JOC Article

Convergent Stereocontrol in Peterson Olefinations. Application to the Synthesis of (±)-3-Hydroxybakuchiol and Corylifolin

Joe B. Perales, Narubumi F. Makino, and David L. Van Vranken*

Department of Chemistry, University of California, Irvine, California 92697-2025

dlvanvra@uci.edu

Received May 17, 2002

The iron-catalyzed Kirmse reaction was used to generate neopentyl α-silyl thioethers that were elaborated to meroterpenes using two complementary routes: one route involved a sila-Pummerer rearrangement, and the other route involved a Peterson olefination. While severe eclipsing interactions undermined the efficiency of the stereospecific sila-Pummerer rearrangement, they made it possible to stereoselectively generate *E* olefins without isolation or separation of *syn*- and *anti*-*β*-silyl alkoxides. Addition of a neopentyl α-silyl alkyllithium intermediate to an aryl aldehyde generated a mixture of *syn*- and *anti*-*β*-silyl alkoxides. The *syn*-*β*-silyl alkoxide eliminated stereospecifically at −78 °C to give an *E* olefin, whereas the *anti*-*β*-silyl alkoxide was unreactive. The reaction mixture was then acidified and heated to induce stereospecific elimination of the anti isomer to give the same *E* olefin via a complementary cationic pathway. This route was used to complete the first synthesis of the meroterpene (±)-3-hydroxybakuchiol. In addition, we synthesized another meroterpene corresponding to the natural product corylifolin and offer evidence that the structure of corylifolin was misassigned.

I. Introduction

The precise construction of carbon−carbon bonds is a central challenge in organic synthesis. Bonds to quaternary carbons are among the most difficult to form, yet the metal-catalyzed Kirmse reaction[1] of allyl sulfides provides a powerful efficient method for the creation of quaternary centers. When used in conjunction with trimethylsilyldiazomethane (TMSD), iron catalysts obviate the need for syringe pump addition.[2] Kirmse reactions with TMSD can be used to generate α-silyl thioethers attached to vinyl-substituted quaternary centers (Scheme 1). α-Silyl thioethers are versatile handles for further elaboration.[3]

Corylifolin, a newly isolated meroterpene, is a weak inhibitor of DNA polymerase.[4] However, more complex meroterpenes such as bakuchiol have diverse biological activities, including antitumor, antimutagenic, anti-inflammatory, insect hormonal, and *Staphylococcus aureus* inhibitory activity.[5] Bakuchiol is highly sensitive to acid and oxygen due to the electron-rich hydroxystyrene moiety. 3-Hydroxybakuchiol **1** isolated from *Psoralea glandulosa*, Linné, "Jesuit tea", is even more sensitive than bakuchiol and has not been previously synthesized.[6]

Vinyl-substituted quaternary centers are central to meroterpene structure. If there existed an efficient method to convert α-silyl thioethers to *E*-styrenes, the Kirmse reaction would be ideally suited for the synthesis of meroterpenes. We hoped to develop a method to convert α-silyl thioethers to *E*-styrenes and then use the method to synthesize 3-hydroxybakuchiol **1** and corylifolin **2** (Figure 1).

II. Results and Discussion

A. Generation of Homoallyl α-silyl Thioethers Using the Iron-Catalyzed Kirmse Reaction. The α-silyl thioethers **4** were accessed by an iron(II)-catalyzed Kirmse reaction of allyl thioethers **3** with trimethylsilyldiazomethane, TMSD (Scheme 1).[7] Reactions were carried out by heating the allylic sulfide **3** with 5 mol % iron(II) chloride diphenylphospinoethane (dppeFeCl$_2$) in refluxing 1,2-dichloroethane for 1 h followed by addition of TMSD to give the α-silyl thioether **4**. Preincubation of

* To whom correspondence should be addressed. Fax: 949-824-5871.

(1) Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994−1003.

(2) (a) Aggarwal, V. K.; Ferrara, M.; Hainz, R.; Spey, S. E. *Tetrahedron Lett.* **1999**, *40*, 8923−8927. (b) Carter, D. S.; Van Vranken, D. L. *Org. Lett.* **2000**, *2*, 1303−1305.

(3) (a) Block, E.; Aslam, M. *Tetrahedron* **1988**, *44*, 281−324. (b) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245−3252. (c) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183−194. (d) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 195−204.

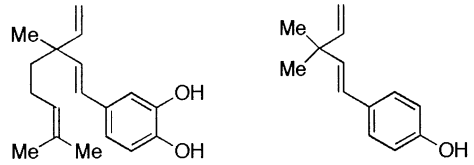
(4) (a) Sun, N. J.; Woo, S. H.; Cassady, J. M.; Snapka, R. M. *J. Nat. Prod.* **1998**, *61*, 362−366. (b) Backhouse, C. N.; Delporte, C. L.; Negrete, R. E.; Erazo, S.; Zuñiga, A.; Pinto, A.; Cassels, B. K. *J. Ethnopharmacology* **2001**, *78*, 27−31.

(5) (a) Kaul, R. *Arzneim.-Forsch.* **1976**, *26*, 486-489. (b) Bhan, P.; Soman, R.; Dev, S. *Agric. Biol. Chem.* **1980**, *44*, 1483−1487. (c) Prikhod'ko, V. A.; Bondarenko, A. S.; Mishenkova, E. L. *Mikrobiol. Zh. (Kiev)* **1980**, *42*, 646−650. (d) Smirnov, V. V.; Romanenko, V. M.; Prikhod'ko, V. A. *Mikrobiol. Zh. (Kiev)* **1984**, *46*, 72−74. (e) Wall, M. E.; Wani, M. C.; Manikumar, G.; Abraham, P.; Taylor, H.; Hughes, T. J.; Warner, J.; McGivney, R. *J. Nat. Prod.* **1988**, *51*, 1084−91. (f) Ryu, S. Y.; Choi, S. U.; Lee, C. O.; Zee, O. P. *Arch. Pharm. Res.* **1992**, *15*, 356−359. (g) Ferrandiz, M. L.; Gil, B.; Sanz, M. J.; Ubeda, A.; Erazo, S.; Gonzalez, E.; Negrete, R.; Pacheco, S.; Paya, M.; Alcaraz, M. J. *J. Pharm. Pharmacol.* **1996**, *48*, 975−980.

(6) Labbe, C.; Faini, F.; Coll, J.; Connolly, J. D. *Phytochemistry* **1996**, *42*, 1299−1303.

(7) Warning, diazo compounds are potentially explosive.

10.1021/jo0259459 CCC: $22.00
Published on Web 08/29/2002

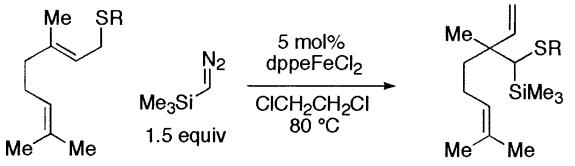


1 (±)-3-hydroxybakuchiol **2** corylifolin

FIGURE 1.

the catalyst with the allylic sulfide is required for consistent and efficient conversion.[8] While the mechanistic details have yet to be determined, it is presumed that the reaction proceeds through an iron carbene intermediate that is attacked by the thioether to form a sulfonium ylide complex.[2b,9] The sulfonium ylide could undergo a [2,3]-sigmatropic rearrangement either with[10] or without involvement of the metal.

SCHEME 1. Iron-Catalyzed Kirmse Reaction of Allyl Thioethers



3a R = Et 91%
3b R = Ph 92%

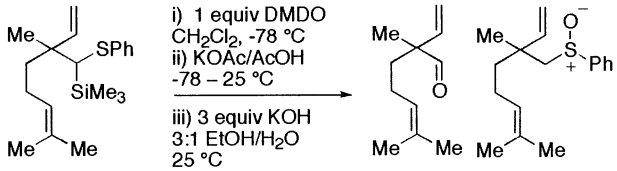
4a 89%, ds 3.4:1
4b 91%, ds 2:1
4b 89%, ds 2:1 **5 g scale**

Both alkyl and aryl thioethers give good yields. The smaller more nucleophilic ethyl thioether **3a** gave a slightly higher level of diastereoselection (3.4:1) than the phenyl thioether **3b** (2:1). In a previous study, the Kirmse reaction of phenyl methallyl thioether **17** with ferrous bromide and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl gave a good yield but no enantioselection.[2b] Consequently, the issue of enantioselection was set aside for this study. When the catalyst loading was reduced from 5 to 2 mol %, the yield of α-silyl thioether **4b** was diminished (63%). However with 5 mol % catalyst, the reaction can be scaled up (up to 5 g) without a significant decrease in yield.

We considered two methods to convert the α-silyl thioether into an *E*-styryl moiety: (1) an oxidative approach involving sulfoxide formation, sila-Pummerer reaction, and Horner−Wadsworth−Emmons olefination and (2) a reductive approach involving reductive lithiation followed by Peterson olefination. Peterson olefinations employing α-silyl thioethers generate mixtures of *E* and *Z* isomers with yields between 60 and 70%. Unfortunately, when the α-silyl thioether is adjacent to a quaternary center the olefination yields do not exceed 35%.[3c] While the Peterson olefination is more direct than the oxidative approach, the discouraging precedents led us to first explore the longer but more propitious oxidative approach.

B. Homologation of the Neopentyl α-silyl Thioether Using a Sila-Pummerer Reaction. To induce the sila-Pummerer reaction, typical conditions (*m*-CPBA, −40 °C) were employed for oxidation of α-silyl thioether **4b** to the corresponding sulfoxide.[11] Unfortunately, at −40 °C, where *m*-CPBA has good solubility, the syn α-silyl sulfoxide **7** underwent sila-Pummerer rearrangement to generate a thioacetal that competitively consumed the oxidizing agent. Insufficient oxidant left unreacted α-silyl thioether **4b**; however, excess oxidant would have epoxidized the trisubstituted olefin if the temperature were raised. Rather than optimize the oxidant stoichiometry, we switched to dimethyldioxirane (DMDO),[12] which is more soluble than *m*-CPBA. Sila-Pummerer rearrangement is much slower than sulfide oxidation at −78 °C. Thus, 1 equiv of DMDO at −78 °C cleanly generated the sulfoxide. Since thiacarbenium ions can participate in thia-Prins cyclizations, a solution of potassium acetate in acetic acid was added to favor formation of the desired thioacetal intermediate. The thioacetal was hydrolyzed to aldehyde **5** using aq potassium hydroxide. The overall yield of aldehyde **5** was 52% (Scheme 2).

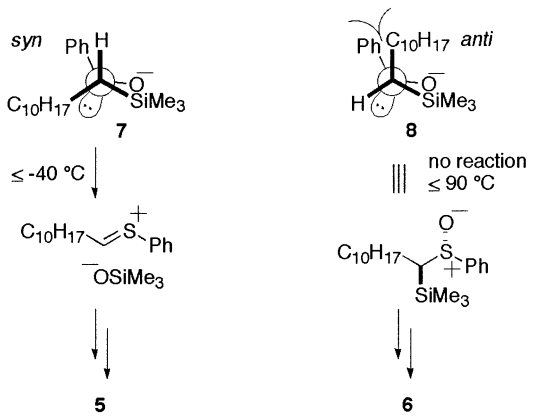
SCHEME 2. Stereospecific Reaction of α-Silyl Sulfoxides



4b **5** 52% **6** 40%

The desired aldehyde **5** was accompanied by a desilylated sulfoxide **6** (40%). Since the sila-Pummerer proceeds through a syn-elimination, eclipsing interactions are important in the transition state. Vedejs has shown that different diastereomers of highly congested α-silyl sulfoxides undergo Pummerer rearrangements at significantly different rates.[13] The syn α-silyl sulfoxide **7** readily eliminates at a temperature less than −40 °C (Scheme 3). In contrast, the anti α-silyl sulfoxide **8** is incapable of adopting the required syn conformation, even up to a temperature of 90 °C. Under the saponification conditions, the remaining α-silyl sulfoxide **8** is desilylated to give sulfoxide **6**. Ethyl thioether **4a** gave similar results in the sila-Pummerer reaction.

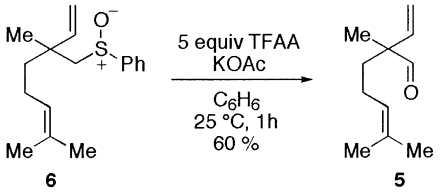
SCHEME 3. Stereospecific Reaction of α-Silyl Sulfoxides



(8) Prabharasuth, R.; Van Vranken, D. L. *J. Org. Chem.* **2001**, *66*, 5256−5258.
(9) McCrindle, R.; Arsenault, G. J.; Farwaha, R.; McAlees, A. J.; Sneddon, D. W. *J. Chem. Soc., Dalton Trans.* **1989**, 761−766.

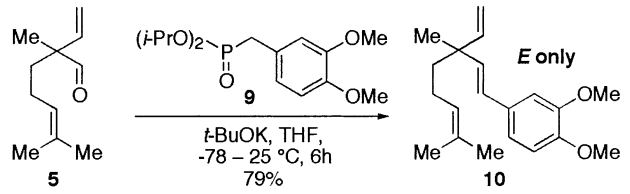
Although 40% of the α-silyl thioether did not produce the desired aldehyde **5**, the remaining sulfoxide **6** was converted to aldehyde **5** by a traditional Pummerer rearrangement. Addition of a solution of potassium acetate in trifluoroacetic anhydride to a solution of sulfoxide **6** produced aldehyde **5** in 60% yield (Scheme 4). Thus, the overall yield of aldehyde **5** from α-silyl thioether **4b** was 76%.

SCHEME 4. Pummerer Oxidation of Sulfoxide 6



Stereoselective olefination of aldehyde **5** was accomplished with a Horner−Wadsworth−Emmons reaction. Deprotonation of phosphonate **9** with potassium *tert*-butoxide followed by addition of aldehyde **5** provided olefin **10** with greater than 100:1 *E*/*Z* selectivity as determined by GC (Scheme 5).

SCHEME 5. Stereoselective Horner−Wadsworth−Emmons Olefination



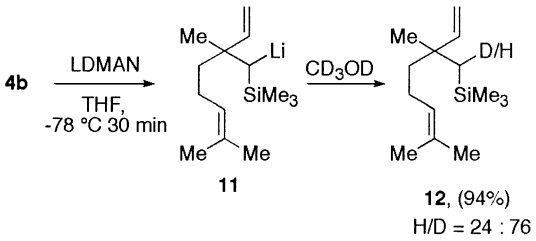
Thus the desired styrene **10** was obtained in 60% overall yield with high *E* selectivity from the α-silyl thioether **4b**. Unfortunately, failure of the anti α-silyl sulfoxide **8** to undergo the sila-Pummerer rearrangement had forced us to salvage unreacted sulfoxide in a second step prior to olefination. Given the lengthiness of this reaction sequence, we turned our attention to the more direct reductive approach for conversion of the α-silyl thioether **4b** to a styryl moiety.

C. Homologation of the Neopentyl α-silyl Thioether Using a Peterson Olefination. Hindered α-silyl thioethers are poor substrates for the reductive lithiation/Peterson olefination sequence when lithium naphthalenide is used for the reductive lithiation step.[3c] However, improvements have been reported for each step of this sequence. First, lithium 1-(dimethylamino) naphthalenide (LDMAN) offers the promise of a higher reduction potential and easier removal of byproducts. Second, potassium salts facilitate formation of the four-membered-ring siliconate intermediate in the Peterson olefination step.[14]

Cohen has reported that when 1-(dimethylamino)-naphthalene (DMAN) is reduced with lithium wire at −70 °C in THF, lithium 1-(dimethylamino)naphthalene (LDMAN) is formed in 60−70% yield after 8 h.[15] Consistent with this report, when LDMAN was formed at −45 °C in THF from lithium wire (scrubbed free of the passivation layer), residual lithium wire remained after 3.5 h. Since the presence of the unreacted lithium was obscured by the dark opaque solution, the LDMAN solution was separated from the residual lithium using a cannula chilled with dry ice.

When thioether was reductively lithiated with LDMAN at −78 °C over 30 min and then quenched with CD_3OD, the desulfurated product **12** was isolated in 94% yield as a 76:24 mixture of deuterated and protonated products (Scheme 6). Thus, within less than 30 min at −78 °C, about one-fourth of the α-silyl alkyllithium **11** was protonated by a species in the reaction mixture.

SCHEME 6. Competitive Protonation of α-Silyllithium 11



When the α-silyl alkyllithium **11** was quenched immediately with CD_3OD at −78 °C, the ratio of deuterated product to protonated product **12** was increased to 90:10. Thus, the available neopentyllithium intermediate **11** was generated from the thioether **4b** in about 85% yield but had to be used immediately.

When 3,4-dibenzyloxybenzaldehyde **13** was added to α-silyl alkyllithium **11** at −78 °C and allowed to warm to rt over 8 h, the olefination products were formed as a disappointing 1.7:1 ratio of *Z* and *E* isomers, respectively. Under basic conditions, the Peterson olefination proceeds through a stereospecific syn elimination. Thus, the formation of *E* and *Z* isomers can be attributed to uncontrolled formation of *syn*- and *anti*-*β*-silyl alkoxides in the addition step. With no way to control addition to the aldehyde, the prospects for stereoselective olefination seemed bleak. According to a comprehensive 1990 review[16] of the Peterson olefination, "To be a useful reaction for the stereoselective synthesis of alkenes, the Peterson reaction requires the stereospecific preparation of *β*-hydroxysilanes." This fatalistic view of the Peterson olefination has not changed in the past 10 years.

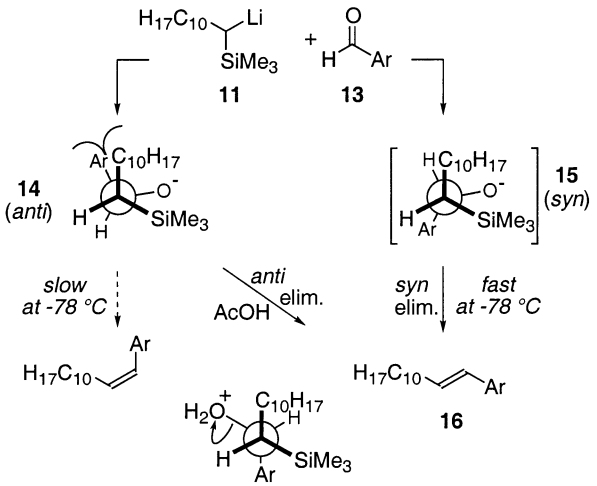
To our delight, when the Peterson olefination was quenched at −78 °C, only the *E* isomer was obtained. Presumably, at low temperature, elimination of the *syn*-*β*-silyl alkoxide **15** was facile whereas elimination of the *anti*-*β*-silyl alkoxide **14** was prevented by severe eclipsing interactions (Scheme 7). However, there are two comple-

(10) Wu, Y. D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421142−3.
(11) (a) Kocienski, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1096−1097. (b) Kocienski, P. J. *Tetrahedron Lett.* **1980**, *21*, 1559−1562.
(12) (a) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800−2803. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(13) (a) Vedejs, E.; Mullins, M. *Tetrahedron Lett.* **1975**, *24*, 2017−2020. (b) Carey, F. A.; Dailey, J. D. J.; Hernandez, O.; Tucker, J. R. *J. Org. Chem.* **1976**, *41*, 3975−3978.
(14) (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−161. (b) Cohen, T.; Jung, S. H.; Romberger, M. L.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 25−26.
(15) Cohen, T.; Kreethadumrongdat, T.; Liu, X.; Kulkarni V. *J. Am. Chem. Soc.* **2001**, *123*, 3478−3483.
(16) Ager, D. J. *Org. React.* **1990**, *38*, 1−223.

mentary ways to generate *E*-alkenes form *β*-hydroxysilanes. Under basic conditions, *syn*-*β*-hydroxysilanes generate *E*-alkenes via *syn*-siloxide eliminations.[17] Under acidic conditions, *anti*-*β*-hydroxysilanes generate *E*-alkenes via *β*-silylcarbocations. Thus, the severe eclipsing interactions that debilitated the sila-Pummerer approach could provide a unique advantage in the Peterson olefination.

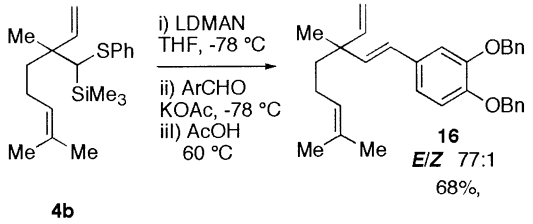
We hypothesized that we could use acid to induce elimination of the unreacted *anti*-*β*-hydroxysilane **14** via a cationic pathway (Scheme 7). If successful, this would allow us to execute a stereoselective Peterson olefination from a mixture of *syn*- and *anti*-*β*-hydroxysilanes.

SCHEME 7. Stereoconvergent Peterson Olefination from a Mixture of Diastereomeric *β*-Silyl Alkoxides



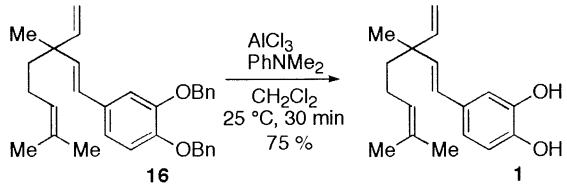
To implement this convergent strategy, aldehyde **13** was added to α-silyl alkyllithium **11** at −78 °C, followed by anhydrous potassium acetate. After 3 h at −78 °C, acetic acid was added and the reaction was warmed to rt over 5 min. The acid-catalyzed elimination was slow even at rt, so the reaction was heated at 60 °C for 8 h. This sequence of basic and acidic Peterson olefination conditions (Scheme 8) afforded the *E* olefin **16** in 68% yield with exceptional selectivity (77:1 *E*/*Z* by GCMS).

SCHEME 8. Stereoselective Synthesis of *E*-Alkenes by a Peterson Olefination



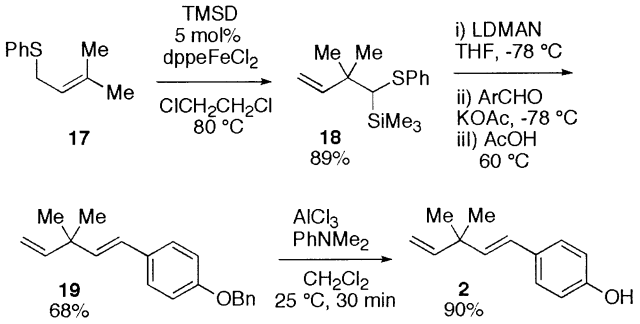
The *p*-hydroxystyrene moiety of bakuchiol makes it unstable to both oxygen[6] and acid,[18] so it is not surprising that 3-hydroxybakuchiol **1** was converted to the diacetate prior to full characterization. To accommodate the sensitive catechol moiety, the deprotection of **16** was carried out using the Akiyama protocol ($AlCl_3$/dimethylaniline) to afford (±)-3-hydroxybakuchiol in 75% yield (Scheme 9).[19] Neither the optical rotation or the absolute stereochemistry of 3-hydroxybakuchiol have been reported. 3-Hydroxybakuchiol decomposes in the presence of oxygen; a ^{1}H NMR sample stored in DMSO-d_6 at rt underwent nearly complete decomposition over 12 h. However, samples frozen in DMSO are stable.

SCHEME 9. Synthesis of (±)-3-Hydroxybakuchiol



D. Synthesis of "Corylifolin". To test the generality of our synthetic route to the meroterpenes, we used the reductive/Peterson olefination strategy for the synthesis of corylifolin, a meroterpene recently isolated from *Psoralea corylifolia*.[4a] The iron-catalyzed Kirmse reaction of methallyl phenylthioether **17**[2b] proceeded in 89% yield using 5 mol % dppeFeCl$_2$ (Scheme 10). The α-silyl thioether **18**[2b] was reductively lithiated using LDMAN and then subjected to the convergent sequence of stereospecific eliminations previously described to produce *E*-styrene **19** in 68% yield as the desired *E* isomer (>50:1 diastereoselection). Deprotection of the phenol generated *E*-styrene **2** in 90% yield.

SCHEME 10. Synthesis of Corylifolin



The structure of **2** was confirmed using ^{1}H NMR, ^{13}C NMR, IR, and low- and high-resolution mass spectrometry. Unfortunately, while the spectroscopic data for compound **2** and corylifolin were similar, they clearly did not match. In the spectra of synthetic compound **2**, the methyl groups are magnetically equivalent, consistent with an achiral structure. In contrast, in the ^{1}H NMR and ^{13}C NMR data reported for corylifolin the two methyl groups were magnetically inequivalent, suggesting a diastereotopic relationship.

At the present time, it is not possible to assign a structure for corylifolin based on the published data. However, it seems clear that corylifolin does not have the structure originally reported.

III. Conclusion

In conclusion, we have used the iron-catalyzed Kirmse reaction to generate neopentyl α-silyl thioethers that

(17) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464−1468.

(18) Prakasa Rao, A. S. C.; Nayak, U. R.; Dev, S. *Tetrahedron* **1974**, *30*, 1107−1114.

(19) Akiyama, T.; Hirofuji, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1321−1324.

were elaborated to meroterpenes using two complementary routes: the first route involved a sila-Pummerer rearrangement and the second route involved a Peterson olefination. Severe eclipsing interactions undermined the efficiency of the sila-Pummerer rearrangement. Steric effects limited the yield of the sila-Pummerer rearrangement to about 50%. The *syn*-α-silyl sulfoxide **7** underwent facile sila-Pummerer rearrangement at − 40 °C, whereas the *anti*-α-silyl sulfoxide **8** failed to undergo the sila-Pummerer reaction up to 90 °C. Fortunately, the type of eclipsing interactions that thwarted the sila-Pummerer route proved to be indispensable in the Peterson olefination route. Even though addition of the neopentyl α-silyllithium **11** to aldehyde **13** generated an inseparable mixture of *syn*- and *anti*-*β*-silyl alkoxides, we were able to convergently transform them into *E* styrenes with high stereoselectivity. The *syn*-*β*-silyl alkoxide eliminated stereospecifically at −78 °C to give the *E* olefin **16**, whereas the anti *β*-silyl alkoxide was unreactive. The reaction mixture was then acidified and heated to induce stereospecific elimination of the anti isomer to give the same *E* olefin **16** via the complementary cationic pathway. This route was used to complete the first synthesis of the meroterpene (±)-3-hydroxybakuchiol **1**. In addition, we synthesized meroterpene **2** corresponding to the natural product corylifolin. The spectroscopic data reported for corylifolin do not match the data we obtained for meroterpene **2** and were not consistent with the proposed achiral structure.

Experimental Section

General Experimental Procedures. Reactions, analysis, purification, identity, and purity were performed or determined as previously described.[20] Additionally, dimethyldioxirane (DMDO) was prepared and titrated immediately before use.[12] Potassium *tert*-butoxide and aluminum trichloride were purified by sublimation, trifluoroacetic anhydride was distilled from P_2O_5 and lithium wire was washed with hexane and scraped free of oxides under an argon atmosphere prior to use. All Peterson olefination reactions were run with an oven dried glass encased magnetic stir bar under an argon atmosphere. The transfer of LDMAN solutions employed a cannula that was chilled with an aluminum foil cover that contained dry ice.

α-Silyl Thioether 4a. A solution of allyl sulfide **3a**[21] (0.14 g, 0.71 mmol) and [1,2-bis(diphenylphosphino)ethane]dichloroiron(II) (21 mg, 4.0×10^{-5} mol) in 1,2-dichloroethane was refluxed for 1 h. A solution of trimethylsilyldiazomethane (2.0 M in hexanes, 0.59 mL, 1.2 mmol) was added. The reaction mixture was refluxed for 1 h, filtered through a plug of silica gel (1:9 EtOAc/hexanes) to remove iron salts, and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica gel (hexanes) to give α-silyl thioether **4a** as a colorless oil (0.19 g, 89%): R_f = 0.34 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, J = 17.5, 10.8 Hz, 1H), 5.07 (t, J = 7.1 Hz, 1H), 5.03 (dd, J = 10.8, 1.4 Hz, 1H), 4.95 (dd, J = 17.5, 1.4 Hz, 1H), 2.62 (dq, J = 11.8, 7.5 Hz, 1H), 2.49 (dq, J = 11.8, 7.4 Hz, 1H), 1.85 (m, 2H), 1.68 (m, 4H), 1.58 (s, 3H), 1.51 (m, 2H), 1.19 (m, 3H), 1.11 (s, 2.3H), 1.08 (s, 0.7H), 0.14 (s, 7.4H), 0.12 (s, 1.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 131.1, 124.9, 112.2, 45.6, 45.2, 40.1, 31.5, 25.7, 23.4, 21.9, 17.7, 14.6, 0.9; IR (thin film) 3078, 2963, 1633, 1449, 1004, 861, 833 cm^{-1}; MS (EI) 284, 255, 147; HRMS (EI) m/z calcd for $C_{20}H_{32}SSi$ 284.1994, found 284.1985. Anal. Calcd for $C_{16}H_{32}SSi$: C, 67.53; H, 11.33. Found: C, 67.63; H, 11.45.

α-Silyl Thioether 4b. A solution of allyl sulfide **3b** (5.00 g, 20.3 mmol) and [1,2-bis(diphenylphosphino)ethane]dichloroiron(II) (533 mg, 1.02 mmol) in 1,2-dichloroethane was refluxed for 1 h. A solution of trimethylsilyldiazomethane (2.0 M in hexanes, 15.2 mL, 31 mmol) was added. The reaction mixture was refluxed for 1 h, filtered through a plug of silica gel (1:9 EtOAc/hexanes) to remove iron salts, and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica gel (hexanes) to give α-silyl thioether **4b** a colorless oil (6.00 g, 89%): R_f = 0.29 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.26 (m, 2H), 7.15 (m, 1H), 5.87 (dd, J = 17.5, 10.8 Hz, 0.33H), 5.82 (dd, J = 17.5, 10.8 Hz, 0.67H), 5.00 (m, 3H), 2.53 (s, 0.33H), 2.51 (s, 0.67H), 1.82 (m, 2H), 1.67 (s, 2H), 1.65 (s, 1H), 1.60 (m, 1H), 1.55 (s, 2H), 1.53 (s, 1H), 1.48 (m, 1H), 1.16 (s, 1H), 1.15 (s, 2H), 0.24 (s, 6H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 146.1, 131.1, 131.0, 129.2, 128.7, 128.6, 125.5, 125.4, 124.8, 124.7, 112.7, 112.5, 47.7, 47.2, 45.6, 45.1, 25.6, 23.4, 23.0, 22.3, 21.4, 17.5, 1.0, 0.9; IR (thin film) 3069, 2963, 1637, 1482, 1408, 1024, 914, 837, 735 cm^{-1}; MS (EI) 332, 255, 195; HRMS (EI) m/z calcd for $C_{20}H_{32}SSi$ 332.1994, found 332.1985. Anal. Calcd for $C_{20}H_{32}SSi$: C, 72.22; H, 9.70. Found: C, 72.14; H, 9.79.

Aldehyde 5 and Sulfoxide 6. To a cooled (−78 °C) solution of thioether **4b** (1.50 g, 4.52 mmol) in CH_2Cl_2 (29 mL) was added dimethyldioxirane (0.074 M in acetone, 61.0 mL, 4.5 mmol). A solution of potassium acetate in acetic acid (5% v/v, 70 mL) was added after 30 min, and the reaction mixture was allowed to warm to rt. After 6 h at rt, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil (1.60 g).

The mixture of thioacetal and un-rearranged α-silyl sulfoxide was dissolved in ethanol (41 mL), and aq KOH (1.0 M, 13.6 mL, 13.6 mmol) was added. After being stirred for 1 h, the reaction mixture was diluted with saturated aq NaCl, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The oil was chromatographed over silica gel (2% EtOAc in hexanes and 10% EtOAc in hexanes) to give aldehyde **5** as a colorless oil (0.39 g, 52%). Spectroscopic data for aldehyde **5** matched the literature values.[22] Sulfoxide **6** was also obtained as a colorless oil in 95% purity as determined by ^{1}H NMR (0.50 g, 40%): R_f = 0.24 (10:90 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.4 Hz, 2H), 7.63 (m, 1H), 7.54 (m, 2H), 5.79 (dd, J = 17.4, 10.8 Hz, 1H), 5.05 (t, J = 7.0 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.97 (d, J = 17.4 Hz, 1H), 3.15 (s, 2H), 1.89 (m, 2H), 1.66 (s, 3H), 1.59 (m, 2H), 1.57 (s, 3H) 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 141.8, 133.4, 131.8, 129.1, 127.8, 123.9, 113.2, 65.4, 40.6, 40.5, 25.6, 22.8, 22.7, 17.6; IR (thin film) 2967, 2919, 1633, 1576, 1371, 1148, 1086, 1023, 914, 690 cm^{-1}; MS (EI) 276, 258, 177, 149, 135; HRMS (EI) m/z calcd for $C_{17}H_{24}OS$ 276.1548, found 276.1547.

Aldehyde 5, by Pummerer Oxidation. To a solution of sulfoxide **6** (49 mg, 0.17 mmol) in benzene (1.0 mL) was added trifluoroacetic anhydride (0.13 mL, 0.89 mmol). The solution was poured into saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aq NaCl, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The oil was chromatographed over silica gel (3% EtOAc in hexanes) to give aldehyde **5** as a colorless oil (18 mg, 60%).

Phosphonate 9. To 3,4-dimethoxybenzyl alcohol (4.3 mL, 30 mmol) was added a solution of phosphorus tribromide (1.0 M, 59 mL, 60 mmol). After 7 h, the reaction mixture was poured into a cold (0 °C) solution of H_2O and $NaHCO_3$ (15 g, 180 mmol). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil (6.4 g). The oil was dissolved in *o*-xylene (100 mL), and

(20) Perales, J. B.; Van Vranken, D. L. *J. Org. Chem.* **2001**, *66*, 7270−7274.

(21) Torii, S.; Uneyama, K.; Ishihara, M.; Ito, K. JP Patent 51 133 252, 1976.

(22) Michelot, D.; Lorne, R.; Huynh, C.; Julia, S. *Bull. Soc. Chim. Fr.* **1976**, 1482−1488.

triisopropyl phosphite (7.5 mL, 30 mmol) was added. The solution was heated at reflux for 79 h. The solution was cooled to 25 °C, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed over silica gel (EtOAc) to give a pale yellow oil that was further purified by Kugelrohr distilation (0.1 mmHg, 165 °C) to yield phosphonate **9** as a colorless oil (5.89 g, 63%): R_f = 0.28 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (m, 1H), 6.89 (m, 2H), 4.66 (d,sept J = 6.2, 1.5 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.11 (d, J = 21.2 Hz, 2H), 1.34 (d, J = 6.2 Hz, 6H), 1.24 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.9, 124.3 (d, 9.0 Hz), 122.0 (d, 7.8 Hz), 113.1 (5.8 Hz), 111.1, 70.4 (d, 6.9 Hz), 55.9, 55.8, 34.2 (d, 139.8 Hz), 24.1 (d, 3.5 Hz), 23.9 (d, 5.0 Hz); IR (thin film) 1595, 1514, 1243, 1105, 995, cm^{-1}; MS (FAB) 317, 289, 233, 154; HRMS (FAB) m/z calcd for $C_{15}H_{25}O_5P$ 316.1440, found 316.1430. Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97. Found: C, 56.84; H, 8.17.

***trans*-Styrene 10.** To a cooled (0 °C) solution of phosphonate **9** (1.57 g, 4.96 mmol) in THF (16.5 mL) was added potassium *tert*-butoxide (557 mg, 4.96 mmol). After 1 h at 0 °C, the solution of phosphonate anion was cooled to −78 °C, and a solution of aldehyde **5** (235 mg, 1.41 mmol) in THF (6.0 mL) was added. After 1 h at −78 °C, the reaction mixture was warmed to rt, stirred for 2 h, and quenched with aq NH_4Cl. The biphasic mixture was extracted with ether, washed with saturated aq NaCl, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil which was chromatographed over silica gel (4% EtOAc in hexanes) to give *trans*-styrene **10** as a colorless oil (336 mg, 79%): R_f = 0.19 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, D_3CN) δ 7.00 (d, J = 1.9 Hz, 1H), 6.90 (dd, J = 8.2, 1.9 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.28 (d, J = 16.3 Hz, 1H), 6.17 (d, J = 16.3 Hz, 1H), 5.94 (dd, J = 17.1, 11.1 Hz, 1H), 5.13 (m, 1H), 5.03 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 1.97 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.50 (m, 2H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, D_3CN) δ 150.3, 149.7, 147.2, 136.8, 132.1, 132.0, 127.8, 125.8, 120.0, 112.8, 112.3, 110.1, 56.4, 56.3, 43.4, 42.1, 25.8, 24.1, 23.6, 17.7; IR (thin film) 2967, 1600, 1510, 1029, 910, 795 cm^{-1}; MS (EI) 300, 285, 257, 217; HRMS (EI) m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2091. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.05; H, 9.56.

Alkylsilane 12. To a cooled (−45 °C) mixture of lithium (13 mg, 1.9 mmol) in THF (4.4 mL) was added 1-(dimethylamino)naphthalene (0.28 mL, 1.7 mmol). The reaction mixture was maintained at −45 °C for 3.5 h and then cooled to −78 °C. A solution of α-silyl thioether **4b** (0.23 g, 0.68 mmol) in THF (4.4 mL) was then added. After 5 min at −78 °C, the solution of alkyllithium was quenched with saturated aq NH_4-Cl and warmed to 25 °C. The reaction mixture was poured into ether and washed with aq KOH (1.0 M), aq HCl (1.0 M), aq saturtaed $NaHCO_3$, and aq saturated NaCl. The solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed over silica gel (hexanes) to give alkylsilane **12** (0.14 g, 92%). When the alkyllithium was quenched with CD_3OD, after 25 min, the reduced product **12** was isolated in 94% yield as a 76:24 mixture of deuterated and protonated product: R_f = 0.55 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (dd, J = 17.5, 10.8 Hz, 1H), 5.07 (m, 1H), 4.91 (dd, J = 10.8, 1.5 Hz, 1H), 4.88 (dd, J = 17.5, 1.5 Hz, 1H), 1.86 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.32 (m, 2H), 1.04 (s, 3H), 0.75 (s, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 130.9, 125.0, 110.2, 44.4, 39.4, 30.7, 25.7, 25.4, 23.3, 17.6, 0.9; IR (thin film) 3072, 2957, 1633, 1410, 1252, 1000, 838 cm^{-1}; MS (EI) 224, 209; HRMS (EI) m/z calcd for $C_{14}H_{28}Si$ 224.1960, found 224.1963.

***trans*-styrene 16.** To a cooled (−45 °C) mixture of lithium wire (71 mg, 10 mmol, about 1 cm) in THF (6.0 mL) was added 1-(dimethylamino)naphthalene (0.40 mL, 2.4 mmol). The reaction mixture was maintained at −45 °C for 3.5 h and then transferred to a cooled (−78 °C) flask under argon using a chilled cannula. A solution of α-silyl thioether **4b** (210 mg, 0.62 mmol) in THF (4.0 mL) was then added followed immediately by a solution of 3,4-dibenzyloxybenzaldehyde (0.40 g, 1.3 mmol) in THF (4.0 mL). Potassium acetate (0.50 g, 5.1 mmol) was added along with potassium hydride (0.30 mL, 30 wt % dispersion in mineral oil, approximately 2.2 mmol). The solution was maintained at −78 °C for 3 h.

Acetic acid (15 mL) was added, and the frozen mixture was then warmed to 60 °C to induce anti elimination of the remaining β-silyl alcohol. The solution was maintained at 60 °C for 8 h and then cooled to 25 °C. The solution was diluted with H_2O, and excess acetic acid was neutralized with $NaHCO_3$. The aqueous solution was extracted with ether, and the ether layer was then washed with 1.0 M aq KOH, 1.0 M aq HCl, saturated aq $NaHCO_3$, and saturated aq NaCl and dried over $MgSO_4$. The mixture was then filtered and concentrated in vacuo to give a yellow oil. The oil was chromatograhped with silica gel (3% EtOAc in hexanes) to give *trans*-styrene **16** as a colorless oil (186 mg, 68%): R_f = 0.35 (10:90 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.4 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.32 (m, 6H), 7.00 (s, 1H), 6.87 (s, 2H), 6.20 (d, J = 16.2 Hz, 1H), 6.01 (d, J = 16.2 Hz, 1H), 5.86 (dd, J = 17.5, 10.7 Hz, 1H), 5.16 (s, 2H), 5.14 (s, 2H), 5.10 (t, J = 7.1 Hz, 1H), 5.03 (dd, J = 10.7, 1.3 Hz, 1H), 5.00 (dd, J = 17.5, 1.3 Hz, 1H), 1.94 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.48 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 148.3, 145.9, 137.4, 137.4, 136.4, 131.9, 131.3, 128.5, 128.4, 127.8, 127.7, 127.4, 127.3, 126.7, 124.8, 119.7, 115.3, 112.9, 111.9, 71.5, 71.5, 42.5, 41.3, 25.7, 23.4, 23.2, 17.6; IR (thin film) 3024, 2967, 2909, 2861, 1600, 1576, 1505, 1452, 1424, 1129, 1014, 967, 905, 795, 729 cm^{-1}; MS (EI) 452, 361, 281, 207, 177, 91; HRMS (EI) m/z calcd for $C_{32}H_{36}O_2$ 452.2715, found 452.2718.

3-Hydroxybakuchiol 1. To a solution of bis-benzyl ether **16** (53 mg, 0.12 mmol) and dimethylaniline (0.10 mL, 0.78 mmol) in CH_2Cl_2 (0.6 mL) was added $AlCl_3$ (89 mg, 0.67 mmol). An exothermic reaction ensued, and the reaction mixture turned dark red. After 30 min, the reaction mixture was poured into aq HCl (1.0 M) and saturated with sodium potassium tartrate. The mixture was extracted with EtOAc, washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over $MgSO_4$, and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed with silica gel (40% ether in pentane) to give 3-hydroxybakuchiol **1** as a colorless oil (27 mg, 75%). As previously described,[6] pure 3-hydroxybakuchiol was unstable, either neat or as a solution in $CDCl_3$ or DMSO, with complete decompositon occurring within 24 h. 3-Hydroxybakuchiol was stable when frozen in DMSO: R_f = 0.22 (40:60 ether/pentane); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 2H), 6.79 (s, 1H), 6.65 (m, 2H), 6.11 (d, J = 16.3 Hz, 1H), 5.95 (d, J = 16.3 Hz, 1H), 5.88 (dd, J = 17.5, 10.7 Hz, 1H), 5.10 (t, J = 7.1 Hz, 1H), 5.01 (d, J = 10.7 Hz, 1H), 4.98 (d, J = 17.5 Hz, 1H), 1.89 (m, 2H), 1.63 (s, 3H), 1.53 (s, 3H), 1.43 (m, 2H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.9, 145.3, 144.8, 133.9, 130.5, 128.9, 126.8, 124.7, 117.7, 115.6, 112.8, 111.8, 42.0, 30.4, 25.5, 23.0, 22.8, 17.5; IR (thin film) 3273, 2967, 2919, 1600, 1514, 1024, 995, 971, 900, 819, 800 cm^{-1}; MS (EI) 272, 257, 189; HRMS (EI) m/z calcd for $C_{18}H_{24}O_2$ 272.1776, found 272.1778.

***trans*-Styrene 19.** To a cooled (−45 °C) mixture of lithium (38 mg, 5.4 mmol) in THF (4.5 mL) was added 1-(dimethylamino)naphthalene (0.30 mL, 1.8 mmol). The reaction mixture was maintained at −45 °C for 3.5 h and then transferred to a cooled (−78 °C) flask under argon with a chilled cannula. A solution of α-silyl thioether **18** (160 mg, 0.60 mmol) in THF (2.0 mL) was added followed immediately by a solution of 4-benzyloxybenzaldehyde (260 mg, 1.2 mmol) in THF (2.0 mL). Potassium acetate (0.50 g, 5.1 mmol) was added along with potassium hydride (0.30 mL, 30 wt % dispersion in mineral oil, approximately 2.2 mmol). The reaction mixture was maintained at −78 °C for 3 h.

Acetic acid (20 mL) was added, and the frozen mixture was warmed to 60 °C to induce anti elimination of the remaining β-silyl alcohol. The reaction mixture was maintained at 60 °C for 10 h and then cooled to 25 °C. The reaction mixture was

diluted with H_2O, and excess acetic acid was neutralized with $NaHCO_3$. The aqueous solution was extracted with ether, and the ether layer was then washed with 1.0 M aq KOH, 1.0 M aq HCl, saturated aq $NaHCO_3$, and saturated aq NaCl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a yellow solid. The solid was chromatographed on silica gel (2% ether in pentane) to give *trans*-styrene **19** as a white solid (114 mg, 68%): mp 58−60 °C (CH_2Cl_2); R_f = 0.31 (2:98 ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.4 Hz, 2H), 7.37 (dd, J = 7.4, 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.26 (d, J = 16.2 Hz, 1H), 6.07 (d, J = 16.2 Hz, 1H), 5.89 (dd, J = 17.4, 10.6 Hz, 1H), 5.06 (s, 2H), 5.01 (dd, J = 17.4, 1.2 Hz, 1H), 4.97 (dd, J = 10.6, 1.2 Hz, 1H), 1.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 147.1, 137.1, 137.0, 130.9, 128.6, 127.9, 127.4, 127.2, 125.6, 114.9, 110.8, 70.1, 39.3, 27.1; IR (KBr) 2957, 1600, 1510, 1171, 1010, 967, 905, 824, 805; MS (EI) 278, 263, 187; HRMS (EI) *m*/z calcd for $C_{20}H_{22}O$ 278.1671, found 278.1672. Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.22; H, 8.21.

"Corylifolin" 2. To a solution of benzyl ether **19** (46 mg, 0.17 mmol) and dimethylaniline (0.090 mL, 0.71 mmol) in CH_2Cl_2 was added $AlCl_3$ (71 mg, 0.53 mmol). An exothermic reaction ensued, and the reaction mixture turned dark red. After 1 h, the solution was poured into an aqueous solution of HCl (1.0 M) and saturated with sodium potassium tartrate. The mixture was extracted with EtOAc, washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over $MgSO_4$, and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on silica gel (15% EtOAc in hexane) to give *trans*-styrene **2** as a white solid (28 mg, 90%): mp 68−74 °C (CH_2Cl_2); R_f = 0.22 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.27 (s, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.28 (d, J = 16.5 Hz, 1H), 6.09 (d, J = 16.5 Hz, 1H), 5.92 (dd, J = 17.5, 10.5 Hz, 1H), 5.01 (d, J = 17.5 Hz, 1H), 4.95 (d, J = 10.5 Hz, 1H), 1.19 (s, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.6, 148.1, 136.4, 130.3, 128.1, 126.9, 116.2, 110.0, 39.9, 27.4; IR (KBr) 2947, 1605, 1590, 1095, 995, 971, 805, 676 cm^{-1}; MS (CI, NH_4^+) 206, 189, 173; HRMS (EI) *m*/z calcd for $C_{13}H_{16}O$ 188.1201, found 188.1202. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.91; H, 8.84.

Acknowledgment. This research was generously supported by the National Science Foundation CHE-9623903. D.L.V.V. is a Research Fellow of the Alfred P. Sloan Foundation. J.B.P. is a recipient of a 2001 Glaxo-Wellcome Graduate Fellowship in Synthetic Organic Chemistry. N.F.M. was supported by an Allergan Summer Research Fellowship.

Supporting Information Available: NMR spectra ^{1}H and ^{13}C for compounds **1**, **2**, **6**, **12**, **16**, and **19** are included. This information is available free of charge via the Internet at http://pubs.acs.org.

JO0259459