Nonsteroidal Benzophenone-Containing Analogues of Cholesterol

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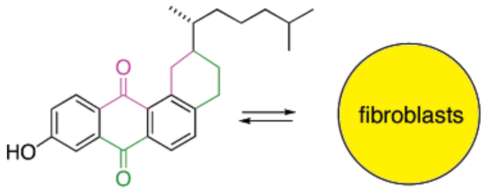


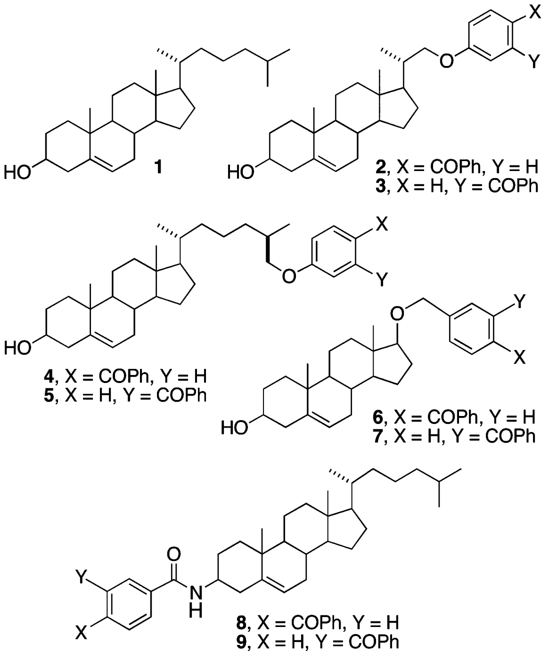
10, — **12**, —

The four benzophenones, **10**−**13**, containing the natural side chain of cholesterol (**1**) have been synthesized to explore whether the tetracyclic nucleus of **1** is essential for its biochemical properties. The syntheses of analogues **10**, **11**, and **13** feature efficient introduction of the alkyl side chain by Suzuki coupling. Preliminary biochemical evaluation of **10** and **12** suggests that the sterol tetracyclic nucleus is not required for biological compatibility with **1**.

Introduction

As part of a study of cellular cholesterol efflux and HDL formation, we have been synthesizing benzophenone-containing analogues of cholesterol (**1**) for use as photoaffinity labels. One of these analogues, compound **2**, designated FCBP, has already been used to substitute successfully for 47% of cellular **1** without perturbing smooth muscle cell function,[1] to photolabel caveolin, a key protein involved in cholesterol efflux, to obtain evidence that the **1** transferred to apolipoprotein A−I (apo A−I) was mainly derived from caveolin-rich domains,[1] and to help elucidate the mechanism of platelet-derived growth-factor-dependent caveolin phosphorylation.[2] Seven additional benzophenone-containing analogues of **1**, compounds **3**−**9**, have also been synthesized and have been shown, along with **2**, to substitute effectively for **1** in apo A−I-dependent cellular sterol efflux.[3] These eight compounds are the first demonstrated to replace cholesterol successfully in a complex pathway of multiple intracellular steps.

Analogues **2**−**7** have the benzophenone moiety extending or replacing part of the sterol alkyl side chain. In analogues **8** and **9**, the photophore is attached at the other end of the structure via an amide linkage. The success of these compounds as cholesterol surrogates led naturally to consideration of whether analogues in which a benzophenone group replaced a major portion of the tetracycle would also be accepted intracellularly. To test this idea, we have prepared compounds **10**−**13** as prospective cholesterol surrogates, and these syntheses and the preliminary biochemical evaluation of **10** and **12** are described



1

2, X = COPh, Y = H
3, X = H, Y = COPh

4, X = COPh, Y = H
5, X = H, Y = COPh

6, X = COPh, Y = H
7, X = H, Y = COPh

8, X = COPh, Y = H
9, X = H, Y = COPh

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10.1021/jo060481q CCC: $33.50

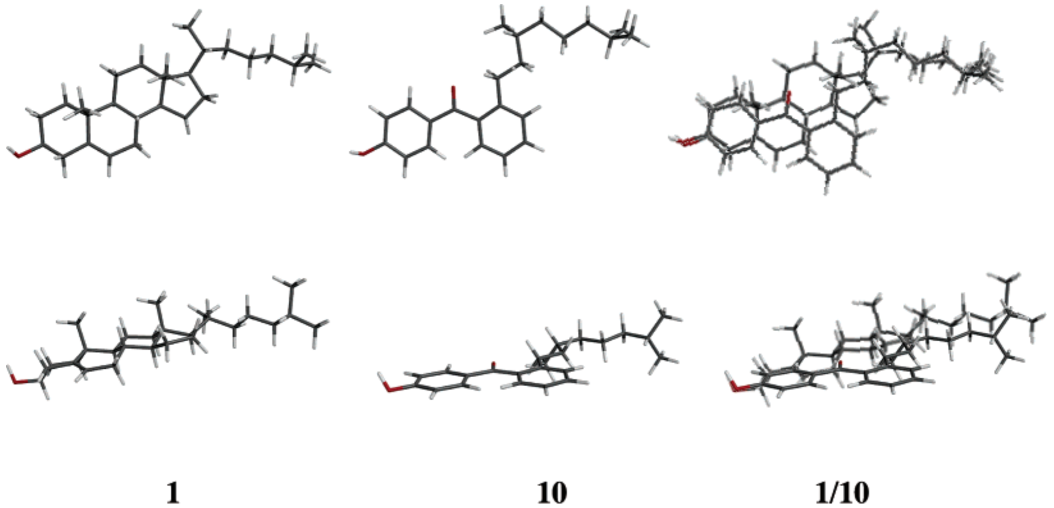
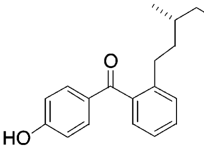


FIGURE 1. Spartan molecular modeling structures of cholesterol (**1**), analogue **10**, and **1** superimposed on **10** in top and side views. The structure of **1** was energy minimized and that of **10** was conformationally manipulated for most effective overlap using Dreiding models as a guide.

in this paper. Compounds with similarly placed hydroxybenzophenone groups have previously shown biological activity as ligands for steroid 5α-reductase[4] and the estrogen receptor.[5] Comparison of structures **10**−**13** with cholesterol (**1**) by use of the Spartan molecular modeling program indicated a reasonable overall correspondence of size and shape, as illustrated for compound **10** in Figure 1.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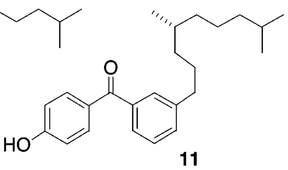
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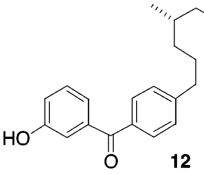
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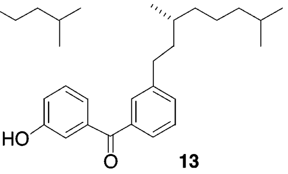
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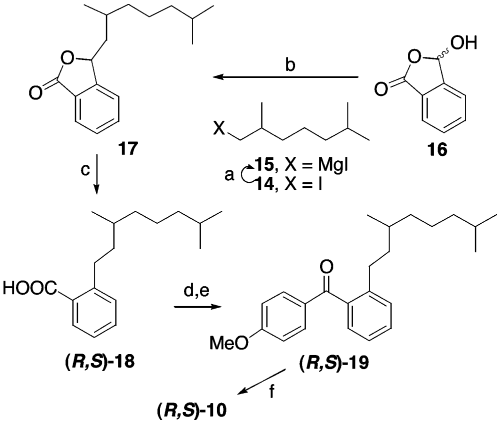
Results and Discussion

Syntheses of 10. The first successful approach to **10**, conducted initially to afford racemic product, involved reaction of Grignard reagent **15**, derived from (*R*,*S*)-iodide **14**,[6] with *o*-carboxybenzaldehyde (**16**) to afford **17**, a diastereomeric mixture, in a disappointing 50% yield (Scheme 1). It had been anticipated that reduction of **17** to acid **18** would be facile, but catalytic hydrogenation, without[7] or with added $HClO_4$,[8] dissolving metal reduction,[9,10] triethylsilane and Wilkinson's catalyst,[11] and trimethylsilyl iodide[12] followed by $NaBH_4$,[13] all failed to afford the desired product. Formation of **18** from **17** was finally achieved in a modest 36% yield by the use of triphenylsilane and *tert*-butyl peroxide.[14] The (*R*,*S*)-**18** thus obtained was converted via Friedel−Crafts reaction of its acyl chloride with anisole to afford (*R*,*S*)-**19** in 79% yield, followed by methyl ether cleavage with HI to afford (*R*,*S*)-**10**.

SCHEME 1. Synthesis of *rac*-10[a]



[a] Reagents and conditions: (a) Mg, Et_2O, rt; (b) THF, **15** in Et_2O, rt, 3 h; (c) Ph_3SiH, *t*BuOO*t*Bu, 140 °C, 5 h; (d) ClCOCOCl, PhH, Δ, 1 h; (e) MeOPh, $AlCl_3$, 140 °C, 4 h; (f) 57% HI, HOAc, Δ, 3.5 h.

Since the overall yield of **10** by this approach was poor, an alternate strategy was adopted for synthesis of enantiomerically pure **10**. As shown in Scheme 2, iodomethoxybenzophenone **21**[15] was prepared in 86% yield by Friedel−Crafts acylation of anisole with the acid chloride of **20** and then combined with the known (*R*)-3,7-dimethyloctene (**22**)[16] by the Suzuki coupling

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[6] Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253−3256 report preparation of the *R* enantiomer of **14**. In the present work, (*R*,*S*)-**14** was prepared via the corresponding (*R*,*S*)-bromide as described in Supporting Information.

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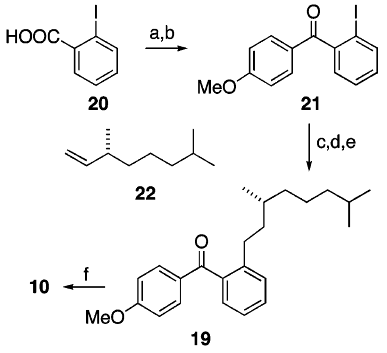
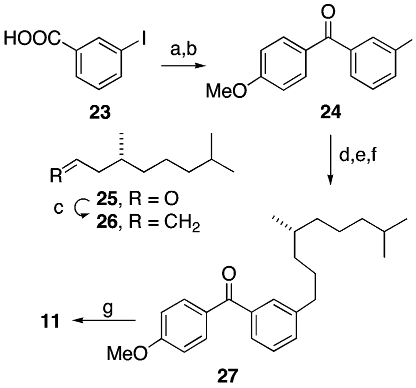
SCHEME 2. Synthesis of 10[a]



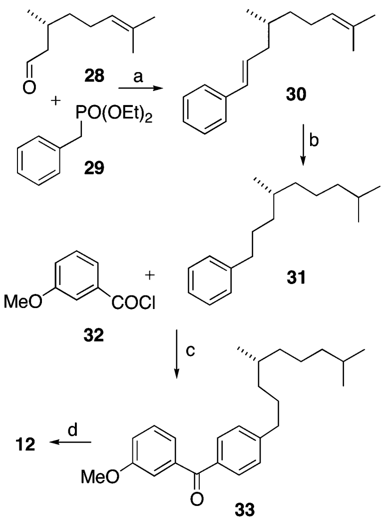
[a] Reagents and conditions: (a) ClCOCOCl, PhH, Δ, 1 h; (b) MeOPh, $AlCl_3$, 140 °C, 4 h; (c) Pd(dppf)Cl_2, Cs_2CO_3, $AsPh_3$, THF, DMF, H_2O; (d) product from **22** + 9-BBN, 4 h, rt; (e) Δ, overnight; (f) 57% HI, HOAc, Δ, 5 h.

SCHEME 3. Synthesis of 11[a]



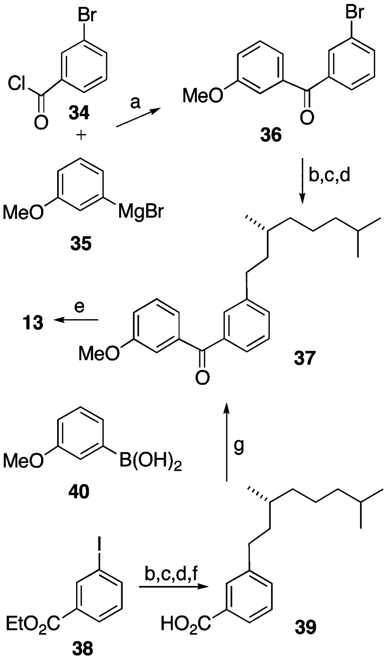
[a] Reagents and conditions: (a) $SOCl_2$, PhH, Δ, 16 h; (b) MeOPh, $AlCl_3$, 0 °C, 12 h; (c) Ph_3PCH_2, THF; (d) Pd(dppf)Cl_2, Cs_2CO_3, $AsPh_3$, THF, DMF, H_2O; (e) product from **26** + 9-BBN, 4 h, rt; (f) Δ, overnight; (g) 57% HI, HOAc, Δ, 5 h.

SCHEME 4. Synthesis of 12[a]



[a] Reagents and conditions: (a) NaH, PhMe, 20 h, rt; (b) 55 psi H_2, 10% Pd/C, 95% EtOH, 4 days; (c) $AlCl_3$, CS_2, Δ, 5 h; MeOPh, $AlCl_3$, 0 °C, 12 h; (d) 57% HI, HOAc, Δ, 5 h.

SCHEME 5. Synthesis of 13[a]



[a] Reagents and conditions: (a) **34**, PBu_3, THF, 20 min, rt, then **35**, THF, 10 min, rt; (b) Pd(dppf)Cl_2, Cs_2CO_3, $AsPh_3$, THF, DMF, H_2O; (c) product from **22** + 9-BBN, 4 h, rt; (d) Δ, overnight; (e) 57% HI, HOAc, Δ, 5 h; (f) NaOH, EtOH, H_2O, rt, overnight; (g) **40**, PPh_3, Pd(OAc)$_2$, pivalic anhydride, THF, 60 °C, 15 h.

procedure of Johnson and Braun[17] to produce 65% of **19**. Hydriodic acid cleavage of **19** then gave 84% yield of (*R*)-**10**.

Synthesis of 11. The second 4-hydroxybenzophenone analogue **11** was prepared via a Suzuki coupling route analogous to that used to prepare **10** (Scheme 3). 3-Iodobenzoic acid (**23**) was converted in 65% yield to benzophenone **24**, and this was coupled with (*R*)-4,8-dimethylnonene (**26**),[18] prepared by Wittig methylenation of **25**, to afford 72% of **27**, which was demethylated in 81% yield to **11**.

Synthesis of 12. Synthesis of the isomeric cholesterol analogue candidate **12** took advantage of the fact that Wittig condensation of (*R*)-citronellal (**28**) with diethyl benzylphosphonate (**29**) to produce **30** (Scheme 4) had been reported.[19] Hydrogenation of **30** thus prepared afforded **31** quantitatively. Friedel−Crafts acylation of **31** with **32** afforded 94% of benzophenone **33**, which was converted to **12** in 81% yield by treatment with hydriodic acid.

Syntheses of 13. Compound **13** was prepared by two comparably efficient routes (Scheme 5). Following the procedure of Maeda et al.,[20] 3-bromobenzoyl chloride (**34**) and 3-methoxyphenylmagnesium bromide (**35**) afforded 98% of benzophenone **36**, which was subjected to Suzuki coupling with **22** to afford **37** in 69% yield. Methyl ether cleavage as usual gave 74% of **13**. Alternatively, Suzuki coupling of ethyl 3-iodobenzoate (**38**) with **22** followed directly by ester hydrolysis gave 42% of **39**, which was coupled with 3-methoxyphenylboronic acid (**40**) in the presence of pivalic anhydride[21] to give 91% of **37**.

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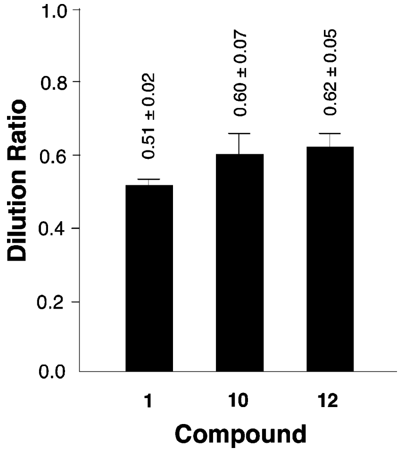

FIGURE 2. The dilution of [^{3}H]cholesterol ([^{3}H]**1**) label in fibroblast monolayers by **1**, **10**, or **12**. The dilution ratio is the reduction in [^{3}H]**1** efflux, induced by apolipoprotein A−I, to the cellular medium after fibroblast monolayers were equilibrated (48 h, 37 °C) with 10 μCi [^{3}H]**1** plus unlabeled **1** or analogue equal to the total sterol content of cells and medium compared with cells labeled with the same level of tracer [^{3}H]**1** only. Complete equilibration between sterol pools is indicated by a dilution ratio of 0.5. Values shown represent means ±1 standard deviation of three independent experiments, each including triplicate dishes of fibroblasts incubated as described in detail in ref 3 and in the Supporting Information.

Preliminary Biochemical Evaluation. To determine whether steroidal benzophenone-containing analogues **2**−**9** had the potential to serve as substitutes for cholesterol (**1**) in intact cells, an isotope dilution assay of apolipoprotein A−I-induced cellular efflux of **1** was developed.[3] To compete successfully with **1** in this assay, an analogue must enter the cells, equilibrate with **1** in major cellular pools, including membranes, and undergo efflux from the cells at a rate comparable to that of **1**. Thus, this assay sets a high standard for success as a cholesterol surrogate, and it was gratifying, albeit unexpected, that each of **2**−**9** met this demanding criterion.

In the present work, analogues **10**−**13**, having the sterol tetracyclic framework replaced by a benzophenone with the photoactivatable cross-linking atom at the top (**10** and **11**) or the bottom (**12** and **13**) of the ring B region of **1**, have been synthesized as described above, and a representative of each type, **10** and **12**, has been evaluated in the same isotope dilution assay. As shown in Figure 2, both **10** and **12** can also successfully replace **1** through the entire process of apolipoprotein A−I-induced cellular efflux of **1**.

Previous evaluations of compounds as cholesterol surrogates have, when conducted at all, almost always tested the ability either to bind proteins that have **1** as a ligand[22−25] or to replace **1** in model membrane bilayers.[24,26−30] 7,7-Azocholestanol has been reported[31] to mimic **1** in its distribution between intracellular membrane compartments. In one recent study, Zhang et al.[32] showed that dehydroergosterol can replace **1** in living fibroblasts. Very recently, we showed by fluorescence microscopy that an analogue of **1** in which the benzophenone moiety of FCBP (**2**) had been replaced by a fluorenone group adopts a distribution similar to **1** in smooth muscle cells.[33] Another recent study[34] reports that palmitoyl ceramides also can displace **1** from membrane bilayers. All these results suggest that there is a much greater biochemical tolerance for variations in the "cholesterol" structure than had been previously believed.[35] The present results with **10** and **12**, which also indicate that the sterol tetracyclic nucleus is not an essential part of a successful cholesterol surrogate, add further support to this idea of structural tolerance in analogues of cholesterol, at least with respect to its bulk roles in cells, as in membranes.

Experimental Section

3-(2,6-Dimethylheptyl)phthalide (17). To 1.52 g (62.5 mmol) of magnesium in 20 mL of ether was added a solution of 15.38 g (60.5 mmol) of **14** in 80 mL of ether. Formation of Grignard reagent **15** was evidenced by boiling and clouding of the ethereal solution. To the stirred **15** was added a solution of 3.66 g (24.4 mmol) of *o*-carboxybenzaldehyde (**16**) in 30 mL of THF, and the resulting mixture was stirred at rt under N_2 pressure for 3 h, then quenched with 100 mL of 1 M aqueous HCl and stirred at rt for 2 h. The aqueous layer was extracted with ether, and the combined organic layers were washed with 5% aqueous $Na_2S_2O_3$ and brine, dried, filtered, and evaporated to afford 8.9 g of residue which was chromatographed with EtOAc:hexane to afford 3.2 g (50%) of **17** as a viscous, pale yellow oil. Rechromatography with 1:6 ether: hexane gave analytically pure **17**: ^{1}H NMR (300 MHz) δ 7.90 (d, $J = 7.5$ Hz, 1H), 7.69−7.66 (m, 2H), 7.54−7.51 (m, 2H), 7.45−7.42 (m, 2H), 5.56−5.52 (m, 2H), 1.93−1.86 (m, 4H), 1.73−1.69 (m, 2H), 1.64−1.49 (m, 4H), 1.41−1.14 (m, 10H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 6H), 0.86 (d, $J = 6.5$ Hz, 6H); ^{13}C NMR (75 MHz) δ 170.9, 170.9, 151.0, 150.9, 134.1, 134.1, 129.2, 129.2, 126.1, 125.9, 125.9, 122.0, 121.9, 80.3, 79.9, 43.0, 42.8, 39.4, 39.3, 38.0, 36.7, 30.2, 29.9, 28.1, 24.7, 22.9, 22.8, 22.8, 22.7, 20.4, 19.3. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.58; H, 9.38.

(*R*,*S*)-2-(3,7-Dimethyloctyl)benzoic acid ((*R*,*S*)-18). According to the procedure of Sano et al.,[14] a mixture of 1.58 g (6.0 mmol) of **17**, 0.88 g (6.0 mmol) of di-*tert*-butylperoxide, and 7.7 g (30 mmol) of triphenylsilane was heated at 140 °C for 5 h, then cooled to rt, diluted with 40 mL of ether, treated with 40 mL of 1 M hydrochloric acid, and stirred for 70 h. The phases were separated, and the organic layer was extracted with 0.5 M NaOH solution. The basic extracts were acidified and extracted with ether, and these ethereal extracts were washed with H_2O, dried, filtered, and evaporated to afford 1.3 g of pale yellow oil. Chromatography with EtOAc:hexane afforded 0.561 g (36%) of (*R*,*S*)-**18** as a yellow oil. Rechromatog-

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raphy with 1:2 ether:hexane gave analytically pure (*R*,*S*)-**18**: ^{1}H NMR (300 MHz) δ 8.06−8.03 (m, 1H), 7.51−7.45 (m, 1H), 7.31−7.26 (m, 2H), 3.14−2.93 (m, 2H), 1.67−1.15 (m, 10H), 0.97 (d, $J = 6.3$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz) δ 173.0, 146.7, 133.1, 131.8, 131.4, 128.2, 126.0, 39.5, 37.3, 33.4, 32.6, 28.2, 25.0, 22.9, 22.9, 19.8. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.80; H, 9.86.

(*R*,*S*)-2-(3,7-Dimethyloctyl)-4′-hydroxybenzophenone ((*R*,*S*)-10). According to a procedure reported by Bhatt and Kulkarni,[36] a mixture of 44 mg (0.12 mmol) of (*R*,*S*)-**19**, prepared as described in Supporting Information, 2 mL of 57% HI solution, and 0.4 mL of glacial acetic acid was heated at reflux for 3.5 h. The reaction mixture was then poured over ice and extracted with ethyl acetate. The combined organic extracts were washed with 5% sodium $Na_2S_2O_3$ solution, saturated Na_2CO_3 solution and brine, dried, filtered, and evaporated to afford 57 mg of yellow solid, which was chromatographed with EtOAc:hexane to afford 21 mg (50%) of **10** as a clear oil, which had ^{1}H and ^{13}C NMR spectra identical with those of **10** described below.

(*R*)-2-(3,6-Dimethyloctyl)-4′-methoxybenzophenone (19). According to the procedure of Johnson and Braun,[17] to a solution of 0.90 g (6.4 mmol) of **22** in 8 mL of anhydrous THF was added 14.5 mL of 0.5 M 9-BBN (7.25 mmol) in THF dropwise. The resulting mixture was stirred at rt for 4 h, then transferred via syringe to a mixture of 1.31 g (1.60 mmol) of Pd(dppf)Cl_2, 7.85 g (24.1 mmol) of Cs_2CO_3, 0.49 g (1.61 mmol) of AsPh_3, and 2.72 g (8.03 mmol) of **21** in a mixture of 16 mL of THF, 16 mL of DMF, and 4 mL of H_2O. The resulting mixture was heated at reflux under N_2 overnight, then passed through a short Celite pad. The filtrate was evaporated, diluted with 50 mL of water, and extracted with ether. The combined organic layers were washed with brine, dried, filtered, and evaporated to give 4.6 g of brown oil, which was chromatographed with 1:10 ether:hexane to give 1.5 g (65%) of colorless oily **19**: ^{1}H NMR δ 7.83−7.80 (m, 2H), 7.41−7.22 (m, 4H), 6.95−6.92 (m, 2H), 3.88 (s, 3H), 2.71−2.56 (m, 2H), 1.57−1.52 (m, 1H), 1.48 (hept, $J = 6.5$ Hz, 1H), 1.39−1.33 (m, 2H), 1.12−1.02 (m, 6H), 0.85 (d, $J = 6.4$ Hz, 6H), 0.81 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR δ 197.7, 163.9, 141.8, 139.4, 132.8, 131.1, 130.2, 130.0, 128.1, 125.3, 113.9, 55.7, 39.5, 39.3, 37.2, 33.0, 31.1, 28.2, 24.9, 23.0, 22.9, 19.8; $[\alpha]_D^{28} = -5.03°$ (*c* 1.63, $CHCl_3$). Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.93; H, 9.17.

2-(3,7-Dimethyloctyl)-4′-hydroxybenzophenone (10). As in the preparation of (*R*,*S*)-**10**, except that the reaction mixture was heated for 5 h, 260 mg (0.71 mmol) of **19** gave 210 mg (84%) of colorless oily **10**: ^{1}H NMR δ 7.77−7.74 (m, 2H), 7.42−7.38 (m, 1H), 7.32−7.31 (m, 1H), 7.28−7.23 (m, 2H), 6.90−6.87 (m, 2H), 6.51 (br s, 1H), 2.69−2.54 (m, 2H), 1.55−1.50 (m, 1H), 1.47 (hept, $J = 6.5$ Hz, 1H), 1.37−1.29 (m, 2H), 1.23−1.00 (m, 6H), 0.83 (d, $J = 6.5$ Hz, 6H), 0.76 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR δ 198.5, 161.0, 141.7, 139.0, 133.2, 130.7, 130.2, 130.1, 128.1, 125.3, 115.6, 39.4, 39.2, 37.1, 32.9, 31.0, 28.1, 24.8, 22.9, 22.8, 19.6; $[\alpha]_D^{28} = -5.29°$ (*c* 0.68, $CHCl_3$). Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.60; H, 9.09.

3-(4,8-Dimethylnonyl)-4′-methoxybenzophenone (27). As in the preparation of **19**, 324 mg (2.10 mmol) of **26** was combined with 9-BBN and then with 887 mg (2.63 mmol) of **24** to give 1.36 g of brown oil which was chromatographed with 1:10 ether:hexane to give 551 mg (72%) of colorless oily **27**: ^{1}H NMR δ 7.87−7.84 (m, 2H), 7.60 (br s, 1H), 7.58−7.56 (m, 1H), 7.41−7.37 (m, 2H), 7.00−6.97 (m, 2H), 3.91 (s, 3H), 2.70−2.65 (m, 2H), 1.73−1.60 (m, 12H), 1.53 (hept, $J = 6.5$ Hz, 1H), 1.45−1.06 (m, 9H), 0.88−0.87 (m, 9H); ^{13}C NMR δ 196.1, 163.3, 143.3, 138.5, 132.8, 132.3, 130.6, 129.8, 128.2, 127.5, 113.7, 55.7, 39.5, 37.4, 36.9, 36.4, 32.9, 29.2, 28.2, 25.0, 22.9, 22.8, 19.9. Anal. Calcd for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 82.04; H, 9.35.

(*R*)-3-(4,8-Dimethylnonyl)-4′-hydroxybenzophenone (11). As in the preparation of **10**, 182 mg (0.50 mmol) of **27** gave 580 mg of residue which was chromatographed to give 145 mg (81%) of colorless oily **11**: ^{1}H NMR δ 7.81−7.79 (m, 2H), 7.70 (br s, 1H), 7.61−7.57 (m, 2H), 7.43−7.38 (m, 2H), 6.98−6.95 (m, 2H), 2.71−2.64 (m, 2H), 1.71−1.56 (m, 2H), 1.52 (hept, $J = 6.5$ Hz, 1H), 1.46−1.07 (m, 9H), 0.88−0.86 (m, 9H); ^{13}C NMR δ 197.5, 161.1, 143.4, 138.2, 133.3, 132.6, 130.0, 129.8, 128.3, 127.6, 115.6, 39.5, 37.4, 36.9, 36.3, 32.8, 29.1, 28.1, 25.0, 22.9, 22.8, 19.8. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.25.

(*R*)-4,8-Dimethylnonyl-3′-methoxybenzophenone (33). According to the method of Kumar et al.,[37] to a stirred solution of 1.71 g (1.00 mmol) of *m*-anisoyl chloride (**32**) in 30 mL of CS_2 under N_2 at rt were added 2.32 g (1.00 mmol) of **31** and 1.60 g (1.00 mmol) of $AlCl_3$. The mixture was heated at reflux for 5 h, cooled to rt, treated with 200 g of ice and 5 mL of concentrated HCl, and extracted with dichloromethane. The organic layer was washed with brine, dried, filtered, and evaporated to give 4.10 g of oil which was chromatographed with 1:50 EtOAc:hexane to give 3.4 g (94%) of golden oily **33**: ^{1}H NMR δ 7.78−7.76 (m, 2H), 7.40−7.27 (m, 5H), 7.14 (m, 1H), 3.88 (s, 3H), 2.72−2.67 (m, 2H), 1.75−1.60 (m, 2H), 1.54 (hept, $J = 6.5$ Hz, 1H), 1.47−1.08 (m, 9H), 0.89−0.88 (m, 9H); ^{13}C NMR δ 196.4, 159.7, 148.4, 139.4, 135.2, 130.5, 129.3, 128.5, 128.5, 122.9, 118.7, 114.4, 55.6, 39.5, 37.4, 36.9, 36.5, 32.8, 28.9, 28.1, 25.0, 22.9, 22.8, 19.8. Anal. Calcd for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 82.06; H, 9.51.

(*R*)-4-(4,8-Dimethylnonyl)-3′-hydroxybenzophenone (12). As in the preparation of **10**, 182 mg (0.50 mmol) of **33** gave 145 mg (81%) of oily **12**: ^{1}H NMR δ 7.78−7.76 (m, 2H), 7.46 (m, 1H), 7.32−7.28 (m, 4H), 7.16−7.14 (m, 1H), 2.71−2.64 (m, 2H), 1.72−1.60 (m, 2H), 1.56 (hept, $J = 6.5$ Hz, 1H), 1.47−1.10 (m, 9H), 0.91−0.90 (m, 9H); ^{13}C NMR δ 197.9, 156.5, 148.9, 138.9, 134.8, 130.8, 129.5, 128.5, 122.6, 120.3, 116.9, 39.5, 37.3, 36.9, 36.5, 32.8, 28.1, 24.9, 22.9, 22.8, 19.8. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.55; H, 9.25.

3-Bromo-4-methoxybenzophenone (36). According to the procedure of Maeda et al.,[20] to a solution of 1.00 g (0.60 mL, 4.56 mmol) of 3-bromobenzoyl chloride (**34**) in 10 mL of THF was added 0.97 g (1.2 mL, 4.6 mmol) of PBu_3 dropwise at −22 °C (dry ice/CCl_4). The resulting mixture was stirred for 20 min, treated rapidly with 4.6 mL of 1.0 M 3-methoxyphenylmagnesium bromide (**35**) in THF, stirred for 10 min, diluted with 10 mL of 1 M HCl, and extracted with ether. The combined organic layers were washed with brine, dried, filtered, and evaporated to give 2.60 g of yellow oil which was chromatographed with 1:15 ether:hexane to give 1.31 g (98%) of colorless oily **36**: ^{1}H NMR δ 7.96−7.95 (m, 1H), 7.74−7.72 (m, 2H), 7.43−7.32 (m, 4H), 7.19−7.16 (m, 1H), 3.89 (s, 3H); ^{13}C NMR δ 194.9, 159.9, 139.7, 138.4, 135.5, 133.0, 130.1, 129.7, 128.8, 123.0, 122.8, 119.4, 114.6, 55.7. Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found: C, 57.99; H, 3.78.

(*R*)-(3,7-Dimethyloctyl)benzoic acid (39). As in the preparation of **19**, 415 mg (2.96 mmol) of **22** was combined with 9-BBN and then with 851 mg (3.08 mmol) of ethyl 3-iodobenzoate (**38**) to give 812 mg of brown oil, which was chromatographed with 1:10 ether:hexane to give 428 mg of colorless oil, which was then treated with 843 mg (21.1 mmol) of NaOH in a mixture of 2 mL of EtOH and 2 mL of H_2O at rt overnight. The mixture was then evaporated, and the residue was acidified with concentrated HCl to pH = 1 and extracted with ether. The combined organic layers were washed, dried, filtered, and evaporated to give 534 mg of colorless oil which was chromatographed with 1:1 ether:hexane to give 321 mg (42%) of colorless oily **39**: ^{1}H NMR δ 8.00−7.98 (m, 2H), 7.48−7.40 (m, 2H), 2.79−2.64 (m, 2H), 1.72−1.67 (m, 1H), 1.57 (hept, $J = 6.8$ Hz, 1H), 1.54−1.48 (m, 2H), 1.41−1.16 (m, 6H), 0.99 (d, $J = 6.0$ Hz, 3H), 0.91 (d, $J = 6.5$ Hz, 6H); ^{13}C NMR δ 173.1, 143.9, 134.2, 130.3, 129.5, 128.7, 127.8, 39.6, 39.1, 37.4, 33.5, 32.7, 28.2, 25.0, 23.0, 22.9, 19.8. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.91; H, 10.15.

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(*R*)-3-(3,7-Dimethyloctyl)-4′-methoxybenzophenone (37). Method A: From 36. As in the preparation of **19**, 110 mg (0.79 mmol) of **22** was combined with 9-BBN and then with 191 mg (0.66 mmol) of **36** to give 341 mg of brown oil, which was chromatographed with 1:10 ether:hexane to give 161 mg (69%) of colorless oily **37**: ^{1}H NMR δ 7.67 (br s, 1H), 7.62−7.60 (m, 1H), 7.44−7.35 (m, 5H), 7.16−7.14 (m, 1H), 3.89 (s, 3H), 2.77−2.63 (m, 2H), 1.70−1.65 (m, 1H), 1.54 (hept, $J = 6.5$ Hz, 1H), 1.50−1.45 (m, 2H), 1.38−1.13 (m, 6H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 6H); ^{13}C NMR δ 197.0, 159.8, 143.7, 139.3, 137.8, 132.8, 130.0, 129.4, 128.3, 127.8, 123.1, 119.1, 114.5, 55.7, 39.5, 39.1, 37.3, 33.6, 32.7, 28.2, 24.9, 22.9, 22.9, 19.8. Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.54; H, 9.18. **Method B. From 39.** According to the procedure of Goossen and Ghosh,[21] to a solution of 67 mg (0.26 mmol) of **39** in 1 mL of THF were added 3 mg (0.011 mmol) of PPh_3, 2 mg (0.009 mmol) of $Pd(OAc)_2$, 47 mg (0.31 mmol) of 3-methoxyphenylboronic acid (**40**), and 73 mg (0.39 mmol) of pivalic anhydride. The resulting mixture was heated overnight at 60 °C and passed through a short pad of Celite. The pad was washed with EtOAc, and the combined organic layers were evaporated to give 212 mg of brown oil which was chromatographed with 1:6 ethyl acetate:hexane to give 84 mg (91%) of colorless oily **37**, which had ^{1}H and ^{13}C NMR spectra identical to those of **37** from **36**.

(*R*)-3-(3,7-Dimethyloctyl)-4′-hydroxybenzophenone (13). As in the preparation of **10**, 161 mg (0.46 mmol) of **37** gave 114 mg (74%) of colorless oily **13**: ^{1}H NMR δ 7.67−7.60 (m, 2H), 7.45−7.28 (m, 5H), 7.14−7.12 (m, 1H), 2.76−2.61 (m, 2H), 1.68−1.63 (m, 1H), 1.54 (hept, $J = 6.5$ Hz, 1H), 1.50−1.44 (m, 2H), 1.36−1.13 (m, 6H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 7$ Hz, 6H); ^{13}C NMR δ 198.1, 156.5, 143.8, 139.1, 137.5, 133.2, 130.2, 129.6, 128.4, 128.0, 123.1, 120.4, 116.9, 39.5, 39.1, 37.3, 33.6, 32.7, 28.2, 24.9, 22.9, 22.8, 19.8. Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.40; H, 8.82.

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Supporting Information Available: General experimental methods, descriptions of preparation of compounds **14**, (*R*,*S*)-**19**, **21**, **22**, **24**, **25**, **26**, **30**, and **31**, details of the isotope dilution assay, ^{1}H and ^{13}C NMR spectra of all new compounds and some known intermediates, atom coordinates for molecular modeling of compounds **1** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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