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Asymmetric Synthesis of 6′-Hydroxyarenarol: The Proposed Biosynthetic Precursor to Popolohuanone E

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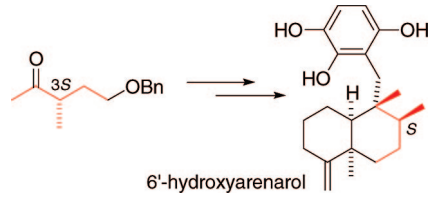
Received June 27, 2008



The first synthesis of (+)-6′-hydroxyarenarol **3**, the proposed biogenetic precursor to popolohuanone E (**1**), is described. An enantioselective route to key iodide intermediate **12** has been developed allowing the asymmetric synthesis of the known *cis*-decalin **22**. Conditions which allow the removal of the methyl ether protecting groups on the hydroxyarene leaving the exocyclic methylene moiety in tact have also been developed to complete this synthesis.

Introduction

Popolohuanone E (**1**) is a marine natural product isolated from the sponge *Dysidea* in 1990 as a dark purple solid (Figure 1).[1] The molecule has a trihydroxylated dibenzofuran-1,4-dione core to which are appended two identical *cis*-decalin units each containing four contiguous stereocenters. Aside from its unique structure, **1** demonstrates interesting biological activity being a potent inhibitor of Topoisomerase II and showing selective cytotoxicity against the A549 nonsmall human lung cancer cell line.[1]

Popolohuanone E and a related compound, arenarol (**2**),[2] bearing the same sesquiterpene unit and also isolated from *Dysidea* sp., have attracted much interest from the synthetic community. There have been several reported syntheses of arenarol, in both racemic[3] and enantiopure form,[4] including a formal racemic synthesis published by our group.[5] No total synthesis of **1** has been published as yet, although Katoh et al. very nearly achieved this goal in preparing 8-*O*-methylpopolohuanone E in 2001.[6]

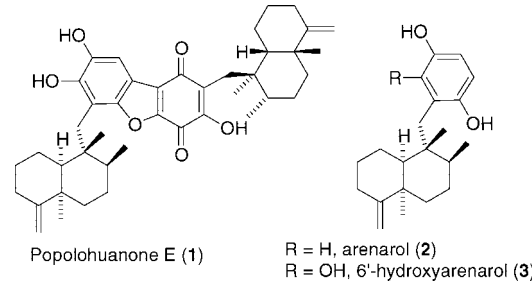


FIGURE 1. Popolohuanone E and related compounds.

For a number of years our group has been interested in pursuing a total synthesis of **1**, in particular, in testing the biosynthetic hypothesis that popolohuanone E is derived from oxidative dimerization of the, as yet unreported, 6′-hydroxyarenarol **3**.[1,7] This strategy is very efficient and especially appealing for a total synthesis as the tricyclic core should be generated without the need for protection on the hydroxyl groups. We were keen to avoid the difficulties that Katoh et al. had experienced when trying to deprotect the core of the molecule in the latter stages of their synthesis. In 2005 we demonstrated

(1) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727. *Popolohua* means *purplish blue as the sea* in Hawaiian.

(2) Arenarol (**2**) was first isolated from *Dysidea arenaria* in 1984 and subsequently from a *Fenestraspongia* species, see:(a) Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241. (b) Carte, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785.

(3) Watson, A. T.; Park, D. F.; Wiemer, D. F.; Scott, W. J. *J. Org. Chem.* **1995**, *60*, 5102.

(4) Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7769.

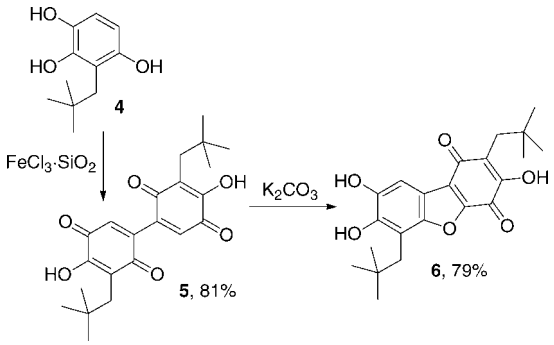
(5) Anderson, J. C.; Pearson, D. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2023.

(6) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terishima, S. *Org. Lett.* **2001**, *3*, 2701.

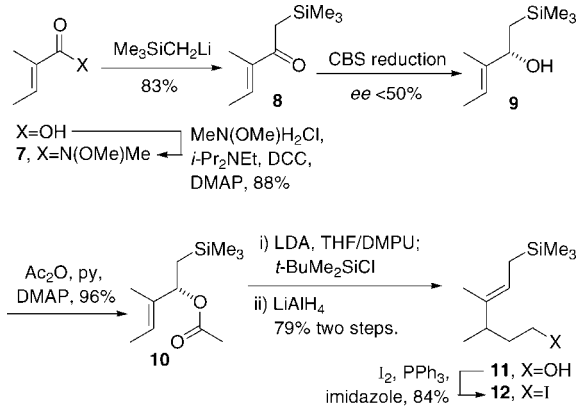
(7) While 6′-hydroxyareranol has not been isolated the related compound 6′-hydroxyavarol the $\Delta^{3,4}$ isomer and C-5 epimer has been isolated from *Dysidea*cinerea: Hirsh, S.; Rudi, A.; Kashman, Y.; Loya, Y. *J. Nat. Prod.* **1991**, *54*, 92.

10.1021/jo801404u CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/18/2008

SCHEME 1. Model Study for Biosynthesis of 1[8]



SCHEME 2. Initial Route to Key Iodide Intermediate 12

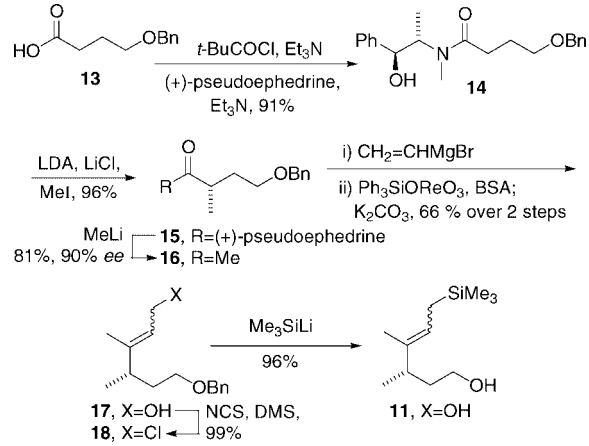


this approach to be feasible, generating the dibenzofuran-1,4-dione core from a model trihydroxyarene with a neopentyl group in place of the decalin unit (Scheme 1).[8] Treatment of trihydroxyarene **4** with silica-supported $FeCl_3$ effected oxidative dimerization and further oxidation to the bisquinone **5**. Subsequent biquinone rearrangement was brought about under very mild conditions with use of K_2CO_3 in acetone to give the tricyclic dibenzofuran-1,4-dione core of popolohuanone E **6**. In an analogous fashion we reasoned that oxidative coupling of **3** followed by further oxidation would give a bisquinone that could then undergo rearrangement to **1**. To investigate this hypothesis, we report the first asymmetric synthesis of 6′-hydroxyarenarol.

Results and Discussion

Our initial studies focused on the asymmetric synthesis of the *cis*-decalin unit. We envisaged this could be achieved by modifying the route we had used from Tokoroyama[9] in our formal synthesis of (±)-**2**.[5] An asymmetric synthesis would require generating iodide **12** in enantiomerically pure form. In the literature racemic route, **12** had been generated from tiglic aldehyde by using a Claisen rearrangement as a key step. A route from tiglic acid was developed (Scheme 2), the success of which required allylic alcohol **9** to be generated in enantiomerically pure form and for chirality to be transferred through the Claisen rearrangement. Although it was found that chirality could be transferred exclusively through an Ireland Claisen rearrangement[10] this route eventually proved unsuccessful as

SCHEME 3. Asymmetric Synthesis of Alcohol 11



CBS reduction[11] failed to give allylic alcohol **9** with an ee of more than 50% despite extensive screening.[12] That, coupled with the instability of alcohol **9** due to its tendency to undergo Peterson elimination, led us to develop an alternative route utilizing a chiral auxiliary to introduce the methyl stereocenter (Scheme 3).

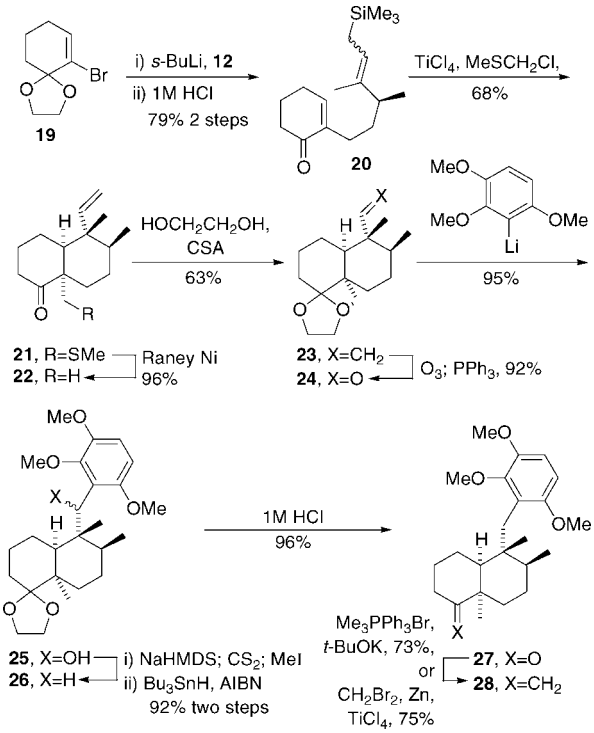
Alkylation precursor **14** was formed from γ-butyrolactone via acid **13**.[13] Asymmetric alkylation with the pseudoephedrine auxiliary[14] gave higher yield and ee than the Evans' oxazolidinone and allowed direct conversion to methyl ketone **16**.[15] Standard Wittig reaction failed to introduce the allyl silane moiety directly therefore a four-step protocol was employed: addition of vinyl magnesium bromide and isomerization of the resulting tertiary allylic alcohol gave primary allylic alcohol **17**.[16] This was converted to allylic chloride **18** and the chloride ion was displaced by using TMSLi, serendipitously also cleaving the benzyl protecting group to give **11**. Finally, the alcohol was converted to the enantiomerically pure iodide under standard conditions to give key intermediate **12**.

With this in hand, methodology that had been used in the racemic synthesis could be used without modification to generate aldehyde **24**.[5,9] Vinyl bromide **19** and iodide **12** were coupled and the ketal deprotected to give the precursor to the Hosomi−Sakurai reaction. Treatment of **20** with Lewis acid in the presence of $MeSCH_2Cl$ gave *cis*-decalin **21** as a single diastereoisomer in 68% yield along with 9% of the proton quenched product. Reduction of the sulfide, protection of the ketone, and cleavage of the alkene then gave the desired aldehyde **24**, also an intermediate in Katoh's synthesis.[17]

The next challenge was to construct the very sterically hindered benzylic bond. From previous work we knew that this

(8) Anderson, J. C.; Denton, R. M.; Wilson, C. *Org. Lett.* **2005**, *7*, 123.
(9) Tokoroyama, T.; Tsukamoto, M.; Asada, T.; Iio, H. *Tetrahedron Lett.* **1987**, *28*, 6645.
(10) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
(11) (a) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769. (b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (c) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275. (d) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.
(12) Since our studies in this area CBS reduction on the same substrate with $SiMe_2Ph$ instead of TMS has been successfully carried out albeit with 0.4 equiv of CBS catalyst. Rodgen, S. A.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4929.
(13) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.
(14) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
(15) Enantiomeric purity measured by HPLC against a racemic standard, using a Chiralcel OJ-H column of ^{i}PrOH/hexane (2:98), 0.25 mL min^{-1}. R_t: *R* (minor) 75.1 min, *S* (major) 79.7 min. Absolute configuration was assumed from the Myers mnemonic.[14]
(16) (a) Bellemin-Laponnaz, S.; Le Ny, J. P.; Osborn, J. A. *Tetrahedron Lett.* **2000**, *41*, 1549. (b) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842.

SCHEME 4. Synthesis of trimethyl-6′-hydroxyarenarol 28.



could be achieved in high yield by addition of an aryl lithium to **24** provided the protecting groups on the hydroxyls were small.[5] Katoh had demonstrated that the resulting benzylic alcohol could be deoxygenated in high yield using a modified Barton procedure and we also found this to be more efficient than direct hydrogenation.[5] Therefore reaction of ortho-lithiated 1,2,5-trimethoxybenzene with aldehyde **24** gave benzylic alcohol **25** as a 6:1 inseparable mixture of diastereoisomers in excellent yield and subsequent deoxygenation proceeded smoothly to give **26** (Scheme 4).

At this point we wanted to introduce the exocyclic methylene as this would be more difficult once deprotection of the hydroxyl groups had taken place. Ketal deprotection gave **27** and the exocyclic double bond could be introduced by using Nysted's reagent in 75% yield. It was found to be crucial to add $TiCl_4$ slowly as a solution in CH_2Cl_2 to avoid isomerization of the double bond. While experiencing problems with this step it was also discovered that the exocyclic methylene could be installed by using an operationally much simpler Wittig reaction, using *t*-BuOK to form the ylide and refluxing in toluene.[18] This gave a comparable yield and the use of basic conditions avoided any possibility of double bond isomerization.

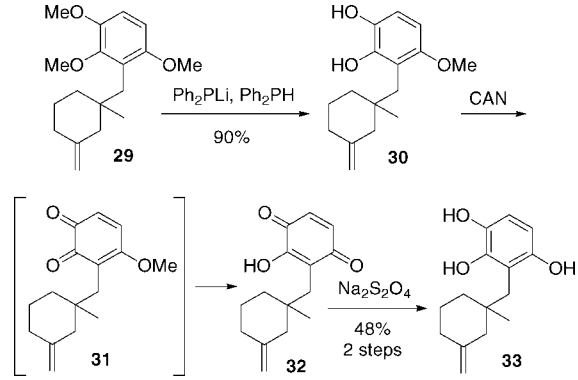
With trimethyl-6′-hydroxyarenarol **28** in hand all that was needed to complete the synthesis of **3** was the removal of the three methyl ether protecting groups. Standard Lewis acidic conditions usually employed for the removal of phenolic methyl ethers were thought to be unsuitable as they would result in isomerization of the double bond to the more stable endocyclic position. Therefore model compound **29** was synthesized[19] to find a strategy whereby deprotection could be accomplished

(17) $[\alpha]_D$ +8.4 (*c* 0.81, $CHCl_3$) [lit. $[\alpha]_D$ +7.4 (*c* 1.01, $CHCl_3$)]. The optical rotation obtained was the same sign and within experimental error leading us to believe that ee had not been eroded through the route.

(18) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586.

(19) See the Supporting Information.

SCHEME 5. Deprotection of Model Compound 29



without double bond isomerization.[20] Initial attempts focused on thiolates and it was found that monodemethylation at C-2[21] could be achieved by using EtSNa in DMF at 110 °C in 86% yield[22] or Ph_2PK in refluxing THF in an unoptimized yield of 63%. Any attempts to further deprotect this monodemethylated compound were unsuccessful. Didemethylation to give **30** could be effected by using PhSH and K_2CO_3 in NMP at 190 °C; however, the 22% isolated yield would not be viable for use in a synthesis. The suggested structure **30** is consistent with literature precedence in that once the methyl ether at C-2 has been removed[21] and the hydroxyl protonated an intramolecular hydrogen bond between this proton and the methoxy group at C-3 can assist cleavage of the second methyl ether.[23] In addition the detection of an *o*-quinone possessing an OMe group from the oxidation of **30** is also consistent with this assignment (vide infra). It was eventually found that the same didemethylated compound **30** could be obtained in an excellent yield of 90% (along with 9% of compound having undergone didemethylation, presumably at C-2[21] and C-6), using Ph_2PLi generated from *n*-BuLi and an excess of Ph_2PH. Prolonged exposure or resubmission of the monomethylated compound to these conditions did not result in the removal of the final methyl ether protecting group. After much experimentation it was found that **30** could be converted to fully deprotected compound **33** by using an oxidation−reduction protocol.[24] Treatment of dihydroxyarene **30** with Salcomine/O_2 resulted in formation of the unstable *o*-quinone **31**. This transformation could also be facilitated with CAN and it was noted that if the reaction was stirred for a longer period of time the *o*-quinone was completely converted to another compound, which proved to be *p*-quinone **32**. Direct reduction with $Na_2S_2O_4$ gave model trihydroxyarene **33** in good overall yield over 3 steps with the exocyclic methylene still intact (Scheme 5).

Application of the deprotection conditions developed in the model system to trimethyl-6′-hydroxyarenarol **28** proceeded presumably via the analogous diol **34** to accomplish the first synthesis of (+)-6′-hydroxyarenarol (**3**) (Scheme 6).

In summary, the first synthesis of (+)-6′-hydroxyarenarol, the proposed precursor of popolohuanone E in nature, has been

(20) It should be noted that all attempts to deprotect this model compound with acetal, ketone, or protected alcohol in place of the exocyclic methylene under Lewis acidic conditions (BBr_3/TMSI) failed.[22]

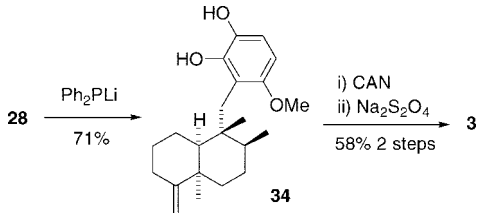
(21) This is consistent with literature precedent for the demethylation of phenols. Methyl ethers with two ortho-substituents have been shown to be deprotected first: Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072.

(22) Denton, R. M. Ph.D. Thesis, University of Nottingham, 2005.

(23) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 6406.

(24) A similar oxidation reduction protocol has been used previously: See ref 3 and 4.

SCHEME 6. Deprotection of 28 To Give 3



completed. The introduction of the key stereocenter in iodide **12** was introduced by using Myers ephedrine auxiliary enolate alkylation methodology for use in the Tokoroyama route to prepare enantiomerically pure decalin **22**. Subsequent addition of 1,2,5-trimethoxybenzene, functional group manipulations, and a three-step deprotection of the phenolic methyl ethers led to (+)-6′-hydroxyarenarol (**3**). Investigations toward the biomimetic total synthesis of popolohuanone E (**1**) have proven not to be as straightforward as anticipated and work toward this goal is ongoing.[25]

Experimental Section

(*S,S*)-4-Benzyloxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylbutyramide (14). To a solution of carboxylic acid **13**[13] (19.8 g, 102 mmol) in Et_2O (750 mL) at rt under N_2 was added Et_3N (14.3 mL, 102 mmol) and the mixture was stirred at rt for 15 min. The solution was cooled to 0 °C and *t*-BuCOCl (12.6 mL, 102 mmol) was added. A thick white precipitate formed immediately. This mixture was warmed to rt and stirred for 1 h after which time the mixture was recooled to 0 °C. To this mixture was added a solution of (+)-pseudoephedrine (13.0 g, 78.7 mmol) and Et_3N (11.0 mL, 78.7 mmol) in THF (190 mL + 20 mL wash) rapidly via cannula. The mixture was stirred at 0 °C for 0.5 h, warmed to rt, and stirred for a further 0.5 h after which time the excess anhydride was quenched by addition of H_2O. The organic layer was separated and washed with sat. aq $NaHCO_3$ and 1 M HCl, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc−petrol) gave pseudoephedrine amide **12** (24.4 g, 91%) as a colorless oil: IR ν_{max} (thin film) 3385, 2933, 2860, 1621 cm^{-1}; ^1H NMR (1:2.2 rotamer ratio, asterix denotes signals due to minor rotamer) δ 0.98* (3H, d, J = 6.8 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.92−2.04 (2H, m), 2.47 (1H, dt, J = 7.4, 4.7 Hz), 2.34−2.64 (1H, m), 2.83 (3H, s), 2.91* (3H, s), 3.52 (2H, t, J = 6.0 Hz), 3.56* (2H, t, J = 6.1 Hz), 4.05 (1H, m), 4.50 (2H, s), 4.52* (2H, s), 4.4−4.61 (1H, m), 7.28−7.38 (10H, m); ^{13}C NMR (asterix denotes signals due to minor rotamer) δ 14.4 (CH_3), 15.3*(CH_3), 25.2 (CH_2), 25.5* (CH_2), 30.2* (CH_2), 30.8 (CH_2), 26.8* (CH_3), 32.6 (CH_3), 58.3 (CH), 69.4 (CH_2), 69.7* (CH_2), 72.7 (CH_2), 72.8 (CH_2), 75.4* (CH), 76.4 (CH), 126.4 (CH), 126.9 (CH), 127.5 (CH), 127.6 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 138.4 (Cq), 138.5* (Cq), 141.5* (Cq), 142.4 (Cq), 173.8* (Cq), 175.0 (Cq); *m/z* (ES) 342 (100%, M^+); HRMS found 342.2052, $C_{21}H_{28}NO_3$ requires 342.2069; $[\alpha]_D$ +75.9 (*c* 1.08, $CHCl_3$).

(1*S*,2*S*,2′*S*)-4′-Benzyloxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2′-methylbutyramide (15). To LiCl (15.9 g, 376 mmol), flame dried under vacuum and cooled under an atmosphere of Ar, was added THF (70 mL) and *i*-Pr_2NH (17.0 mL, 121 mmol) and the resulting suspension was stirred at −78 °C under N_2. A solution of *n*-BuLi (2.5 M in hexanes; 45.0 mL, 113 mmol) was added dropwise over 15 min and the mixture was warmed to 0 °C for 5 min and then recooled to −78 °C. A solution of pseudoephedrine amide **14** (18.3 g, 53.7 mmol) in THF (160 mL) was added via cannula over 30 min. The reaction mixture was stirred at −78 °C for 1 h, 0 °C for 15 min, and rt for 5 min, then recooled to 0 °C whereupon MeI (10.0 mL, 161 mmol) was added. The mixture was stirred at 0 °C for 15 min and then quenched by the addition of sat. aq NH_4Cl. The mixture was partitioned between sat. aq NH_4Cl and EtOAc and the aqueous layer was separated and extracted with EtOAc. The combined organics were washed with 1 M HCl, dried, and concentrated in vacuo. Purification by flash column chromatography (Et_2O) gave alkylated product **15** (18.4 g, 96%) as a colorless oil: IR ν_{max} (thin film) 3380, 2933, 2869, 1615, 1453, 1089 cm^{-1}; ^1H NMR (1:3.1 rotamer ratio, asterix denotes signals due to minor rotamer) δ 0.97* (3H, d, J = 6.8 Hz), 1.04 (3H, d, J = 6.8 Hz), 1.13 (3H, d, J = 7.0 Hz), 1.17* (3H, d, J = 6.7 Hz), 1.68 (1H, m), 2.01 (1H, m), 2.81 (3H, s, N*Me*), 2.93* (3H, s, N*Me*), 2.88−2.97 (1H, m, COC*H*Me), 3.43 (1H, m, CH_2OBn), 3.51 (1H, m), 4.24−4.44 (1H, m, NC*H*Me), 4.47 (2H, s, OCH_2Ph), 4.53- 4.63 (1H, m, C*H*OH), 7.25−7.37 (10H, m); ^{13}C NMR (asterix denotes signals due to minor rotamer) δ 14.6 (CH_3), 15.7* (CH_3), 17.7 (CH_3), 17.9* (CH_3), 27.1* (CH), 27.4 (CH), 32.4* (CH_3), 33.3 (CH_3), 34.3 (CH_2), 34.8* (CH_2), 57.8 (CH), 68.1 (CH_2), 68.2* (CH_2), 73.1 (CH_2), 75.7* (CH), 76.5 (CH), 126.4 (CH), 127.1 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 128.8 (CH), 138.5 (Cq), 142.6 (Cq), 177.9* (Cq), 178.9 (Cq); *m/z* (ES) 356 (100%, M^+) HRMS found 356.2207, $C_{22}H_{30}NO_3$ requires 356.2226; $[\alpha]_D$ +93.6 (*c* 1.88, $CHCl_3$).

(3*S*)-5-Benzyloxy-3-methylpentan-2-one (16). To a solution of pseudoephedrine amide **15** (18.4 g, 51.8 mmol) in THF (450 mL) at −78 °C under N_2 was added MeLi (1.6 M in Et_2O; 78.0 mL, 124 mmol) over 30 min. The solution was warmed to 0 °C once the addition was complete and stirred for 15 min at 0 °C. The reaction was quenched by addition of *i*-Pr_2NH (7.3 mL, 52 mmol) and stirred at 0 °C for a further 15 min after which time a solution of acetic acid in Et_2O (20% v/v, 140 mL) was added. The reaction mixture was diluted with Et_2O and H_2O and the layers separated. The aqueous layer was extracted with Et_2O and the combined organics washed with sat. aq $NaHCO_3$ and brine, dried, and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc−petrol) gave ketone **16** (8.64 g, 81%, 90% ee by HPLC[15]) as a colorless oil: IR ν_{max} (thin film) 2932, 2859, 1710, 1454, 1361, 1099 cm^{-1}; ^1H NMR δ 1.11 (3H, d, J = 7.1 Hz), 1.63 (1H, dq, J = 14.1, 6.0 Hz), 2.03 (1H, m), 2.14 (3H, s), 2.74 (1H, sex, J = 6.9 Hz), 3.49 (2H, t, J = 6.3 Hz), 4.47 (2H, s), 7.29−7.36 (5H, m); ^{13}C NMR δ 16.5 (CH_3), 28.4 (CH_3), 32.8 (CH_2), 44.1 (CH), 68.0 (CH_2), 73.1 (CH_2), 127.7 (CH), 127.7 (CH), 128.5 (CH), 138.4 (Cq), 212.5 (Cq); *m/z* (ES) 229 (100%, MNa^+); HRMS found 229.1200, $C_{13}H_{18}O_2Na$ requires 229.1204. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H 8.80. Found: C, 75.38; H, 8.67. $[\alpha]_D$ +10.7 (*c* 0.98, $CHCl_3$).

(4*S*)-6-Benzyloxy-3,4-dimethylhex-2-en-1-ol (17). A solution of vinyl magnesium bromide (1 M in THF; 54 mL, 54 mmol) was added dropwise over 25 min to methyl ketone **16** (5.58 g, 27.1 mmol) stirred in THF (200 mL) at −78 °C under N_2. The reaction mixture was warmed to rt and stirred for 4 h before sat. aq NH_4Cl was added and the layer separated. The aqueous layer was extracted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude tertiary allylic alcohol (6.2 g).

A solution of $Ph_3SiOReO_3$ (0.67 g, 1.32 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (7.8 mL, 32 mmol) were stirred in Et_2O (250 mL) at 0 °C under N_2 for 10 min. A solution of crude tertiary allylic alcohol (6.2 g, 26.5 mmol) in Et_2O (60 mL + 20 mL wash) was added rapidly via cannula. The reaction was allowed to stir and warmed to rt for 14 h after which time Et_3N (2.6 mL) was added and the solvent was removed in vacuo. To the residue was added MeOH (270 mL) and K_2CO_3 (7.3 g, 53 mmol) and the mixture was stirred at rt for 3 h after which time sat. aq NH_4Cl was added. The layers were separated and the aqueous was extracted

(25) Trihydroxyarene **3** seems to be stable in air and in solution of a variety of solvents ($CDCl_3$, CH_2Cl_2, Et_2O, EtOAc, MeCN). Subjection of **3** to the oxidative dimerization conditions developed for model system **4** (Scheme 1)[8] only resulted in oxidation to hydroxy *p*-quinone. Other preliminary experiments with other oxidants, discredited on the model system **4**, have unsurprisingly proven unfruitful.

with DCM. The combined organics were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (20% Et_2O−petrol) gave allylic alcohol **17**[26] (4.18 g, 66% over 2 steps) as a colorless oil as a 4:1 mixture of double bond isomers: IR ν_{max} (thin film) 3392, 2930, 2869, 1454, 1102 cm^{-1}; ^1H NMR (only signals due to major isomer quoted) δ 1.03 (3H, d, $J = 6.9$ Hz), 1.60 (3H, s), 1.55−1.75 (2H, m), 2.34 (1H, sex, $J = 7.2$ Hz), 3.42 (2H, t, $J = 6.5$ Hz), 4.14 (2H, d, $J = 6.4$ Hz), 4.47 (1H, d, $J = 12.0$ Hz), 4.51 (1H, d, $J = 12.0$ Hz), 5.42 (1H, tq, $J = 6.8$, 0.7 Hz), 7.25−7.4 (5H, m); ^{13}C NMR δ 12.7 (CH_3), 19.6 (CH_3), 34.6 (CH_2), 39.4 (CH), 59.4 (CH_2), 68.7 (CH_2), 73.0 (CH_2), 123.4 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 138.7 (Cq), 143.1 (Cq); *m*/*z* (ES) 257 (70%, MNa^+), 217 (100%, $M^+ - OH$); HRMS found 257.1521, $C_{15}H_{22}O_2Na$ requires 257.1517; $[\alpha]_D$ +15.8 (*c* 0.37, $CHCl_3$).

(3*S*)-(6-Chloro-3,4-dimethylhex-4-enyloxymethyl)benzene (18). To a stirred solution of *N*-chlorosuccinimide (1.18 g, 8.83 mmol) in CH_2Cl_2 (40 mL) at 0 °C under N_2 was added Me_2S (0.71 mL, 9.6 mmol) dropwise and the resulting white suspension was cooled to −20 °C. Allylic alcohol **17** (1.88 g, 0.803 mmol) in CH_2Cl_2 (8 mL) was added dropwise via cannula over 10 min. The reaction mixture was stirred at 0 °C for 1 h after which time it was poured onto ice cold brine and the layers separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give allylic chloride **18** (2.01 g, 99%) as a yellow oil: IR ν_{max} (thin film) 2960, 2930, 2859, 1656, 1453, 1104, 697 cm^{-1}; ^1H NMR (only signals due to major isomer quoted) δ 1.03 (3H, d, $J = 6.9$ Hz), 1.6−1.75 (2H, m), 1.66 (3H, s), 2.33−2.34 (1H, sex, $J = 7.2$ Hz), 3.41 (2H, m), 4.09 (2H, d, $J = 8.0$ Hz), 4.49 (2H, s), 5.48 (1H, t, $J = 7.9$ Hz), 7.25−7.40 (5H, m); ^{13}C NMR δ 12.4 (CH_3), 19.3 (CH_3), 34.7 (CH_2), 39.3 (CH), 41.1 (CH_2), 68.5 (CH_2), 73.2 (CH_2), 120.3 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 138.7 (Cq), 146.3 (Cq); *m*/*z* (ES) 217 (80%, $M^+ - Cl$); HRMS found 217.1583, $C_{15}H_{21}O$ requires 217.1592; $[\alpha]_D$ +7.3 (*c* 0.44, $CHCl_3$).

(3S)-(*E*,*Z*)-3,4-Dimethyl-6-trimethylsilylhex-4-en-1-ol (11). To a solution of hexamethyldisilane (0.75 mL, 3.7 mmol) in HMPA (3 mL) at 0 °C under N_2 was added MeLi (1.5 M in Et_2O as a complex with LiBr; 1.95 mL, 2.93 mmol). The reaction mixture was stirred at 0 °C for 15 min whereupon THF (15 mL) was added rapidly and the solution immediately cooled to −78 °C. Allyl chloride **18** (98 mg, 0.39 mmol) in THF (4 mL) was added dropwise via cannula over 5 min. The reaction was allowed to stir and warmed slowly to rt o/n. The reaction mixture was poured onto petrol and sat. aq NH_4Cl. The layers were separated and the organics washed with H_2O and brine, filtered through a silica plug, and concentrated in vacuo. Purification by flash column chromatography (10% Et_2O−petrol) gave alcohol **11**[5] (75 mg, 96%) as a colorless oil: $[\alpha]_D$ +8.3 (*c* 1.26, $CHCl_3$).

(4*S*)-(6-Iodo-3,4-dimethylhex-2-enyl)trimethylsilane (12). To a solution of alcohol **11** (0.404 g, 2.02 mmol) in MeCN (35 mL) at 0 °C under N_2 was added imidazole (0.18 g, 2.6 mmol) and PPh_3 (0.69 g, 2.6 mmol). Solid iodine (0.62 g, 2.4 mmol) was added in small portions over 30 min and the reaction stirred at rt for 3 h before being poured onto 0.5 M HCl and the layers separated. The aqueous was extracted with Et_2O and the combined organics washed with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (petrol) gave iodide **12**[5] (0.54 g, 87%) as a colorless oil: $[\alpha]_D$ +22.6 (*c* 0.495, $CHCl_3$).

(4a*R*,5*S*,6*R*,8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronaphthalene-1-spiro-2′-(1′,3′-dioxolane) (26). To a solution of alcohol **25** (72 mg, 0.17 mmol) in THF (5 mL) under N_2 at −78 °C was added NaHMDS (2 M in THF; 0.26 mL, 52 mmol). The reaction mixture was stirred at −78 °C for 30 min after which time CS_2 (66 μL, 1.1 mmol) was added and the reaction warmed to −55 °C over 1 h. The reaction was cooled to −78 °C and MeI (34 μL, 0.55 mmol) was added and the reaction warmed to −55 °C over 1 h after which time sat. aq NaS_2O_4 was added and the reaction mixture warmed to rt. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (20% Et_2O−petrol) to yield the xanthates as a yellow oil (81 mg). The xanthates were transferred to a Schlenk flask under Ar and dried for 2 h under vacuum before toluene (5 mL) was added. To this solution was added Bu_3SnH (0.17 mL, 0.62 mmol) and AIBN (2.5 mg, 15 μmol) and the mixture was degassed by a freeze, pump, thaw procedure. The reaction mixture was heated at 110 °C for 2 h, allowed to cool to rt, filtered, and concentrated in vacuo. Purification by flash column chromatography (gradient elution: petrol then 10% EtOAc−petrol) gave **26** (64 mg, 92% over 2 steps) as a colorless oil: IR ν_{max} (thin film) 2937, 2835, 1484, 1463, 1090 cm^{-1}; ^1H NMR δ 0.83 (3H, d, $J = 6.6$ Hz), 0.93 (3H, s), 1.20−1.42 (2H, m), 1.44 (3H, s), 1.45−1.74 (9H, m), 1.86 (1H, dt, $J = 14.0$, 4.8 Hz), 2.62 (1H, d, $J = 13.1$ Hz), 2.92 (1H, d, $J = 13.1$ Hz), 3.73 (3H, s), 3.75 (3H, s), 3.83 (3H, s), 3.91−3.93 (4H, m), 6.52 (1H, d, $J = 8.9$ Hz), 6.73 (1H, d, $J = 8.9$ Hz); ^{13}C NMR δ 18.6, 19.0, 22.8, 24.8, 28.6, 30.4, 30.8, 36.1, 36.4, 41.9, 43.0, 48.8, 55.3 (CH_3), 56.2 (CH_3), 60.0 (CH_3), 64.5 (CH_2), 64.6 (CH_2), 104.7 (CH), 109.9 (CH), 114.5 (Cq), 124.1 (Cq), 147.1 (Cq), 149.6 (Cq), 153.5 (Cq); *m*/*z* (ES) 441 (100%, MNa^+), 357 (25%), 181 (57%, $C_{10}H_{13}O_3^+$); HRMS found 441.2609, $C_{25}H_{38}O_5Na$ requires 441.2617; $[\alpha]_D$ +12.0 (*c* 0.40, $CHCl_3$).

(4a*R*,5*S*,6*R*,8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronaphthalen-1(2*H*)-one (27). To a solution of ketal **24** (126 mg, 0.301 mmol) in THF (4 mL) was added 1 M HCl (4 mL) and the reaction was stirred vigorously at rt for 4.5 h until TLC analysis showed complete consumption of starting material. The layers were separated and the aqueous extracted with Et_2O (3 × 2 mL). The combined organics were washed with brine (4 mL), dried ($MgSO_4$), and concentrated in vacuo to give ketone **27**[5] (109 mg, 96%) as a very viscous colorless oil: ^1H NMR δ 0.82 (3H, s, C*Me*), 0.88 (3H, d, $J = 6.0$ Hz, CH*Me*), 1.18 (3H, s, C*Me*), 1.20−1.40 (5H, m), 1.80−2.20 (7H, m), 2.65 (1H, d, $J = 13.4$ Hz, CH_2Ar), 2.73 (1H, d, $J = 13.4$ Hz, CH_2Ar), 3.74 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 6.53 (1H, d, $J = 8.9$ Hz, Ar*H*), 6.75 (1H, d, $J = 8.9$ Hz, Ar*H*); ^{13}C NMR δ 17.8 (CH_3), 18.8 (CH_3), 21.3 (CH_2), 24.6 (CH_2), 28.4 (CH_2), 30.8 (CH_3), 34.6 (CH_2), 34.7 (CH_2), 36.5 (CH_2), 38.9 (CH), 44.2 (Cq), 48.4 (Cq), 51.8 (CH), 55.3 (CH_3), 56.1 (CH_3), 60.0 (CH_3), 104.7 (CH), 110.0 (CH), 123.1 (Cq), 147.0 (Cq), 149.6 (Cq), 153.3 (Cq), 217.8 (Cq); $[\alpha]_D$ +21.0 (*c* 0.78, $CHCl_3$).

(4a*R*,5*S*,6*R*,8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-1-methylene-5,6,8a-trimethyldecahydronaphthalene (28). Nysted's reagent (20% wt in THF; 0.14 mL, 74 μmol) was added to ketone **27** (7.9 mg, 21 μmol) stirred in CH_2Cl_2 (1 mL) at −78 °C under N_2. To this was added $TiCl_4$ (1 M in DCM; 63 μL, 63 μmol) dropwise over 5 min. The solution was stirred at −78 °C for a further 30 min and then stirred at rt o/n. Et_3N (0.1 mL) was added in one portion and the solution was stirred for 10 min before being passed through a celite plug, eluting with EtOAc, and concentrated in vacuo. Purification by flash column chromatography (10% Et_2O−petrol) gave **28**[5] (5.9 mg, 75%) as a colorless oil: ^1H NMR δ 0.87 (3H, d, $J = 6.1$ Hz, CH*Me*), 0.89 (3H, s, C*Me*), 1.05 (3H, s, C*Me*), 1.15−1.66 (3H, m), 1.50−1.68 (2H, m), 1.69−1.97 (4H, m), 1.99−2.06 (1H, m), 2.10 (1H, dd, $J = 13.9$, 5.2 Hz), 2.43 (1H, dt, $J = 13.5$, 6.6 Hz), 2.62 (1H, d, $J = 13.3$ Hz, CH_2Ar), 2.70 (1H, d, $J = 13.3$ Hz, CH_2Ar), 3.73 (3H, s, O*Me*), 3.74 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 4.66 (1H, s, C=CH_2), 4.69 (1H, s, C=CH_2), 6.52 (1H, d, $J = 8.9$ Hz, Ar*H*), 6.74 (1H, d, $J = 8.9$ Hz, Ar*H*); $[\alpha]_D$ +24.6 (*c* 0.56, $CHCl_3$).

Or to a suspension of *t*-BuOK (53 mg, 0.48 mmol) in benzene (1.5 mL) at rt under Ar was added $MePPh_3Br$ (170 mg, 0.48 mmol) and the resulting white suspension was heated at reflux for 1 h to give a yellow solution. After cooling to rt the solvent was taken off under reduced pressure (under Ar) and the residue dried under

(26) Tokoroyama, T.; Aoto, T. *J. Org. Chem.* **1998**, *63*, 4151.

vacuum for 30 min. The residue was dissolved in toluene (2 mL) and ketone **27** (8.9 mg, 24 μmol) in toluene (1 mL) was added via cannula. The reaction mixture was heated at reflux o/n, cooled to rt, and diluted with H_2O (4 mL) and Et_2O (2 mL). The layers were separated and the aqueous extracted with Et_2O (3 × 2 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (5% Et_2O−petrol) gave alkene **28** (6.5 mg, 73%) as a colorless oil. Data were as above.

(4a*R*,5*S*,6*R*,8a*S*)-6-Methoxy-1-(1,2,4a-trimethyl-5-methylene decahydronaphthalen-1-ylmethyl)benzene-2,3-diol (34). To a solution of diphenylphosphine (0.46 mL, 0.27 mmol) in THF (5 mL) under Ar at 0 °C was added *n*-BuLi (2.5 M in hexanes; 0.96 mL, 0.24 mmol) dropwise. The reaction was stirred at rt for 30 min after which time arene **28** (49.6 mg, 0.133 mmol) in THF (1 mL + 0.5 mL wash) was added via cannula. The reaction mixture was heated at reflux o/n, allowed to cool to rt, and H_2O (5 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organics were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (gradient elution: 10% EtOAc−petrol then 20%) gave diol **34** (32.7 mg, 71%) as a colorless oil; IR ν_{max} ($CHCl_3$) 3601 (OH), 3547 (OH), 2931 (CH), 1489, 1463, 1083 cm^{-1}; ^1H NMR δ 0.91 (3H, d, J = 6.0 Hz, CH*Me*), 0.92 (3H, s, C*Me*), 1.07 (3H, s, C*Me*), 1.18−1.28 (2H, m), 1.48 (2H, m), 1.60−1.68 (1H, m), 1.71−2.01 (4H, m), 2.03−2.16 (2H, m), 2.45 (1H, td, J = 13.6, 7.2 Hz), 2.65 (1H, d, J = 14.0 Hz, CH_2Ar), 2.71 (1H, d, J = 14.0 Hz, CH_2Ar), 3.71 (3H, s, O*Me*), 4.68 (1H, s, C=CH_2), 4.71 (1H, s, C=CH_2), 6.27 (1H, d, J = 8.7 Hz, Ar*H*), 6.70 (1H, d, J = 8.7 Hz, Ar*H*); ^{13}C NMR δ 18.4 (CH_3), 19.0 (CH_3), 23.0 (CH_2), 25.3 (CH_2), 28.2 (CH_2), 30.4 (Cq), 32.2 (CH_2), 33.2 (CH_3), 35.0 (CH_2), 37.7 (CH_2), 39.6 (CH), 44.5 (Cq), 48.8 (CH), 55.2 (CH_3), 101.3 (CH), 105.7 (CH_2), 112.5 (CH), 116.1 (Cq), 125.6 (Cq), 137.2 (Cq), 144.7 (Cq), 153.8 (Cq); *m*/*z* (EI^+) 344 (7%, M^+), 154 (100%, $C_8H_{10}O_3^+$); HRMS found 344.2355, $C_{22}H_{32}O_3$ requires 344.2351; $[\alpha]_D$ +30.4 (*c* 0.67, $CHCl_3$).

6′-Hydroxyarenarol (3). A solution of CAN (131 mg, 0.238 mmol) in MeCN:H_2O (2 mL:1 mL) was added fast dropwise to diol **35** (32.7 mg, 95.1 μmol) in MeCN:H_2O (4 mL:2 mL) at 0 °C to give a dark red solution. TLC analysis after 5 min showed complete consumption of starting material to an orange spot (R_f 0.28, 30% EtOAc−petrol) (*o*-quinone). After a further 30 min the ice bath was removed and the reaction stirred at rt for a further 3 h until the solution had lightened to yellow and TLC analysis showed complete conversion of the original orange spot to a yellow spot (R_f 0.74). The reaction mixture was partitioned between H_2O (10 mL) and Et_2O (10 mL) and the phases separated. The aqueous phase was extracted with Et_2O (10 mL) and the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude *p*-quinone. The residue was dissolved in Et_2O (20 mL) and shaken with a solution of $Na_2S_2O_4$ (0.5 g) in H_2O (20 mL) in a separating funnel for 10 min until the organic layer had turned from yellow to colorless and TLC analysis showed complete consumption of starting material. The layers were separated and the organic layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc−petrol) gave triol **3** (18.2 mg, 58% from **34**) as a yellow oil: IR ν_{max} ($CHCl_3$) 3603 (OH), 3544 (OH), 2933 (CH), 2870 (CH), 1632, 1487, 1461, 1110 cm^{-1}; ^1H NMR δ 0.93 (3H, d, J = 5.6 Hz, CH*Me*), 0.96 (3H, s, C*Me*), 1.10 (3H, s, C*Me*), 1.20−1.32 (2H, m), 1.49−1.56 (3H, m), 1.60−1.78 (2H, m), 1.90−2.09 (3H, m), 2.13 (1H, dd, J = 13.7, 5.2 Hz), 2.45 (1H, td, J = 13.6, 6.6 Hz), 2.65 (1H, d, J = 14.5 Hz, CH_2Ar), 2.70 (1H, d, J = 14.5 Hz, CH_2Ar), 4.51 (1H, s, O*H*), 4.69 (1H, s, C=CH_2), 4.72 (1H, s, C=CH_2), 5.46 (1H, s, O*H*), 6.22 (1H, d, J = 8.5 Hz, Ar*H*), 6.62 (1H, d, J = 8.5 Hz, Ar*H*); ^{13}C NMR δ 18.3 (CH_3), 18.9 (CH_3), 23.0 (CH_2), 25.2 (CH_2), 28.2 (CH_2), 32.1 (CH_2), 33.2 (CH_3), 35.8 (CH_2), 37.7 (CH_2), 39.7 (Cq), 40.0 (CH), 44.5 (Cq), 49.2 (CH), 105.9 (CH_2), 106.1 (CH), 113.3 (CH), 114.6 (Cq), 136.6 (Cq), 144.9 (Cq), 149.9 (Cq), 153.5 (Cq); *m*/*z* (EI^+) 330 (6%, M^+), 191 (68%, $M^+ - C_7H_7O_3$), 149 (100%); HRMS found 330.2189, $C_{21}H_{30}O_3$ requires 330.2195; $[\alpha]_D$ +34.8 (*c* 0.27, $CHCl_3$).

Acknowledgment. We thank the EPSRC, GSK, and Pfizer Central Research for funding, Dr. N. Parr and Dr J. Åhmen for helpful discussions, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra, and Dr T. Liu for microanalytical data.

Supporting Information Available: General experimental details, experimental procedures, and data for compounds **7**−**11**, **25**, and **29**−**33**, optical rotation data for **20**−**24**, and copies of ^1H and ^{13}C NMR spectra for **3**, **7**−**12**, **14**−**18**, **25**−**28**, and **30**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801404U