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ENTRIES INTO PROSTANOID MODELS VIA THE HYDROBORATION OF ENOL SILYL ETHERS

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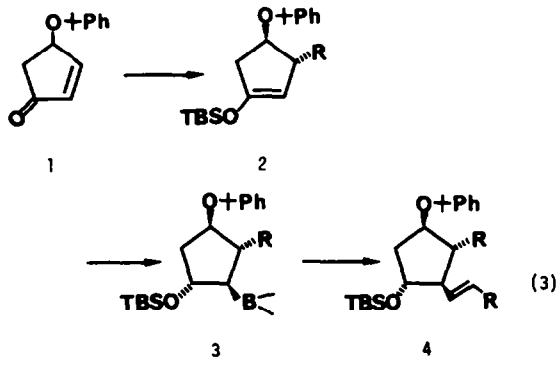
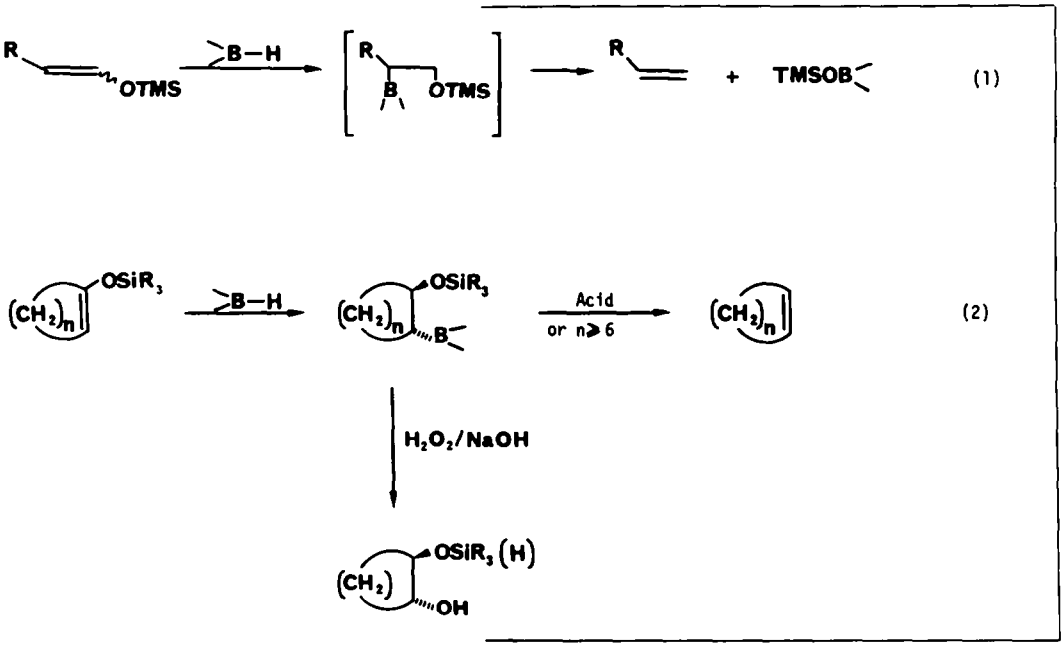
Abstract—The hydroboration of enol silyl ether (2), readily available from Stork's enone (1) with thexylborane gives the highly functionalized mixed organoborane (3). The remaining B–H bond of 3 can be used to hydroborate a terminal acetylene or a 1-bromoacetylene to give vinylboranes, which can then be utilized to introduce a *trans* vinyl group at C-12 of a prostanoid system in moderate yield. Although the yields are modest, the fact that 2 can be converted to the diprotected prostanoid system (see 19 or 21) in a one flask operation from readily available terminal acetylenes or 1-bromoacetylenes makes the methodology more attractive. In one attempt to use organoborane chemistry to introduce the *cis*-5-hepten-6-yl sidechain of the PGE_2 and related series 2 was converted to the exomethylene system 27 which was converted to 28 in 30% yield again in a single flask operation.

The hydroboration of enol silyl ethers has been shown to occur in a regio and stereoselective manner placing the B atom on the β C and, as expected for cyclic systems, *trans* to the silyloxy group[2] (eqn 1). The resulting β-silyloxy organoboranes from the acyclic enol silyl ethers are unstable, undergoing a facile elimination.[3] On the other hand, the *trans*-β-silyloxy organoboranes from the enol silyl ethers of cyclic ketones (eqn 2), though unstable to acid[4] are stable to basic or neutral conditions and at least to refluxing THF temperatures, and as such are potentially useful synthetic intermediates.[5] This is not true, however, if the ring size is greater than eight carbons where elimination does occur upon hydroboration.[6]



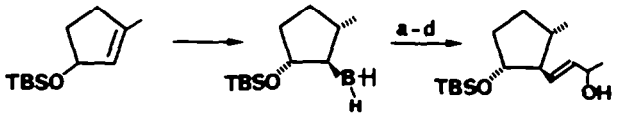


We were intrigued by the possibility of employing the high regio and stereoselectivity of the hydroboration of cyclic enol silyl ethers in the preparation of prostanoids. We report herein on the results of the conversion of Stork's enone (1) to the diprotected prostanoid model system (4) in moderate yield in a two step process involving readily available starting materials.

Two reports on the use of organoboranes in the synthesis of prostanoid model systems have appeared[7,8] both of which indicated that the reactions were quite susceptible to the reaction conditions and substrates used. In the first of these reports Corey and Ravindranathan[6] were able to show that the β-silyloxy organoborane (6), obtained via hydroboration of protec-

ted allyl alcohol (5), could be converted to the prostanoid *model* system (7). The enlightening facts were the high stereoselectivity in the ring for the diastereomer shown, the fact that the β-(t-butyldimethylsilyloxy) organoborane was stable to the reaction conditions, the high stereoselectivity for the *trans* double bond, and the fact that the protected 1-bromo propargyl alcohol could be used in the reaction.

Since several elegant syntheses of prostaglandins have appeared[9] we limited our study to routes that (1) would not suffer from loss of one of the cyclopentyl units; (2) would use readily available acetylenes or 1-bromoacetylenes as the eventual sidechains and (3) would be, at least in principle, amenable to a chiral synthesis. Based on both the Corey and Evans studies, which showed that the protected propargyl alcohols (14 and 15)

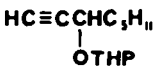


5 6 7 (4)

a. $BrC{\equiv}CCHC_5H_{11}$ b. NaOMe c. $Ag(NH_3)_2NO_3$ d. NaOAc/HOAc

The second study by Evans *et al.*[8] used 1-ethylcyclopentene (8) as starting material and organoboranes 9, 10 and 11 as intermediates as outlined in Scheme 1. Only the yields of the various conversions along with these respective units used to compose the C-12 side chain are given, the reader is referred to the original articles for the details on this thorough study. The conversion of 9 to 12 occurred in good yield although it suffers from the loss of one of the cyclopentene units (8). On the other hand, the organoborane (10) though readily available was converted to the unnatural *cis* isomer 12 in only moderate yield with complications from thexyl group migration. The best approach turned out to be the reaction of the dimethylboronate (11) with either the appropriate *Z* or *E* vinyllithium reagent shown which leads to 12 or 13 in good yield, but does require the preparation of the dimethylboronate and the use of a stereoselectivity generated vinyllithium reagent.

could be used in an organoborane approach to prostanoids we simplified our study somewhat by using the simple units, 1-hexyne, 1-bromohexyne and 1-bromopentyne as sidechain precursors.



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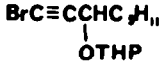

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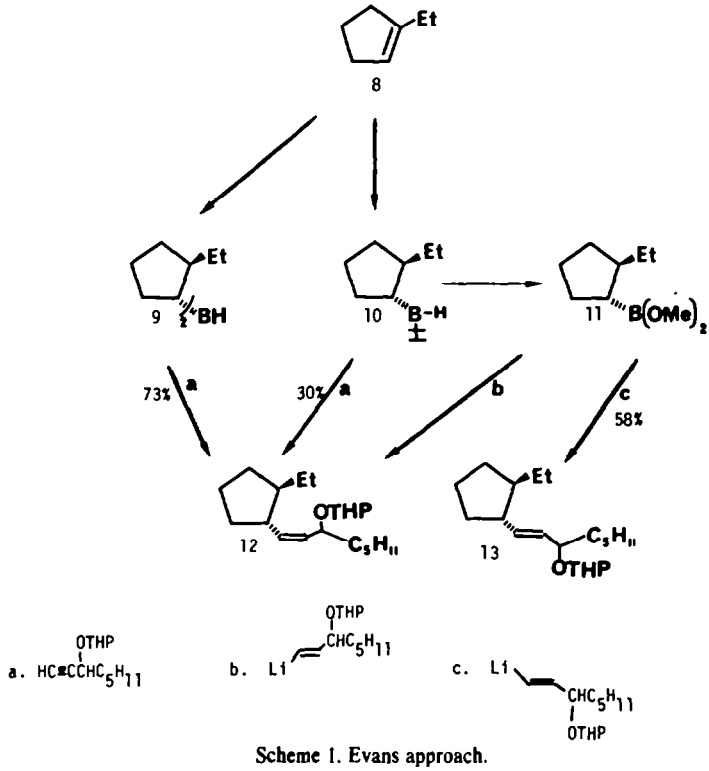
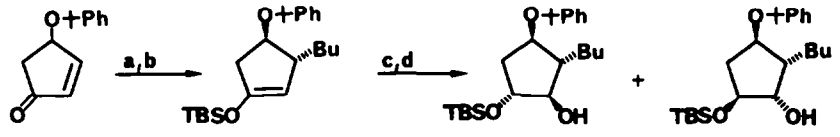
Thus hydroboration of 2 to 3 and the conversion of 3 to prostanoid model systems would (1) establish the viability of the hydroboration of enol silyl ethers as a potential route to these systems, (2) would give information about the effect, if any, of the cumyloxy group at C-9 (prostaglandin numbering) on the stereochemistry of the hydroboration (3) would lead to prostanoids of the correct stereochemistry and finally would have the



Scheme 1. Evans approach.

potential for a chiral synthesis via the use of a chiral hydroborating agent.[10]

We then turned our attention to the 1-bromoacetylene approach to the introduction of the vinyl C-12 sidechain.



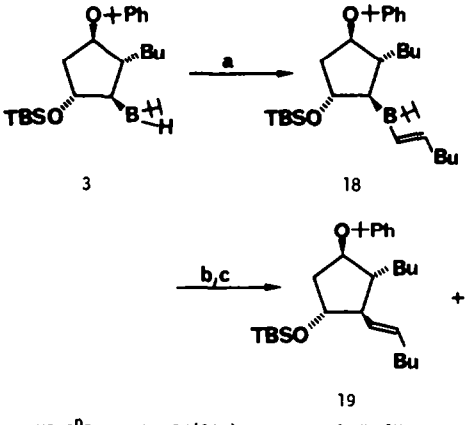
(5)

1 2 16 17

a. $^{n}Bu_2CuLi/Et_2O$ b. TBSCl/HMPA c. $H-BH_2$ d. $H_2O_2/NaOH$

Stork's enone **1**[11] was readily converted to the enol silyl ether **2** in 54% yield. The hydroboration of **2** with one molar equivalent of borane in THF followed by oxidation gave a 2:1 mixture of **16** and **17** in 87% yield. The use of thexylborane[12] gave complete stereoselectivity yielding **16** in 72% yield. Thus the desired intermediate organoborane **3** forms in good yield.

Our first approach to the introduction of the vinyl unit was to react **3** with 1-hexyne to give the mixed organoborane **18** which was treated with iodine in a solution of methanolic sodium methoxide.[8,18] This gave less than 5% of the desired product by NMR analysis and a number of by-products some of which were the result of apparent oxidation of the protected hydroxyls. On the other hand, treatment of **18** with Pd(II) acetate, based on a procedure



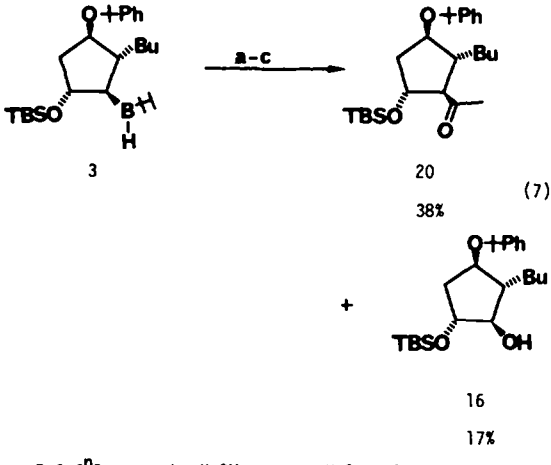
3 18 19 15

(6)

a. $HC{\equiv}C^{n}Bu$ b. $Pd(OAc)_2$ c. $H_2O_2/NaOH$

of Yamamoto *et al.*,[14] followed by oxidation gave the diprotected prostanoid **19** in 37% yield along with 24% of **16**. Although the yield is moderate the sequence is a short one and it does establish the correct relative stereochemistry in a single step. Unfortunately, none of several variations on this reaction, improved on the 37% yield. It is worthy to note, however, that no evidence was found for migration of the thexyl group in this Pd(II) reaction. The structure of **18** was assumed based on the preferred attack of the thexylborane on the side opposite that of the adjacent Bu group as seen in the Corey study[7] and consistent with Brown's hydroboration of 3-methylcyclopentene.[15] The *trans* geometry of the double bond was supported by an IR absorbance at 970 cm^{-1}. The ^{13}C-NMR spectrum was consistent with a single diastereomer although the two diastereotopic Me's of the cumyloxy group appeared at 28.3 and 28.1 ppm.

This method of converting organoboranes to *trans* olefins was first reported by Zweifel *et al.*[16] and employed by Corey.[7] Treatment of **3** sequentially with 1-bromohexyne, sodium methoxide, and alkaline hydrogen peroxide gave the ketone **20** in 38% yield together with 17% of **16**.



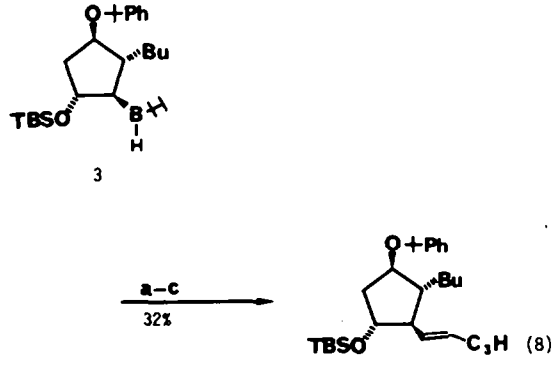
3 20 16

38% 17%

(7)

a. $BrC{\equiv}C^{n}Bu$ b. NaOMe c. $H_2O_2/NaOH$

Attempte protodeboronation of the presumed vinylborane with isobutyric acid gave none of the desired **19**. However, treatment of **3** sequentially with 1-bromopentyne, sodium methoxide and silver ammonium nitrate[7] gave **21** in 32% yield.



3 21

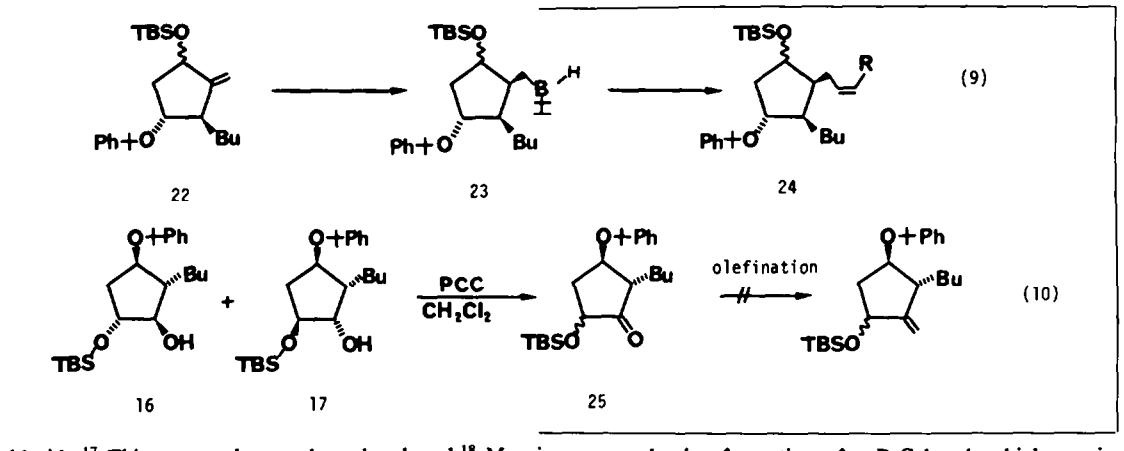
(8)

a. $BrC{\equiv}CC_3H_7$ b. NaOMe c. $Ag(NH_3)_2NO_3$

At this point our attention turned to the possibility of a borane approach to the introduction of the C-8 sidechain of PGE_2 analogs. For this we required the exomethylenecyclopentane **4** which could be hydroborated and the organo-borane converted to the prostanoid model system **24**. Clearly in this system the relative stereochemistry is not the natural one so that this would have to be attended to after deprotection–oxidation at C-9 and epimerization at C-8. Our concern, however, was the preparation of **22** and its conversion to **24**. Our first attempt to prepare **22** involved hydroboration–oxidation of **2** to a mixture of **16** and **17** (eqn 4) further oxidation of **16** and **17** to ketone **25** and finally olefination of **25**. We were unable to convert **25** to **22** using the Wittig reagent or the Peterson reagent, trimethylsilylmethylmagnesium chloride.[17] This approach was thus abandoned.[18] Murai *et al.*[19] had reported the direct conversion of trimethylsilyl enol ethers to the trimethylsilyl ethers of 1-methylenecycloalkanols via their treatment with Simmons-Smith reagent. Happily this worked equally well on enol silyl ether **2** (R = "Bu) to give **27**. With the exomethylene group as desired, but unfortunately with premature loss of the cumyloxy protecting group. The stereochemistry noted in **27** is based on cyclopropanation of the double bond from the α-face followed by hydride shift from C-8 to C-9 (prostaglandin numbering) from the β-face. This now creates two problems, those being the relative stereochemistry of the O functions at C-9 and C-11 and a lack of specificity of the hydroboration of **26**. Both of these problems are rather inconsequential if one converts the silyloxy group at C-9 to a CO, which will at the same time allow epimerization at C-8.[17]

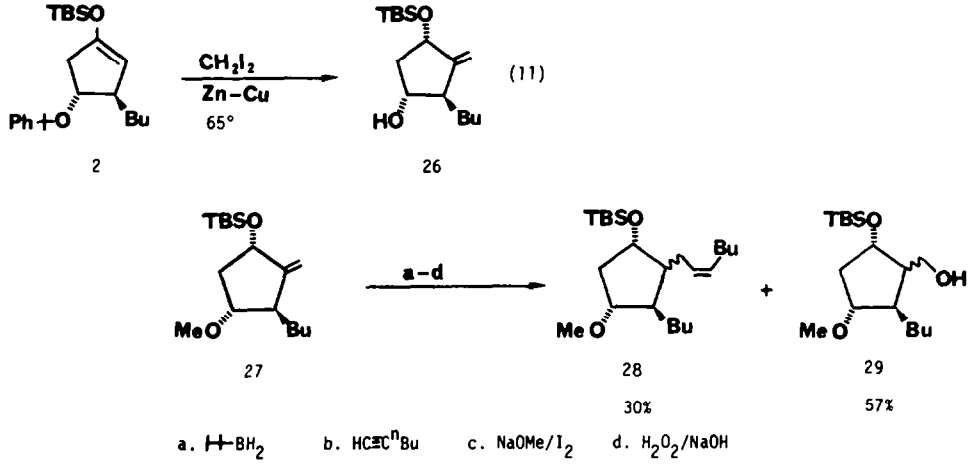
The alcohol **26** was methylated to give **27** and this subjected to hydroboration with thexylborane followed by treatment of the intermediate organoborane with 1-hexyne, sodium methoxide and alkaline hydrogen peroxide to give a 30% yield of **28** as a mixture of diastereomers and a 57% yield of the alcohols **29**. Although this conversion (**27** → **28**) is easily carried out and gives the double bond stereoselectively, the moderate yield coupled with the difficulty in obtaining the exomethylene system along with a low stereoselectivity in the hydroboration step does not make it a very attractive entry into the PGE_2 series.

In conclusion, it has been shown that the hydroboration of the enol silyl ethers of highly substituted cyclopentanones can lead to the highly regio and stereoselective formation of a B-C bond, which can in turn be employed for the formation of C–C bond in a single flask operation. This allows the regio and stereoselective introduction of the C-12 sidechain in prostaglandins wherein the sidechain precursor is a simple terminal acetylene or its 1-bromo analog. In addition the hydroboration of exomethylenecyclopentanes (*cf* **28**) permits the introduction of this *cis* olefinic C-8 sidechain of prostaglandins, such as PGE_2.



EXPERIMENTAL

General methods. Reactions were carried out in a flame-dried, standard apparatus consisting of reflux condenser, N_2 inlet and no-air stopper under an atmosphere of N_2. IR spectra were recorded on Perkin–Elmer 283 spectrophotometer, mass spectra on a Hewlett-Packard 5995 GC-MS at 70 eV, ^{1}H-NMR spectra on a Jeol FX-90Q spectrometer. Flash chromatography was done according to Still *et al.*[20] Solvents were distilled from calcium



hydride or sodium benzophenone prior to use. Reagents were obtained from the normal sources and purified when necessary.

Preparation of trans-1-(*t-butyldimethylsilyloxy*)-3-*n-butyl*-4-*cumyloxy*-1-*cyclopentene* (**2**). Following the procedure of Johnson and Dutra,[21] lithium di-n-butylcuprate was prepared from 5.7 g (30 mmol) CuI, 60.6 mmol n-BuLi (33.5 mL of 1.81 M hexane soln) in 40 mL ether at −30°. This soln was cooled to −78° and treated with 6.3 g (30 mmol) 4-cumyloxy-2-cyclopentenone[22] in 15 mL ether. After 15 min the mixture was diluted with THF (60 mL) and Et_3N (5 mL) added followed by the addition of 4.5 g (30 mmol) t-butyldimethylchlorosilane in 35 mL THF:HMPA (4:1). The reaction was stirred at r.t. overnight and poured onto a mixture of hexane (300 mL) and H_2O (200 mL). The organic layer was separated, dried ($MgSO_4$), concentrated at reduced pressure, dissolved in 50 mL dimethylsulfoxide and the enol silyl ether recovered by extraction with hexane (4 × 50 mL). The organic extracts were washed with 10% $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and concentrated at reduced pressure. The crude material was distilled to give 6.3 g (54%) of **2** b.p. 157–158°/0.25; n_D^{25} 1.4894; IR (neat) 1645 cm^{-1}; ^{1}H-NMR (CCl_4) 7.15 (m, 5H), 4.35 (m, 1H), 3.37 (m, 1H) 2.73–2.00 (m, 3H), 1.46 (d, 6H), 1.38–0.57 (m, 18H) and 0.13 (s, 6H); ^{13}C-NMR ($CDCl_3$) 151.5, 146.8, 104.0, 76.7, 76.5, 50.3, 43.1, 33.7, 29.9, 29.4, 27.9, 25.6, 22.8, 18.1, 14.0, −4.6, −4.7. MS 388 (0.5), 270(9), 269(44), 213(7), 155(4), 121(6), 120(7), 119(71), 111(100), 91(75), 84(6), 75(16), 73(33), 55(12), 43(14), 18(39). (Found: C, 74.38; H, 10.46. Calc.: C, 74.15; H, 10.38).

Preparation of 2-*n-butyl*-5-(*t-butyldimethylsilyloxy*)-3-*cumyloxy*-1-*cyclopentanol* (**16**). Thexylborane was prepared from 4.5 mL (5 mmol) 1.1 M borane·THF soln and 0.6 g (5 mmol) 2,3-dimethyl-2-butene at 0° over 15 min. The addition of 1.9 g (5 mmol) of **2** followed by stirring at 0° for 0.5 hr oxidation with 4 mL 3 N NaOH and 4 mL 30% H_2O_2 and work-up gave the crude material which was purified by column chromatography on silica gel (petroleum ether–benzene 1:1) to give 1.5 g (72%) of **16** as a single isomer. n_D^{25} 1.4888; IR (neat) 3431 cm^{-1}; ^{1}H-NMR (CCl_4) 7.14 (m, 5H), 3.88–3.5 (m, 3H), 2.38–1.68 (m, 2H), 1.48 (s, 6H), 1.41–0.61 (m, 19H), and 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$) 147.0, 127.8, 126.8, 126.2, 78.4, 77.4, 76.1, 76.3, 48.5, 42.7, 30.5, 29.3, 28.3, 25.9, 23.0, 18.1, 13.9, and −4.6; MS 213(20), 187(10), 139(4), 131(8), 129(6), 120(12), 119(100), 103(5), 97(6), 91(14), 79(5), 77(6), 75(29), 73(15), 69(5), 58(10), 57(7), 55(9), 43(33), 41(13), 39(5), 29(5), 18(33), 17(9).

Preparation of **19** *from* **2**—*Palladium acetate approach.* Compound **2** was hydroborated with thexylborane as above on a 3 mmol scale. This was followed by the addition of 0.25 g (3 mmol) 1-hexyne and the reaction stirred for 1 hr at r.t. In a separate flask was prepared a mixture of Pd(II) acetate (0.67 g; 3 mmol), Et_3N (0.33 g; 3 mmol)in 20 mL THF. The organoborane soln was transferred via syringe to the second flask and this allowed to stir overnight at r.t. The solvent was removed at reduced pressure and 20 mL hexane and a small amount of alumina added to remove the Pd formed. This was then filtered through celite 503, evaporated and the crude product oxidized by the addition of 2 mL 3 N NaOH and 2 mL 30% H_2O_2. Work-up and evaporation of the solvent gave the crude product which was purified by flash chromatography eluting with 2% EtOAc–hexane to give 0.50 g (36.7%) of **19**. ^{1}H-NMR (CCl_4) 7.55 (m, 5H), 6.00–4.93 (m, 2H), 4.10–3.20 (m, 2H), 2.87–0.67 (m, 37H) and 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$) 147.4, 127.8, 132.4, 128.6, 126.7, 126.2, 76.8, 76.3, 52.6, 48.1, 44.0, 32.4, 30.8, 30.3, 29.5, 28.3, 28.1, 25.9, 23.0, 21.1, 18.1, 13.9, 13.8 and −4.6. Also was eluted 0.30 g (24%) of **16**.

Preparation of **21** *from* **2**. Compound **2** was hydroborated as above on a 5 mmol scale with thexyl–borane after which 0.7 g (5 mmol) 1-bromopentyne was added and stirring continued at 0° for 2 hr after which time 5 mL of 1 M NaOMe in MeOH was added to effect the migration. This soln was stirred at 0° for 5 min and 3 hr at r.t. The mixture was then oxidized by the addition of 5 mL 3 N NaOAc and 5 mL 30% H_2O_2 at r.t. for 1 hr. The mixture was then saturated with NaCl, extracted with ether (3 × 15 mL) and dried ($MgSO_4$). Solvent evaporation gave 2.2 g of crude material which was chromatographed over 25 g silica gel with petroleum ether to give 0.9 g (38%) of **21**, n_D^{25} 1.4743 IR (neat) 1708; ^{1}H-NMR (CCl_4) 7.18 (m, 5H), 3.70–2.88 (m, 2H), 2.68–0.43 (m, 36H), and 0.08 (s, 6H); MS 417(9), 300(5), 299(23), 281(6), 223(9), 187(5), 169(6), 129(4), 120(23), 119(100), 101(5), 91(24), 85(13), 75(16), 73(12), 57(11), 43(7), 41(11). In addition 0.9 g (47.6%) of **16** was obtained eluting with benzene–ether (2:1).

Preparation of **26** *from* **2**. A soln of 1.16 g (9 mmol) Zn–Cu couple, 1.61 g (6 mmol) CH_2I_2 and 1.16 g (6 mmol) CH_2I_2 and 1.16 g (3 mmol) of **9** in 3 mL ether was heated to reflux for 48 hr, diluted with ether (10 mL), filtered through celite and washed with 1.5 M HCl, 10% $NaHCO_3$ and H_2O, dried (Na_2SO_4) and the crude purified by flash chromatography with 7% EtOAc–hexane yielding 0.56 g (65%) of **26** as a single isomer. IR (neat) 3370 and 3075 cm^{-1}; ^{1}H-NMR (CCl_4) 5.16 (m, 1H), 5.00 (m, 1H), 4.47 (t, 1H, J = 5.1 Hz), 3.89 (m, 1H), 3.68 variable on dilution (m, 1H, OH), 2.52 (m, 1H), 2.25–1.56 (m, 2H), 1.38 (m, 6H), 0.90 (s, 12H) and 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$) 156.6, 109.2, 76.7, 75.6, 51.6, 42.8, 33.4, 29.5, 25.8, 22.9, 18.1, 14.0, −4.6, −4.7; MS 227(18), 209(12), 127(5), 107(5), 95(8), 93(23), 91(7), 79(11), 77(11), 76(8), 75(100), 73(20), 59(7), 57(14), 56(22), 55(10), 47(10). (Found: C, 67.32; H, 11.36. Calc.: C, 67.54; H, 11.34).

Preparation of **27** *from* **26**. Following the procedure of Johnstone and Malcolm[23] 0.94 g (13 mmol) powdered KOH was dissolved in 3 mL DMSO and this stirred for 5 min after which time 0.9 g (6 mmol) of **26** added followed by the addition of 0.9 g (6 mmol) MeI. The mixture was stirred for 2 hr, diluted with water (20 mL) and extracted with hexane (3 × 20 mL) and dried over Na_2SO_4. The combined organic layers were washed with water (5 × 10 mL) and dried over Na_2SO_4. The solvent was removed at reduced pressure and the crude material chromatographed on florisil with 2% EtOAc–hexane to give 0.32 g (52%) of **27**, n_D^{20} 1.4587; IR (neat) 3080 cm^{-1}; ^{1}H-NMR (CCl_4) 5.10 (m, 1H), 4.90 (m, 1H), 4.82–4.07 (m, 1H), 4.02–3.47 (m, 1H), 3.29 (s, 3H), 2.80–1.10 (m, 13H), 0.90 (s, 9H) and 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$) 155.4, 106.7, 82.8, 72.4, 56.4, 48.0, 40.2, 33.7, 29.1, 25.8, 22.8, 18.2, 14.0, −4.7; MS 241(16), 135(30), 109(5), 107(14), 94(5), 93(42), 91(18), 90(9), 89(100), 81(6), 79(23), 75(12), 76(5), 75(65), 73(49), 59(39), 57(41), 56(10), 55(18), 53(9), 47(10), 45(36), 43(29).

Preparation of **28** *and* **29**. The hydroboration of 0.30 g (1 mmol) of **27** was carried out with 1 mmol thexylborane at 0° for 1 hr. To the resulting mixed organoborane was then added 0.08 g (1 mmol) 1-hexyne and the soln stirred for 1.5 hr at −15° over a 15 min period. Aqueous sodium thiosulfate was added until the excess I_2 color disappeared and the mixture was oxidized by the addition of 0.4 mL 3 N NaOH and 0.4 mL 30% H_2O_2. The reaction was then worked-up in the usual way and the crude material flash chromatographed with 4% EtOAc hexane to give 0.11 g (30%) of the desired **28** as a mixture of two diastereomers. IR (neat) 3065 cm^{-1}, ^{1}H-NMR ($CDCl_3$) 5.44 (m, 2H), 3.40 and 3.26 (two s, 3H, ratio 1:2 for two OCH_3 groups), 0.88 and 0.86 (two s, 9H), 0.10 and 0.07 (two s, 6H) in addition to multiplet at about 2–1. ^{13}C-NMR ($CDCl_3$) 130.5, 130.3, 128.9, 128.4, 85.1, 84.4, 75.6, 74.3, 49.3, 48.0, 45.0, 44.7, 57.7, 56.4, 40.1, 37.5.

7% EtOAc–hexane eluted 0.09 g of the first of the two isomeric alcohols **29**; IR (neat) 3450 cm^{-1}, ^{1}H-NMR ($CDCl_3$) 4.40 (m, 1H), 3.80 (m, 2H), 3.30 (s, 3H), 2.93 (m, 1H), 2.15–1.06 (m, 14H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C-NMR ($CDCl_3$) 85.0, 73.0, 62.7, 56.7, 49.4, 44.5, 39.8, 33.4, 29.6, 25.7, 23.0, 17.9, 13.9, −4.6, −5.2.

9% EtOAc–hexane eluted 0.09 (28%) of the second isomer of **29** IR (neat) 3440 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 4.32–3.38 (m, 4H), 3.27 (s, 3H), 3.14–1.05 (m, 14H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$) 84.5, 75.0, 62.2, 56.3, 50.7, 44.0, 40.6, 30.4, 27.8, 25.8, 22.9, 17.9, 13.9, −4.3, −4.9.

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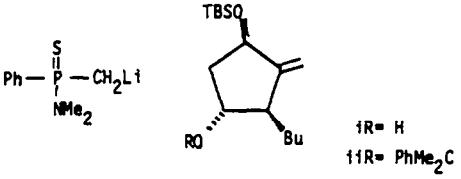

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