A Remarkable Substituent Effect on the Enantioselectivity of Tandem Asymmetric Epoxidation and Enantiospecific Ring Expansion of Cyclopropylidene Alcohols: A New Enantiocontrolled Synthesis of (-)-Debromoaplysin and (-)-Aplysin

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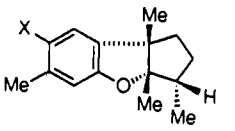
A remarkable substituent effect by the *tert*-butyldimethylsiloxy group on the enantioselectivity of the tandem asymmetric epoxidation and enantiospecific ring expansion of 2-[2-(*tert*-butyldimethylsiloxy)-4-methylphenyl]-2-cyclopropylideneethanol (18), affording (S)-(-)-2-[2-(*tert*-butyldimethylsiloxy)-4-methylphenyl]-2-hydroxymethylcyclobutanone (21) in high yield and high enantiomeric excess, was observed. This enabled us to accomplish a concise and highly enantioselective total synthesis of (-)-debromoaplysin (2) and (-)-aplysin (1), providing a new and general strategy for the enantioselective synthesis of biologically important substances having the dihydrobenzofuran framework.

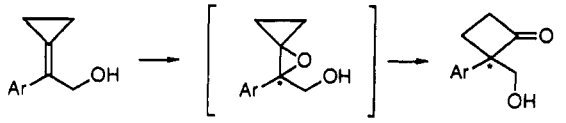
(-)-Aplysin (1) is representative of the first class of halogenated sesquiterpenes isolated from the sea hare, *Aplysia kurodai*,[1] which inhabits the eastern Pacific and from the opisthobranchs[2] which inhabit the coasts of North America. This compound displays antifeedant properties that help protect the host mollusks from raptorial advances. The cooccurrence of (-)-debromoaplysin (2), the unhalogenated form, suggests that this might function as an antioxidant and scavenge reactive halogens (Chart 1). Because of these interesting features, compounds 1 and 2 have aroused synthetic interest for the past few years.[3] During our work[4] directed toward the enantioselective construction of cyclobutanones and its application to the synthesis of biologically desirable compounds, we developed a new enantiocontrolled approach to (-)-aplysin (1) and (-)-debromoaplysin (2). This synthesis consists of the highly enantiocontrolled creation of geminally substituted cyclobutanones 5 *via* the tandem Katsuki-Sharpless asymmetric epoxidation of 2-aryl-2-cyclopropylideneethanols 3 followed by the enantiospecific ring expansion of chiral bicyclooxapentanes 4 (Scheme 1). Herein we describe these results.

Chart 1



(-)-aplysin (X = Br) (1)
(-)-debromoaplysin (X = H) (2)

Scheme 1



3 4 5

Results and Discussion

In a preceding study,[4f] we showed that the tandem asymmetric epoxidation and enantiospecific ring expansion reaction of aryl-substituted cyclopropylideneethanols 3 did not proceed in a highly enantioselective manner, especially in the cases of tolyl and *p*-methoxyphenyl substituents relative to alkyl-substituted cases. So, we sought first to delineate the substituent effect of the aromatic ring bearing suitable substituents for the synthesis of (-)-aplysin (1) and (-)-debromoaplysin (2) on the enantioselectivity of this tandem reaction sequence.

The syntheses of the cyclopropylideneethanols 11, 14, and 18 were straightforward (Scheme 2). The hydroxamate 8, prepared by silylation (100%) of methyl glycolate (6), followed by hydroxamate formation[5] (97%) of the resulting silyl ether 7, was condensed with 4-lithio-3-[(methoxymethyl)oxy]toluene[6] generated *in situ* by lithiation of 3-[(methoxymethyl)oxy]toluene to give the ketone 9 (80%). Compound 9 was then converted to the cyclopropylidene ether 10 in 94% yield by Wittig reaction with cyclopropylidenetriphenylphosphorane under McMurry's conditions[7] using tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a catalyst. Desilylation with $^{n}Bu_4N^{+}F^{-}$ and

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(3) For the synthesis of racemic form: (a) Yamada, K.; Yazawa, H.; Uemura, D.; Toda, M.; Hirata, Y. *Tetrahedron* **1969**, *25*, 3509-3520. (b) Ronald, R. C. *Tetrahedron Lett.* **1976**, 4413-4416. (c) Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R., III. *J. Org. Chem.* **1980**, *45*, 3989-3993. (d) Ghosh, A.; Biswas, S.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1988**. 1421. (e) Biswas, S.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1990**, *55*, 3498-3502. For the synthesis of optical active form *via* resolution: (f) Ronald, R. C.; Gewali, M. B.; Ronald, B. P. *J. Org. Chem.* **1980**, *45*, 2224-2229. For chiral synthesis: (g) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329-332.

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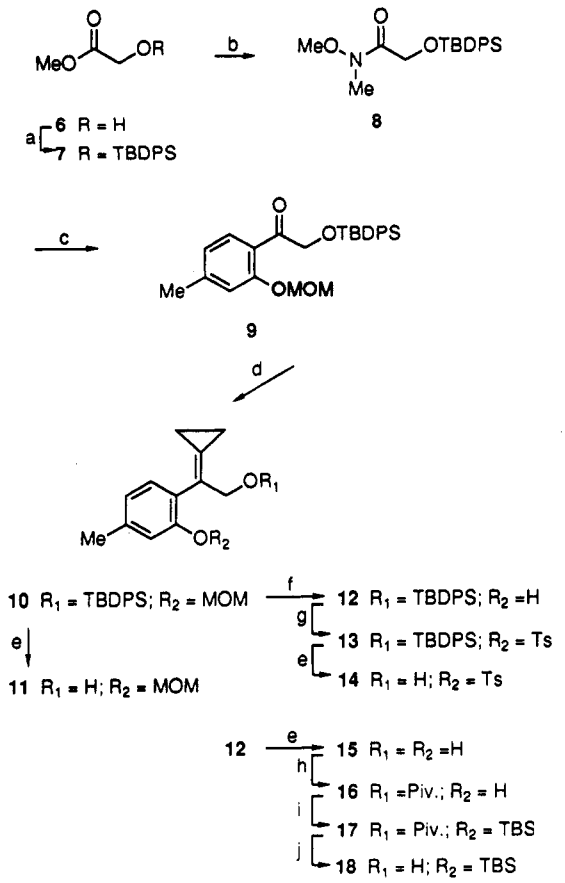
Scheme 2



[a] Steps: (a) TBDPSCl, DMAP, imidazole, DMF, rt, 10 h; (b) MeO(Me)NH·HCl, Me_3Al, CH_2Cl_2, −15 °C, 2 h; (c) 3-[(methoxymethyl)oxy]toluene, ^tBuLi, Et_2O, 0 °C, 2 h then **8**, −78 °C → 0 °C, 1 h; (d) cyclopropyltriphenylphosphonium bromide, NaH, THF, 62 °C, 10 h, then **9**, TDA-1, 62 °C, 1 h; (e) $^nBu_4N^+F^-$, THF, rt, 3 h; (f) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 30 min → −23 °C, 1.5 h; (g) TsCl, DMAP, pyridine, rt, 24 h; (h) pivaloyl chloride, pyridine, rt, 2 h; (i) TBSCl, DMAP, imidazole, DMF, 0 °C, 10 h; (j) DIBAL, CH_2Cl_2, −23 °C, 30 min.

deprotection of the methoxymethyl group of **10** afforded the alcohol **11** (100%) and the phenol **12** (91%), respectively. Tosylation (64%) of phenol **12**, followed by desilylation (98%) of the resulting tosylate **13**, gave the alcohol **14**. The ester **16**, prepared by desilylation (99%) of **12** and selective esterification with pivaloyl chloride (85%) of the resulting alcohol **15**, was then subjected to silylation (86%), followed by the reductive deprotection of the pivaloyl group with DIBAL (100%) to furnish the alcohol **18**, via the ester **17**.

The tandem asymmetric epoxidation and 1,2-rearrangement of the cyclopropylidene alcohols **11**, **14**, and **18** was examined with *tert*-butyl hydroperoxide (TBHP) in the presence of diethyl L-(+)-tartrate [(+)-DET] or diisopropyl L-(+)-tartrate [(+)-DIPT], titanium tetraisopropoxide [$Ti(O^iPr)_4$], and 3-Å molecular sieves[8] (Table 1). Although the substrate **11** showed very low enantioselectivity (55% ee) giving the cyclobutanone **19** in 61% yield, the substrates **14** and **18** resulted in a moderate (81% ee) and high (95% ee) enantioselectivity in 65 and 98% yields, respectively. It should be noted that the enantioselectivity of the silyl ether **18** was much higher than that of the simple tolyl case[4f] (79–83% ee). This remarkable substituent effect could be rationalized by steric congestion between the OR and hydroxymethyl and cyclopropyl groups in the presumed intermediates **A** or **B**, respectively, giving the chiral cyclobutanones, in which the developing positive charge at the chiral center is stabilized by overlap with the π-electron system of the phenyl group, providing an opportunity for epimerization. On the other hand, the developing positive charge at the chiral center of the preferred conformation **C** or **D**, which lacks the steric congestion of **A** and **B**, cannot be stabilized by the π-electron system of the phenyl group and thus cannot epimerize, leading to high enantioselectivity (Chart 2).

These findings encouraged us to develop our enantiocontrolled synthesis of (−)-aplysin (**1**) and (−)-debromoaplysin (**2**) (Scheme 3). Thus, the direct substitution of the hydroxy group of **21** with a phenylthio group was achieved by following Hata's procedure[10] to give the sulfide **22** (96%) which was then desulfurized by Raney Ni(W_2) in acetone to afford the methyl analogue **23** (81%). Grignard reaction of vinylmagnesium bromide (91%) and the cyclobutanone **23** (91%), followed by silylation by triethylsilyl trifluoromethanesulfonate of the resulting cyclobutanol **24** (95%), afforded the silyl ether **25** as a single product. This was then subjected to the palladium-mediated ring expansion reaction[11] [$PdCl_2(MeCN)_2$] to give the unsaturated cyclopentanone **26** (59%). This ring expansion reaction was performed more effectively (89%) with triphenylarsine ($AsPh_3$) and palladium acetate [$Pd(OAc)_2$] as ligand and catalyst, respectively. The reaction of **26** with methylcerium reagent generated *in situ* (MeLi, $CeCl_3$) proceeded in a stereoselective manner to give the alcohol **27** (92%).[9] The deprotection of the alcohol **27** afforded the phenol **28** (88%). The cyclization of **28** was effected by the oxymercuration–reduction procedure to give the dihydrobenzofuran **29** (88%). Upon dehydration with $POCl_3$, **29** afforded the olefin **30** (100%) [$[\alpha]^{25}_D$ −113° (*c* 0.20, $CHCl_3$) (lit.[3g] $[\alpha]_D$ −124.9° (*c* 0.61, $CHCl_3$)]. By following the reported procedure,[3g] the olefin **30** was converted into (−)-debromoaplysin (**2**) (79%) [$[\alpha]^{25}_D$ −61.8° (*c* 0.16, $CHCl_3$) (lit.[3f] $[\alpha]^{21}_D$ −68° (*c* 0.088, $CHCl_3$), lit.[3g] $[\alpha]^{29}_D$ −66.5° (*c* 0.72, $CHCl_3$))] and then (−)-aplysin (**1**) (84%) [$[\alpha]^{25}_D$ −83.2° (*c* 0.15, $CHCl_3$), mp 85.5–86.5 °C

(7) Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531–2534.

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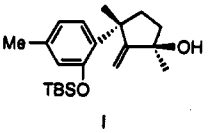
(9) The product **27** was shown to contaminate 8% of the stereoisomer **i** judged by the integration of exomethylene hydrogens in the ^1H NMR spectrum of the product since these isomers could not be separated.



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(10) (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409–1412. (b) Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315–1318. (c) Watanabe, Y.; Araki, T.; Ueno, Y.; Endo, T. *Tetrahedron Lett.* **1986**, *27*, 5385–5388.

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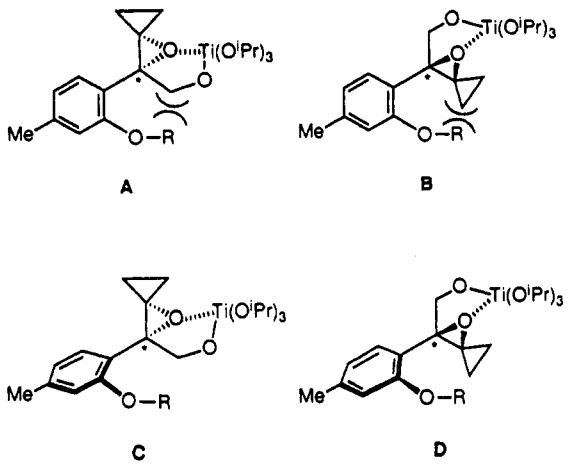
Table 1. Tandem Asymmetric Epoxidation and 1,2-Rearrangement[a]

11, 14, 18 19, 20, 21

entry	substrate R	tartrate	$Ti(O^iPr)_4$ (equiv)	TBHP (equiv)	time (h)	temp (°C)	product R (%)	$[\alpha]_D$ (deg)	opt yield[b] (% ee)
1	11: MOM	(+)-DET	1	3	72	−50	(S)-19: MOM (61)	−48.0	55
2	14: Ts	(+)-DIPT	1	3	72	−50	(S)-20: Ts(65)	−156.1	81
3	18: TBS	(+)-DIPT	1	3	48	−50	(S)-21: TBS, (98)	−118.2	95

[a] Unless otherwise stated, the reaction was carried out in CH_2Cl_2 in the presence of 3-Å molecular sieves. [b] Estimated by ^1H NMR analysis (500 MHz) of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) using corresponding racemic samples which were prepared by the epoxidation [*m*-chloroperbenzoic acid (*m*-CPBA)] accompanied by 1,2-rearrangement of 11, 14, and 18.

Chart 2



(lit.[1] $[\alpha]^{27}_D$ −85.4° ($CHCl_3$), mp 85–86 °C, lit.[3g] $[\alpha]_D$ −83.5° (*c* 0.31, $CHCl_3$), mp 84.5–85.5 °C)].

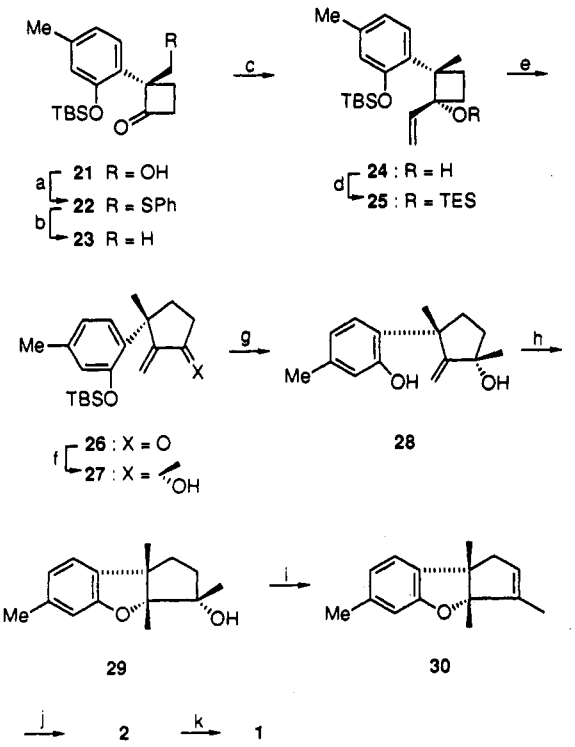
Thus, we disclose a highly enantioselective procedure for the construction of *o*-hydroxyphenyl-substituted cyclobutanones, which leads a new enantioselective synthesis of (−)-debromoaplysin (2) and (−)-aplysin (1). This methodology could provide a new, general strategy for the enantioselective synthesis of biologically important substances having the dihydrobenzofuran framework.[13]

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry N_2 unless indicated otherwise. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone, and DMSO, DMF, CH_2Cl_2, and Et_3N were distilled from CaH_2 and kept over 4-Å molecular sieves. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Silica gel column chromatography was carried out with Wako gel C-200, while Merck Kieselgel 60 Art. 9385 was used for flash chromatography.

(13) See: (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds, Vol. I, Acetogenins, Shikimates, and Carbohydrates*; Academic Press: New York, 1975; *Vol. II, Terpenes*; Academic Press: New York, 1972. (b) Siuda, J. F.; DeBernardis, J. F. *Lloydia* **1973**, *36*, 107–143. (c) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley: New York, 1983; Vol. 5, p 235. (d) *Terpenoids and Steroids*; The Chemical Society: London, 1975; Vol. 5, pp 1–12. (e) Lau, C. K.; Bélanger, P. C.; Dufresne, C.; Scheigetz, J.; Therien, M.; Fitzsimmons, B.; Young, R. N.; Ford-Hutchinson, A. W.; Riendeau, D.; Denis, D.; Guay, J.; Charleson, S.; Piechuta, H.; McFarlane, C. S.; Chiu, S.-H. L.; Eline, D.; Alvaro, R. F.; Miwa, G.; Walsh, J. L. *J. Med. Chem.* **1992**, *35*, 1299–1318 and references cited herein.

Scheme 3



[a] Steps: (a) PhSSPh, $^nBu_3P$, THF, reflux, 7 h; (b) Raney Ni(W2), acetone, rt, 15 min; (c) vinylmagnesium bromide, $CeCl_3$, THF, −78 °C, 2 h; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min; (e) (i) $PdCl_2(MeCN)_2$, THF, reflux, 2 h or (ii) $Pd(OAc)_2$, $AsPh_3$, CH_2Cl_2, rt, 3 h; (f) MeLi, $CeCl_3$, Et_2O, −78 °C, 2 h; (g) $^nBu_4N^+F^-$, THF, rt, 2 h; (h) $Hg(OCOCF_3)_2$, THF, rt, 2 h; then 10% NaOH, $NaBH_4$; (i) $POCl_3$, pyridine, rt, 18 h; (j) H_2, PtO_2, EtOH, rt, 3 h; (k) Br_2, $NaHCO_3$, $CHCl_3$, rt, 10 min.

Methyl 2-(*tert*-Butyldimethylsiloxy)acetate (7). To a stirred solution of methyl glycolate (6) (3.0 mL, 38.9 mmol), imidazole (3.2 g, 47.0 mmol), and a catalytic amount of DMAP in DMF (60 mL) was added TBDPSCl (11.0 mL, 42.3 mmol) at 0 °C, and stirring was continued for 10 h at room temperature. The reaction mixture was washed with 10% HCl, saturated aqueous $NaHCO_3$, and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (97:3 v/v) as eluant to give the silyl ether 7 (12.8 g, 100%) as a colorless oil: IR (neat) 1760, 1740 (C=O) cm^{-1}: ^1H NMR (90 MHz, $CDCl_3$) δ 1.09 (9H, s), 3.64 (3H, s), 4.24 (2H, s), 7.31–7.77 (10H, m); MS *m/e* 271 (M^+ − 57). Anal. Calcd for $C_{19}H_{22}O_3Si$: C, 69.47; H, 7.36. Found: C, 69.71; H, 7.33.

***N*-Methoxy-*N*-methyl-2-(*tert*-butyldiphenylsiloxy)acetamide (8).** To a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (20.9 g, 63.7 mmol) in CH_2Cl_2 (200 mL) was added a 1.0 M solution of trimethylaluminum in hexane (125 mL, 125

mmol) at −15 °C, and stirring was continued for 30 min at the same temperature and then for 35 min at room temperature. To this solution was added a solution of the silyl ether **7** (20.9 g, 63.7 mmol) in CH_2Cl_2 (40 mL) at −15 °C, and stirring was continued for 2 h at room temperature. The reaction mixture was treated with 10% HCl solution and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (7:3 v/v) as eluant to give the hydroxamate **8** (22.1 g, 97%) as colorless prisms: mp 57–58 °C (from hexane); IR ($CHCl_3$) 1690 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.10 (9H, s), 3.13 (3H, s), 3.44 (3H, s), 4.41 (2H, s), 7.29–7.86 (10H, m); MS *m/e* 300 (M^+ − 57). Anal. Calcd for $C_{20}H_{27}NO_3Si$: C, 67.19; H, 7.61; N, 3.92. Found: C, 67.06; H, 7.50; N, 3.95.

(*tert*-Butyldiphenylsiloxy)methyl 2-[(Methoxymethyl)oxy]-4-methylphenyl Ketone (9). To a stirred solution of 3-[(methoxymethyl)oxy]toluene (1.65 g, 10.8 mmol) in Et_2O (40 mL) was added 1.7 M solution of ^{t}BuLi in hexane (6.4 mL, 10.9 mmol) at 0 °C, and stirring was continued for 2 h at 0 °C. To this stirred solution was added a solution of the hydroxamate **8** (2.98 g, 8.34 mmol) in Et_2O (20 mL) at −78 °C, and stirring was continued for 1 h at 0 °C. The reaction mixture was treated with 10% HCl solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (24:1 v/v) as eluant to give the ketone **9** (3.0 g, 80%) as colorless prisms: mp 69–70 °C (from hexane); IR ($CHCl_3$) 1685 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.11 (9H, s), 2.32 (3H, s), 3.20 (3H, s), 4.84 (2H, s), 5.00 (2H, s), 6.80–7.77 (13H, m); MS *m/e* 391 (M^+ − 57). Anal. Calcd for $C_{27}H_{32}O_4Si$: C, 72.29; H, 7.19. Found: C, 72.52; H, 7.33.

1-(*tert*-Butyldiphenylsiloxy)-2-cyclopropylidene-2-[2-[(methoxymethyl)oxy]-4-methylphenyl]ethane (10). To a stirred suspension of NaH (190 mg, of 60% oil suspension, 4.75 mmol) in THF (8 mL) was added cyclopropyltriphenylphosphonium bromide (1.8 g, 4.7 mmol) at room temperature. After the mixture had been stirred for 10 h at 62 °C, a solution of the ketone **9** (713 mg, 1.59 mmol) and tris[2-(2-methoxyethoxy)-ethyl]amine (0.05 mL, 0.156 mmol) in THF (4 mL) was added in 30 min, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (97:3 v/v) as eluant to give the cyclopropylideneethyl silyl ether **10** (704 mg, 94%) as a colorless oil: IR (neat) 1605 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (9H, s), 1.07 (4 H, br s), 2.34 (3H, s), 3.32 (3H, s), 4.69 (2H, br s), 5.01 (2H, s), 6.78 (1H, br d, J = 7.4 Hz), 6.89 (1H, br s), 7.74 (1H, d, J = 7.4 Hz), 7.28–7.66 (10H, m); MS *m/e* 472 (M^+). Anal. Calcd for $C_{30}H_{36}O_3Si$: C, 76.23; H, 7.68. Found: C, 76.09; H, 7.68.

2-Cyclopropylidene-2-[2-[(methoxymethyl)oxy]-4-methylphenyl]ethanol (11). To a stirred solution of the silyl ether **10** (53.2 mg, 0.113 mmol) in THF (1.5 mL) was added 1 M solution of ^{n}Bu$_4$N$^+$F$^-$ in THF (0.22 mL, 0.22 mmol) at room temperature, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (3:2 v/v) as eluant to give the alcohol **11** (26.3 mg, 100%) as a colorless oil: IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.26 (4H, br s), 1.57 (1H, br s), 2.35 (3H, s), 3.48 (3H, s), 4.60 (2H, br s), 5.20 (2H, s), 6.84 (1H, br d, J = 7.4 Hz), 6.95 (1H, br s), 7.22 (1H, d, J = 7.4 Hz); MS *m/e* 234 (M^+); HRMS calcd for $C_{14}H_{18}O_3$ 234.1255 (M^+), found 234.1241.

1-(*tert*-Butyldiphenylsiloxy)-2-cyclopropylidene-2-(2-hydroxy-4-methylphenyl)ethane (12). To a stirred solution of the MOM ether **10** (1.56 g, 3.30 mmol) and EtSH (3.0 mL, 40.5 mmol) in CH_2Cl_2 (25 mL) was added BF_3·Et_2O (0.8 mL, 6.5 mmol) at −78 °C. After stirrring had been continued for 30 min at −78 °C and then 1.5 h at −23 °C, the reaction mixture was treated with pH 7 phosphate buffer and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (49:1 v/v) as eluant to give the phenol **12** (1.3 g, 91%) as colorless prisms: mp 103–104 °C (from hexane); IR ($CHCl_3$) 3270 (OH), 1620 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.78–1.34 (4H, m), 1.09 (9H, s), 2.32 (3H, s), 4.53 (2H, s), 6.65 (1H, br d, J = 8.0 Hz), 6.81 (1H, br s), 7.09 (1H, d, J = 8.0 Hz), 7.34–7.78 (10H, m), 9.02 (1H, s); MS *m/e* 428 (M^+). Anal. Calcd for $C_{28}H_{32}O_2Si$: C, 78.46; H, 7.52. Found: C, 78.46; H, 7.54.

1-(*tert*-Butyldiphenylsiloxy)-2-cyclopropylidene-2-[2-[(*p*-toluenesulfonyl)oxy]-4-methylphenyl]ethane (13). To a stirred solution of the phenol **12** (31 mg, 0.072 mmol) and a catalytic amount of DMAP in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (30 mg, 0.157 mmol) at room temperature, and stirring was continued for 24 h at the same temperature. The reaction mixture was treated with 10% HCl solution and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (49:1 v/v) as eluant to give the tosylate **13** (26.4 mg, 64%) as a colorless oil: IR ($CHCl_3$) 1610, 1595 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.84 (4H, br s), 0.95 (9H, s), 2.29 (3H, s), 2.35 (3H, s), 4.31 (2H, br s), 6.98–7.68 (17H, m); MS *m/e* 525 (M^+ − 57); HRMS calcd for $C_{31}H_{29}O_4SSi$ 525.1554 (M^+ − 57), found 525.1544.

2-Cyclopropylidene-2-[2-[(*p*-toluenesulfonyl)oxy]-4-methylphenyl]ethanol (14). To a stirred solution of the silyl ether **13** (25 mg, 0.043 mmol) in THF (1.5 mL) was added a 1 M solution of ^{n}Bu$_4$N$^+$F$^-$ in THF (0.45 mL, 0.45 mmol) at room temperature, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (2:1 v/v) as eluant to give the alcohol **14** (14.5 mg, 98%) as a colorless oil: IR (neat) 3560, 3400 (OH), 1615, 1605 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.91–1.24 (4H, m), 2.30 (3H, s), 2.44 (3H, s), 4.48 (2H, s), 6.91 (1H, br s), 7.07 (1H, br d, J = 9.0 Hz), 7.25 (1H, d, J = 9.0 Hz), 7.26 and 7.66 (each 2H, each d, J = 9.0 Hz); MS *m/e* 344 (M^+); HRMS calcd for $C_{19}H_{20}O_4S$ 344.1081 (M^+), found 344.1083.

2-Cyclopropylidene-2-(2-hydroxy-4-methylphenyl)ethanol (15). To a stirred solution of the silyl ether **12** (1.29 g, 3.01 mmol) in THF (1.5 mL) was added a 1 M solution of ^{n}Bu$_4$N$^+$F$^-$ in THF (7.0 mL, 7.0 mmol) at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (85:15 v/v) as eluant to give the alcohol **15** (565 mg, 99%) as a colorless oil: IR (neat) 3150 (OH), 1620 (C=C) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (4H, s), 2.29 (3H, s), 4.55 (2H, s), 6.66 (1H, br d, J = 7.6 Hz), 6.73 (1H, br s), 7.12 (1H, d, J = 7.6 Hz); MS *m/e* 190 (M^+); HRMS calcd for $C_{12}H_{14}O_2$ 190.0993 (M^+), found 190.1000.

2-Cyclopropylidene-2-(2-hydroxy-4-methylphenyl)-ethyl Pivalate (16). To a stirred solution of the alcohol **15** (395 mg, 2.08 mmol) in pyridine (3 mL) was added pivaloyl chloride (0.26 mL, 2.11 mmol) at room temperature, and stirring was continued for 2 h at the same temperature. The reaction mixture was treated with 10% HCl solution and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (19:1 v/v) as eluant to give the ester **16** (485 mg, 85%) as a colorless oil: IR (neat) 3425 (OH), 1720 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.14 (9H, s), 1.15–1.38 (4H, m), 2.30 (3H, s), 4.95 (2H, s), 6.35 (1H, br), 6.70 (1H, br d, J = 8.0 Hz), 6.74 (1H, br s), 7.06 (1H, d, J = 8.0 Hz); MS *m/e* 274 (M^+); HRMS calcd for $C_{17}H_{22}O_3$ 274.1568 (M^+), found 274.1573.

2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-cyclopropylideneethyl Pivalate (17). To a stirred solution of the ester **16** (480 mg, 1.75 mmol), imidazole (260 mg, 3.82 mmol), and a catalytic amount of DMAP in DMF (5 mL) was added TBSCl (500 mg, 3.32 mmol) at 0 °C, and stirring was continued for 10 h at the same temperature. The reaction mixture was treated with 10% HCl solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (49:1 v/v) as eluant to give the silyl ether **17**

(585 mg, 86%) as a colorless oil: IR (neat) 1725 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.93 (9H, s), 1.10 (9H, s), 1.01–1.29 (4H, m), 2.30 (3H, s), 5.03 (2H, br s), 6.63 (1H, br s), 6.72 (1H, br d, J = 7.8 Hz), 7.06 (1H, d, J = 7.8 Hz); MS m/e 388 (M^+); HRMS calcd for $C_{23}H_{36}O_3Si$ 388.2432 (M^+), found 388.2483.

2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-cyclopropylideneethanol (18). To a stirred solution of the ester 17 (155 mg, 0.399 mmol) in CH_2Cl_2 (3 mL) was added a 1.0 M solution of DIBAL in hexane (1.10 mL, 1.10 mmol) at −23 °C, and stirring was continued for 30 min at the same temperature. The reaction mixture was diluted with Et_2O and treated with saturated aqueous NH_4Cl (0.32 mL). After stirring had been continued for 1 h at room temperature, the mixture was treated with $MgSO_4$ and filtered through Celite. The residue upon evaporation of the filtrate was chromatographed on silica gel with hexane–AcOEt (93:7 v/v) as eluant to give the alcohol 18 (121 mg, 100%) as a colorless oil: IR (neat) 3400 (OH), 1610 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.13 (6H, s), 0.93 (9H, s), 1.05–1.30 (4H, m), 2.00 (1H, br), 2.30 (3H, s), 4.55 (2H, br s), 6.64 (1H, br s), 6.76 (1H, br d, J = 7.6 Hz), 7.10 (1H, d, J = 7.6 Hz); MS m/e 304 (M^+); HRMS calcd for $C_{18}H_{28}O_2Si$ 304.1857 (M^+), found 304.1852.

General Procedure for Tandem Katsuki–Sharpless Asymmetric Epoxidation and 1,2-Rearrangement of Cyclopropylidene Alcohols. Preparation of (*S*)-(−)-2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-(hydroxymethyl)cyclobutanone (21). To a stirred solution of the cyclopropylidene alcohol 18 (124 mg, 0.408 mmol) and L-(+)-DIPT (150 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was added 3-Å molecular sieves (100 mg) at −20 °C. After the solution was stirred for 30 min at −20 °C, $Ti(O^iPr)_4$ (0.15 mL, 0.501 mmol) was added, and stirring was continued for 30 min at the same temperature. To this reaction mixture was added a 3.5 M solution of ^{t}BuOOH in CH_2Cl_2 (0.35 mL, 1.23 mmol) at −78 °C, and stirring was continued for a further 48 h at −50 °C. The reaction mixture was treated with a solution of citric acid monohydrate (106 mg, 0.504 mmol) in Et_2O–acetone (9:1 v/v) (5 mL), stirred for 1 h, and filtered through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (92:8 v/v) as eluant to give the cyclobutanone 21 (128 mg, 98%) as colorless needles: mp 73–74 °C (from hexane); $[\alpha]^{23}_D$ −118.2° (c 1.04, $CHCl_3$); IR ($CHCl_3$) 3400 (OH), 1765 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.31 and 0.34 (each 3H, each s), 1.03 (9H, s), 1.85 (1H, t, J = 6.1 Hz), 2.28 (3H, s), 2.30–2.71 (2H, m,), 2.93–3.13 (2H, m), 3.91 (2H, d, J = 6.1 Hz), 6.66 (1H, br s), 6.70 (1H, br d, J = 8.0 Hz), 7.31 (1H, d, J = 8.0 Hz); MS m/e 263 (M^+ − 57); HRMS calcd for $C_{14}H_{19}O_3Si$ 263.1102 (M^+ − 57), found 263.1083. Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.59; H, 8.88.

(*S*)-(−)-2-(Hydroxymethyl)-2-[2-[(methoxymethyl)oxy]-4-methylphenyl]cyclobutanone (19): yield 61%; colorless oil; $[\alpha]^{23}_D$ −48.0° (c 0.71, $CHCl_3$); IR (neat) 3450 (OH), 1765 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.28–2.48 (2H, m), 2.98–3.18 (2H, m), 3.48 (3H, s), .4.00 (2H, m), 5.19 (2H, s), 6.79 (1H, br d, J = 8.1 Hz), 6.95 (1H, br s), 7.31 (1H, d, J = 8.1 Hz); MS m/e 250 (M^+); HRMS calcd for $C_{14}H_{18}O_4$ 250.1204 (M^+), found 250.1197.

(*S*)-(−)-2-(Hydroxymethyl)-2-[2-[(*p*-toluenesulfonyl)oxy]-4-methylphenyl]cyclobutanone (20): yield 65%; colorless oil; $[\alpha]^{22}_D$ −156.08° (c 0.85, $CHCl_3$); IR ($CHCl_3$) 3500 (OH), 1780 (C=O), 1620, 1600 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.85 (1H, m), 2.27 (3H, s), 2.49 (3H, s), 2.25–2.50 (2H, m), 2.92–3.13 (2H, m), 3.88 (2H, d, J = 5.8 Hz), 6.88–7.95 (7H, m); MS m/e 360 (M^+); HRMS calcd for $C_{19}H_{20}O_6S$ 360.1030 (M^+), found 360.1009.

General Procedure for the Preparation of (±)-(Hydroxymethyl)cyclobutanones. Preparation of 2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-(hydroxymethyl)-cyclobutanone (21). To a stirred solution of the cyclopropylidene alcohol 18 (124 mg, 0.408 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (80% active, 105 mg, 0.487 mmol) at 0 °C, and stirring was continued for 15 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% NaOH and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–Et_2O (3:1 v/v) as eluant to give the (±)-cyclobutanone 21 (115 mg, 96%) as a colorless oil. Other (±)-cyclobutanones were also prepared by following the same procedure described above, and all the spectral data were identical with those of the corresponding chiral samples.

General Preparation and Analysis of Mosher's Esters. The reaction was generally run on a 0.1 mmol scale under the modified procedure of Mosher's original procedure.[12] To a stirred solution of DMAP (0.1 mmol, 1.0 equiv), Et_3N (0.1 mL), and (*S*)-(−)-MTPA (28 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added a solution of trifluoromethanesulfonyl chloride (TfCl) (20 mg, 0.12 mmol) at 0 °C. Immediately, a solution of the (hydroxymethyl)cyclobutanone (0.1 mmol) in CH_2Cl_2 (0.5 mL) was added. After ensuring complete reaction by monitoring the reaction by TLC, the reaction mixture was diluted with CH_2Cl_2 and washed with 10% HCl, saturated aqueous $NaHCO_3$, and NaCl. The residue upon workup was passed through a short plug of silica gel with hexane–AcOEt (10:1 v/v) as eluant. ^1H NMR analysis in $CDCl_3$ at 500 MHz focused on CH_2OMTPA. These protons were typically observed as a diastereomeric pair of singlets at δ 4.43 and AB doublets centered at δ 4.30 and 4.45 for **20** and singlet at δ 4.54 and AB doublets centered at δ 4.38 and 4.62 for **21**. In the case of **19**, these protons were observed as a diastereomeric pair of AB doublets centered at δ 4.47 and 4.72 and δ 4.61 and 4.66. The integration of these protons was compared to determine the enantiomeric excess.

(*R*)-(−)-2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-[(phenylthio)methyl]cyclobutanone (22). After a solution of the cyclobutanone 21 (44 mg, 0.137 mmol), diphenyl disulfide (90 mg, 0.412 mmol), and tri-*n*-butylphosphine (0.14 mL, 0.562 mmol) in THF (3 mL) had been refluxed for 7 h under stirring, the reaction mixture was diluted with Et_2O and washed with aqueous 10% NaOH and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–benzene (4:1 v/v) as eluant to give the sulfide **22** (54.5 mg, 96%) as a colorless oil: $[\alpha]^{23}_D$ −91.3° (c 1.06, $CHCl_3$); IR ($CHCl_3$) 1775 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.27 and 0.29 (each 3H, each s), 1.00 (9H, s), 2.27 (3H, s), 2.31–2.78 (2H, m), 2.95–3.14 (2H, m), 3.33 and 3.51 (each 1H, each d, J = 12.8 Hz), 6.63 (1H, br s), 6.78 (1H, br d, J = 8.0 Hz), 7.11–7.35 (6H, m); MS m/e 355 (M^+ − 57). Anal. Calcd for $C_{24}H_{32}O_2SSi$: C, 69.85; H, 7.82; S, 7.77. Found: C, 69.83; H, 7.83; S, 7.89.

(*S*)-(−)-2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-methylcyclobutanone (23). To a stirred solution of the sulfide **22** (53.5 mg, 0.13 mmol) in acetone (2 mL) was added Raney $Ni(W_2)$ (600 mg) at room temperature. After being stirred for 15 min at room temperature, the reaction mixture was filtered through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–Et_2O (97:3 v/v) as eluant to give the cyclobutanone **23** (31.9 mg, 81%) as a colorless oil: $[\alpha]^{25}_D$ −105.0° (c 1.794, $CHCl_3$); IR ($CHCl_3$) 1775 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.31 and 0.34 (each 3H, each s), 1.03 (9H, s), 1.52 (3H, s), 1.97–2.62 (2H, m), 2.27 (3H, s), 2.97–3.17 (2H, m), 6.66 (1H, br s), 6.68 (1H, br d, J = 8.1 Hz), 7.25 (1H, d, J = 8.1 Hz); MS m/e 304 (M^+); HRMS calcd for $C_{18}H_{28}O_2Si$ 304.1857 (M^+), found 304.1853. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 71.06; H, 9.21.

(1*R*,2*S*)-(+)-2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-methyl-1-vinylcyclobutanol (24). To a stirred suspension of cerium chloride (170 mg, 0.7 mmol) in THF (2.5 mL) was added a 1.0 M solution of vinylmagnesium bromide in THF (1.0 mL, 1.0 mmol) at −78 °C. After stirring had been continued for 1 h, a solution of the cyclobutanone **23** (27.0 mg, 0.09 mmol) in Et_2O (3 mL) was added dropwise to this reaction mixture at the same temperature and the temperature was then raised to room temperature in 2 h. The reaction mixture was treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the cyclobutanol **24** (26.7 mg, 91%) as a colorless oil: $[\alpha]^{25}_D$ +7.9° (c 1.01, $CHCl_3$); IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.31 and 0.35 (each 3H, each s), 1.03 (9H, s), 1.47 (3H, s), 1.66–2.13 (4H, m), 2.25 (3H, s), 2.52 (1H, s), 4.88 (1H, dd, J = 9.9 and 2.0 Hz), 5.27 (1H, dd, J = 16.2 and 2.0 Hz), 5.92 (1H, dd, J = 16.2 and 9.9 Hz), 6.52–7.00 (3H, m); MS m/e 275 (M^+ − 57); HRMS calcd for $C_{16}H_{23}O_2Si$ 275.1467 (M^+ − 57), found 275.1458.

(1*R*,2*S*)-(−)-2-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-2-methyl-1-(triethylsiloxy)-1-vinylcyclobutanol (25). To a stirred solution of the cyclobutanol **24** (202.1 mg, 0.61 mmol) and 2,6-lutidine (0.21 mL, 1.80 mmol) in CH_2Cl_2 (2.5 mL) was added portionwise triethylsilyl trifluoromethanesulfonate (TESOTf) (0.20 mL, 0.88 mmol) at 0 °C, and stirring was continued for 30 min at the same temperature. The reaction mixture was then diluted with CH_2Cl_2 and washed with 10% HCl, saturated aqueous $NaHCO_3$, and NaCl. The residue upon workup was chromatographed on silica gel with hexane as eluant to give the silyl ether **25** (258.7 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −26.5° (*c* 1.61, $CHCl_3$); IR (neat) 1610 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.23 and 0.26 (each 3H, each s), 0.66 (6H, q, *J* = 8.4 Hz), 0.99 (9H, s), 0.99 (9H, t, *J* = 8.4 Hz), 1.43 (3H, s), 1.90–2.36 (4H, m), 2.23 (3H, s), 4.92 (1H, dd, *J* = 10.5 and 3.0 Hz), 5.21 (1H, dd, *J* = 18.0 and 3.0 Hz), 5.92 (1H, dd, *J* = 18.0 and 10.5 Hz), 6.51 (1H, s), 6.59 and 6.93 (each 1H, each d, *J* = 7.5 Hz); MS *m/e* 446 (M^+); HRMS calcd for $C_{26}H_{46}O_2Si_2$ 446.3036 (M^+), found 446.3042.

(3*R*)-(−)-3-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-3-methyl-2-methylidenecyclopentanone (26). (i) A solution of the silyl ether **25** (80.8 mg, 0.18 mmol) and bis(acetonitrile)-palladium(II) chloride (58.0 mg, 0.20 mmol) in THF (3 mL) was refluxed for 2 h. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (99:1 v/v) as eluant to give the enone **26** (35.2 mg, 59%) as a colorless oil: $[\alpha]^{25}_D$ −121.5° (*c* 0.63, $CHCl_3$); IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (6H, s), 0.99 (3H, s), 1.59 (3H, s), 2.30 (3H, s), 1.14–2.86 (4H, m), 5.08 and 6.07 (each 1H, each s), 6.66 (1H, s), 6.67 and 7.09 (each 1H, each d, *J* = 7.5 Hz); MS *m/e* 330 (M^+); HRMS calcd for $C_{20}H_{30}O_2Si$ 330.2015 (M^+), found 330.1991.

(ii) A mixture of the silyl ether **25** (3.5 mg, 0.008 mmol), palladium(II) acetate (1.9 mg, 0.007 mmol), triphenylarsine (2.0 mg, 0.007 mmol), and CH_2Cl_2 (1 mL) was stirred for 3 h at room temperature. By following the same workup procedure described above, the enone **26** (2.3 mg, 89%) was obtained as a colorless oil which was identical with the sample prepared above in all aspects.

(1*S*,3*R*)-3-[2-(*tert*-Butyldimethylsiloxy)-4-methylphenyl]-1,3-dimethyl-2-methylidenecyclopentanol (27). To a stirred suspension of cerium chloride (70 mg, 0.28 mmol) in THF (2.5 mL) was added 1.4 M solution of methyllithium in Et_2O (0.20 mL, 0.28 mmol) at −78 °C, and stirring was continued for 1 h at the same temperature. To this reaction mixture was added dropwise a solution of the cyclopentanone **26** (18.6 mg, 0.056 mmol) in Et_2O (3 mL) at −78 °C, and then the temperature was raised to room temperature in 2 h. The reaction mixture was treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the cyclopentanol **27** (18.0 mg, 92%) as a colorless oil: IR (neat) 3425 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.34 (6H, s), 1.04 (9H, s), 1.43 (3H, s), 1.51 (3H, s), 1.56–2.58 (4H, m), 2.26 (3H, s), 5.02 and 5.54 (each 0.92H, each s), 5.07 and 5.58 (each 0.08H, each s), 6.64 (1H, d, *J* = 8.4 Hz), 6.65 (1H, s), 7.25 (1H, d, *J* = 8.4 Hz); MS *m/e* 346 (M^+); HRMS calcd for $C_{21}H_{34}O_2Si$ 346.2330 (M^+), found 346.2328.

(1*S*,3*R*)-3-(2-Hydroxy-4-methylphenyl)-1,3-dimethyl-2-methylidenecyclopentanol (28). To a stirred solution of the silyl ether **27** (37.0 mg, 0.11 mmol) in THF (2.5 mL) was added a 1.0 M solution of $^nBu_4N^+F^-$ in THF (0.16 mL, 0.16 mmol) at room temperature, and stirring was continued for 2 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (4:1 v/v) as eluant to give the phenol **28** (21.8 mg, 88%) as a colorless oil: IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (3H, s), 1.57 (3H, s), 1.40–2.60 (4H, m), 2.28 (3H, s), 4.82 and 5.23 (each 1H, each s), 6.68 (1H, s), 6.69 (1H, d, *J* = 7.8 Hz), 7.27 (1H, d, *J* = 7.8 Hz); MS *m/e* 232 (M^+); HRMS calcd for $C_{15}H_{20}O_2$ 232.1463 (M^+), found 232.1426.

(3*S*,3a*R*,8b*S*)-(−)-2,3,3a,8b-Tetrahydro-3-hydroxy-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran (29). To a stirred solution of the phenol **28** (3.4 mg, 0.015 mmol) in THF (1.5 mL) was added mercuric trifluoroacetate (6.1 mg, 0.015 mmol) at room temperature, and stirring was continued for 2 h at the same temperature. The reaction mixture was then treated with aqueous 10% NaOH (0.2 mL) and $NaBH_4$ (3.0 mg, 0.079 mmol) successively, saturated with NaCl, diluted with AcOEt, and passed through silica gel. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the alcohol **29** (3.0 mg, 88%) as a colorless oil: $[\alpha]^{25}_D$ −6.6° (*c* 0.56, $CHCl_3$); IR (neat) 3550 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, s), 1.25 (3H, s), 1.36 (3H, s), 1.54–1.79 (4H, m), 2.30 (3H, s), 2.77 (1H, s), 6.57 (1H, s), 6.71 (1H, d, *J* = 7.5 Hz), 6.93 (1H, d, *J* = 7.5 Hz); MS *m/e* 232 (M^+); HRMS calcd for $C_{15}H_{20}O_2$ 232.1463 (M^+), found 232.1466.

(3a*S*,8b*S*)-(−)-3a,8b-Dihydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran (30). To a stirred solution of the alcohol **29** (6.3 mg, 0.027 mmol) in pyridine (1.0 mL) was added dropwise phosphorus oxychloride (0.01 mL, 0.11 mmol) at 0 °C, and stirring was continued for 18 h at room temperature. The reaction mixture was diluted with Et_2O and treated with 7 N H_2SO_4. The aqueous layer was extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the olefin **30** (5.8 mg, 100%) as a colorless oil: $[\alpha]^{25}_D$ −113.0° (*c* 0.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, s), 1.43 (3H, s), 1.72 (3H, s), 2.28 (3H, s), 2.38–2.74 (2H, m), 5.41 (1H, m), 6.56 (1H, s), 6.67 (1H, d, *J* = 7.8 Hz), 7.00 (1H, d, *J* = 7.8 Hz); MS *m/e* 214 (M^+); HRMS calcd for $C_{15}H_{18}O$ 214.1358 (M^+), found 214.1358.

(3*S*,3a*S*,8b*S*)-(−)-2,3,3a,8b-Tetrahydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran [(−)-Debromoaplysin] (2). The mixture of the olefin **30** (2.5 mg, 0.012 mmol), a catalytic amount of platinum oxide, and EtOH (2.0 mL) was stirred for 3 h at room temperature under an atmosphere of hydrogen and then passed through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (99:1 v/v) as eluant to give (−)-debromoaplysin (**2**) (2.0 mg, 79%) as a colorless oil: $[\alpha]^{25}_D$ −61.8° (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, *J* = 6.6 Hz), 1.29 (3H, s), 1.33 (3H, s), 2.28 (3H, s), 6.53 (1H, s), 6.65 (1H, d, *J* = 7.2 Hz), 6.92 (1H, d, *J* = 7.2 Hz); MS *m/e* 216 (M^+); HRMS calcd for $C_{15}H_{20}O$ 216.1514 (M^+), found 216.1494.

(−)-Aplysin (1). To a stirred mixture of (−)-debromoaplysin (**2**) (2.0 mg, 0.0093 mmol), $NaHCO_3$ (1.3 mg, 0.015 mmol), and $CHCl_3$ (1.0 mL) was added a 0.1 M solution of bromine in $CHCl_3$ (0.14 mL, 0.014 mmol) at 0 °C, and stirring was continued for 10 min at room temperature. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (98:2 v/v) as eluant to give (−)-aplysin (**1**) (2.3 mg, 84%) as colorless needles: mp 85.5–86.5 °C (from MeOH); $[\alpha]^{25}_D$ −83.2° (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, d, *J* = 7.0 Hz), 1.28 (3H, s), 1.31 (3H, s), 1.03–1.20 and 1.50–1.90 (5H, m), 2.31 (3H, s), 6.58 (1H, s), 7.14 (1H, s); MS *m/e* 296 (M^+ + 2) and 294 (M^+); HRMS calcd for $C_{15}H_{19}OBr$ 296.0599 (M^+ + 2) and 294.0620 (M^+), found 296.0574 and 294.0612.

Supplementary Material Available: ^1H NMR spectra of **1**, **2**, **11**, **13–18**, **19**, **20**, and **24–30** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.