Highly Enantioselective Synthesis of Natural Phyllodulcin†

Alessio Ramacciotti,‡ Rita Fiaschi,‡ and Elio Napolitano*,‡,§

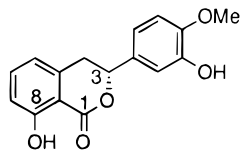
Università di Pisa, Dipartimento di Chimica Bioorganica, Via Bonanno 33, 56126 Pisa, Italy, and Scuola Normale Superiore, Piazza dei Cavalieri, 56127 Pisa, Italy

Received February 20, 1996⊗

(*S*)-[4-Methoxy-3-[(triisopropylsilyl)oxy]phenyl)oxirane (prepared from isovanillin by consecutive silylation, olefination, Sharpless asymmetric *cis*-dihydroxylation, and dehydration) reacted with [3-(methoxymethoxy)phenyl]lithium (prepared from 3-bromophenol by consecutive methoxymethylation and bromine−lithium exchange) to yield (*R*)-1-[4-methoxy-3-[(triisopropylsilyl)oxy]phenyl)-2-[3-(methoxymethoxy)phenyl]ethanol. The last compound underwent selective hydrogen−metal exchange with excess of butyllithium affording (after carbonation, lactonization, and deprotection of phenolic groups) the title compound [(*R*)-3,4-dihydro-8-hydroxy-3-(4-methoxy-3-hydroxyphenyl)-isocoumarin].

Introduction

Natural 3-aryl-3,4-dihydroisocoumarins constitute a small class of secondary metabolites particularly abundant in the *Hydrangea* genus (Saxifragacee).[1] Members of the class differ from each other by the number and type of oxysubstituents on the aromatic rings; the presence of an 8-hydroxy group is very frequent. Phyllodulcin (**1**) is probably the most interesting representative among 3-aryl-3,4-dihydroisocoumarins. It has long been known as the sweet component of the plant named amacha in Japan (*Hydrangea macrophylla* Seringe var. *thumbergii*), whose leaves, fermented and dried, are infused to make a traditional beverage. Because of its refreshing taste and strong sweetening power (almost a thousand times that of sucrose), phyllodulcin (**1**) has become the lead compound in studies of structure−activity relationship aimed at the development of a new class of low-calories sweeteners, designated as isovanillins because of the presence of a 3-hydroxy-4-methoxyphenyl group as a common feature.[2] Furthermore, phyllodulcin (**1**) exhibits antimicrobial activity, a property shared with other congeners.[1]



1

A number of different methods are available for building the carbon framework of natural 3-aryl-3,4-dihydroisocoumarins and to place regioselectively the oxy functions on the two aromatic rings (particularly the hydroxy group at C-8);[3e] however, in spite of the relatively simple stereochemical problems involved (only one asymmetric carbon present) no chemical synthesis of natural 3-aryl-3,4-dihydroisocoumarins, featuring an effective control of the absolute configuration, has been published. To the best of our knowledge, only one study has dealt with the asymmetric synthesis of **1**, but with only partial success, owing to the ease of racemization of the benzylic chiral center; the latter, although introduced in the appropriate chirality and with high enantioselectivity, proved to be configurationally unstable under the hydrogenolytic or strongly acidic conditions required for the completion of the synthesis.[3] On the other hand, the possibility of obtaining substances related to **1** in optically pure form might lead to a better understanding of the relationship between structure and taste of **1** and, more generally, to the structure−activity relationships of 3-aryl-3,4-dihydroisocoumarins.

In previous publications we have outlined a possibly wide scope approach to chiral 3-alkyl-3,4-dihydroisocoumarins, which is shown retrosynthetically in Scheme 1 (structures **2a**−**5a**).[4] According to this approach: (a) the *ortho*-metalation promoted by a *β*-functionalized alkyl group followed by carbonation was adopted for the regioselective introduction of C(1) of the targets; (b) the enantioselective construction of the intermediate 2-phenylethyl alcohol **3a** was accomplished by addition of an organometallic reagent prepared from **4** to the appropriate enantiopure terminal epoxide **5a**; (c) the introduction of the desired chirality at C(3) of the targets was ultimately based on the very efficient methods for olefin oxidation developed by Sharpless. We report here the extension of the above approach to the first successful enantioselective synthesis of **1**, as the representative of natural 3-aryl-3,4-dihydroisocoumarins.

For such an extension, at least two specific problems were foreseen, which were not encountered in our previ-

† Dedicated to Professor A. Marsili on the occasion of his 65th birthday.

‡ Università di Pisa.

§ Scuola Normale Superiore.

⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) (a) For the literature prior to 1985, see: Hill, R. A. *Progr. Chem. Nat. Compd.*, **1986**, *49*, 1. For recent isolation of **1** from natural sources, see: (b) Hashimito, T.; Tori, M.; Asakawa, Y. *Phytochemistry* **1987**, *12*, 3323. (c) Yoshikawa, M.; Uchida, E.; Chatani, N.; Murukami, N.; Yamahara, *J. Chem. Pharm. Bull.* **1992**, *40*, 3121. (d) Yoshikawa, M.; Uchida, E.; Chatani, N.; Kobayashi, H.; Naitoh, Y.; Okuno, Y.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1992**, *40*, 3352.

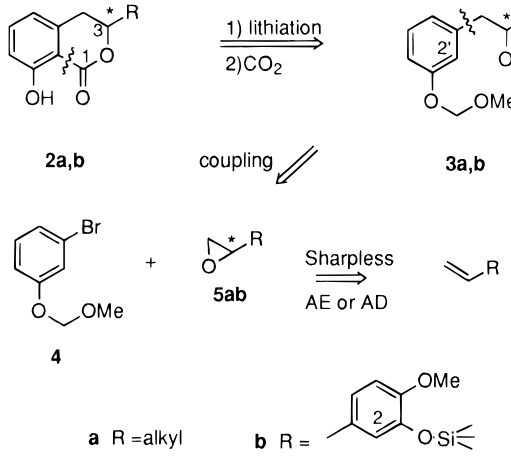
(2) Arnoldi, A.; Bassoli, A.; Merlini, L.; Ragg, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1359 and references cited therein.

(3) (a) Takeuchi, N.; Nakano, T., Goto, K., Tobinaga, S. *Heterocycles* **1993**, *35*, 289. (b) Mali, R. S, Shelke, D. W. *Indian J. Chem.* **1993**, *32B*, 822. (c) Kessar, S. V.; Gupta, Y. P.; Singh, S. *Indian J. Chem.* **1993**, *32B*, 668. (d) Kessar, S. V., Singh, P.; Vohra, R.; Kaur, N. P.; Venugopal, D. *J. Org. Chem.* **1992**, *57*, 6716. (e) Arnoldi. A.; Bossoli, A.; Merlini, L., Ragg, E. *Gazz. Chim. Ital.* **1992**, *122*, 403. (f) Napolitano, E.; Ramacciotti, A.; Fiaschi, R. *Gazz. Chim. Ital.* **1988**, *118*, 101. (g) Watanabe, M.; Sahara, M.; Kubo, M.; Furukawa, S.; Billedeau, R. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 742. See also ref 1a for earlier synthetic work.

(4) (a) Synthesis of (−)-mellein: Napolitano, E. *Gazz. Chim. Ital.* **1991**, *121*, 455. (b) Synthesis of isocoumarin portion of AI77-B: Bertelli, L.; Fiaschi, R.; Napolitano, E. *Gazz. Chim. Ital.* **1993**, *123*, 669.

S0022-3263(96)00338-6 CCC: $12.00

Scheme 1. Retrosynthesis of 3,4-Dihydroisocoumarins Based on the Lithiation of Aromatic Rings Promoted by β-Functionalized Alkyl Groups



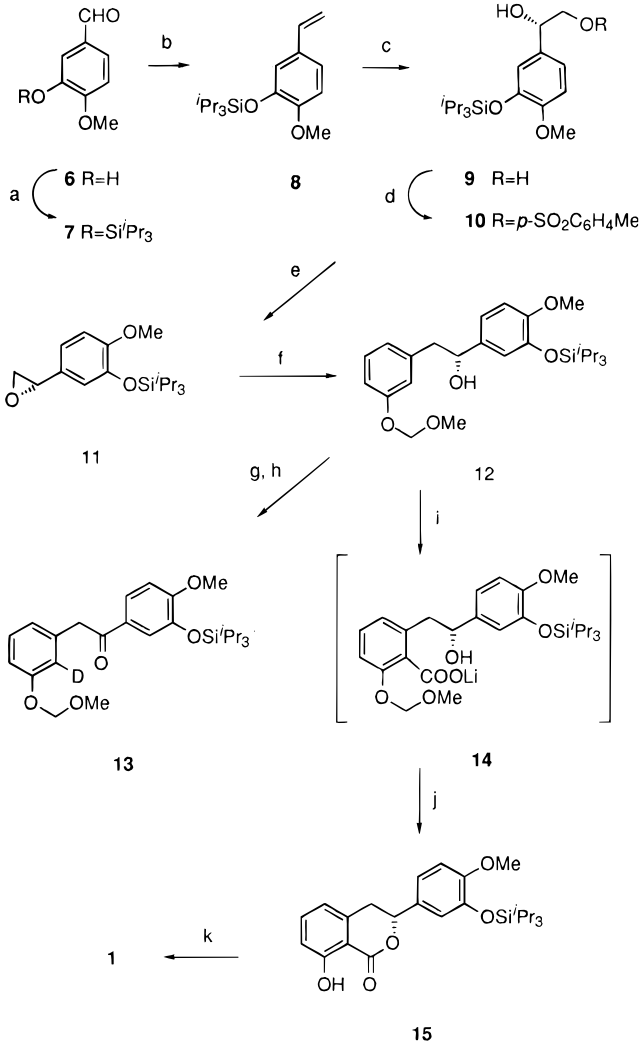
ous enantioselective syntheses of isocoumarins, where the C(3) substituent of the target was an alkyl (such as in **2a**) rather than aryl group such as in **2b**. First, whereas alkyloxiranes **5a** are generally and quite selectively attacked by carbon nucleophiles at the less substituted carbon atom, with aryloxiranes such as **5b**, the attack of nucleophiles at the benzylic position as well as the rearrangement of the epoxide to an arylacetaldehyde prior to the formation of the new carbon−carbon bond can be serious side reactions, which obviously lead to unwanted products.[5] Secondly, on the basis of our pervious work with ketalized deoxybenzoins,[6] a competition between positions 2 and 2′ could be expected in the reaction of **3b** with the lithiating agent, which would lead to a benzyl phthalide rather than to the desired dihydroisocoumarin **2b**.

We hoped to solve the first problem by an appropriate choice metal atom to couple **4** and **5b**. As to the second problem, we decided to rely on the use of a hindered silyl group for the protection of the phenolic OH of the aryl fragment providing the C(3)−aryl substituent in the final compound: the use of such a group was expected to disfavor lithiation at C(2) of **3b**;[7] furthermore, such a silyl group, besides offering a good protection of the phenol throughout the synthesis, was expected to be cleaved under mild conditions, hopefully avoiding racemization.

Results and Discussion

Isovanillin (**6**) was almost quantitatively converted into the styrene derivative **8** by condensation with triisopropylsilyl chloride followed by Wittig olefination of the intermediate silylated aldehyde **7** with triphenylmethylenephosphorane. Asymmetric dihydroxylation according to the Sharpless procedure (AD-mix-α)[8] converted **8** into the diol **9** (97% yield) with an enantiomeric excess of 95.1%, as determined by chromatography of its diacetate using a chiral stationary phase (see Experimental Section). Diol **9** (first chiral intermediate) was converted

Scheme 2. Enantioselective Synthesis of Phyllodulcin[a]



[a] Conditions: (a) $^{i}Pr_3SiCl$, imidazole, DMF. (b) $Ph_3MeP^+Br^-$, BuLi, THF. (c) AD-mix-α, H_2O, $^{t}BuOH$. (d) *p*-$MeC_6H_4SO_2Cl$, pyridine. (e) NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2/H_2O. (f) **4**, BuLi, THF. (g) BuLi, cyclohexane, 16 h, rt; then D_2O. (h) PCC, CH_2Cl_2. (i) BuLi, cyclohexane, 16 h, rt; then CO_2. (j) Ac_2O, and then HCl (6 M)/ Et_2O. (k) $Bu_4N^+F^-$, THF.

into its monotosylate **10** (96% yield, 94.8% ee) and finally into the epoxide**11** (100% yield, enantiomeric excess could not be determined). The reaction of the epoxide **11** with the lithiated derivative obtained by halogen−metal exchange between the protected bromophenol **4** and butyllithium gave the desired alcohol **12** (65% yield, 94% ee), with no evidence of alternative addition products.[5] There are precedents for such a result of the reaction between aryllithium reagents and aryloxiranes,[9] although its scope seems to have been overlooked. Also, it is interesting to note that the protected bromophenol **4** underwent clean halogen−metal exchange, although it could be considered as a good candidate for hydrogen−metal exchange, owing to the presence of a hydrogen *ortho* to a methoxymethoxy group and to a bromine atom.[10] In agreement with our expectations, the alcohol **12**, when exposed to a 3-fold excess of butyllithium in cyclohexane

(5) Gorzinski Smith J. *Synthesis* **1984,** 629.
(6) (a) Napolitano, E.; Ramacciotti, A.; Morsani, M.; Fiaschi, R. *Gazz. Chim. Ital.* **1991**, *121*, 257. (b) Napolitano, E.; Giannone, E., Fiaschi, R., Marsili, A. *J. Org. Chem.* **1983,** *48*, 3653.
(7) For a precedent of such a use of a hindered silyloxy group, see: Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.
(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994,** *94*, 2483.
(9) Cristol, S. J.; Douglass, J. R.; Meek, J. S. *J. Am. Chem. Soc.* **1951**, *73*, 816. For a recent application to the synthesis of the natural diarylethanol derivative named combretastatin, see: Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *Tetrahedron*: *Asymmetry* **1996**, *4*, 1101.

for 18 h at room temperature, was cleanly metalated at C(2′), as demostrated by the almost quantitative deuterium incorporation upon quenching with deuterium oxide; the site and the extent of deuterium incorporation was determined unambiguously by conversion of the deuterated alcohol **12** to the corresponding ketone **13**; in this compound the aromatic protons give well-separated signals in the ^{1}H-NMR spectrum. The use of the triisopropylsilyl group was essential in order to get a clean metalation and to minimize the formation of secondary products, probably arising from desilylation; poorer results were obtained with the dimethyl *tert*-butylsilyl group, whereas the trimethylsilyl group was totally unsatisfactory. Treatment of metalated **12** with carbon dioxide led to the intermediate lithium carboxylate **14** which was not characterized but used as a crude product in the subsequent step. Reaction of **14** in a two-phase system (ether and aqueous hydrochloric acid) led to the cyclized and partially deprotected isocoumarin **15**; however, extensive racemization occurred under these conditions, the enantiomeric excess of **15** ranging from 60 to 40%, depending on the pH of the water phase. We noticed however that the cyclized product itself was configurationally quite stable to the above conditions, suggesting that racemization had probably occurred at the level of an open-chain precursor of **15** and that cyclization called for milder reaction conditions. Treatment of **14** with acetic anhydride prior to hydrolysis in the two-phase system described above proved to be suitable to induce the lactonization and partial deprotection of **14**; silylated phyllodulcin **15** was in fact obtained by this sequence in reasonable overall yield from **12** and with 93.5% ee. The final removal of the silyl group from **14** using tetrabutylammonium fluoride afforded the target compound **1** in quantitative yield and with an optical purity of 94%, which rose to 98% after one recrystallization, as determined by comparison with the reported optical rotation of phyllodulcin[1b] (HPLC determination of the ee was unsatisfactory with the column employed.)

In conclusion, the first enantioselective synthesis of the problematic natural isocoumarin phyllodulcin (**1**) has been accomplished by using the Sharpless asymmetric dihydroxylation for the introduction of the chirality and the lithiation of an aromatic ring promoted by a β-functionalized alkyl group as a key step, for the regioselective introduction of the 8-hydroxy group. The approach should in principle be applicable to the synthesis of other chiral 8-hydroxy-3,4-dihydroisocoumarins.

Experimental Section

^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) specta were obtained a samples dissolved in $CDCl_3$ unless otherwise stated; chemical shifts are in ppm downfield from tetramethylsilane as internal standard; IR spectra were taken with a FTIR spectrophotometer (film of pure substance for liquids or Nujol mulls for solids on KBr disks), and the most intense or representative bands are reported (in cm^{-1}). Melting points were obtained with a Kofler hot stage apparatus and are uncorrected. Boiling points refer to the oven temperature and were obtained with a bulb-to-bulb distillation apparatus. For the evaluation of the enantiomeric excess, a Chiracel OD-H column (0.46 cm i.d., 25 cm) and with a UV detector operating at 250 nm was used; mixtures of hexane (H) and 2-propanol (P) were used for the elution. For chromatographies, the flash technique was applied;[11] unless otherwise stated, the eluant was a mixture of hexane (H) and ethyl acetate (EA). Dry solvents were obtained by distillation from sodium powder (Aldrich) under nitrogen. For the thin-layer chromatographies (TLC), silica gel on aluminum foils was used; for the visualization of the spots, the plates were dipped into an ethanolic solution, containing phosphomolybdic acid (5%) and sulfuric acid (5%), and heated by means of an heat gun. $MgSO_4$ was used as the drying agent, unless otherwise stated.

4-Methoxy-3-[(triisopropylsilyl)oxy]benzaldehyde (7). A solution of isovanillin (**6**) (2.00 g, 13.2 mmol), imidazole (3.20 g, 46 mmol), and triisopropylsilyl chloride (3.2 g, 16.5 mmol) in DMF (10 mL) was allowed to react at room temperature for 16 h. The reaction mixture was partitioned between hexane and water; the organic phase was washed with water, dried, and evaporated to yield pure **7** (4.1 g, 98% yield) as an oil. The analytical sample was purified by distillation: bp 180−5 °C/ 0.1 mmHg; ^{1}H NMR δ 1.06−1.32 (m, 21H), 3.86 (s, 3H), 6.94 (d, J = 8 Hz 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.44 (dd, J= 8 and 2 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR δ 13.47, 18.50, 56.14, 111.71, 119.92, 126.77, 130.74, 146.66, 157.18, 191.55. Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 72.8; H, 10.1. Found: C, 72.4; H, 9.9.

4-Methoxy-3-[(triisopropylsilyl)oxy]styrene (8). To a stirred suspension of methyltriphenylphosphonium bromide (4,64 g, 13 mmol) in THF (40 mL) was added dropwise butyllithium (13 mmol, 8.1 mL of a 1.6 M hexane solution) followed, after 15 min, by the protected isovanillin **6** (3.90 g, 12.6 mmol). The progress of the reaction was monitored by TLC (H/EA 9:1); after 1 h of stirring at room temperature the reaction was complete. The reaction mixture was partitioned between ether and water; the upper organic phase was washed with brine, dried, and evaporated to afford a residue from which **8** (3.88 g, 100%yield) was obtained by chromatography (H/EA 9:1) as an oil: ^{1}H NMR δ 1.08−1.31 (m, 21H), 3.8 (s, 3H), 5.1 (dd, J = 0.7 and 11.0 Hz, 1H), 5.55 (dd, J = 0.7 and 17.5 Hz , 1H), 6.60 (dd, J = 11.0 and 17.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.93 (dd, J = 2.1 and 8.2 Hz, 1H), 6.97 (d, J = 2.1 Hz, 1H); ^{13}C NMR δ 13.56, 18.59, 56.15, 112.10, 112.46, 118.45, 120.52, 131.32, 137.10, 146.13, 151.52. Anal. Calcd for $C_{18}H_{30}O_2Si$: C, 70.5; H, 9.9. Found: C, 70.6; H, 9.6.

(*S*)-1-[4-Methoxy-3-[(triisopropylsilyl)oxy]phenyl]-1, 2-ethanediol (9). A mixture containing AD-mix-α[8] (Aldrich, 14.0 g) and the styrene **8** (3.00 g, 9.7 mmol) in a 1:1 *tert*-butyl alcohol/water (100 mL) was stirred in an ice−water bath for 18 h. Solid sodium sulfite (15 g) was then added and the mixture, after 30 min of stirring at the room temperature, was partitioned between ether and brine; the organic phase was dried and evaporated to leave a residue from which pure **9** (3.22 g, 97%) was obtained by chromatography (H/EA 3:2) as an oil which solidified on standing: mp 45−46.5 °C; ^{1}H NMR δ 1.06−1.28 (m, 21H), 3.57−3.63 (m, 2H), 3.78 (s, 3H), 4.67 (dd, J = 3.9 and 7.9 Hz, 1H), 6.77−6.88 (m, 3H); ^{13}C NMR δ 13.53, 18.54, 56.12, 68.61, 74.78, 112.58, 119.00, 119.56, 133.65, 146.11, 151.20; $[\alpha]_D$ +19.75 (c = 10.37, methanol). Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.5 H, 9.5. Found: C, 63.2; H, 9.8.

For the determination of the enantiomeric eccess, diol **9** (100 mg, 0.29 mmol) was allowed to react for 2 h at room temperature with acetic anhydride (1 mL) in pyridine (2 mL) to yield quantitatively a *diacetate*: oil; ^{1}H NMR δ 1.09 (d, J = 6.2 Hz, 18H), 1.16−1.38 (m, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 3.79 (s, 3H), 4.18−4.32 (m, 2H), 5.91 (dd, J = 4.5 and 7.5 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.87−6.92 (m, 2H); ^{13}C NMR δ 13.53, 18.53, 21.40, 21.73, 30.34, 56.07, 66.75, 73.52, 112.50, 119.56, 120.54, 129.50, 146.17, 151.73, 170.63, 171.26; ee 95.1% (eluant: 99:1 H/P).

(*S*)-1-[4-Methoxy-3-[(triisopropylsilyl)oxy]phenyl]-2-[(*p*-toluenesulfonyl)oxy]ethanol (10). *p*-Toluenesulfonyl chloride (2.1 g, 11 mmol) was added to an ice-cold solution of the diol **9** (3 g, 8.8 mol) in pyridine (3 mL). After 2 h, a few

(10) For a case of preference for hydrogen rather than bromine exchange in a related compound, see: Kles, A.; Kadirof, R.; Börner, A.; Holz, J.; Kagan, A. B. *Tetrahedron Lett.* **1995**, *36*, 4601. For a recent study of hydrogen-metal exchange in bromobenzene derivatives, see: Coe, P. L.; Waring, A. J.; Yarwood, T. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2729.

(11) Still, W. C.; Kahn, M.; Mitra, A. P. *J. Org. Chem.* **1978**, 43. 2923.

drops of water were added to dissolve the precipitate, and after 15 min the mixture was partitioned between ether and ice−water containing 3 mL of concentrated hydrochloric acid. The organic phase was washed with water and then with brine, dried, and evaporated to afford a residue from which pure **10** (4.2 g, 96.2%) was obtained by chromatography (H/EA 2:1) as an oil, which solidified on standing: mp 57−60 °C; ^{1}H NMR δ 1.06 (d, J = 6.3 Hz, 18H), 1.16−1.19 (m, 3H), 2.44 (s, 3H), 3.77 (s, 3H), 3.97−4.10 (m, 2H), 4.84 (dd, J = 8.2 and 3.6 Hz, 1H), 6.79−6.86 (m, 3H), 7.33 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 13.55, 18.56, 22.34, 56.10, 72.07, 75.07, 112.56, 119.05, 119.77, 128.63, 130.57, 131.43, 133.80, 145.90, 146.26, 151.90; $[\alpha]_D$ +14.69 (c = 10.32, methanol); ee 94.8% (eluant: 9:1 H/P). Anal. Calcd for $C_{25}H_{38}O_6SSi$: C, 60.7; H, 7.7. Found: C, 60.6; H, 7.3.

(*S*)-[4-Methoxy-3-[(triisopropylsilyl)oxy]phenyl]oxirane (11). A solution of the monotosylate **10** (4.00 g, 8 mmol) in methylene chloride (40 mL) was stirred for 2h with water (5 mL) containing sodium hydroxide (1.28 g, 32 mmol) and tetrabutylammonium hydrogen sulfate (100 mg). The mixture was diluted with ether, and the organic layer was washed with brine, dried, and evaporated to afford a residue from which pure **11** (2.58 g, 99.5% yield) was obtained by chromatography (H/EA 9:1) as an oil; ^{1}H NMR δ 1.052−1.59 (m, 21H), 2.75 (dd, J = 2.60 and 5.39 Hz, 1H), 3.09 (dd, J = 4.0 and 5.4 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, J = 2.6 and 4.0 Hz), 6.75−6.87 (m, 3H); ^{13}C NMR δ 13.57, 18.58, 51.71, 52.87, 56.18, 112.63, 118.10, 119.43, 130.54, 146.39, 151.66; $[\alpha]_D$ −3.27 (c = 10.41, methanol). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.0; H, 9.4. Found: C, 67.9; H, 9.7.

(*R*)-2-[3-(Methoxymethoxy)phenyl]-1-[4-methoxy-3-[(triisopropylsily)oxy]phenyl]ethanol (12). To a solution of 3-(methoxymethoxy)bromobenzene (2.20 g, 10.1 mmol) in tetrahydrofuran (30 mL) stirred under nitrogen at −78 °C was added butyllithium (10.1 mmol, 5.05 mL of a 2 M hexane solution). After 1 h epoxide **11** (2.27g, 7 mmol) was added, and the solution was allowed to warm up to room temperature over 3 h. After 12 h, the reaction mixture was partitioned between ether and water; the organic phase was washed with brine, dried, and evaporated to afford a residue from which **12** (2.25 g, 70% yield) was obtained after chromatography (H/EA 4:1) as an oil: ^{1}H NMR δ 1.08−1.32 (m, 21H), 2.96 (d, J = 6.7 Hz, 2H), 3.47 (s, 3H), 3.80 (s, 3H), 4.79 (t, J = 6.7 Hz, 1H), 5.15 (s, 2H), 6.77−6.92 (m, 6H), 7.19 (t, J = 7.7 Hz, 1H); ^{13}C NMR δ 13.53, 18.59, 46.54, 56.15, 56.63, 75.50, 95.03, 112.46, 114.86, 117.99, 118.91, 119.41, 123.72, 130.03, 137.04, 140.47, 146.02, 150.97, 157.95; $[\alpha]_D$ +42.49 (c = 6.63, methanol); ee 94% (eluant: 97:3 H/P). Anal. Calcd for $C_{26}H_{40}O_5Si$: C, 67.8; H, 8.8. Found: C, 67.9; H, 8.7.

2′-Deuterio-4-methoxy-3′-(methoxymethoxy)-3-[(triisopropylsilyl)oxy]deoxybenzoin (13). Butyllithium (1 mmol, 0.5 mL of a 2.0 M cyclohexane solution) was added dropwise to a solution of alcohol **12** (200 mg, 0.43 mmol) in cyclohexane, and the mixture was allowed to react for 16 h. The reaction flask was cooled to −78 °C, deuterium oxide (1 mL) was added, and the mixture was allowed to equilibrate with the room temperature and then partitioned between ether and water. The organic phase was dried and evaporated to afford a residue (deuteriated **12**) which was taken up in methylene chloride (2.5 mL); to the solution was added, pyridinium chlorochromate (215 mg, 1 mmol) and after 3 h of stirring the mixture was diluted with ether, filtered through a short pad of Florisil, and evaporated to afford a residue from which **13** (195 mg, 0.42 mmol) was obtained by chromatography (H/EA 4:1) as an oil: ^{1}H NMR δ 0.96−1.31 (m, 21H), 3.46 (s, 3H), 3.86 (s, 3H), 4.17 (s, 2H), 5.14 (s, 2H), 6.80-6.92 (m, 4H), 7.22 (dd, J = 7.0 and 8.6 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 2.1 and 8.4 Hz, 1H); ^{13}C-NMR δ 13.44, 18.52, 45.93, 56.16, 56.69, 95.09, 111.49, 115.09, 118.04, 121.02, 123.62, 124.08, 130.25, 137.27, 145.95, 156.04, 158.12, 191.65, 196.73. Anal. Calcd for $C_{26}H_{38}O_5Si$: C, 68.1; H, 8.4. Found: C, 67.9; H, 8.6.

(*R*)-3, 4-Dihydro-8-hydroxy-3-[4-methoxy-3-[(triisopropylsilyl)oxy]phenyl]isocoumarin (15). To a solution of diarylethanol **12** (2.00 g, 4.4 mmol) in cyclohexane (25 mL) was added butyllithium (10 mmol, 5 mL of a 2 M cyclohexane solution). After 18 h of stirring at room temperature, the mixture was poured into ether (100 mL) saturated with dry ice, and the mixture was allowed to warm up to room temperature under stirring. The solvent was evaporated, and the was residue suspended in acetic anhydride (20 mL). After 3 h of stirring, the mixture was partitioned between 6 M aqueous hydrochloric acid and ether, and the two phases were further stirred for additional 30 min. The organic phase was washed with water, with 10% sodium hydrogen carbonate, and with brine; finally, it was dried and evaporated to afford a residue from which pure **14** (1.06 g, 53% yield) was obtained by chromatography (H/EA 7:3) as a solid (needles): mp 168−172 °C; IR ν_{CO} 1680 cm^{-1}; ^{1}H NMR δ 1.05−1.32 (m, 21H), 3.09 (dd, J = 16.6 and 3.7 Hz, 1H), 3.29 (dd, J = 11.2 and 16.6 Hz, 1H), 3.81(s, 3H), 5.49 (dd, J = 3.7 and 11.2 Hz, 1H), 6.71−7.01 (m, 5H), 7.39 (dd, J = 8.3 and 7.6 Hz, 1H), 11.00 (s, 1H); ^{13}C NMR δ 13.54, 18.55, 35.53, 56.10, 81.31, 112.50, 116.98, 118.62, 119.19, 120.24, 130.91, 136.93, 140.02, 146.23, 152.01, 162.89, 170.56, 201.21; $[\alpha]_D$ +31.98 (c = 3.83, methanol); ee 93.5% (eluant: 93:7 H/P). Anal. Calcd for $C_{25}H_{33}O_5Si$: C, 68.0; H, 7.5. Found: C, 68.0; H, 7.5.

(*R*)-3,4-Dihydro-8-hydroxy-3-(4-methoxy-3-hydroxyphenyl)isocoumarin (1, phyllodulcin). To a solution of the isocoumarin **14** (0.50 g, 1.08 mmol) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (1.5 mmol, 1.5 mL of a 1 M tetrahydrofuran solution). After 1 h the solution was partitioned between ether and dilute hydrochloric acid; the organic phase was washed with brine, dried, and evaporated to afford a residue from which pure 1 (0.3 g, 95% yield) was obtained by recrystallization from ether/hexane as a white solid: mp 117.5−120 °C (lit.[1b] 118−120 °C); ^{1}H NMR δ 3.08 (dd, J = 3.4 and 16.5 Hz, 1H), 3.31 (dd, J = 11.9 and 16.5 Hz, 1H), 3.91 (s, 3H), 5.50 (dd, J = 3.4 and 11.9 Hz, 1H), 5.69 (s, 1H), 6.73 (d, J = 7.4 Hz), 6.85−7.03 (m, 4H), 7.44 (dd, 7.5 and 8.2 Hz), 11.01 (s, 1H); ^{13}C NMR δ 0.70, 35.71, 56.71, 81.36, 109.14, 111.26, 113.29, 117.08, 118.65, 118.92, 131.76, 137.01, 140.05, 146.51, 147.67, 162.95, 170.51; $[\alpha]_D$ +74.4 (c = 1.16, methanol); $[\alpha]_D$ +67.4 (c = 1.30, acetone); (lit.[1b] $[\alpha]_D$ +71 (c = 1.31, acetone).

Acknowledgment. The research was supported by Ministero della Ricerca Scientifica e Tecnologica (MURST, Roma).

JO9603385