Regioselectivity in the Palladium-Catalyzed Addition of Carbon Nucleophiles to Dihydropyran Derivatives

Marc-Raleigh Brescia, Yvonne Class Shimshock, and Philip DeShong*

Department of Chemistry and Biochemistry, The University of Maryland College Park, Maryland 20742

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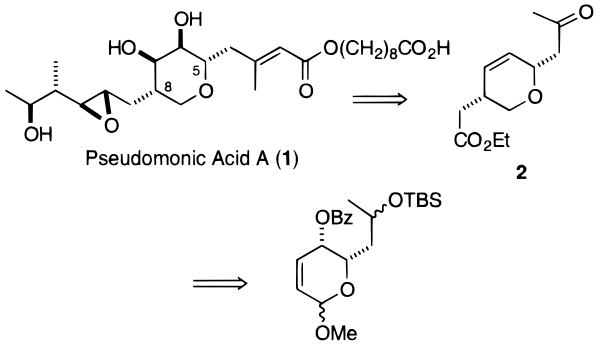
The regioselectivity of Pd-catalyzed malonate or sulfonylacetate addition to dihydropyran derivatives is highly dependent upon the substitution pattern of the dihydropyran nucleus and is governed by electronic, rather than steric factors. In certain instances, subtle steric features also play a role in controlling regioselectivity by altering the conformation of the intermediate η^3-allyl Pd-complex.

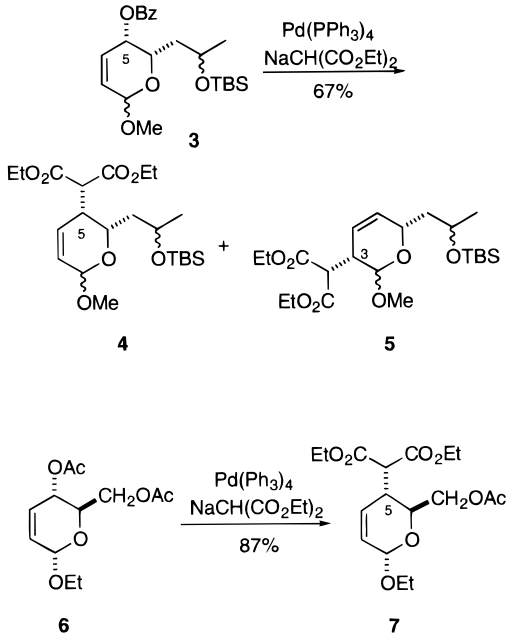
Palladium-catalyzed transformations play a major role in the arsenal of synthetic chemistry.[1,2] Of particular interest is the Pd(0)-catalyzed alkylation of allylic alcohol derivatives by stabilized carbon nucleophiles. This reaction is widely applied in organic synthesis because the alkylation generally proceeds with retention of configuration at the least hindered site of the allylic starting material.[3−5] During the course of our synthesis of pseudomonic acid A[6] (**1**), our strategy was to introduce the C-8 side chain[7] of dihydropyran **2** via Pd-catalyzed alkylation of allylic benzoate **3** as indicated in Scheme 1. In the alkylation, it was anticipated that the nucleophile would be introduced at C-8 (C-3)[7] regioselectively since the alkyl side chain had a larger *A*-value than the corresponding methoxy substituent.[8] However, alkylation did not occur at C-3 of dihydropyran **3**, the least hindered site to produce pyran **5**; rather it occurred regiospecifically at C-5 yielding diester **4** (Scheme 2).

Previous studies of Pd-catalyzed alkylation in carbohydrate derivatives by Baer,[9] Dunkerton,[10] and Curran[11] in addition to other heteroatom-substituted systems[1b] indicated that both steric and electronic factors had a role in controlling the regioselectivity of alkylation of dihydropyran derivatives. For example, Baer and Hanna reported that the sole alkylation adduct of the reaction of pyranoside **6** and diethylmalonate was diester **7**.[9] Baer's results, taken in conjunction with our findings in the pseudomonic acid series, suggested that electronic factors played a more prominent role in influencing the regioselectivity of the Pd-catalyzed alkylations than had been previously recognized. However, the limited number of dihydropyran derivatives studied under these conditions precluded a comprehensive understanding of the relative importance of steric and electronic factors in the regioselectivity of alkylation.[6,9−11] Accordingly, a systematic study of the Pd-catalyzed reaction of dihydropyran derivatives was undertaken to assess the importance of substituents and their relative stereochemistry in the alkylation process. As described below, this study demonstrated that electronic characteristics of substituents is the dominant determinant in control-

Scheme 1



Scheme 2



⊗ Abstract published in *Advance ACS Abstracts,* February, 1; 1997.

(1) (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Permagon Press: New York, 1991; Vol. 4, pp 585−661. (b) For a discussion of the regioselectivity of Pd-catalyzed alkylation in allylic systems with a heteroatom directly attached to the allyl system, see: Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Permagon Press: New York, 1991; Vol. 4, pp 615−635, and references cited therein.

(2) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(3) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615−2649.

(4) Trost, B. M. *Pure Appl. Chem.* **1979**, *51*, 787−800.

(5) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385−393.

(6) Class, Y. J.; DeShong, P. *Tetrahedron Lett.* **1995**, *36*, 7631−7634.

(7) Pseudomonic acid numbering. We shall use pyran numbering throughout the remainder of the manuscript.

(8) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1990; pp 130−139.

(9) Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889−906.

(10) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812−2814.

(11) It was recognized that the relative stereochemistry of the two substituents on dihydropyran **2** would also play a role in controlling the regiochemistry of nucleophilic attack; however, we anticipated that the general features of the addition would not be altered by the relative stereochemistry of the substituents. See also: Curran, D. P.; Suh, Y.-G. *Carbohydrate Res.* **1987**, *171*, 161−191.

S0022-3263(96)01973-1 CCC: $14.00

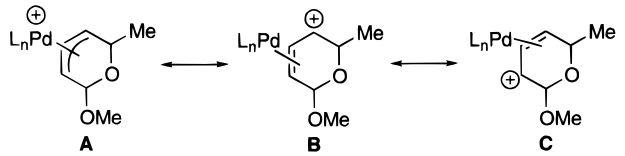
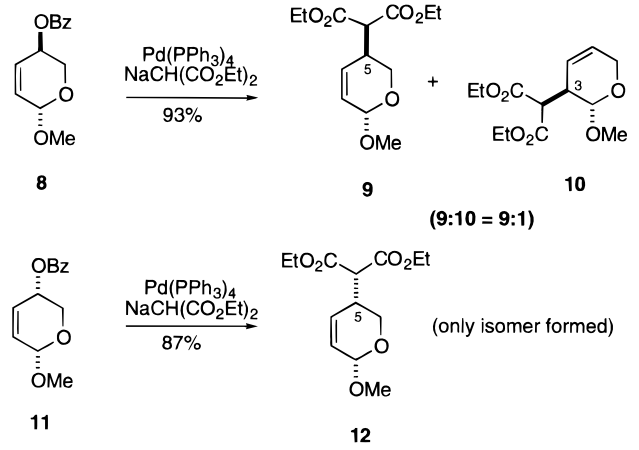
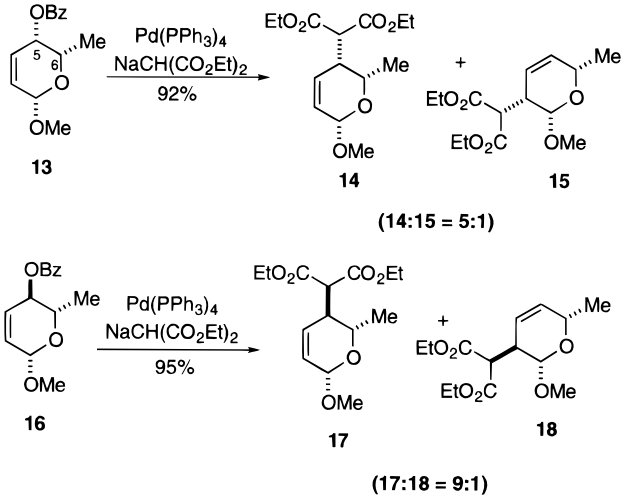


Figure 1.

Scheme 3



Scheme 4



ling the regioselectivity of alkylation in unsymmetrically substituted allylic benzoates such as dihydropyrans **3**, **13**, and **16**, respectively. In the absence of the "anomeric"-like substituent at C-2, however, substituents on the ring also affect the conformation of the π-allyl Pd-complexes and, ultimately, the regioselectivity of alkylations.

Our hypothesis is that alkylation at C-5 in dihydropyrans **3** and **6** is strongly favored due to decreased electrophilicity at C-3. The reasoning for this prediction is that the π-allyl Pd-complex has resonance contributors with cationic character at C-3 and C-5, respectively (**A**−**C**, Figure 1). The presence of two inductively electron-withdrawing oxygens at C-2 decreases the contribution of resonance form **C** to the hybrid and results in increased cationic character at C-5, resonance form **B**.

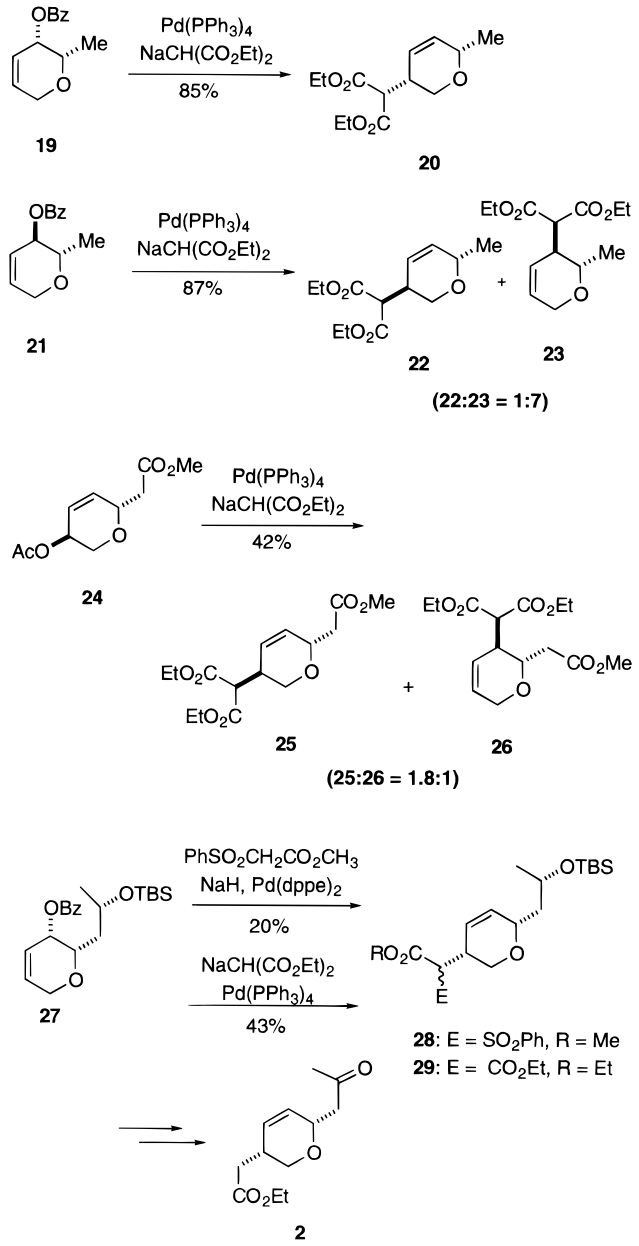
The first set of dihydropyran derivatives studied were diastereomeric benzoates **8** and **11**, respectively. Upon the basis of both steric and electronic considerations, it was anticipated that alkylation would occur at C-5, and this expectation was borne out as summarized in Scheme 3. Irrespective of the relative configuration of the allylic benzoate, the major product arose from alkylation at C-5. Under a standard set of alkylation conditions,[12] *trans*-allylic benzoate **8** gave a 9:1 ratio of diesters **9** and **10**, while *cis*-allylic benzoate **11** gave exclusively diester **12**. The regioselectivity and stereospecificity of each alkylation product was confirmed by homonuclear decoupling experiments. The selectivity is greater with *cis*-allylic benzoate **11** because the incoming diethyl malonate anion must approach the π-allyl Pd intermediate from the same face as the methoxy group at C-2 (vide infra).

In a second series of allylic derivatives, benzoates **13** and **16** were subjected to the alkylation protocol (Scheme 4). These benzoates have a methyl group at C-6 in addition to an anomeric methoxy group at C-2 and were chosen to serve as models for the allylic benzoates employed in the synthesis of pseudomonic acid derivatives (**3** in Scheme 1). Methyl was chosen as the C-6 substituent because its *A*-value is known precisely.[8] Since the *A*-value of the methyl group is more than twice the size of the methoxy group it was anticipated that alkylation should occur regioselectively at C-3 in this series of compounds, assuming that steric factors are more important than electronic factors in controlling the regiochemistry of alkylation. If, on the other hand, electronic factors are more important than steric interactions, one anticipates that C-5 alkylation products would be favored. The experimental results shown in Scheme 4 demonstrate conclusively that C-5 alkylation, the products of electronic control of the regioselectivity, predominated, in analogy with our results in the pseudomonic acid series and Baer and Hanna's findings[9] (Scheme 2). It is particularly noteworthy that the same regioselectivity was observed in the alkylation irrespective of the relative configuration of the two substituents. The slight differences in the regioselectivity of the alkylation of benzoates **13** and **16** of 5:1 vs 9:1, respectively, can be attributed to conformational preferences adopted by the intermediate Pd-complex and will be discussed below.

In the final model system investigated, allylic benzoates **19** and **21** lacking the anomeric methoxy group at C-2 were subjected to alkylation (Scheme 5). On the basis of the hypothesis, it was anticipated that lack of the C-2 methoxy group would remove the electronic bias of the system and favor C-3 alkylation due to steric control of the alkylation. In fact, this was the case with the *cis*-benzoate **19**, which gave diester **20** as the exclusive product of alkylation. However, alkylation of *trans*-benzoate **21** gave a 1:7 ratio of diesters **22** and **23** in which the C-5 regioisomer predominated. Our prediction, as well as the results from other systems,[9−11] was that C-3 alkylation should be the major product of alkylation, even in *trans*-benzoate **21**. For example, Curran observed regioselective C-3 alkylation in the Pd-catalyzed allylic alkylation of *trans*-acetate **24** under similar conditions (Scheme 5).[11] However, in Curran's example, it is unclear whether coordination of the Lewis basic ester moiety could have altered the "inherent" regioselectivity of attack by the nucleophile on the π-allyl Pd intermediate. Benzoate **21**, a compound that has the identical relative configuration of substituents as Curran's acetate **24** and must proceed through a common Pd-complex (at

(12) A standard protocol for the alkylation was employed for these studies in an effort to minimize concerns about the regioselectivity arising from differences in the reaction conditions or catalysts involved. In some instances, the yields of adduct suffered from lack of optimization of reaction conditions.

Scheme 5



(22:23 = 1:7)

least with regard to relative stereochemistry of Pd and C-6 substituents), provided, however, the regioisomeric product (Scheme 5). As shown previously, it has been demonstrated that Pd-catalyzed alkylation of *cis*-benzoate **27** with either sulfonyl anion or malonate gave dihydropyrans **28** and **29**, respectively, with virtually complete regioselectivity.[6]

We attribute the significant difference in regioselectivity of alkylation between diastereomeric benzoates **19** and **21** to distortion in the respective π-allyl Pd intermediates as outlined in Schemes 6 and 7. Treatment of *cis*-benzoate **19** with Pd(0) catalyst resulted in formation of π-allyl Pd intermediate **30**. This complex could exist in two conformations, **30A** and **30B**, where **30A** predominates. A survey of X-ray crystallographic structures of π-allyl Pd-complexes in the Cambridge Crystallographic Database indicated that the substituents *syn* to Pd on the ring favor the pseudoequatorial conformation, presumably to avoid steric interactions with the bulky ligands on Pd.[14] Attack of malonate anion onto Pd-complex **30A** should occur regioselectivity at C-3 thus avoiding eclipsing interactions with the pseudoaxial methyl group (Scheme 6).

The situation was altered dramatically for alkylation of benzoate **21** (Scheme 7). In this case, displacement of the benzoate by Pd(0) provided complex **31** with the methyl group and the Pd having a *syn*-relationship. (For the sake of consistency, the enantiomer of **21** is drawn in this scheme). The methyl group sterically interacts with Pd and its ligands in both conformations **31A** and **31B**, respectively, resulting in a Pd-complex where Pd lies toward C-3 as in complex **32A**. This "distortion" of the π-allyl Pd-complex can be represented as a σ,η^2-complex **32B**.[14] Addition of malonate to the "distorted" Pd-complex **32** occurred in an S_N2'-like fashion regioselectivity at C-5 to afford dihydropyran **23**.

Additional support for the proposal that "distorted" π-allyl Pd-complexes are responsible for the high regioselectivity was provided by the experiments shown in Scheme 8. Treatment of *cis*-benzoate **19** under Stille conditions[14d] with Pd(0)-catalyst and $PhSnMe_3$ gave a 3:2 mixture of dihydropyrans **33** and **34**. Arylation of the π-allyl Pd-complex is known to occur by transmetalation of the aryl group from tin to Pd followed by reductive elimination. Benzoate **19** gave *symmetrical* π-allyl Pd-complex **30**; therefore, arylation was expected to occur nonselectively at either end (C-3 or C-5) of the allyl Pd-complex.

Arylation of *unsymmetrical* Pd-complex **31**, on the other hand, must occur with high regioselectivity at the end of the allylic system distal to the sterically demanding methyl substituent. In this case, the arylation results supported the proposal of a "distorted" intermediate Pd-complex, and a 15:1 mixture of dihydropyrans **35** and **36**, respectively, was obtained (a 4 to 2 ratio of **33** and **34** were also present).

The results summarized above indicated that both electronic and conformational factors exert significant control of the regioselectivity of functionalized pyran derivatives. In particular, substituents on the same face of the pyran as the metal and its ligands result in "distortion" of the π-allyl Pd intermediate and lead to high regioselectivity in subsequent coupling reactions.

We are currently assessing whether these factors also affect the regioselectivity of cyclohexane and cyclopentane derivatives. Application of this strategy to the synthesis of pyran-based natural products is underway, and results will be reported in due course.

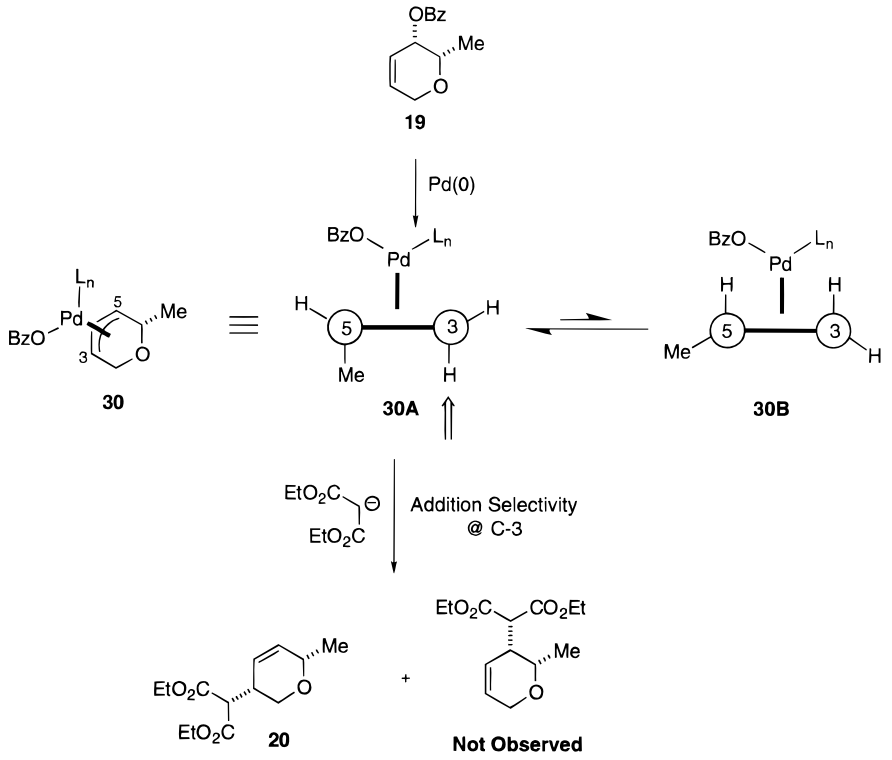
Experimental Section

All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl while methylene chloride (CH_2Cl_2) and dimethylformamide (DMF) were distilled from calcium hydride. Glassware used in the reactions described below was dried overnight in an oven at 120 °C. All reactions were run under an atmosphere of N_2.

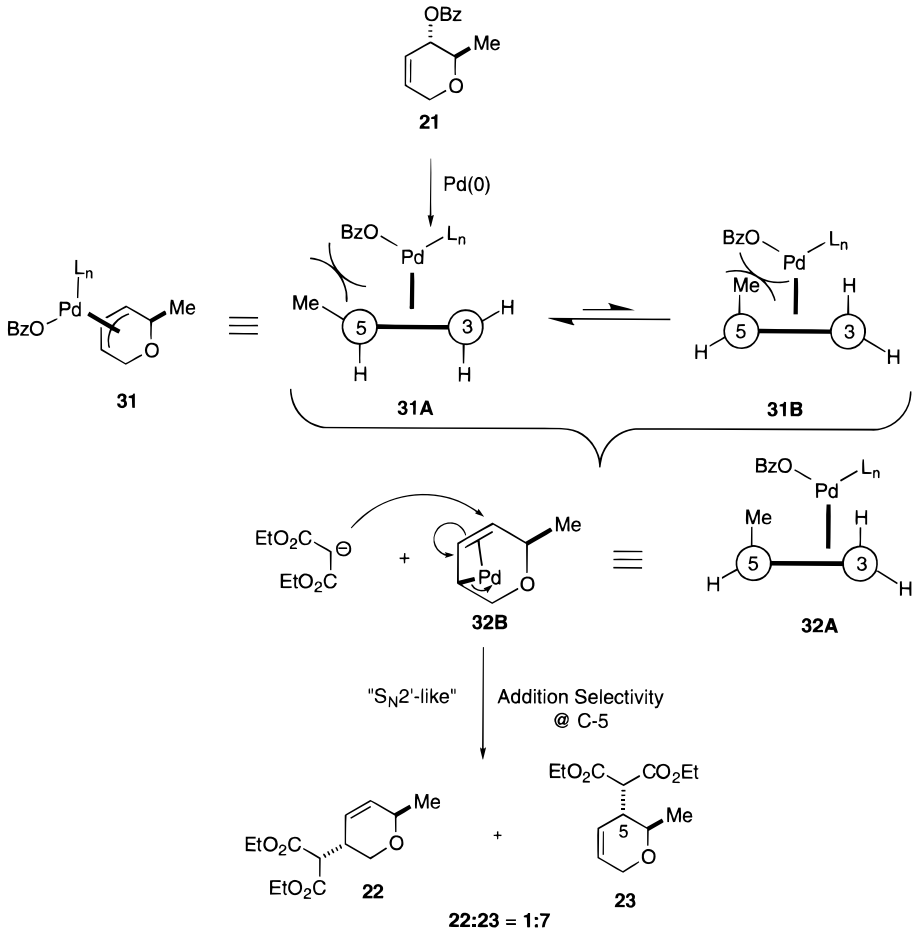
(13) The survey consisted of all ten structures of Pd-complexes in which a π-allyl Pd-complex of a cyclic structure had been determined. For example, see BEXHIV10 or FIDVIX in the Cambridge Crystallographic Database.

(14) The structure of π-allyl Pd-complexes in these reactions remains controversial. The role of η^3 vs σ,η^2-complexes in alkylation reactions has been discussed by several authors. See: (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215−3216. (b) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399−1402. (c) Akermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679−682. (d) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem* **1990**, *55*, 3019−3023.

Scheme 6



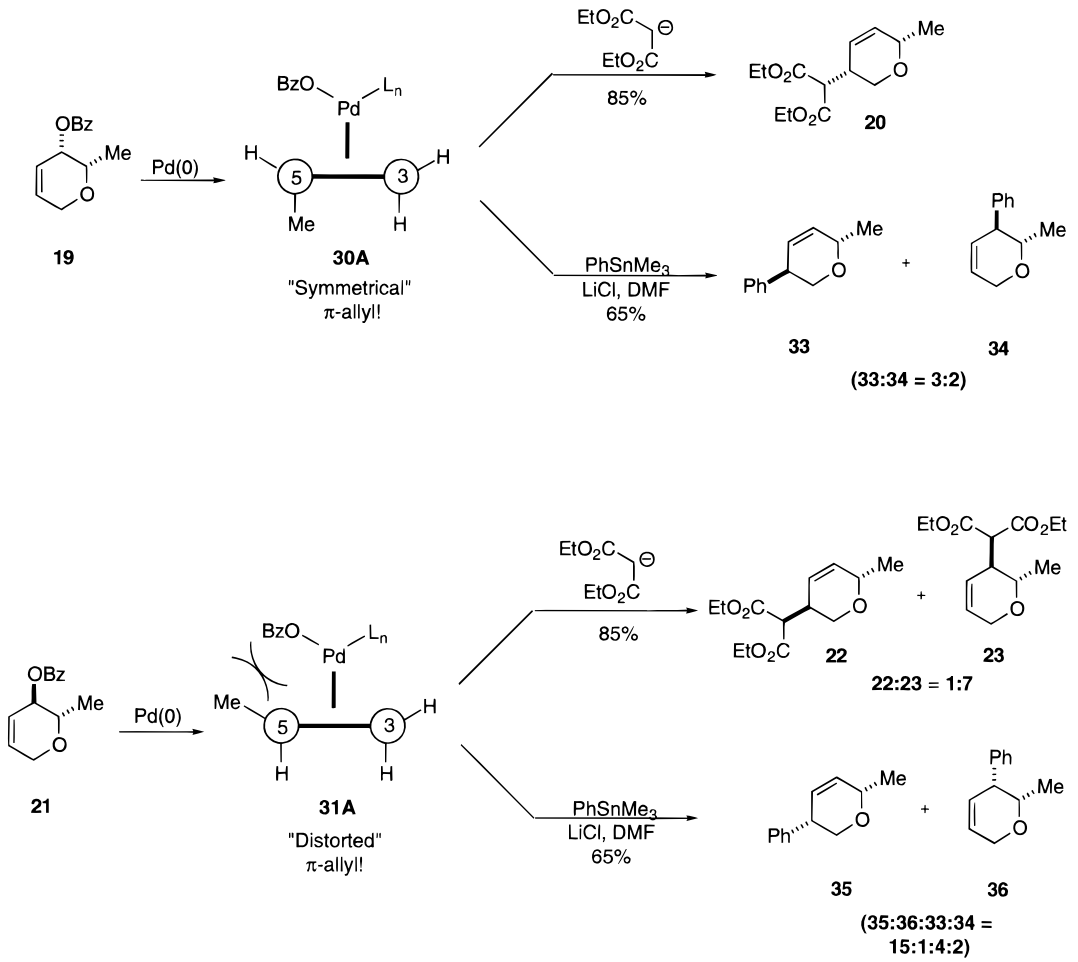
Scheme 7



Gas chromatography was performed using a gas chromatograph equipped with a flame ionization detector and a 25-m capillary column coated with crosslinked methyl silicone. All compounds for which elemental analysis was not obtained were >95% pure as judged by gas chromatographic and NMR spectral analysis unless otherwise noted. ^{1}H-NMR spectra of these substances are included in the Supporting Information.

General Procedure for the Synthesis of Diesters 4, 9, 10, 12, 14, 15, 17, 18, 20, 22, 23, and 29. Sodium hydride (60% dispersion in oil, 0.15 g, 0.38 mmol) was washed with 2

Scheme 8



× 2 mL of hexane and once with 2 mL of THF. To a suspension of oil-free NaH in 5 mL of THF was added diethyl malonate (770 μL, 0.38 mmol). After 15 min of stirring, the resulting diethyl malonate anion solution was added via cannula to a solution of allylic benzoate (0.56 mmol), $Pd(PPh_3)_4$ (45 mg, 0.039 mmol), and triphenylphosphine (100 mg, 0.39 mmol) in 5 mL of THF. The resulting orange mixture was heated at 66 °C for 48 h. The reaction mixture was then separated between 10 mL of distilled H_2O and 10 mL of Et_2O. The aqueous phase was extracted with 3 × 10 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (20 mm, 12 cm, 5−15% Et_2O/hexane) gave the diesters as a colorless oil. The ratio of diesters was determined by gas chromatography and confirmed by ^{1}H-NMR. Both the major and minor diesters were subjected to homonuclear decoupling to determine their regiochemistry. Only the major diester in each reaction was fully characterized (*vide infra*), since the minor diester could not be successfully separated from the major diester.

General Procedure[14d] for the Synthesis of Dihydropyrans 33−36. Phenyltrimethyltin (0.22 mL, 0.90 mmol) was added to a yellow mixture of allylic benzoate (130 mg, 0.60 mmol), $Pd(dba)_2$ (17 mg, 0.030 mmol), and LiCl (76 mg, 1.8 mmol) in 10 mL of DMF. The mixture was degassed and stirred at room temperature for 72 h. The reaction mixture was then separated between 75 mL of distilled H_2O and 75 mL of Et_2O. The organic layer washed with an additional 75 mL of distilled H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (20 mm, 16 cm, 0−10% Et_2O/hexane) gave 63 mg (61%) of a yellow oil. The ratio and regiochemistry of the products was determined in the same manner as the diesters (*vide supra*).

Diester 4. Diester **4** was obtained in 67% yield as a mixture of three diastereomers. TLC R_f = 0.45 (6:1 hexane:EtOAc). IR (CCl_4) 2956 (s), 2931 (s), 2856 (s), 1756 (s), 1737 (s), 1462 (m). ^{1}H-NMR ($CDCl_3$) 0.00−0.10 (m, 6), 0.75−0.88 (m, 9), 1.15−1.30 (m, 9), 1.50−2.03 (m, 3), 2.65−2.85 (m, 1), 3.35−3.50 (m, 3), 3.78−4.31 (m, 6), 4.64−4.96 (m, 1), 5.64−5.79 (m, 1), 5.90−6.02 (m, 1).

Alcohols **40** and **46** have been prepared by Achmatowicz,[15] however, we prepared **40** and **46** using methodology developed in the DeShong lab (Schemes 9 and 10, respectively).[6] Under standard Mitsunobu conditions,[16] **40** was converted to benzoate **8**, while **46** gave benzoate **16**. Alternatively, **40** was treated with *n*-BuLi and BzCl to afford benzoate **11**, while **46** was converted to benzoate **13**. Finally, benzoates **13** and **16** were reduced under Gray conditions[17] to afford benzoates **19** and **21**, respectively (Scheme 11).

Benzoate 8.[18,19] Benzoate **8** was obtained in 67% yield. Mp 49.5−50.5 °C (hexane:Et_2O). TLC R_f = 0.54 (3:2 hexane:EtOAc). IR (CCl_4) 3065 (w), 2995 (m), 2931 (m), 2896 (m), 2826 (m), 1722 (s), 1455 (s), 1272 (s). ^{1}H-NMR ($CDCl_3$) 3.45 (s, 3), 3.96 (dd, 1, J = 1.4, 13.0), 4.23 (dd, 1, J = 2.8, 13.0), 4.92 (d, 1, J = 3.1), 5.17 (ddd, 1, J = 1.4, 2.8, 5.1), 6.06 (dd, 1, J = 3.1, 10.3), 6.18 (dd, 1, J = 5.1, 10.3), 7.50−8.08 (m, 5). ^{13}C-NMR ($CDCl_3$) 55.6, 61.3, 63.8, 94.1, 125.1, 128.3, 129.7, 130.0, 130.8, 133.0, 166.1. HRMS (EI) Calcd for $C_{13}H_{14}O_4$: 234.0892 (M^+). Found: 234.0897.

Diester 9. This compound was obtained as a 9 to 1 ratio of diesters **9** and **10**. TLC R_f = 0.35 (3:1 hexane:EtOAc). IR

(15) Achmatowicz Jr., O.; Buckowski, P.; Szechner, B.; Zierchowska, A.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973−1996.
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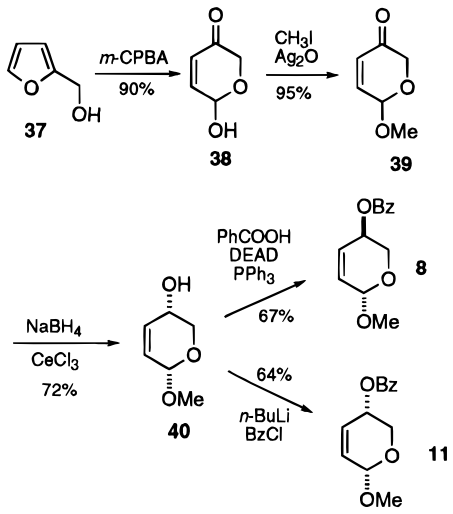
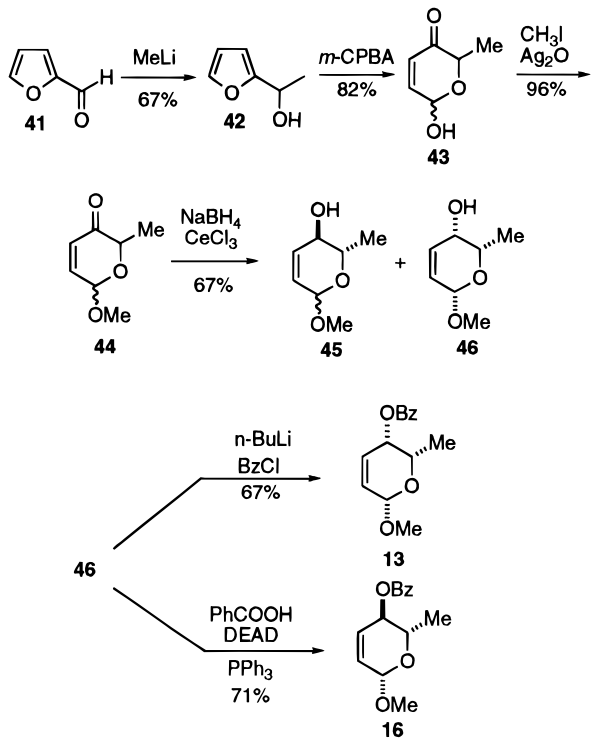
(17) Rolf, D.; Gray, G. R. *J. Am. Chem. Soc.* **1982**, *104*, 3539−3541.
(18) Bock, K.; Pederson, C. *Acta. Chem. Scand.* **1971**, *25*, 2757−2764.
(19) Achmatowicz, O., Jr.; Bukowski, P. *Rocz. Chem.* **1973**, *47*, 99−113.
(20) Dyong, I.; Weigand, J.; Thiem, J. *Liebigs. Ann. Chem.* **1986**, *4*, 577−786.

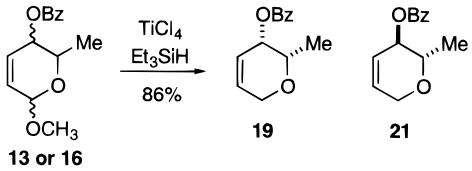
Scheme 9



Scheme 10



Scheme 11



(CCl_4) 3056 (w), 2981 (m), 2931(m), 2888 (m), 1756 (s) 1738 (s), 1450 (m), 1394 (m), 1369 (m). ^{1}H-NMR ($CDCl_3$) 1.24 (t, 6, J = 7.1), 2.68 (ddd, 1, J = 3.4, 5.5, 10.0), 3.38 (s, 3), 3.53 (d, 1, J = 10.0), 3.63 (d, 1, J = 12.0) 4.00, (dd, 2, J = 3.4, 12.0), 4.15 (q, 4, J = 7.1), 4.71 (d, 1, J = 2.7), 5.76 (dd, 1, J = 2.7, 10.2), 5.96 (dd, 1, J = 5.5, 10.2). ^{13}C-NMR ($CDCl_3$) 14.0, 33.4, 53.5, 55.3, 59.5, 61.6, 94.7, 127.7, 129.3, 168.1. HRMS (EI) Calcd for $C_{13}H_{20}O_6$: 272.1260 (M^+). Found: 272.1248.

Benzoate 11.[18,19] Benzoate **11** was obtained in 64% yield. TLC R_f = 0.60 (3:2 hexane:EtOAc). IR (CCl_4) 3063 (w), 2988 (m), 2931 (s), 2888 (s), 2831 (s), 1725 (s), 1606 (m), 1475 (m), 1450 (s). ^{1}H-NMR ($CDCl_3$) 3.45 (s, 3), 3.85−4.01 (m, 2) 4.87 (br s, 1), 5.49−5.78 (m, 1), 5.85−5.92 (dm, 1, J = 10.0), 6.02−6.08 (dm, 1, J = 10.0), 7.36−8.03 (m, 5). ^{13}C-NMR ($CDCl_3$) 55.8, 60.0, 65.4, 95.2, 128.4, 129.0, 129.1, 129.7, 129.8, 133.2, 165.9. HRMS (EI) Calcd for $C_{13}H_{14}O_4$: 234.0892 (M^+). Found: 234.0905.

Diester 12. Diester **12** was obtained in 87% yield. TLC R_f = 0.38 (3:1 hexane:EtOAc). IR (CCl_4) 3050 (w), 2988 (s), 2931 (s), 2906 (s), 2888 (s), 2825 (m), 1756 (s) 1738 (s), 1463 (s), 1444 (s), 1388 (s), 1369 (s). ^{1}H-NMR ($CDCl_3$) 1.21 (t, 3, J = 7.1), 2.98−3.07 (m, 1), 3.18 (d, 1, J = 9.1), 3.34 (s, 3), 3.63−3.73 (m, 2), 4.13, (q, 4, J = 7.1), 4.75−4.77 (m, 1), 5.67−5.74 (dm, 1, J = 10.3), 5.81-5.88 (dm, 1, J = 10.3). ^{13}C-NMR ($CDCl_3$) 13.9, 34.0, 52.9, 55.2, 60.2, 61.5, 95.0, 122.0, 130.2, 167.5. HRMS (EI) Calcd for $C_{13}H_{20}O_6$: 272.1260 (M^+). Found: 272.1273.

Benzoate 13. Benzoate **13** was obtained in 67% yield. Mp 47.5−49.5 °C (hexane/Et_2O). TLC R_f = 0.55 (3:1 hexane:EtOAc). IR (CCl_4) 3063 (w), 2994 (s), 2963 (m), 2938 (s), 2856 (m), 2831 (m), 1719 (s), 1600 (m), 1450 (s), 1400 (s), 1375 (s), 1339 (s), 1318 (s). ^{1}H-NMR ($CDCl_3$) 1.33 (d, 3, J = 6.5), 3.49 (s, 3), 3.97 (dq, 1, J = 2.5, 6.5), 5.04 (d, 1, J = 1.2), 5.21−5.23 (m, 1), 5.94−5.97 (dm, 1, 10.1), 6.10−6.14 (dm, 1, J = 10.1), 7.37−7.41 (m, 2), 7.50−7.54 (m, 1), 8.04−8.07 (m, 2). ^{13}C-NMR ($CDCl_3$) 16.6, 55.1, 66.5, 69.6, 98.0, 127.1, 128.4, 129.8, 129.9, 132.7, 133.1, 166.2. HRMS (EI) Calcd for $C_{14}H_{16}O_4$: 248.1049 (M^+). Found: 248.1048.

Diester 14. This compound was obtained in 92% yield as a 5 to 1 ratio of diesters **14** and **15**. TLC R_f = 0.33 (3:1 hexane:EtOAc). IR (CCl_4) 3050 (w), 2981 (s), 2931 (s), 2906 (s), 2875 (s), 2825 (m), 1762 (s), 1738 (s), 1663 (w), 1469 (s), 1444 (s), 1369 (s). ^{1}H-NMR ($CDCl_3$) 1.14 (d, 3, J = 6.9), 1.20 (t, 6, J = 6.8), 2.95−2.98 (m, 1), 3.36 (s, 1), 3.47 (d, 1, J = 9.3), 3.99 (q, 4, J = 6.8), 4.15 (br q, 1, J = 6.9), 4.97 (br s, 1), 5.66−5.69 (dm, 1, J = 10.3), 5.84−5.88 (dm, 1, J = 10.3). ^{13}C-NMR ($CDCl_3$) 13.9, 17.2, 37.6, 52.0, 54.4, 61.4, 69.0, 97.2, 128.4, 129.6, 168.3. HRMS (EI) Calcd for $C_{14}H_{22}O_6$: 286.1416 (M^+). Found: 286.1419.

Benzoate 16.[20] Benzoate **16** was obtained in 95% yield. IR (CCl_4) 3094 (w), 3063 (m), 2988 (s), 2938 (s), 2875 (s), 2825 (s), 1725 (s), 1606 (m), 1494 (m), 1469 (s), 1450 (s), 1406 (s). ^{1}H-NMR ($CDCl_3$) 1.35 (d, 3, J = 6.5), 3.46 (s, 3), 3.99 (dq, 1, J = 6.5, 6.5), 5.10 (s, 1), 5.27 (d, 1, J = 6.5), 5.89 (d, 1, J = 10.2), 6.01 (d, 1, J = 10.2), 7.39−7.43 (m, 2), 7.52−7.55 (m, 1), 8.00−8.02 (m, 2). ^{13}C-NMR ($CDCl_3$) 18.5, 54.9, 70.1, 71.3, 97.0, 125.9, 129.2, 129.4, 129.6, 130.2, 133.1, 165.9. HRMS (EI) Calcd for $C_{14}H_{16}O_4$: 248.1049 (M^+). Found: 248.1050.

Diester 17. This compound was obtained in 95% yield as a 9 to 1 ratio of diesters **17** and **18**. TLC R_f = 0.19 (9:1 hexane:EtOAc). IR (CCl_4) 3050 (w), 2975 (s), 2931 (s), 2906 (s), 2875 (s), 2825 (s), 1756 (s), 1738 (s), 1444 (m), 1400 (s), 1369 (s). ^{1}H-NMR ($CDCl_3$) 1.22 (t, 6, J = 6.9), 1.32 (d, 3, J = 6.6), 2.67 (ddd, 1, J = 3.4, 4.3, 9.9), 3.38 (s, 3), 3.43 (d, 1, J = 9.9), 3.91 (dq, 1, J = 3.4, 6.6), 4.15 (q, 4, J = 6.9), 4.83 (s, 1), 5.76 (d, 1, J = 10.3), 5.89 (dd, 1, J = 4.3, 10.3). TLC R_f = 0.41 (3:1 hexane:EtOAc). ^{13}C-NMR ($CDCl_3$) 14.0, 20.2, 39.0, 52.0, 53.9, 55.0, 61.4, 61.6, 69.3, 95.4, 127.7, 167.8, 168.2. HRMS (EI) Calcd for $C_{14}H_{22}O_6$: 286.1416 (M^+). Found: 286.1403.

Benzoate 19. Benzoate **19** was obtained in 86% yield. TLC R_f = 0.25 (9:1 hexane:EtOAc). IR (CCl_4) 3063 (m), 2981 (s), 2956 (s), 2913 (s), 2875 (s), 2819 (m), 1720 (s), 1700 (s), 1613 (w), 1594 (w), 1450 (s), 1419 (s). ^{1}H-NMR ($CDCl_3$) 1.29 (d, 3, J = 6.4), 3.83 (dq, 1, J = 2.2, 6.4), 4.15−4.32 (m, 2), 5.19−5.21 (m, 1), 6.02−6.10 (m, 2), 7.38−7.55 (m, 3), 8.07 (d, 2, J = 7.2). ^{13}C-NMR ($CDCl_3$) 16.4, 65.5, 66.9, 71.9, 122.6, 128.1, 129.6, 129.9, 132.1, 132.8, 166.4. HRMS (EI) Calcd for $C_{13}H_{14}O_3$: 218.0943 (M^+). Found: 218.0952.

Diester 20. Diester **20** was obtained in 85% yield. TLC R_f = 0.27 (9:1 hexane:EtOAc). IR (CCl_4) 3038 (w), 2981 (s), 2963 (s), 2938 (m), 2906 (m), 2869 (m), 2825 (m), 1756 (s), 1738 (s), 1463 (m), 1444 (m), 1369 (s). ^{1}H-NMR ($CDCl_3$) 1.19 (d, 3, J = 6.9), 1.24 (t, 6, J = 7.1), 2.69−2.76 (dm, 1, J = 10.0), 3.55 (d, 1, J = 10.0), 3.72 (dd, 1, J = 3.3, 11.9), 3.85 (d, 1, J = 11.9), 4.09−4.23 (m, 5), 5.71-5.73 (m, 2). ^{13}C-NMR ($CDCl_3$) 14.1, 20.9, 34.2, 54.9, 61.4, 61.5, 66.2, 70.8, 124.6, 134.0, 168.0. HRMS (EI) Calcd for $C_{13}H_{20}O_5$: 257.1389 ($M - H^+$). Found: 257.1402.

Benzoate 21. Benzoate **21** was obtained in 86% yield. TLC R_f = 0.32 (9:1 hexane:EtOAc). IR (CCl_4) 3069 (w), 3044 (m),

2981 (s), 2938 (s), 2869 (m), 2831 (s), 1725 (s), 1606 (m), 1450 (s), 1375 (s). ^{1}H-NMR ($CDCl_3$) 1.28 (d, 3, J = 6.5), 3.77 (dq, 1, J = 6.5, 6.5), 4.13−4.25 (m, 2), 5.26−5.28 (m, 1), 5.81−5.84 (dm, 1, J = 10.3), 5.91−5.94 (dm, 1, J = 10,3), 7.41 (t, 2, J = 7.6), 7.53 (t, 1, J = 7.6), 8.02 (d, 2, J = 7.6). ^{13}C-NMR ($CDCl_3$) 18.1, 64.6, 71.1, 72.0, 124.4, 128.3, 129.6, 129.7, 130.1, 133.0, 166.0. HRMS (EI) Calcd for $C_{13}H_{14}O_3$: 218.0943 (M^+). Found: 218.0935.

Diester 23. This compound was obtained in 87% yield as a 1 to 7 ratio of diesters **23** and **24**. TLC R_f = 0.18 (9:1 hexane:EtOAc). IR (CCl_4) 3044 (w), 2981 (s), 2938 (s), 2906 (m), 2875 (m), 2831 (m), 1756 (s), 1731 (s), 1456 (m), 1438 (s), 1394 (s). ^{1}H-NMR ($CDCl_3$) 1.13−1.24 (m, 9), 2.59−2.64 (m, 1), 3.46 (d, 1, J = 6.7), 3.69 (dq, 1, J = 6.1, 6.1), 3.97−4.05 (m, 2), 4.08−4.21 (m, 4), 5.66−5.79 (m, 2). ^{13}C-NMR ($CDCl_3$) 13.9, 14.0, 18.1, 40.0, 53.8, 61.2, 61.5, 62.5, 70.4, 123.9, 127.6, 168.0. HRMS (EI) Calcd for $C_{13}H_{20}O_5$: 257.1389 ($M - H^+$). Found: 257.1402.

Diester 29. Diester **29** was obtained in 43% yield. TLC R_f = 0.24 (9:1 hexane:EtOAc). IR (CCl_4) 3038 (w), 2956 (s), 2931 (s), 2090 (w), 2856 (m), 1756 (s), 1738 (s), 1463 (m), 1369 (m), 1256 (s). ^{1}H-NMR ($CDCl_3$) 0.03 (s, 6), 0.83 (s, 9), 1.15 (d, 3, J = 6.2), 1.25 (t, 6, J = 7.2), 1.44−1.51 (m, 1), 1.73−1.79 (m, 1), 2.72−2.77 (dm, 1, J = 10.0), 3.52 (d, 1, J = 10.0), 3.67−3.72 (dm 1, J = 11.7), 3.79−3.82 (dm, 1, J = 11.7), 3.96−4.01 (m, 1), 4.09−4.22 (m, 5), 5.75−5.78 (m, 2). ^{13}C-NMR ($CDCl_3$) −4.8, −4.3, 14.0, 14.1, 23.5, 34.3, 44.9, 54.7, 61.3, 61.4, 65.5, 65.9, 72.0, 124.9, 132.7, 168.3. HRMS (FAB) Calcd for $C_{21}H_{37}O_6Si$: 415.2516 ($M - H^+$). Found: 415.2531.

Dihydropyrans 33 and 34. This compound was obtained in 65% yield as a 3 to 2 ratio of dihydropyrans **33** and **34**. Data for **33**: TLC R_f = 0.45 (9:1 hexane:EtOAc). IR (CCl_4) 3088 (w), 3063 (s), 3031 (s), 2981 (s), 2969 (s), 2931 (s), 2875 (s), 2850 (s), 2825 (s), 1606 (s). ^{1}H-NMR ($CDCl_3$) 1.29 (d, 3, J = 6.7), 3.45 (dd, 1, J = 9.8, 11.1), 3.61−3.66 (m, 1), 4.09−4.13 (m, 1), 4.28−4.31 (m, 1), 5.80−5.84 (dm, 1, J = 10.2), 5.86−5.90 (dm, 1, J = 10.2), 7.19−7.23 (m, 3), 7.30−7.34 (m, 2). ^{13}C-NMR ($CDCl_3$) 21.2, 41.5, 70.3, 71.4, 126.8, 128.0, 128.1, 128.5, 131.9, 141.3. HRMS (EI) Calcd for $C_{12}H_{14}O$:174.0966 (M^+). Found: 174.0965.

Data for **34**: TLC R_f = 0.41 (9:1 hexane:EtOAc). ^{1}H-NMR ($CDCl_3$) 1.14 (d, 3, J = 6.1), 3.21−3.23 (m, 1), 3.52 (dq, 1, J = 2.8, 6.1), 4.29−4.32 (m, 2), 5.74−5.78 (dm, 1, J = 10.2), 5.89−5.93 (dm, 1, J = 10.2), 7.17−7.25 (m, 3), 7.29-7.33 (m, 2). Dihydropyran **34** could not be separated completely from **33** so it was not further characterized.

Dihydropyran 35. This mixture of dihydropyrans was obtained in 65% yield as a 4:2:15:1 ratio of **33**−**36**, respectively. TLC R_f = 0.45 (9:1 hexane:EtOAc). IR (CCl_4) 3088 (w), 3063 (s), 3031 (s), 2981 (s), 2931 (s), 2906 (s), 2875 (s), 2850 (s), 2819 (s). ^{1}H-NMR ($CDCl_3$) 1.31 (d, 3, J = 6.8), 3.28−4.30 (m, 1), 3.81 (dd, 1, J = 4.2, 11.1), 3.95 (dd, 1, J = 4.2, 11.1) 4.27−4.30 (m, 1), 5.81−5.87 (m, 2), 7.20−7.24 (m, 2), 7.27−7.32 (m, 3). ^{13}C-NMR ($CDCl_3$) 20.8, 40.9, 69.1, 69.8, 126.5, 126.9, 128.1, 128.3, 131.8, 142.7. HRMS (EI) Calcd for $C_{12}H_{14}O$: 174.1044 (M^+). Found: 174.1038.

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Supporting Information Available: ^{1}H-NMR spectra of compounds **4**, **9**, **12**−**14**, **17**, **19**−**21**, **23**, **29,** and **33**−**35** (14 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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