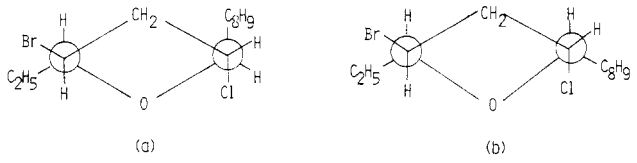
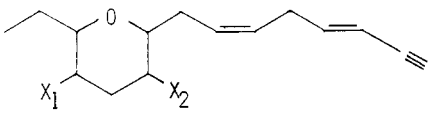


Figure 1. Newman projection of **2**: (a) C_8 side chain axial; (b) C_8 side chain equatorial.

halogen, and two doublets at δ 128.48 and 126.04 to an isolated olefin. The compound must therefore be monocylic. Analysis of the ^1H NMR spectrum (Table I) including decoupling experiments allowed unambiguous assignment of all protons and hence definition of a structural framework (**3**), which received support from



3 X_1, X_2 = Br or Cl

mass spectral fragments corresponding to successive losses from the parent ion of C_2H_4, C_8H_9, HBr, and Cl. The proton data also placed the isolated double bond at C-6. Its cis stereochemistry was deduced from the ^{13}C chemical shift of the doubly allylic methylene at C-5, which resonates at δ 30.87 (or 31.08). Analogous methylenes in fatty acids are observed at δ 25.7 (cis–cis), 30.5 (cis–trans), or δ 35.7 (trans–trans).[5] Confirmation of the C-6,7 cis stereochemistry was provided by the 200-MHz ^1H NMR spectrum of **2** in deuteriobenzene, where the cis- and trans-olefin signals do not overlap. Computer simulation of the two cis protons using a chemical shift difference of 11.5 Hz and a J value of 11 Hz resulted in a pattern that fits the observed signals. Yet to be elucidated were the positions of the halogens and the stereochemistry at the four chiral centers.

A coupling constant of J = 10.2 Hz between H-12 and H-13 denotes a trans diaxial relationship, thus demanding diequatorial configuration for X_1 and the C_2 side chain. On the other hand, H-10 lacks large coupling (J = 3.4, 3.0, 1.75 Hz), thereby necessitating axial configuration for X_2. Orientation of the C_8 side chain remains to be settled, once the identities of X_1 and X_2 are known.

The relatively large chemical shift difference between the C_{14} protons ($\Delta\delta$ = 0.48) suggests interaction with a bulky group at C-12, most likely an equatorial bromine. This was proven by single-frequency on-resonance ^1H–^{13}C decoupling experiments in deuteriobenzene. In that solvent the H-10 and H-12 protons are separated by 60 Hz. Irradiation of CHX_1 at 79.542 438 Hz collapsed the HC–Br doublet at δ 46.5 to a singlet. Conversely, the HC–Cl doublet at δ 60.5 collapsed to a singlet when it was irradiated at 79.542 378 Hz, Hence X_1 = Br and X_2 = Cl.

Finally, the orientation of the C_8 side chain could be determined. In the fully coupled ^{13}C NMR spectrum of **2** the C-11 methylene appears as a doublet of doublets ($^1J_{CH}$ = 139, 128 Hz), further split by $^2J_{CCH}$ and $^3J_{CCCH}$ couplings of about 1 Hz. The maximum width of the pattern due to long-range coupling is about 4 Hz. Such a pattern can be obtained only if all geminal and vicinal couplings are equal to one another and are about 1 Hz. In Figure 1 it may be seen that both C-11–C-12–H-12 and C-11–C-10–H-10 angles are about 109°, which renders the $^2J_{CCH}$ coupling constants about equal and small, 1–2 Hz. Vicinal coupling ($^3J_{CCCH}$) between carbon and hydrogen depends on the dihedral angle between CCC and CCH bonds and is governed by a Karplus relationship.[6] If the C_8 side chain is axial (Figure 1a), this dihedral angle will be 180°, leading to an 8-Hz coupling. The resulting pattern is resolvable as a doublet. This is not observed. If, however, C_8 is equatorial (Figure 1b), a dihedral angle of 60° results, about equal to the situation with the C_2 side chain, which is known to be equatorial. Hence orientation of the C_8 side chain is equatorial.

Experimental Section

Mass spectra were obtained on a MAT 311 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 467 spectrometer. A Beckman ACTA 111 spectrophotometer was used to measure UV spectra. ^1H NMR spectra were determined on a Varian XL-200 NMR spectrometer. Natural abundance ^{13}C NMR spectra (noise, off-resonance, and specific proton decoupled) were recorded on a Varian FT-80 spectrometer.

Isolation. *A. oculifera* were collected at Duwa, Sri Lanka, at low tide from a reef where the animals were browsing. The animals were about 30 mm long and exuded a purple pigment on contact. The animals (450 g) were frozen and later homogenized with acetone. Filtration and concentration at reduced pressure gave a dark brown residue, which was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 solubles (1.5 g) were chromatographed on Bio-Sil A (hexane/CH_2Cl_2, 65:35) followed by HPLC (Partisil, hexane/CH_2Cl_2, 80:20) to give **2** as a colorless liquid: $[\alpha]_D$ +7.14° (c 0.98, CH_2Cl_2); $\lambda_{max}^{(MeOH)}$ 227 nm (ϵ 13 600); IR (CH_2Cl_2) 3300, 3020, 2960, 2850, 2100, 1100, 1082 (sh), 960, 818 cm^{-1}; HRMS, m/z 332.0364, calcd for $C_{15}H_{20}{}^{81}Br^{35}ClO$, 332.0366; MS, m/z 334, 332, 330 (M^+), 306, 304, 302 ($M^+ - C_2H_4$), 297, 295 (M^+ – Cl), 255, 253, 251 ($M^+ - C_6H_7$), 229, 227, 225 ($M^+ - C_8H_9$), 215 (M^+ – HBrCl), 201, 199, 197 ($M^+ - C_{10}H_{13}$), 81 (C_8H_9, base peak); ^{13}C NMR ($CDCl_3$) and ^1H NMR ($CDCl_3$), see Table I; ^1H NMR (C_6D_6) δ 6.24 (1 H dt), 5.53 (1 H m), 5.34 (2 H m), 4.25 (1 H, ddd), 3.44 (1 H ddd), 3.22 (1 H ddd), 3.07 (1 H dt), 2.7–1.9 (10 H, complex), 1.67 (1 H qdd), 1.08 (1 H t).

Acknowledgment. We thank Professor E. Alison Kay for identifying the organism; the East-West Center for an open grant to E.D.deS. and for enabling his field study in Sri Lanka; and the National Science Foundation for generous financial support.

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Stereochemistry and Carbon-13 Nuclear Magnetic Resonance Spectroscopy of the Histamine-Liberating Sesquiterpene Lactone Thapsigargin. A Modification of Horeau's Method

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Recently, thapsigargin (**1**) and thapsigargicin (**2**), the two major skin irritants of *Thapsia garganica* (Apiaceae = Umbelliferae) have been isolated,[1] and the relative con-

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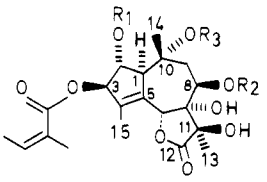
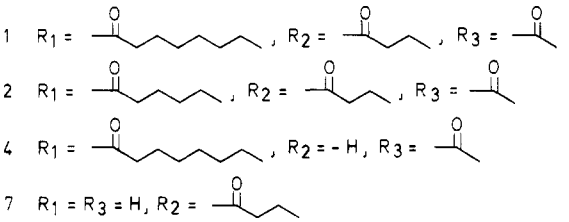
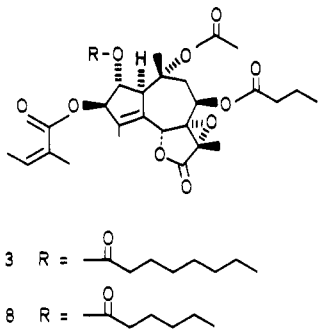


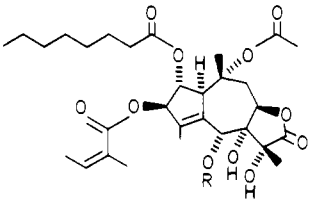


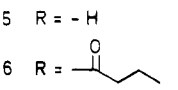
figurations at all the asymmetric centers except those bearing the hydroxy groups have been established by an X-ray analysis performed on the 7,11-epoxide (**3**).[2] On



the basis of the reactivity of **1** and its derivatives toward periodic acid and with the support of nuclear Overhauser experiments, we have assigned the relative configurations of these two hydroxy groups, which seem to be of special importance to the biologic activity.[2] The absolute configuration as represented by formula **1** has been established by a modification of Horeau's method. Furthermore, assignments of the signals in the ^{13}C NMR spectrum of **1** were performed in order to facilitate the structure elucidation of six other 2,3,8,10-tetraesterified 2,3,7,8,10,11-hexaoxygenated 6,7-guaianolides isolated from species of the genus *Thapsia*.[3]

During the structure elucidation of **1** a sodium carbonate catalyzed saponification was shown to yield a mixture of **4**, **5**, and unreacted **1**.[2] The inertness of **4** toward periodic acid strongly indicates the hydroxy group at C(7) to be trans to the two other hydroxy groups. Thus, the β-position of the oxygen at C(8), as evidenced by the X-ray crystallographic analysis of **3**,[2] implies the hydroxy groups at C(7) and C(11) to be α and β, respectively. Like **4**, thapsigargin did not react with periodic acid. A trans configuration of the hydroxy groups at the lactone ring of **4** necessitates a cis configuration to be present in **5**, since the latter compound must be formed by an opening of the lactone followed by a rotation around the C(7)–C(11) bond. Accordingly, **6**, formed by selective butanoylation of the secondary hydroxy group in **5**, reacted quantitatively when treated with periodic acid. The ^1H NMR spectrum of the periodate reaction mixture contained a prominent peak

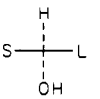




at δ 2.50 assignable to the methyl group in pyruvate. Lability of the product prohibited its chromatographic isolation and full characterization.

The cis configuration of the hydroxy group at C(7) relative to the proton at C(1) was further confirmed by nuclear Overhauser experiments performed on a Me_2SO-d_6 solution of **1**. Saturation of the low-field signal due to one of the two hydroxy protons (found at 6.10 ppm) afforded a 3% increment of the intensity of the signal due to H(1). In contrast, saturation of the high-field hydroxy proton signal (found at 6.02 ppm) did not result in a significant increment of the intensity of any signal. Since inspections of Dreiding stereomodels establish an unlikely great distance between H(1) and OH(11) for a nuclear Overhauser interaction irrespectively of the stereochemistry of the hydroxy group, the low-field hydroxy signal was assigned to OH(7). An interaction between OH(7) and H(1) is only likely if a cis relationship is assumed.

Application of the Horeau method established the absolute configuration at C(8) of debutanoylthapsigargin (**4**) as *R* and consequently that of thapsigargin as depicted in formula **1**. This method is based on an empirical rule which states that esterification of an asymmetric alcohol, I, where L is a bigger substitutent than S in a steric sense,



I

by an excess of optically inactive α-phenylbutyric anhydride results in preferential combination with the *S* antipode of the acid.[4] The enantiomeric alcohol will preferentially combine with the *R* antipode of the acid. This principle has been used extensively to establish the absolute configuration of a number of natural products or synthons.[5] In general, the preferential formation of formed (*R*)- or (*S*)-α-phenylbutyrate has been established in an indirect way, either by measuring the sign of rotation of the recovered acid[4,5] or by chromatographic investigations of the recovered acid[6] or derivatives thereof.[7] A method based on a ^1H NMR spectroscopic or gas chromatographic investigation of the epimeric esters formed after reactions of the alcohol with two partly resolved enantiomeric α-phenylbutyric anhydrides has, however, been published.[8]

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Table I. ^{13}C NMR Spectral Data of the Sesquiterpene Nuclei

C	chemical shift, ppm		
	1[a]	1[b]	9[b]
1	58.4 (dm, $^1J = 138$)	59.1 (d)	52.6 (d)
2	78.6 (dt, $^1J = 149$, $^2J = 5$)	79.5 (d)	33.3 (t)
3	84.8 (dm, $^1J = 151$)	85.8 (d)	81.2 (d)
4	140.9 (sm)	141.4 (s)	142.8 (s)
5	132.3 (sm)	133.1 (s)	134.5 (s)
6	76.9 (dt, $^1J = 150$, $^3J = 6$, $^3J = 6$)	78.4 (d)	78.7 (d)
7	79.3 (sm)[c]	79.7 (s)	79.7 (s)[c]
8	66.5 (dd, $^1J = 146$, $^2J = 6$, $^2J \approx 0$)	67.7 (d)	67.7 (d)
9	38.6 (ts, $^1J = 130$, $^2J \approx 0$)	39.5 (t)	39.8 (t)
10	84.7 (sm)	86.3 (s)	87.0 (s)
11	78.9 (sm)[c]	79.7 (s)	79.5 (s)[c]
12	175.9 (sq, $^3J = 4$)	178.7 (s)	178.4 (s)
13	16.0 (qs, $^1J = 128$)	16.2 (q)	15.9 (q)
14	22.9 (qm, $^1J = 128$)	23.4 (q)	23.4 (q)
15	12.6 (qs, $^1J = 127$)	13.2 (q)	13.2 (q)

[a] Recorded at 67.9 MHz in CD_3CN. Shifts in parts per million downfield from Me_4Si. Multiplicities are from a gated decoupled spectrum. Numerical values of coupling constants given in hertz. The assignments are based on incremental varying of a proton decoupler frequency and on SPT experiments as described in the text. [b] Recorded at 67.9 MHz in CD_3OD. Multiplicities are from an off-resonance-decoupled spectrum. [c] Assignments interchangeable.

In the case of debutanoylthapsigargin (**4**) the two epimeric esters formed by pyridine-catalyzed reaction with optically inactive α-phenylbutyric anhydride[9] were separated by HPLC, and the ratio was estimated from the peak heights.[10]

The minor product cochromatographed with the ester obtained by a 4-(dimethylamino)pyridine-catalyzed reaction between **4** and the anhydride of (*S*)-α-phenylbutyric acid.[9] This catalyst was chosen since the anhydride reacts very slowly with **4** in a pyridine solution, but it undergoes rapid racemization in this solvent.[11] Replacing pyridine with 4-(dimethylamino)pyridine in the reaction between **4** and optically inactive α-phenylbutyric anhydride required a considerably shorter reaction time but also afforded a smaller preponderance of the major product. A lower reaction temperature again increased the ratio between the two epimeric esters. The preferential formation of the ester of **4** and (*R*)-phenylbutyric acid established an *R* configuration of C(8), if it is assumed that the C(7) group is the larger one. This assumption has been found valid for pseudoguaianolides[12] but invalid for one germacranolide and two eudesmanolides.[13]

The possibility of converting thapsigargin (**1**) as well as thapsigargicin (**2**) into **7** and the almost identical rotations of the epoxides **3** and **8** established the absolute and relative configuration of thapsigargicin as depicted in formula **2**.

In the previously described ^{13}C NMR spectrum of thapsigargin (**1**),[2a] a distinction between the signals of C(2), C(3), C(6), and C(8) was not possible since coincidence of the ^1H NMR signals of the attached protons prohibited selective decoupling. Separation of the signals originating from H(2) and H(8) was obtained by using acetonitrile-d_3 as the solvent, and the assignments (given in Table I) of the signals of the connected carbons were verified by incrementally varying the decoupler frequency in the δ 4.7–6.0 range of the proton spectrum.[14] Comparison of the ^{13}C NMR spectrum of **1** and the 2-deoxy analogue, trilobolide (**9**),[15] made a distinction between C(3) and C(6) possible. The assignments of the C(15) signal is based on SPT experiments.[16] Excitation of H(15) produced changes in the intensity of the signals due to one of the sp^2 hybridized carbons, thus permitting assignment of this signal to C(4).

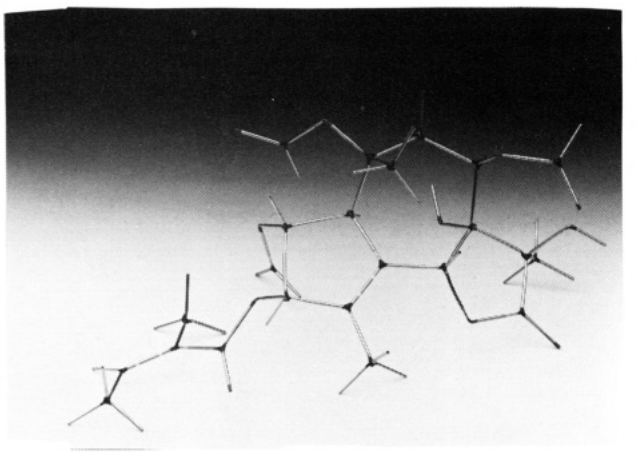
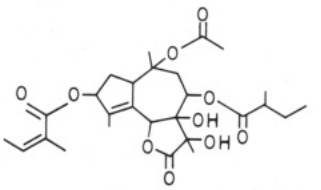


Figure 1. Dreiding stereomodel of **1**. For clarity the acyl moieties of octanoyl, butanoyl, and acetyl have been replaced by a formyl group.



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According to Dreiding stereomodels, a torsion angle of approximately 180° between C(8)–H(8) and C(9)–H(9β) is present in one of the two possible low-energy conformations of **1**, whereas an angle of approximately 60° is found in the other low-energy conformation (Figure 1). The observed values of 3 Hz for the coupling constants between H(8) and both H(9β) and H(9α) indicate the latter conformation to be the favored one. Furthermore, the weak C(9)–H(8) and C(8)–H(9α) couplings (Table I) can be explained by the orientation of O(8) in this conformation.[17] Likewise, the torsion angles of approximately 180° between C(6)–C(7) and C(8)–H(8), between C(14)–C(10) and C(1)–H(1), and between C(14)–C(10) and C(9)–H(9α) are in agreement with the observed C(6)–H(8) coupling constant and the observed pattern for C(14).[18] Selective decoupling of H(1) has verified a C(6)–H(1) coupling, although a low signal to noise ratio impeded clear-cut conclusions. A lack of investigated model structures[18] has

(9) The ^1H NMR spectrum of the product established that only the secondary hydroxy group was acylated under these conditions. Since the chemical shift values of especially H(1), H(9), and H(13) are very dependent on the concentration, Horeau methods based on comparisons of ^1H NMR spectra[8] should be used with circumspection in this case.

(10) Direct measurement of the product composition enables establishment of the preponderant ester even though only a minute amount of alcohol is esterified. This is especially advantageous if the alcohol, as in the case of **4**, reacts extremely slowly with the anhydride.

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made an interpretation of the coupling impossible.

Experimental Section

For NMR spectroscopy samples were prepared as approximately 10% (w/v) solutions in CD_3CN and 3% (w/v) in Me_2SO-d_6, with Me_4Si added as an internal standard. ^1H spectra were obtained on a Bruker HX-270S spectrometer in the FT mode by using quadrature detection. For NOE measurement the 5-mm-o.d. sample tube was degassed by several freeze–pump–thaw cycles before sealing. The NOE experiment was performed by using a spectral width of 4000 Hz and 16K data points. The on-line- and off-line-irradiated spectra were sequentially obtained and stored on disk. The delay between each scan was 5 s and the saturation period 2 s. The total number of scans accumulated was 7200. The NOE effect was determined by subtraction from the two FIDs of a weight factor (1.*xx*), leading to the disappearance of the enchanced signal having *xx*% NOE effect.

The SPT (selective population transfer) ^{13}C spectra were obtained on the same instrument. Inversion of proton signals was effected by 50-ms pulses. The spectral width was 20 000 Hz, 32 K data points were used, and 2000 scans were accumulated with a delay of 5 s between each scan.

^1H NMR data of **1** (CD_3CN): δ 5.64 [br s, H(6) and H(3)], 5.49 [t, J = 3 Hz, H(8)], 5.38 [t, J = 4 Hz, H(2)], 4.19 [br s, H(1)], 2.90 [dd, J = 15, 3 Hz, H(9)], 1.77 [br s, H(15)], 1.33 and 1.31 [2 s, H(13) and H(14)]. The signals from the acyl moieties, found as expected, cover the signal due to one of the protons attached to C(9).

Periodic acid treatment was performed by leaving a methanolic solution of equal amounts of compound and periodic acid at room temperature for 18 h. After addition of water the mixture was extracted with ether. The residue obtained by concentration of the organic layer was investigated by ^1H NMR or HPLC over Lichrosorb RP 18 [7 μm; eluent, MeOH–H_2O(3:1); 4600 theoretical plates calculated for **4**].

Butanoylation of 5 was performed by leaving a solution of **5** (8 mg), butyric anhydride (20 μL), and 4-(dimethylamino)-pyridine (7 mg) in methylene chloride (2 mL) for 45 min. The organic layer obtained after addition of 2 M hydrochloric acid (10 mL) and ether (10 mL) followed by occasional shaking for 10 min was washed with 0.5 M aqueous sodium carbonate, water, and 0.5 M hydrochloric acid and concentrated to give an oil, from which **6** (5 mg) was isolated by column chromatography over silica gel [60–80 mesh; eluent; toluene–EtOAc (3:1)]: ^1H NMR data ($CDCl_3$) δ 5.88 [br s, H(6)], 5.69 [br s, H(3)], 5.41 [dd, J = 4, 5 Hz, H(2)], 5.18 [dd, J = 14, 4 Hz, H(8)], 3.72 [br s, H(1)], 2.85 [dd, J = 14, 4 Hz, H(9)], 1.90 [br s, H(15)], 1.45 [s, H(14)]. The signals from the acyl moieties, found as expected, cover the signals due to Me(11) and due to one of the protons attached to C(9).

Horeau analyses were performed by leaving a solution of **4** (5 mg) and optically inactive α-phenylbutyric anhydride (20 μL) in either pyridine (0.5 mL) or a 0.5% solution of 4-(dimethylamino)pyridine in methylene chloride (1 mL). After an adequate period of time [2 days for the pyridine-catalyzed reaction, 1 h for the 4-(dimethylamino)pyridine-catalyzed reaction at room temperature, 4 h at 0 °C, 16 h at −23 °C, and 9 days at −78 °C], the solution was mixed with water and stirred for a further 2 h. After addition of ether (5 mL) the organic layer was separated, washed with 0.5 M aqueous sodium carbonate (5 mL) and 0.25 M hydrochloric acid (5 mL), dried, and concentrated to yield a residue, which was dissolved in methylene chloride (5 mL). A sample (5 μL) of this solution was investigated by HPLC over Polygosil 60-5 [120 × 4.6 mm, eluent 2-propanol–hexane (2:98), detection 220 nm, flow rate 1 mL/min, 1600 teoretical plates as calculated for the ester of **4** and (*S*)-α-phenylbutyric acid]. Retention times: the ester of **4** and (*R*)-α-phenylbutanoic acid, 9.4 min; the ester of **4** and (*S*)-α-phenylbutanoic acid, 10.8 min. The ratio of (*R*)-α-phenylbutanoate/(*S*)-α-phenylbutanoate for the pyridine-catalyzed reaction was 3:2, and those for the 4-(dimethylamino)pyridine-catalyzed reaction were as follows: room temperature, 5:4; 0 °C, 4:3; −23 °C, 3:2; −78 °C, 3:1.

^1H NMR data of **4** esterified with (*R*)-α-phenylbutyric acid (0.75 mg in 400 μL of $CDCl_3$): δ 5.69 [br s, H(6) or H(3)], 5.55 [t, J = 3 Hz, H(8) or H(2)], 5.54 [H(6) or H(3)], 5.35 [H(8) or H(2)], 4.16 [br s, H(1)], 2.92 [dd, J = 12, 3 Hz, H(9)], 1.85 [s, H(15)], 1.49 [s, H(14)]. The signals from the acyl moieties, found as expected, cover the signals due to Me(11) and due to one of the protons attached to C(9).

^1H NMR data of **4** esterified with (*S*)-α-phenylbutyric acid (0.25 mg in 400 μL of $CDCl_3$): δ 5.69 [br s, H(3) or H(6)], 5.54 [H(8) or H(2)], 5.43 [H(8) or H(2)], 5.35 [H(3) or H(6)], 4.12 [br s, H(1)], 2.91 [dd, J = 12, 3 Hz, H(9)], 1.81 [s, H(15)], 1.39 [s, H(14)], 1.20 [s, H(13)]. The signals from the acyl moieties, found as expected, cover the signal due to one of the protons attached to C(9).

The reaction between 4 and (*S*,*S*)-α-phenylbutyric anhydride ($[\alpha]^{23}_D$ +123° (*c* 0.1, C_6H_6)) was performed as described above for the 4-(dimethylamino)pyridine-catalyzed reaction between the optically inactive anhydride and **4** at room temperature. Approximately 8% of the *R* ester could be detected in the product by HPLC.

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Palladium-Mediated Reaction of Enol Ethers with Organomercuric Acetates

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Regiospecific palladium-mediated coupling of heterocyclic or arylmercuric salts with cyclic or acylic enol ethers and acetates has been reported.[2-11] We have now extended the study of this coupling reaction utilizing selected reactant arylmercuric acetates and enol ethers to explore the scope of the reaction and to examine reaction parameters such as cyclic enol ether ring size, steric factors in both enol ether and organometallic reactants, and reaction solvent effects. For this study, the mercuric acetates used were (see Chart I) [1,3-dimethyl-2,4(1*H*,3*H*)-dioxopyrimidin-5-yl]mercuric acetate[2,3,6,7] (**1**), (4-methoxyphenyl)mercuric acetate[12] (**2**), (2-methoxynaphthyl)-mercuric acetate (**3**), and (4-methoxynaphthyl)mercuric acetate (**4**); the enol ethers used were 2,3-dihydrofuran (**5**), 3,4-dihydro-2*H*-pyran (**6**), 5-methyl-2,3-dihydrofuran (**7**), and *n*-butyl vinyl ether (**8**). All reactions utilized stoichiometric palladium acetate and were carried out at room temperature. The results of the study are summarized in Tables I and II.

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