C-3′), 129.2 (C, C-1′), 129.4 (CH, C-2′), 133.3 (CH, C-4′), 134.2 (C, C-11), 144.5 (C, C-4), 151.8 (C, C-12), 152.6 (C, $CCl_3CH_2OCO_2$), 164.1 (C, O_2CPh), 169.7 [C, O_2CCH_3 (C-9 or C-7)], 169.8 [C, O_2CCH_3 (C-7 or C-9)]; FABMS (NBA) *m*/*z* 713 [MH − H_2O]$^+$, 609−615 [MH − $PhCO_2H$]$^+$, 591 [MH − $PhCO_2H$−H_2O]$^+$, 549−566 [MH − $PhCO_2H$ − AcOH]$^+$, 533 [MH − $PhCO_2H$ − AcOH − H_2O]$^+$.

5,13-Bis(Troc)brevifoliol (6). Troc-Cl (12 μL, 0.087 mmol) was added to a solution of **1** (26 mg, 0.047 mmol) in pyridine (0.5 mL) containing 4 Å-ms (200 mg). The reaction mixture was stirred at room temperature for 3 h. More Troc-Cl (12 μL, 0.087 mmol) was added, and the mixture was stirred for an additional 15 h. The salts that formed were filtered through Celite and washed with CH_2Cl_2 (2 mL) and EtOAc (2 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by radial chromatography (2−5% EtOAc−CH_2Cl_2), giving 15.4 mg (36%) of **6** and 16.4 mg (48%) of **5**, as white powders. The derivative **6** had the following physical characteristics: mp 177−179 °C; $[\alpha]^{23}_D$ −17.0° (*c* 0.91, CH_2Cl_2); IR (KBr) ν_{max} 3578, 2976, 1752, 1663, 1600, 1438, 1374, 1248, 1132, 1090, 1067, 1033, 938, 920, 882, 822, 788, 714, 602, and 570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (3H, s, H-19), 1.12 (3H, s, H-16), 1.35−1.45 (1H, m, H-14α), 1.38 (3H, s, H-17), 1.53 (1H, d, J = 14 Hz, H-2α), 1.76 (3H, s, O_2CCH_3, C-9 or C-7), 1.95 (1H, td, J = 14, 3.5 Hz, H-6*β*), 2.07 [3H, s, O_2CCH_3 (C-7 or C-9)], 2.09 (3H, s, H-18), 2.20 (1H, dd, J = 14, 4.2 Hz, H-6α), 2.45 (1H, dd, J = 14, 9 Hz, H-2*β*), 2.54 (1H, dd, J = 13.9, 7.4 Hz, H-14*β*), 2.70 [1H, br s, OH (C-15)], 2.73 (1H, d, J = 9 Hz H-3α), 4.68 [1H, d, J = 11.8 Hz, CCl_3CH_2O (C-5 or C-13)], 4.79 [2H, br dd, CCl_3CH_2O (C-5 or C-13)], 4.99 [2H, br s, H-20a + CCl_3CH_2O (C-5 or C-13)], 5.27 (1H, t, J = 3.5 Hz, H-5*β*), 5.38 (1H, s, H-20b), 5.53 (1H, br t, J = 7.4 Hz, H-13*β*), 5.65 (1H, dd, J = 10, 4.2 Hz, H-7α), 6.15 (1H, br d, J = 10.3 Hz, H-9*β*), 6.67 (1H, br d, J = 10.3 Hz, H-10α), 7.45 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.55 (1H, t, J = 7.5 Hz, H_{p-Ph}), 7.88 (2H, d, J = 7.5 Hz, H_{o-Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9 (CH_3, C-18), 12.8 (CH_3, C-19), 20.7 [CH_3, O_2CCH_3 (C-9) or

(C-7)], 21.3 [CH_3, O_2CCH_3 (C-7) or (C-9)], 25.1 (CH_3, C-17), 27.2 (CH_3, C-16), 29.3 (CH_2, C-2), 33.7 (CH_2, C-6), 38.4 (CH, C-3), 43.7 (CH_2, C-14), 44.8 (C, C-8), 62.6 (C, C-1), 69.2 (CH, C-7), 69.5 (CH, C-10), 75.6 (C, C-15), 76.4 (CH_2, Cl_3CH_2O), 76.7 [CH, CH_2, C-9 and Cl_3CH_2O], 79.2 (CH, C-5), 84.2 (CH, C-13), 94.5, (C, CCl_3C), 94.8 (C, CCl_3C), 115.4 (CH_2, C-20), 128.8 (CH, C-3′), 129.1 (C, C-1′), 129.5 (CH, C-2′), 133.4 (CH, C-4′), 136.9 (C, C-11), 144.2 (C, C-4), 146.7 (C, C-12), 153.0 (C, $CCl_3CH_2OCO_2$), 154.2 (C, $CCl_3CH_2OCO_2$), 164.0 (C, O_2CPh), 169.6 [C, O_2CCH_3 (C-7 or C-9)], 169.9 [C, O_2CCH_3 (C-9 or C-7)]; FABMS (thioglycerol) *m*/*z* 904 $[MH]^+$, 787 $[MH - PhCO_2H]^+$, 767 $[MH - PhCO_2H - H_2O]^+$, 727 $[MH - PhCO_2H - AcOH]^+$.

5,13-Bis(TES)brevifoliol (7). TESCl (80 μL, 0,48 mmol) was added to a solution of **1** (106 mg, 0.19 mmol) and pyridine (40 μL) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h, and TESCl (16 μL, 0.096 mmol) and pyridine (8 μL) were added. After stirring 1.5 h, more TESCl (32 μL, 0.19 mmol) and pyridine (16 μL) were added, and the mixture was stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL), cooled to 5 °C for 22 h, and filtered through a pad of Celite (0.5 cm). The solids were washed with EtOAc (2 mL), and the combined filtrate was evaporated. The residue was separated by radial chromatography (EtOAc−Hex, 1:4) to afford 104 mg (69%) of **7** as a white powder: mp 121−123 °C; $[\alpha]^{23}_D$ −10.2° (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3559, 2956, 1741, 1664, 1601, 1458, 1375, 1263, 1089, 1028, 1002, 907, 826, 742, 709, 605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.59 [12H, q, J = 7.6 Hz, 2 $Si(CH_2CH_3)_3$], 0.92 (3H, s, H-19), 0.95 [18H, t, J = 7.6 Hz, 2 $Si(CH_2CH_3)_3$], 1.09 (3H, s, H-16), 1.36−1.43 (2H, m, H-2α + H-14α), 1.37 (3H, s, H-17), 1.77 (3H, s, O_2CCH_3 (C-9 or C-7)], 1.65−1.79 (1H, m, H-6*β*), 1.82 (1H, m, H-6α), 1.98 (3H, s, H-18), 2.04 [3H, s, O_2CCH_3 (C-7 or C-9)], 2.21 (1H, dd, J = 13.2, 6.8 Hz, H-14*β*), 2.32 (1H, br t, J = 13 Hz, H-2*β*), 2.70 [1H, br s, OH (C-15)], 3.01 (1H, d, J = 9.1 Hz, H-3α), 4.25 (1H, br s, H-5*β*), 4.48 (1H, br t, J = 6.8 Hz H-13*β*), 4.69 (1H, br s, H-20a), 5.00 (1H, s, H-20b), 5.70 (1H, dd J = 10.7, 5.5 Hz, H-7α), 6.08 (1H, br d, J = 10.4 Hz, H-9*β*), 6.63 (1H, br d, J = 10.4 Hz, H-10α), 7.43 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.55 (1H, t, J = 7.5 Hz, H_{p-Ph}), 7.89 (2H, br d, J = 7.5 Hz, H_{o-Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.65 (CH_2, $SiCH_2$), 4.75 (CH_2, $SiCH_2$), 6.77 (CH_3, $SiCH_2CH_3$) 6.86 (CH_3, $SiCH_2CH_3$), 11.8 (CH_3, C-18), 12.8 (CH_3, C-19), 20.7 [CH_3, O_2CCH_3 (C-9 or C-7)], 21.4 [CH_3, O_2CCH_3 (C-7 or C-9)], 25.1 (CH_3, C-17), 27.4 (CH_3, C-16), 29.7 (CH_2, C-2), 37.0 (CH, C-3), 37.9 (CH_2, C-6), 45.0 (C, C-8), 47.8 (CH_2, C-14), 61.6 (C, C-1), 70.0 (CH, C-7), 70.7 (CH, C-10), 72.6 (CH, C-5), 76.0 (CH, C-13), 76.9 (CH, C-9), 77.2 (C, C-15), 109.3 (CH_2, C-20), 128.6 (CH, C-3′), 129.4 (CH, C-2′), 129.6 (C, C-1′), 132.7 (C, C-11), 133.0 (CH, C-4′), 151.1 (C, C-4), 151.8 (C, C-12), 164.1 (C, O_2CPh), 169.6 [C, O_2CCH_3 (C-7 or C-9)], 169.9 [C, O_2CCH_3 (C-9 or C-7)]; FABMS (thioglycerol) *m*/*z* 785 $[MH]^+$, 725 $[MH - AcOH]^+$, 663 $[MH - PhCO_2H]^+$, 645 $[MH - PhCO_2H - H_2O]^+$, 603 $[MH - PhCO_2H - AcOH]^+$, 545 $[MH - PhCO_2H - 2\ AcOH]^+$.

5-Acetyl-13-oxobrevifoliol (8). (a) From PCC Oxidation. Pyridinium chlorochromate (PCC, 36 mg, 0.17 mmol) was added to a solution of **2** (100 mg, 0.17 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 16 h, and diethyl ether (10 mL) was added. The solids were filtered through a pad of Florisil (1.5 cm) and washed with ether (3 × 3 mL) and CH_2Cl_2 (5 mL), and the combined filtrate was concentrated. The residue was purified by radial chromatography (2% MeOH−CH_2Cl_2, EtOAc−Hex, 1:1) to give 78 mg (78%) of enone **8** as a white powder: mp 215−219 °C, $[\alpha]^{23}_D$ −2.9° (*c* 1.0, CH_2Cl_2); IR (KBr) ν_{max} 3570, 2972, 1753, 1740, 1716, 1664, 1599, 1451, 1372, 1242, 1087, 1070, 1024, 959, 824, 807, 720, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz at 23 °C) δ 0.88 (3H, s), 0.98 (3H, s), 1.21−1,28 (3H, m), 1.36 (3H, s), 1.64−1,70 (4H, br s), 1.7−2.30 (8H, m), 2.35−2.60 (2H, s), 2.70 (2H, d, J = 14 Hz), 2.79 [1H, br s, OH (C-15)], 4.94 (1H, br s), 5.30 (1H, s), 5.37 (1H, br s), 5.49 (1H, br s), 6.24 (1H, br d), 6.79 (1H, br s), 7.43 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.58 (1H, t, J = 7.5 Hz, H_{p-Ph}), 7.91 (2H, br d, J = 7.5 Hz, H_{o-Ph}); ^1H NMR ($CDCl_3$, 500 MHz at −10 °C) δ 0.88 (3H, s), 0.94 (3H, s), 1.25 (3H, s), 1.37 (3H, s), 1.81 (3H, s), 1.91 (3H, s), 2.10 (3H, s), 2.15 (3H, s), 2.42−2,66 (4H, m), 2.79 [1H, br s, OH (C-15)], 4.94 (1H, br s), 5.30 (1H, s), 5.37 (1H, br s), 5.50 (1H, br s), 6.25 (1H, d, J = 10.7 Hz), 6.88 (1H, d, J = 10.7 Hz), 7.43 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.58 (1H, t, J = 7.5 Hz, H_{p-Ph}), 7.91 (2H, br d, J = 7.5 Hz, H_{o-Ph}, in a 4:1 ratio with δ 8.03), 8.03 (2H, br d, J = 7.5 Hz, H_{o-Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 12.5, 14.0, 26.6 (4 CH_3, C-16, C-17, C-18, and C-19), 20.7, 21.1, 21.2 [3 CH_3, O_2CCH_3 (C-5, C-7, and C-9)], 27.5, 33.6 (2 CH_2, C-2 + C-6), 39.0 (CH, C-3), 45.1 (C, C-8), 49.6 (CH_2, C-14), 59.0 (C, C-1), 69.5, 70.1, 74.0, 77.2 (4 CH, C-5, C-7, C-9, and C-10), 75.2 (C, C-15), 114.3 (CH_2, C-20), 128.8, 129.5 (2 CH, C-2′ + C-3′), 129.4 (C, C-1′), 133.5 (CH, C-4′), 145.0, 147.0 (2 C, C-4 + C-12), 163.6 (C, O_2CPh), 163.9 (C, C-11), 169.5, 169.8, 169.9 [3 C, O_2CCH_3 (C-5, C-7 + C-9)], 207.3 [C, *C*=O (C-13)]; FABMS (NBA) *m*/*z* 597 $[MH]^+$, 579 $[MH - H_2O]^+$, 537 $[MH - AcOH]^+$, 475 $[MH - PhCO_2H]^+$, 457 $[MH - PhCO_2H - H_2O]^+$, 415 $[MH - PhCO_2H - AcOH]^+$, 357 $[MH - PhCO_2H - 2\ AcOH]^+$.

(b) From NMO-TPAP Oxidation.[20] Tetrapropylammonium perruthenate (TPAP, 3 mg, 0.59 mmol) and *N*-methylmorpholine-*N*-oxide (NMO, 45 mg, 0.38 mmol, 2.3 equiv) were added to a solution of **2** (96 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) containing 4 Å-ms (500 mg). The reaction mixture was stirred at room temperature for 2 h, and the disappearance of the starting material, **2**, was monitored by TLC analysis. TPAP (1 mg, 0.20 mmol) was added, and the mixture was stirred for 2 h. One last addition of TPAP (1 mg, 0.20 mmol) was required, and after 1.5 h of stirring, the reaction mixture was filtered in a sintered glass funnel. The solids were washed with EtOAc (2 mL), and the combined filtrate was concentrated and applied on a pad of silica gel (1 cm, Pasteur pipet) and eluted with EtOAc (10 mL). The eluent was removed under reduced pressure, and the residue was purified by radial chromatography (PE:Et_2O, 1:3) to give 38.4 mg (40%) of enone **8**. This material has the same physical properties as that described above.

C-13, C-15 Oxygen Bridge Compound 10. A solution of **1** (26 mg, 0.047 mmol) and *p*-toluenesulfonyl chloride (TsCl, 20 mg, 0.10 mmol) in pyridine (1 mL) containing 4 Å-ms (250 mg) was stirred at room temperature for 6 h. An additional portion of TsCl (5 mg, 0.03 mmol) was added, and the mixture was stirred for another 17 h. The reaction mixture was then filtered through a sintered glass funnel, and the filtrate was concentrated. The crude product was purified by radial chromatography (PE:CH_2Cl_2−EtOH, 15:4:1) to give 10.9 mg (44%) of compound **10** as a white powder: mp 122−123 °C; $[\alpha]^{23}_D$ 6.5° (*c* 0.49, CH_2Cl_2); IR (KBr) ν_{max} 3447, 2957, 1734, 1653, 1601, 1457, 1368, 1267, 1245, 1092, 1067, 1026, 980, 910, 826, 803, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (3H, s, H-17), 1.22 (3H, s, H-19), 1.30 (3H, s, H-16), 1.75 (1H, ddd, J = 13.5, 12.1, 2.8 Hz, H-6*β*), 1.80−2.30 [4H, m, H-2α, H-14α, H-14*β* + OH (C-5)], 1.88 (3H, s, H-18), 1.99 [3H, s, O_2CCH_3 (C-7)], 2.04 [3H, s, O_2CCH_3 (C-9)], 2.08 (1H, ddd, J = 13.5, 4.9, 2.8 Hz, H-6α), 2.22 (1H, dd, J = 14.4, 11.1 Hz, H-2*β*), 3.07 (1H, d, J = 11.0 Hz, H-3α), 4.40 (1H, distorted t, J = 7.7 Hz, H-13α), 4.45 (1H, t, J = 2.5 Hz, H-5*β*), 4.96 (1H, s, H-20a), 5.20 (1H, s, H-20b), 5.22 (1H, d, J = 6.0 Hz, H-9*β*), 5.55 (1H, dd, J = 12.1, 4.9 Hz, H-7α), 6.25 (1H, d, J = 6.0 Hz, H-10α), 7.47 (2H, t, J = 7.5 Hz, H_{m-Ph}), 7.57 (1H, t, J = 7.5 Hz, H_{p-Ph}), 8.0 (2H, d, J = 7.5 Hz, H_{o-Ph}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3 (CH_3, C-19), 11.8 (CH_3, C-18), 20.6 [CH_3, O_2CCH_3 (C-9)], 21.0 [CH_3, O_2CCH_3 (C-7)], 24.8 (CH_2, C-2), 25.3 (CH_3, C-17), 26.4 (CH_3, C-16), 34.1 (CH_2, C-6), 36.3 (CH, C-3), 46.1 (C, C-8), 51.4 (CH_2, C-14), 61.6 (C, C-1), 67.3 (CH, C-10), 70.6 (CH, C-7), 73.1 (CH, C-9 or C-5), 73.2 (CH, C-5 or C-9), 79.4 (C, C-15), 82.9 (CH, C-13), 112.3 (CH_2, C-20), 128.5 (CH, C-3′), 129.5 (CH, C-2′), 129.8 (C, C-1′), 133.0 (CH, C-4′), 137.3 (C, C-11), 146.8 (C, C-12), 150.8 (C, C-4), 165.2 (C, O_2CPh), 169.6 [C, O_2CCH_3 (C-9)], 170.5 [C, O_2CCH_3 (C-7)]; FABMS (NBA) *m*/*z* 538 M^+, 537 $[M - H]^+$, 417 $[MH - PhCO_2H]^+$, 359 $[MH - PhCO_2H - AcOH]^+$, 298 $[MH - PhCO_2H - 2\ AcOH]^+$; *anal.* C 68.98%, H 7.08%, calcd for $C_{31}H_{38}O_8$, C 69.13%, H 7.11%.

Esterification: General Procedure. To a solution containing the alcohol (1 equiv), dipyridyl carbonate[24] (2-DPC, 6 equiv), and dimethylamino pyridine (DMAP, 2 equiv) in dry toluene at room temperature was added the appropriate substituted acid (6 equiv), and the reaction mixture was stirred

overnight. The solvent from the reaction mixture was evaporated under reduced pressure to dryness (without heating) to give a crude mixture. Separation of this mixture with silica gel (1 mm), using the specified eluents, gave the desired ester.

13α- and 5α-[(2′*S*)-3-Phenyllactate]brevifoliol (12 and 13). Following the general procedure, the (*S*)-(−)-acid, **11a** (48 mg, 0.19 mmol), was coupled with **1** (18 mg, 0.032 mmol), and the reaction mixture was stirred at rt for 24 h to give a mixture of the corresponding C-13 (25% yield) and C-5 esters (35% yield) as white solids, which after hydrolysis of the THP group gave **12** and **13**, both in 50% yield as white solids.

13α-[(2′*S*)-3-Phenyllactate]brevifoliol (12): IR (KBr) ν_{max} 3550−3300, 2979, 1742, 1640, 1604, 1450, 1373, 1262, 1104, 1093, 1028, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (3H, br s, H-19), 1.15 (3H, s, H-16), 1.19 (1H, dd, J = 14, 7 Hz, H-14α), 1.35 (3H, s, H-17), 1.45 (1H, d, J = 14 Hz, H-2α), 1.62 [1H, br s, OH (C-5)], 1.75 (3H, br s, O_2CCH_3), 1.80 (1H, dd, J = 14, 11 Hz, H-6β), 1.96 (3H, br s, H-18), 1.98 (1H, dd, J = 14, 5 Hz, H-6α), 2.05 (3H, s, O_2CCH_3), 2.10 [1H, s, OH (C-2′)], 2.36 (1H, br dd, J = 14, 8 Hz, H-2β), 2.55 (1H, dd, J = 14, 7 Hz, H-14β), 2.58−2.65 [1H, br s, OH (C-15)], 2.69 (1H, d, J = 8 Hz, H-3α), 2.92 (1H, dd, J = 14, 8 Hz, H-3′), 3.00 (1H, dd, J = 14, 4 Hz, H-3′), 4.02 (1H, dd, J = 8, 4 Hz, H-2′), 4.46 (1H, br s, H-5β), 4.86 (1H, s, H-20a), 5.25 (1H, s, H-20b), 5.45 (1H, br t, J = 7 Hz, H-13β), 5.56 (1H, dd, J = 11, 5 Hz H-7α), 6.01−6.12 (1H, br m, H-9β), 6.58−6.62 (1H, br d, J = 10 Hz, H-10α), 7.12 (2H, d, J = 7.5 Hz, H_{o-Ph}), 7.15−7.25 (3H, m, H_{Ar}) 7.40 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.84 (2H, d, J = 7.5 Hz, H_{COo-Ph}); *anal.* C 68.08%, H 6.88%, calcd for $C_{40}H_{48}O_{11}$, C 68.16%, H 6.86%.

5α-[(2′*S*)-3-Phenyllactate]brevifoliol (13): IR (KBr) ν_{max} 3565, 2970, 1741, 1715, 1663, 1601, 1445, 1380, 1305, 1250, 1134, 1088, 1070, 963, 805, 759, 716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, br s, H-19), 1.03 (3H, s, H-16), 1.05−1.16 (1H, m, H-14α), 1.34 (3H, s, H-17), 1.35−1.55 [3H, m, H-2α, OH (C-2′) + OH (C-13)], 1.75 (3H, br s, O_2CCH_3), 1.86−1.98 (1H, m, H-6α), 2.04 (3H, s, O_2CCH_3), 2.09 (3H, br s, H-18), 2.15 (1H, br d, J = 14 Hz, H-6β), 2.42 (1H, br dd, J = 14, 9 Hz, H-2β), 2.52 (1H, dd, J = 14, 7 Hz, H-14β), 2.76 (1H, d, J = 8 Hz, H-3α), 2.83 [1H, br s, OH (C-15)], 2.94 (1H, dd, J = 14, 8 Hz, H-3′), 3.12 (1H, dd, J = 14, 6 Hz, H-3′), 4.22 (1H, dd, J = 8, 6 Hz, H-2′), 4.42 (1H, br t, J = 7 Hz H-13β), 4.94 (1H, s, H-20a), 5.31 (1H, br s, H-5β), 5.35 (1H, s, H-20b), 5.59 (1H, dd, J = 11, 5 Hz H-7α), 5.97−6.07 (1H, br d, J = 10 Hz, H-9β), 6.62 (1H, d, J = 10 Hz, H-10α), 7.14 (2H, d, J = 7.5 Hz, H_{o-Ph}), 7.17−7.28 (3H, m, H_{Ar}) 7.42 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.86 (2H, d, J = 7.5 Hz, H_{COo-Ph}); *anal.* C 67.94%, H 6.83%, calcd for $C_{40}H_{48}O_{11}$, C 68.16%, H 6.86%.

13α-Phenylisoserinatebrevifoliol (15). Following the general procedure, (2*R*,3*S*)-(−)-2-(tetrahydropyran-2-yloxy)-3-phenylmethanamido)propanoic acid, **14**[25] (34 mg, 0.092 mmol), was coupled with compound **1** (10 mg, 0.018 mmol) to give the corresponding C-13 ester (13.7 mg, 86% yield). Hydrolysis of the THP group (13.7 mg, 0.016 mmol) with the *p*-toluenesulfonic acid in EtOH gave the alcohol derivative **15** (6.8 mg, 51% yield): mp 150−152 °C; IR (KBr) ν_{max} 3499, 3435, 3017, 2933, 1731, 1660, 1651, 1450, 1370, 1120, 1080, 969, 805, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, br s, H-19), 1.04 (3H, s, H-16), 1,14 (1H, dd, J = 14, 8 Hz, H-14α), 1.23 (3H, s, H-17), 1.27 [1H, d, J = 4,0 Hz, OH (C-5)] 1.73 (3H, s, O_2CCH_3), 1.78 (1H, d, J = 14 Hz, H-2α), 1.92−2.00 (2H, m, H-6α, H-6β), 2.05 (3H, s, O_2CCH_3), 2.09 (3H, s, H-18), 2.28 (1H, dd, J = 14, 9 Hz, H-2β), 2.44 (1H, dd, J = 14, 7 Hz, H-14β), 2.64 [1H, br s, OH (C-15)], 2.98 (1H, d, J = 9 Hz, H-3α), 3.34 [1H, d, J = 3,0 Hz, OH (C-2′)] 4.37 (1H, br s, H-5β), 4.72 (1H, t, J = 3 Hz, H-2′), 5.10 (1H, s, H-20a), 5.33 (1H, s, H-20b), 5.48 (1H, br t, J = 7 Hz H-13β), 5.64−5.72 (2H, m, H-7α + H-3′), 5.97 (1H, br d, J = 10 Hz, H-9β), 6.53 (1H, d, J = 10 Hz, H-10α), 7.11 (1H, d, J = 9.4 Hz, N−H), 7.30−7.61 (11H, m, H_{Ar}), 7.72 (2H, d, J = 7.5 Hz, H_{Ar}), 7.85 (2H, d, J = 8.0 Hz, H_{Ar}); *anal.* C 68.28%, H 6.50%, N 1.70%, calcd for $C_{47}H_{53}NO_{12}$, C 68.50%, H 6.48%, N 1.69%.

5α-Acetyl-13α-cinnamoylbrevifoliol (16). Following the general procedure described above, cinnamic acid (30 mg, 0.20 mmol) was coupled with compound **2** (30 mg, 0.050 mmol) in boiling CH_2Cl_2 for 20 h. Workup and chromatography (CH_2Cl_2−Et_2O, 85:15) gave **16** (16 mg, 53% yield) as a white solid: mp 124−125 °C; IR (KBr) ν_{max} 3581, 2981, 1742, 1718, 1639, 1451, 1373, 1313, 1238, 1093, 1027, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, br s, H-19), 1.12 (3H, s, H-16), 1.31 (1H, dd, J = 14, 7 Hz, H-14α), 1.35 (3H, s, H-17), 1.46 (1H, d, J = 14 Hz, H-2α), 1.73 (3H, br s, O_2CCH_3), 1.88 (1H, td, J = 14, 4 Hz, H-6β), 1.98 (1H, ddd, J = 14, 5, 2 Hz, H-6α), 2.03 (3H, s, O_2CCH_3), 2.05 (3H, s, O_2CCH_3), 2.08 (3H, s, H-18), 2.41 (1H, br dd, J = 14, 8 Hz, H-2β), 2.62 (1H, dd, J = 14, 7.4 Hz, H-14β), 2.70 [1H, br s, OH (C-15)], 2.73 (1H, d, J = 8 Hz, H-3α), 4.88 (1H, s, H-20a), 5.26 (1H, s, H-20b), 5.38 (1H, dd, J = 4, 2 Hz, H-5β), 5.57 (1H, br t, J = 7.4 Hz, H-13β), 5.63 (1H, dd, J = 11.0, 5.0 Hz, H-7α), 6.09 (1H, br d, J = 10.5 Hz, H-9β), 6.32 (1H, d, J = 16 Hz, H-1′), 6.68 (1H, br d J = 10.5 Hz, H-10α), 7.35−7.47 (7H, m, H_{Ar}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.65 (1H, d, J = 16 Hz, $H_{2'}$), 7.86 (2H, d, J = 7.5 Hz, H_{COo-Ph}); *anal.* C 69.37%, H 6.66%, calcd for $C_{42}H_{48}O_{11}$, C 69.21%, H 6.64%.

5α-Acetyl-13α-[(2′*S*)-*O*-(tetrahydropyran-2-yl)-3-phenyllactate]brevifoliol (17). Following the general procedure described above, the (*S*)-(−)-acid, **11a** (33 mg, 0.13 mmol), was coupled with compound **2** (13 mg, 0.021 mmol). Workup and chromatography (Hex−EtOAc, 7:3) gave **17** (10 mg, 55% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, br s, H-19), 1.08 (3H, s, H-16), 1.20−1.30 (1H, m, H-14α), 1.35 (3H, s, H-17), 1.40−1.60 (7H, br m, H-2α + $(CH_2)_3$], 1.73 (3H, br s, O_2CCH_3), 1.75−1.95 (2H, m, H-6α, H-6β), 1.97 (3H, br s, H-18), 2.03 (3H, s, O_2CCH_3), 2.05 (3H, s, O_2CCH_3), 2.35 (1H, br dd, J = 13.9, 9.1 Hz, H-2β), 2.51 (1H, dd, J = 13.9, 7.4 Hz, H-14β), 2.64 [1H, br s, OH (C-15)], 2.68 (1H, d, J = 9.1 Hz, H-3α), 2.92 (1H, dd, J = 14, 6 Hz, H-3′), 3.00 (1H, dd, J = 14, 7.5 Hz, H-3′), 3.32−3.41 (1H, m, OCH_2), 3.75−3.85 (1H, m, OCH_2), 4.25 (1H, dd, J = 7.5, 6 Hz, H-2′), 4.40 (1H, t, J = 3 Hz, R−OC*H*O−R), 4.88 (1H, s, H-20a), 5.28 (1H, s, H-20b), 5.35−5.40 (1H, br s, H-5β), 5.45 (1H, t, J = 7.4 Hz, H-13β), 5.56 (1H, dd, J = 11.0, 5.0 Hz, H-7α), 6.06 (1H, br d, J = 10 Hz, H-9β), 6.65 (1H, d, J = 10.4 Hz, H-10α), 7.10−7.25 (5H, m, H_{Ar}), 7.45 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.87 (2H, d, J = 7.5 Hz, H_{COo-Ph}); *anal.* C 67.72%, H 6.99%, calcd for $C_{47}H_{58}O_{13}$, C 67.92%, H 7.04%.

5α-Acetyl-13α-[(2′*S*)-3-phenyllactate]brevifoliol (18). Hydrolysis of compound **17** (10 mg) was carried out in EtOH (1 mL) in the presence of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 16 h, after which time the solvent was removed under reduced pressure, leaving a crude residue. Separation of this mixture with silica gel (CH_2Cl_2−Et_2O, 85:15) gave compound **18** (5 mg) in 56% yield as a white solid: mp 87−88 °C; IR (KBr) ν_{max} 3560−3300, 2980, 1742, 1452, 1373, 1236, 1093, 1028, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (3H, br s, H-19), 1.10 (3H, s, H-16), 1,19 (1H, dd, J = 14, 7 Hz, H-14α), 1.24 [1H, s, OH (C-2′)], 1.35 (3H, s, H-17), 1.45 (1H, d, J = 14 Hz, H-2α), 1.73 (3H, br s, O_2CCH_3), 1.78−1.92 (2H, m, H-6α, H-6β), 1.96 (3H, br s, H-18), 2.02 (3H, s, O_2CCH_3), 2.05 (3H, s, O_2CCH_3), 2.38 (1H, br dd, J = 14, 8 Hz, H-2β), 2.56 (1H, dd, J = 14, 7.4 Hz, H-14β), 2.53−2.66 [1H, br s, OH (C-15)], 2.64 (1H, d, J = 8 Hz, H-3α), 2.95 (1H, dd, J = 14, 8 Hz, H-3′), 3.08 (1H, dd, J = 14, 4 Hz, H-3′), 4.29 (1H, dd, J = 8.0, 4 Hz, H-2′), 4.88 (1H, s, H-20a), 5.27 (1H, s, H-20b), 5.35−5.40 (1H, br s, H-5β), 5.43−5.48 (1H, br t, J = 7.4 Hz, H-13β), 5.58 (1H, dd, J = 11.0, 5.0 Hz, H-7α), 6.01−6.12 (1H, br m, H-9β), 6.58−6.65 (1H, br d, J = 10 Hz, H-10α), 7.14−7.25 (5H, m, H_{Ar}), 7.42 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.86 (2H, d, J = 7.5 Hz, H_{COo-Ph}); FABMS *m*/*z* 746 (M^+ − PhCO, $-CH_3$), 626, 540, 401, 358, 341, 221, 239, 220, 185, 184, 148, 105, 91; *anal.* C 67.45%, H 6.68%, calcd for $C_{42}H_{50}O_{12}$, C 67.54%, H 6.75%.

5α-Acetyl-13α-[(2′*R*)-3-phenyllactate]brevifoliol (19). Following the general procedure, the coupling of the (2*R*)-(+)-acid, **11b** (62.5 mg, 6 equiv), with compound **2** (24.8 mg, 1 equiv) and subsequent hydrolysis of the THP ether (12.5 mg, 36% yield) gave the corresponding free alcohol **19** (9.2 mg, 86.7% yield), as a white solid: mp 91−92 °C; IR (KBr) ν_{max} 3575−3400, 3000−2900, 1742, 1453, 1372, 1236, 1094, 1027, 915, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (3H, br s,

H-19), 1.11 (3H, s, H-16), 1,23−1.339 (1H, m, H-14α), 1.35 (3H, s, H-17), 1.48 (1H, br d, J = 14 Hz, H-2α), 1.73 (3H, br s, O_2CCH_3), 1.78−2.07 (2H, m, H-6α, H-6β), 1.92 (3H, br s, H-18), 2.02 (3H, s, O_2CCH_3), 2.05 (3H, s, O_2CCH_3), 236−2.44 [2H, br dd, J = 14, 8 Hz, H-2β + OH (C-2′)], 2.54−2.64 (2H, br dd, J = 14, 7 Hz, H14β + OH (C-15)], 2.67 (1H, d, J = 8 Hz, H-3α), 2.92 (1H, dd, J = 14, 8 Hz, H-3′), 3.06 (1H, dd, J = 14, 6 Hz, H-3′), 4.38 (1H, dd, J = 8, 6 Hz, H-2′), 4.94 (1H, s, H-20a), 5.30 (1H, s, H-20b), 5.36−5.44 (1H, br s, H-5β), 5.53−5.67 (2H, m, H-7α and H-13β), 6.05−6.16 (1H, br m, H-9β), 6.60−6.66 (1H, br d, J = 10 Hz, H-10α), 7.15 (2H, d, J = 7.5 Hz, H_{o-Ph}), 7.18−7.20 (3H, m, H_{Ar}), 7.42 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.55 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.86 (2H, d, J = 7.5 Hz, H_{COo-Ph}); FABMS m/z 746 (M^+ − PhCO, $-CH_3$), 626, 540, 401, 358, 341, 238, 221, 220, 185, 184, 148, 105, 91; *anal*. C 67.68%, H 6.72%, calcd for $C_{42}H_{50}O_{12}$, C 67.54%, H 6.75%.

5α-Acetyl-13α-phenylisoserinatebrevifoliol (20). The acid **14**[25] (37 mg, 0.1 mmol) was coupled with compound **2** (10 mg, 0.0167 mmol) as above to give the corresponding C-13 ester (15.6 mg, 45% yield). Hydrolysis of the THP group (4.7 mg, 6.8 × 10^{-2} mmol) with the *p*-toluenesulfonic acid in EtOH gave the alcohol derivative **20** (1.5 mg, 35% yield): IR (KBr) ν_{max} 3437, 2983, 1739, 1713, 1601, 1445, 1320, 1240, 1145, 1070, 955, 809, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (3H, br s, H-19), 1.10 (3H, s, H-16), 1.20−1.32 (1H, m, H-14α), 1.35 (3H, s, H-17), 1.51 (1H, d, J = 14 Hz, H-2α), 1.68−1.78 (3H, br s, O_2CCH_3), 1.82−2.00 (2H, m, H-6α, H-6β), 1.90 (6H, s, 2 × O_2CCH_3), 2.05 (3H, s, H-18), 2.30−2.45 (2H, m, H-2β + H-14β), 2.55−2.66 [1H, br s, OH (C-15)], 2.70 (1H, d, J = 9 Hz, H-3α), 3.24 [1H, d, J = 6.0 Hz, OH (C-2′)], 4.63 (1H, dd, J = 6.0, 2.7 Hz, H-2′), 4.94 (1H, s, H-20a), 5.30 (1H, s, H-20b), 5.39−5.42 (1H, br s, H-5β), 5.56 (1H, dd, J = 11.0, 5.0 Hz, H-7α), 5.62 (1H, dd, J = 9.4, 2.7 Hz, H-3′), 5.68−5.75 (1H, br t, J = 7.4 Hz, H-13β), 6.05−6.12 (1H, br d, J = 10 Hz, H-9β), 6.58−6.64 (1H, br d, J = 10 Hz, H-10α), 6.95 (1H, d, J = 9.4 Hz, N−H), 7.30−7.60 (11H, m, H_{Ar}), 7.72 (2H, d, J = 7.5 Hz, H_{Ar}), 7.84 (2H, d, J = 8.0 Hz, H_{Ar}); *anal*. C 68.04%, H 6.47%, N 1.59%, calcd for $C_{49}H_{55}NO_{13}$, C 67.96%, H 6.40%, N 1.62%.

13α-Acetyl-4α,20-dihydroxybrevifoliol (21). Compound **3** (87 mg, 0.15 mmol) was dihydroxylated with OsO_4 (1.8 mg, 0.0071 mmol, 0.05 equiv) and *N*-methylmorpholine-*N*-oxide (18.7 mg, 1.1 equiv) in acetone (1.5 mL) and water−t-BuOH (6:1). The reaction mixture was stirred at room temperature overnight. Once the reaction was complete, Fluorisil (40 mg), sodium hydrosulfite (25 mg), and water (2 mL) were added. Extraction was carried out in ethyl acetate (6 × 15 mL) and diethyl ether (7 × 5 mL). The combined extracts were dried over $MgSO_4$ and filtered, and then the solvent was removed under reduced pressure to leave a crude material (85 mg). Separation of this material with silica gel (CH_2Cl_2−MeOH, 95:5; 9:1) gave 65.7 mg (72%) of pure triol **21**, which crystallized upon drying under vacuum: mp 134−135 °C; IR (KBr) ν_{max} 3575−3331, 2980, 1733, 1375, 1251, 1031, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (3H, br s, H-19), 1.23−1.26 (1H, m, H-14α), 1.28 (3H, s, H-16), 1.75−1.90 (10H, br s, H-17, H-2α, + 2 × O_2CCH_3), 2.00 (3H, s, O_2CCH_3), 1.95−2.10 (2H, m, H-6β + H-6α), 2.05 (3H, s, H-18), 2.15−2.23 (1H, br s, OH), 2.23−2.34 (2H, m, H-2β + H-3α), 2.38 (1H, dd, J = 14, 7.4 Hz, H-14β), 2.50−2.55 (1H, br s, OH), 3.25−3.35 (1H, m, OH), 3.62−3.75 (3H, br m, H-20 + OH), 4.40 (1H, br s, H-5β), 5.43−5.51 (1H, m, H-9β), 5.51−5.60 (2H, m, H-7α + H-13β), 6.32−6.44 (1H, br s, H-10α), 7.44 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.90 (2H, br d, J = 7.5 Hz, H_{COo-Ph}); *anal*. C 62.78%, H 6.99%, calcd for $C_{33}H_{44}O_{12}$, C 62.64%, H 7.01%.

13α-Acetyl-20-(*t*butyldimethylsilyloxy)-4α-hydroxybrevifoliol (21a). The primary alcohol of triol **21** (17 mg, 0.027 mmol) was treated with *tert*-butyldimethylsilyl chloride (22.2 mg, 0.147 mmol, 5.5 equiv) and imidazole (24.5 mg, 0.36 mmol, 13.5 equiv) in CH_2Cl_2 (2 mL) containing 4 Å-ms (100 mg). The reaction mixture was stirred at rt for 18 h (TLC analysis) and filtered through Celite and then the solvent was removed under reduced pressure. Separation of the crude material with silica gel (Hex−EtOAc, 1:1) gave 17.8 mg (88% yield) of the silyl ether derivative **21a**: mp 111−112 °C; IR (KBr) ν_{max} 3450, 2947, 1731, 1370, 1220, 1162, 1065, 845 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.09 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.90 (3H, s, H-19), 0.92 (9H, s, $Si(CH_3)_3$), 1.07 (3H, s, H-16), 1,00−1.10 (1H, m, H-14α), 1.25 (1H, d, J = 14 Hz, H-2α), 1.28 (3H, s, H-17), 1.60−1.75 (3H, m, H-6β, H-6α + OH), 1.89 (3H, br s, O_2CCH_3), 1.96−2.03 (6H, br s, 2 × O_2CCH_3), 2.06 (3H, s, H-18), 2.22 (1H, m, H-2β), 2.33 (1H, d, J = 8 Hz, H-3α), 2.62 (1H, dd, J = 14, 7.4 Hz, H-14β), 2.85 [1H, br s, OH (C-15)], 3.43−3.50 (1H, br s, OH), 3.55, 3.66 (each 1H, br d, J = 10 Hz, H-20), 3.8 (1H, br s, H-5β), 5.47−5.55 (2H, m, H-13β + H-9β), 5.57 (1H, dd, J = 14, 5.0 Hz, H-7α), 6.36−6.47 (1H, br s, H-10α), 7.42 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.90 (2H, br d, J = 7.5 Hz, H_{COo-Ph}).

13α-Acetyl-20-*tert*-butyldimethylsilyloxy-5-methanesulfonyl-4α-hydroxybrevifoliol (23). The above alcohol precursor (13 mg, 0.0174 mmol) was treated with mesyl chloride (6.75 mL, 0.087 mmol, 5 equiv) in pyridine (3 mL) and 3 Å molecular sieves (50 mg). The reaction mixture was stirred at room temperature for 24 h, then filtered through Celite and rinsed with CH_2Cl_2. Evaporation of the solvents under reduced pressure followed by separation of the crude material with silica gel (CH_2Cl_2−EtOAc, 8:2) gave the mesylated product **23** (31.1 mg, 73% yield): mp 109−110 °C; IR (KBr) ν_{max} 3505, 2933, 1741, 1452, 1372, 1245, 1179, 1086, 1034, 841 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.88 (3H, s, H-19), 0.90 (9H, s, $Si(CH_3)_3$), 1.07 (3H, s, H-16), 1,04−1.13 (1H, m, H-14α), 1.25−1.30 (1H, d, J = 14 Hz, H-2α), 1.30 (3H, s, H-17), 1.70−2.05 (3H, br m, H-6β, H-2β + OH), 1.80 (3H, br s, O_2CCH_3), 1.85 (3H, s, O_2CCH_3), 2.00 (3H, br s, O_2CCH_3), 2.02 (3H, s, H-18), 1.88 (1H, dt, J = 14, 4 Hz, H-6α), 2.23 [1H, s, OH (C-15)], 2.25 (1H, d, J = 8 Hz, H-3α), 2.37 (dd, J = 14, 7.4 Hz, 1H, H-14β), 3.15 (3H, s, O_2SCH_3), 3.52−3.62 (1H, br s, H-20), 3.73 (1H, d, J = 10 Hz, H-20), 5.00 (1H, br s, H-5β), 5.40−5.50 (1H, br m, H-9β), 5.48 (1H, br d, J = 14 Hz, H-7α), 5.56 (1H, br s, H-13β), 6.30−6.43 (1H, br s, H-10α), 7.42 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.54 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.89 (2H, br s, H_{COo-Ph}); *anal*. C 58.35%, H 7.37%, calcd for $C_{40}H_{60}O_{14}SSi$, C 58.23%, H 7.33%.

13α-Acetyl-4α,20-dihydroxy-5-methanesulfonylbrevifoliol (24). Deprotection of the primary alcohol group of **23** (8 mg, 0.01 mmol) with TBAF (dry, 1.0 M solution in THF, 14.5 μL) in THF (1.0 mL) gave derivative **24** (3 mg, 66% yield, based on recovered starting material): IR (KBr) ν_{max} 3455, 2928, 1734, 1446, 1375, 1340, 1220, 1170, 1056, 1048, 843 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.09 (3H, s, H-19), 1.18 (3H, s, H-16), 1.16−1.26 (1H, m, H-14α), 1.30 (3H, s, H-17), 1.53 (1H, d, J = 14 Hz, H-2α), 1.70−1.95 (3H, br m, H-6β, H-2β + OH), 1.77 (3H, br s, O_2CCH_3), 1.89 (3H, s, O_2CCH_3), 1.92 (3H, br s, O_2CCH_3), 1.99 (3H, s, H-18), 2.05 [1H, s, OH (C-15)], 2.15 (1H, dt, J = 14, 4 Hz, H-6α), 2.20 (1H, br d, J = 8 Hz, H-3α), 2.33 (1H, dd, J = 14, 7.4 Hz, H-14β), 3.11 (3H, s, O_2SCH_3), 3.57, 3.66 (each 1H, d, J = 11 Hz, H-20), 4.51 (1H, s, OH), 5.07 (1H, br s, H-5β), 5.24 (1H, dd, J = 14, 5.0 Hz, H-7α), 5.34−5.41 (1H, m, H-9β), 5.51 (1H, br t, J = 7.4 Hz, H-13β), 6.19−6.34 (1H, br s, H-10α), 7.37 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.52 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 7.76−7.86 (2H, br s, H_{COo-Ph}).

Compound 25. Compound **24** (3.0 mg, 0.0044 mmol) was treated with tetrabutylammonium acetate (12 mg, 9 equiv) in butanone (1.0 mL). The reaction mixture was stirred under reflux for 19 h. Separation of this crude mixture with silica gel (CH_2Cl_2−Et_2O, 4:1) gave the hydroxyoxetane derivative **25** (1.2 mg, 44% yield): IR (KBr) ν_{max} 3550, 2958, 1728, 1708, 1445, 1385, 1226, 1171, 1046, 863 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.09 (3H, s, H-19), 1.20 (3H, s, H-16), 1.28 (3H, s, H-17), 1.30 (1H, dd, J = 14, 7 Hz, H-14α), 1.39 (1H, d, J = 14 Hz, H-2α), 1.65 (3H, br s, O_2CCH_3), 1.67−1.84 (2H, br m, H-6β, + OH), 2.01 (3H, s, O_2CCH_3), 2.03 (3H, s, O_2CCH_3), 2.04 (3H, s, H-18), 2.05−2.10 (1H, m, H-6α), 2.30 (1H, br dd, J = 14, 8 Hz, H-2β), 2.58 (1H, dd, J = 14, 7 Hz, H-14β), 2.77 (1H, br d, J = 8 Hz, H-3α), 2.92 [1H, s, OH (C-15)], 4.36 (1H, d, J = 8.1 Hz, H-20a), 4.52 (1H, d, J = 8.1 Hz, H-20b), 5.15 (1H, br s, H-5α), 5.37 (1H, dd, J = 14, 5.0 Hz, H-7α), 5.60 (1H, br t, J = 7 Hz, H-13β), 6.98 (1H, br d, J = 10.5 Hz, H-9β), 7.15 (1H, br d, J = 10.5 Hz, H-10α), 7.46 (2H, t, J = 7.5 Hz, H_{COm-Ph}), 7.62 (1H, t, J = 7.5 Hz, H_{COp-Ph}), 8.04 (2H, d, J = 7.5 Hz, H_{COo-Ph});

FABMS (NBA) *m*/*z* 555 ($M^+ - CH_3CO_2$), 531, 515, 484; *anal.* C 64.39%, H 6.90%, calcd for $C_{33}H_{42}O_{11}$, C 64.48%, H 6.89%.

Acknowledgment. We express our gratitude to UQAM Foundation and the Department of Chemistry, UQAM, for their financial support. Financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and F.C.A.R. Funds (Quebec) are also acknowledged. The authors also wish to acknowledge Prof. E. Piers for supervising part of this work and the Department of Chemistry, University of British Columbia, for the use of laboratory facilities. Special thanks to Dr. H. L. Thanh for recording of the 2D 500 MHz NMR spectra, R. M. Dubois for providing assistance with the editing of data tables, and K. Walsh for providing assistance with the preparation of the manuscript.

Supporting Information Available: Procedures for isolation of **1** and for the preparation of compounds **2**−**4**; Tables S1 of ^{1}H and S2 of ^{13}C NMR spectral data for compounds **1**−**7** and **10**, copies of IR spectra for compounds **1**−**4**, **8**, and **10**, and 300 or 500 MHz ^{1}H and ^{13}C NMR spectra for compounds **1**, **8**, and **10** and 2D NMR spectra for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.
(2) Nicolaou, K. C.; Guy, R.; Potier, P. *Sci. Am.* **1996**, 94−98.
(3) Rowinsky, E. R.; Donehower, R. C. *N. Engl. J. Med.* **1995**, *332*, 1004−1014.
(4) Parmar, V. S.; Jha, A. *Stud. Nat. Prod. Chem.* **1998**, *20*, 79−133.
(5) Deka, V.; Dubois, J.; Thoret, S.; Guéritte, F.; Guénard, D. *Org. Lett.* **2003**, *5*, 5031−5034, and references therein.
(6) For review: Kingston, D. G. I.; Yuan, H.; Jagtap, P. G.; Samala, L. The Chemistry of Taxol and Related Taxoids. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: New York, 2002; Vol. 84.
(7) Ettouati, L.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1991**, *47*, 9823−9838.
(8) Balza, F.; Tachibana, S.; Barrios, H.; Towers, G. H. N. *Phytochemistry* **1991**, *30*, 1613−1614.
(9) Chu, A.; Zajicek, J.; Towers, G. H. N.; Soucy-Breau, C. M.; Lewis, N. G.; Croteau, R. *Phytochemistry* **1993**, *34*, 269−271.
(10) Georg, G. I.; Gollapudi, S. R.; Grunewald, G. L.; Gunn, C. W.; Himes, R. H.; Rao, B. K.; Liang, X.-Z.; Mirhom, Y. W.; Mitscher, L. A.; Vander Velde, D. G.; Ye, Q.-M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1345−1348.
(11) Appendino, G.; Barboni, L.; Gariboldi, P.; Bombardelli, E.; Gabetta, B.; Viterbo, D. *J. Chem. Soc., Chem. Commun.* **1993**, 1587−1589.
(12) Barboni, L.; Gariboldi, P.; Torregiani, E.; Appendino, G.; Cravotto, G.; Bombardelli, E.; Gabetta, B.; Viterbo, B. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3233−3238.
(13) Fuji, K.; Tanaka, K.; Li, B.; Shingu, T.; Yokoi, T.; Sun, H.; Taga, T. *Tetrahedron* **1995**, *51*, 10175−10188.
(14) Chu, M.; Furlan, L. B.; Davin, J.; Zajicek, Towers, G. H. N.; Soucy-Breau, C. M.; Rettig, S. J.; Croteau, R.; Lewis, N. G. *Phytochemistry* **1994**, *36*, 975−985.
(15) Wahl, A.; Guéritte-Voegelein, F.; Guénard, D.; Le Goff, M.-T.; Potier, P. *Tetrahedron*, **1992**, *48*, 6965−6974.
(16) Zamir, L. O.; Zheng, Y. F.; Caron, G.; Sauriol, F.; Mamer, O. *Tetrahedron Lett.* **1996**, *37*, 6435−6438.
(17) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: New York, 1983; p C175.
(18) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Aldrich Chemical: Milwaukee, WI, 1992.
(19) Appendino, G.; Gariboldi, P.; Pisetta, A.; Bombardelli, E.; Gabetta, B. *Fitoterapia* **1993**, *64* (1, Suppl.), 37−46.
(20) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13−19.
(21) (a) Soto, J.; Fuentes, M.; Castedo, L. *Phytochemistry* **1996**, *43*, 313−314. (b) Shen, Y.-C.; Wang, S.-S.; Pan, Y.-L.; Lo, K.-L.; Chakraborty, R.; Chien, C.-T.; Kuo, Y.-H.; Lin, Y.-C. *J. Nat. Prod.* **2002**, *65*, 1848−1852.
(22) Cragg, G. M.; Schepartz, S. A.; Suffness, M.; Grever, M. R. *J. Nat Prod.* **1993**, *56*, 1657−1668.
(23) (a) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401−7416. (b) Bai, J.; Kitabatake, M.; Toyoizumi, K.; Fu, L.; Zhang, S.; Dai, J.; Sakai, J.; Hirose, K.; Yamori, T.; Tomida, A.; Tsuruo, T.; Ando, M. *J. Nat Prod.* **2004**, *67*, 58−63.
(24) Kim, S.; Lee, J. I.; Ko, Y. K. *Tetrahedron Lett.* **1984**, *25*, 4943−4946.
(25) Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939−6942.
(26) Georg, G. I.; Cheruvallath, Z. S.; Vander Velde, D.; Ye, Q.-M.; Mitscher, L. A.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1349−1350.
(27) (a) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599−1600. (b) Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653−659. (c) Isaccs, R. C. A.; DiGrandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938−3941.
(28) Presented in part as a lecture: Breau, L.; Tremblay, S.; Soucy, C.; Branchaud, S.; Francoeur, E. Derivatives of Brevifoliol, an Abeo-Taxane, as Potential PGP inhibitors. 12th Ontario-Québec Minisymposium in Synthetic and Bioorganic Chemistry, U. Sherbrooke, Sherbrooke, PQ, Canada, Nov 2001.
(29) Arakawa, H. *Naturwissenchaften* **1963**, *50*, 441.

NP0304565