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LIMITATIONS IN THE APPLICATION OF ANIONIC OXY-COPE SIGMATROPY TO ELABORATION OF THE FORSKOLIN NUCLEUS

Leo A. Paquette* and Jeffrey A. Oplinger

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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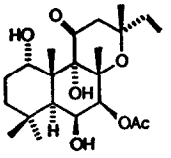
Abstract: The functionalized bicyclo[2.2.2]octenone **6** has been synthesized in four steps from 2,4,4-trimethyl-2-cyclohexenone. This ketone undergoes 1,2-addition with 6-lithiodihydropyran to deliver alcohols **16** and **17** in a 1:1.8 ratio. The potassium salt of **17** experiences oxy-Cope rearrangement in refluxing tetrahydrofuran solution containing 18-crown-6 and gives rise under these conditions to the thermodynamic enolate **19**. This intermediate has been trapped with several electrophiles, the most relevant to elaboration of the forskolin nucleus being phenylselenenyl chloride. A route to tricyclic ketones **25** and **26** is thereby opened. In an attempt to expand upon this chemistry, several more highly functionalized 3,4-dihydro-2H-pyrans were prepared; some were obtained in enantiomerically pure condition since they originated from carbohydrate precursors. The complications associated with metalation of these heterocycles at C-6 are delineated. Since no indication of oxyanionic Cope rearrangement was observed in those adducts (**41**/**42**, **46**, and **51**) which were synthesized, we conclude that steric (and perhaps electronic) influences exert a particularly strong rate-retarding effect on the key [3,3] sigmatropic step.

Structural elucidation in 1977 of forskolin (**1**),[1,2] the major diterpene from the roots of *Coleus forskohlii*, was accompanied by recognition of its interesting blood pressure lowering and cardioactive properties.[3] Forskolin is able not only to activate cardiac adenylate cyclase,[4] but to induce peripheral vasodilation,[4] relax smooth muscle in the absence of guanine nucleotide-binding protein,[5] and reduce intraocular pressure in man.[6] Its bronchospasmolytic,[7] antihypertensive,[8] and ionotropic activities[7,8] are also of considerable medicinal interest.[9]



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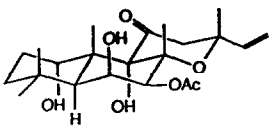
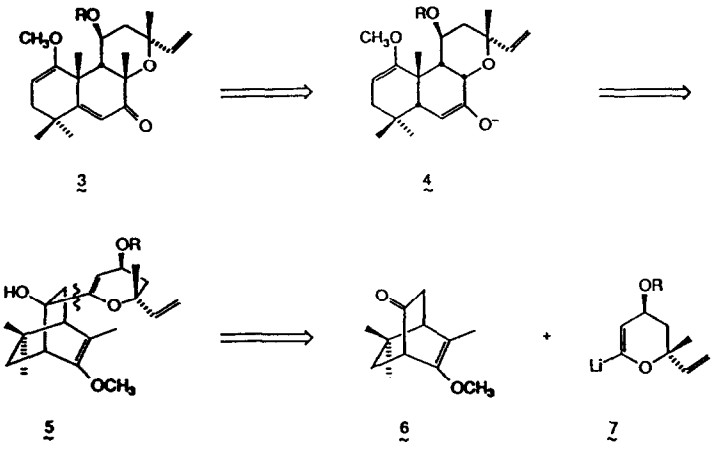


2

In view of the unique structure and fascinating pharmacological properties of **1**, considerable activity has surrounded its structural modification[1b,10] and independent laboratory preparation.[11] A formal total synthesis has recently been completed.[12]

Careful analysis of the labdane ring system within **1** reveals a rather large number of 1,3-diaxial methyl-methyl and methyl-hydroxyl interactions to be present (see **2**). Although the basic tricyclic framework is otherwise in a stable arrangement, this particular collection of pendant groups requires that more than passing consideration be given to their mode of introduction.

Our retrosynthetic plan for the preparation of **1** emerged from an ongoing interest in



3 4 5 6 7

the synthetic utilization of oxyanionic [3,3] sigmatropy.[13] Specifically, the plan called for stereocontrolled 1,2-addition of the enantiomerically pure lithiated glycal 7 having known absolute configuration to racemic ketone 6, under conditions where kinetic control would be achieved.[13j] Following the conjoining of these two segments as in 5, heating of the potassium salt was expected to induce Cope rearrangement with subsequent prototropic shift[13j] to deliver enolate anion 4. For reasons of structural topography, methylation of 4 can only occur from the β direction. Ultimately, conversion to 3 followed by functional group manipulation would deliver enantiomerically pure 1.

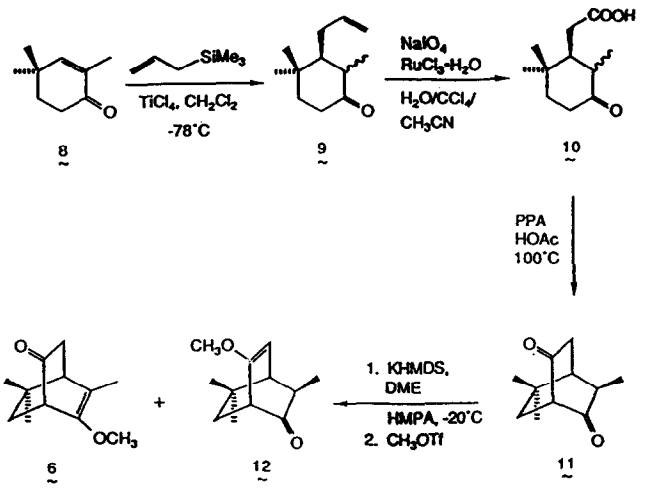
We record below the partial realization of this goal[14] and also delineate those limitations to the scheme that have manifested themselves in the course of this investigation.

Results and Discussion

Construction of Bicyclic Ketone 6. The feasibility of acid-catalyzed intramolecular Claisen condensation as a route to non-enolizable β-diketones has previously been demonstrated.[13j,15] On the assumption that keto acid 10 would respond similarly to cyclization, attention was directed initially to its acquisition. Thus, 8 was prepared by condensation of isobutyraldehyde with ethyl vinyl ketone in the presence of sulfuric acid and subjected to the conditions of the Sakurai reaction.[16] The resulting mixture of epimeric cyclohexanones 9 underwent smooth oxidative cleavage of its terminal double bond without need for carbonyl protection when treated with ruthenium trichloride in the presence of sodium periodate.[17] The conversion of 9 to 10 could also be effected by sequential ozonolysis and Jones oxidation, although in diminished yield (71% overall).

The fact that 10 was also a mixture of stereoisomers proved inconsequential inasmuch as subsequent heating with polyphosphoric acid in acetic acid furnished only 11 in 91% yield. Exclusive adoption by 11 of the exo methyl arrangement is the result of otherwise severe steric congestion that would materialize in the endo environment. Formation of the requisite bicyclo[2.2.2]octanedione ring system proved therefore to be an easy accomplishment.

In contrast, considerable experimentation was required before O-methylation of the thermodynamically more stable enolate in 11 could be satisfactorily realized. Controlled

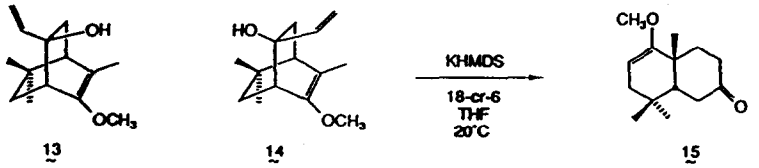


8 9 10 6 12 11

regioselective deprotonation at the methyl-substituted carbon requires removal of a proton that is positioned in a highly hindered environment. The response of 11 is consequently linked intimately to the nature of the base and solvent system utilized during enolate formation. The best conditions involved use of potassium hexamethyldisilazide in 1,2-dimethoxyethane containing HMPA at reduced temperature (-20 °C). Subsequent to the addition of methyl triflate, a 7:1 mixture of 6 and 12 was obtained in 71% yield. These isomers proved to be readily separable by chromatography.

The Prototype Anionic Oxy-Cope Sequence. Demonstration of the feasibility of our synthetic plan next required information relating to the stereoselectivity of capture by 6 of vinylorganometallic reagents. Whereas the right side of its carbonyl group (as drawn) might intuitively be regarded as the more sterically accessible, some structural distortion of the framework was anticipated as a consequence of the gem-dimethyl group. The left surface gains increasingly more exposure when only modest deformation takes place. In addition, there exists little basis for judging the impact of the electron-rich vinyl ether moiety on the preferred direction of nucleophilic approach to 6. Chelation of a metal ion to the exo surface of this double bond could by virtue of its relative location reduce the readiness of syn anion capture. On the other hand, chelation control could exert beneficial kinetic acceleration.[18]

In the event, condensation of 6 with vinylmagnesium bromide gave rise to 13 and 14 in 2:1 ratio. Stereochemical assignment to these alcohols followed from spectral and chemical

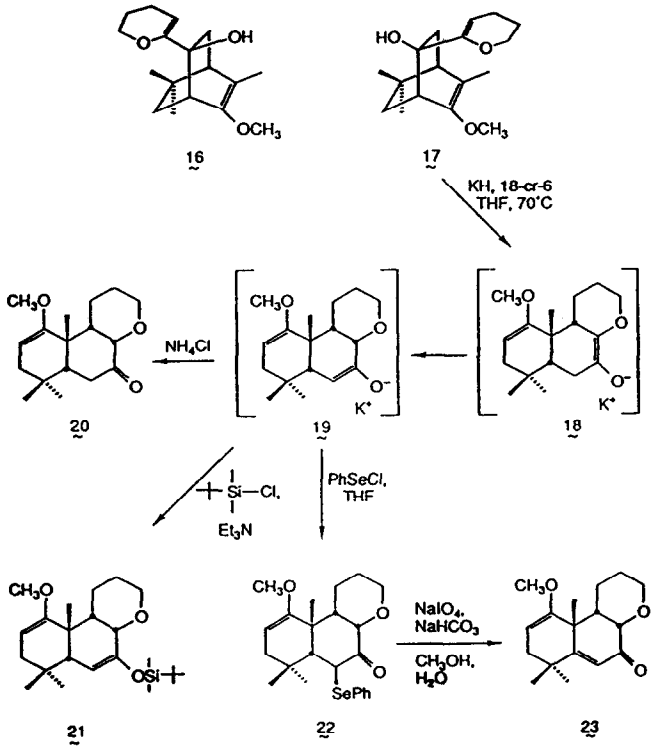


13 14 15

considerations. Most notable in the latter category was the unreactivity of 13 to potassium hexamethyldisilazide and 18-crown-6 in tetrahydrofuran solution at room temperature, conditions which induced the complete conversion of 14 to 15 during 3 h.

When 6 was condensed with 6-lithiodihydropyran,[19] the epimeric alcohols 16 and 17 were formed efficiently in a ratio of 1:1.8. On this basis, it would appear that there may not

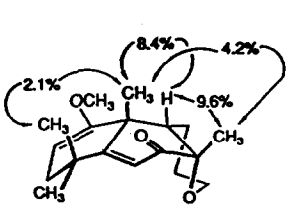
yet be a secure foundation for predicting the preferred course of 1,2-additions to 6 because of a pronounced sensitivity to the steric size and nucleophilicity of the incoming reagent.[20] Whatever the case, the desired [3,3] sigmatropic rearrangement within 17 did not proceed as readily as in 14. Heating of its potassium salt was necessary to drive the reaction forward at a convenient rate. This thermal activation proved to be very well suited to our objectives because the initially formed enolate (18) experiences *complete* equilibration to 19 at 70 °C. The exclusivety of this prototropic shift is most striking.



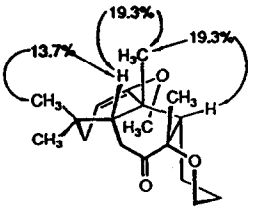
Quenching of the enolate solution with ammonium chloride gave 20 without distinguishing regiochemistry. On the other hand, its reaction with *tert*-butyldimethylsilyl chloride afforded silyl enol ether 21 having *two* vinyl protons clearly evident in its ^{1}H NMR spectrum. With phenylselenenyl chloride as electrophile, 22 was obtained in 79% yield. The subsequent oxidative elimination of benzeneselenenic acid from 22 provided 23, *a substrate capable only of unidirectional enolization.*

In actuality, deprotonation-methylation of 23 furnished a mixture of 24 (39%) and 25 (52%). The co-formation of 24, a compound easily transformed back into 23 by means of mild acid hydrolysis, is presumed to reflect the serious 1,3-diaxial methyl-methyl interaction that necessarily develops with introduction of the new angular methyl group. The conclusion that methyl capture had indeed occurred on the convex face as desired was convincingly established by difference NOE studies at 300 MHz (see A).

The next objective, setting the trans A/B ring juncture, cannot be accomplished by dissolving metal reduction. The cis nature of the B/C ring fusion causes the C_8-O bond in 25 to be axially disposed and subject to more rapid cleavage under these conditions. The search for other methods of achieving 1,4-reduction of the enone in stereospecific trans

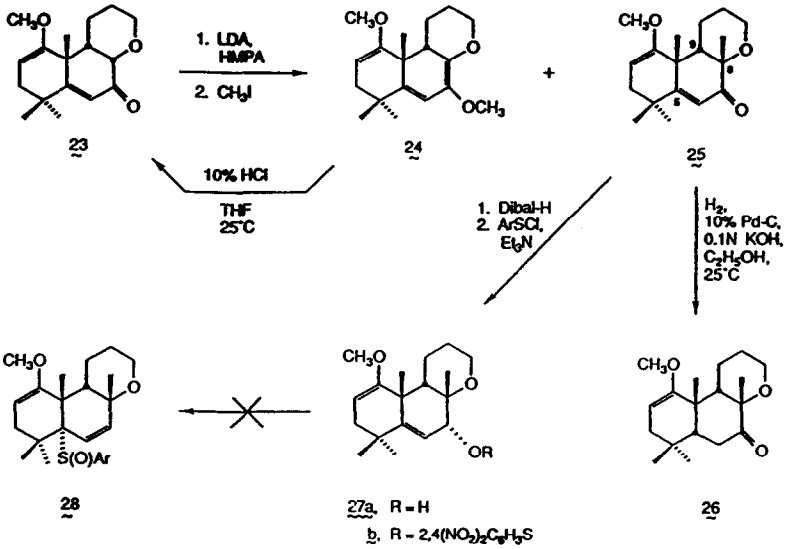


A



B

fashion led us to examine copper hydride,[21] alkaline iron pentacarbonyl,[22] the tris(triphenylphosphine)rhodium(I) chloride-triethylsilane combination,[23] sodium hydrogen telluride,[24] and diisobutylaluminum hydride-methylcopper.[25] In every instance, 25 was recovered unchanged, despite the wide variations in reaction temperature and reaction time that were purposefully implemented. Attempts to realize the Michael addition of sulfhydryl reagents or the conjugate delivery of methyl selenide via $Me_2AlSeMe$[26] were similarly thwarted. While the unresponsiveness to uncatalyzed nucleophilic capture occasioned no surprise,[27] the other failures were construed to be an indicator of prevailing steric congestion about that particular double bond in the substrate (see A).

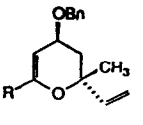


For these reasons, proper *intramolecular* delivery of the requisite hydrogen atom was given consideration. Our inability to convert 25 to its tosylhydrazone did not allow for examination of subsequent catecholborane reduction.[28] However, since its carbonyl group proved subject to stereospecific reduction to 27a in the presence of diisobutylaluminum hydride,[29] conversion to α-sulfoxide 28 by [2,3] sigmatropic rearrangement of a sulfenate ester was deemed worthy of scrutiny.[30] The stereochemical assignment to 27a rests principally on the intense nuclear Overhauser interaction (17.7%) between the β carbinol proton and the proximal cis-oriented angular methyl group. Conversion to 27b was accomplished in moderate yield using 2,4-dinitrobenzenesulfenyl chloride and triethylamine. However, our attempts to isomerize 27b to 28 at temperatures up to that of refluxing toluene gave rise only to decomposition products.

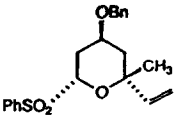
In contrast, high chemoselectivity can be achieved by catalytic hydrogenation over 10% palladium on carbon in 0.1 N ethanolic potassium hydroxide solution.[31] The exclusive product was shown to be 26 by COSY and NOE analyses at 500 MHz (B represents one of several possible conformations).

Although the preceding observations would appear to foreshadow serious problems, Dreiding molecular models reveal that prior establishment of a trans relationship between the substituents at C-8 and C-9 (see 25) as demanded by forskolin imparts considerable conformational rigidity and predisposes the C_8-O bond equatorially. Of course, epimerization at C-9 is critically dependent on the presence of an OR substituent in 5, 7, and the compounds derived therefrom. The likelihood that structural modification in this manner would permit approximate control of stereochemistry was therefore pursued.

Synthesis of Oxygenated 3,4-Dihydro-2*H*-pyrans. An ideal convergent match for (±)-6 was initially considered to be enantiomerically pure 7. However, although levorotatory glycal 29a has proven amenable to synthesis,[32] it has not proven satisfactorily responsive to metalation of its α position (as in 29b), as previously demonstrated for vinyl ethers[33] and certain dihydropyrans.[19,34] Attempts to prepare the trialkyltin derivative 29b for subsequent transmetalation purposes[34d] have also proven unfruitful.[32] Finally, it was likewise not possible to avail ourselves of sulfone 30 in order to take advantage of its synthon relationship to 29b.[35]

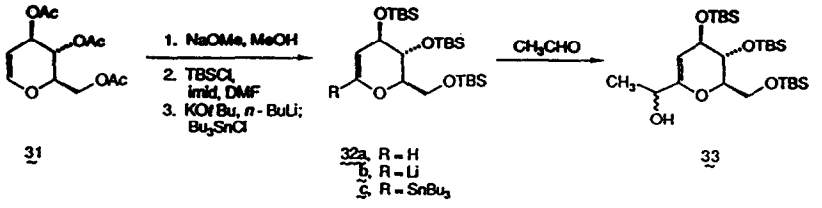


29a, R = H
b, R = Li
c, R = $SnBu_3$



30

In the belief that the benzyloxy substituent in 29 may be a possible source of the problem, other substitution patterns were considered in turn. Thus, *D*-glucal triacetate (31) was subjected to sequential saponification and exhaustive silylation to provide 32a.[34d] Lithiation of 32a with 2 equiv of *tert*-butyllithium in ether at -50 °C successfully generated 32b. Although trapping of this organometallic with acetaldehyde gave rise to a 1:1 mixture of the diastereomeric alcohols 33 in 96% yield, condensation with 6 proved not to be useful, presumably because simple enolization was competing effectively. Recourse to the combined use of anhydrous cerium trichloride[33c-e,g-h,36] was not advan-



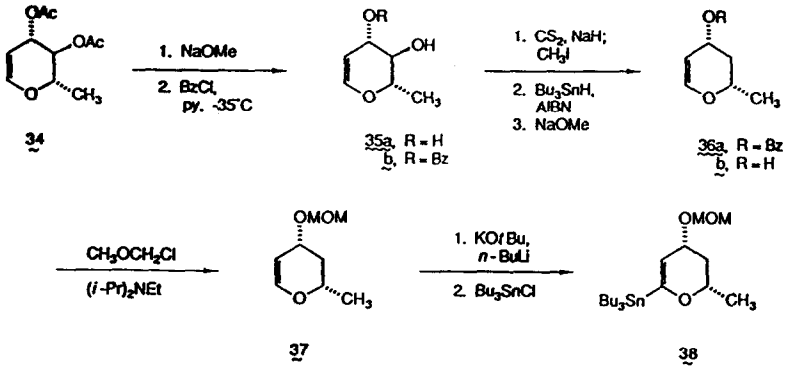
31

32a, R = H
b, R = Li
c, R = $SnBu_3$

33

tageous. Stannane 32c was prepared and converted to 32b through the agency of *n*-butyllithium. However, condensation with 6 proved not to be more efficacious than before.

In an attempt to reduce the steric bulk and level of oxygenation within the glycal, commercially available[37] *L*-rhamnal diacetate (34) was converted to 35b by selective monobenzoylation of diol 35a. Free radical deoxygenation of 35b by means of the Barton protocol[38] ultimately afforded 36b after ester saponification. Following formation of the MOM ether 37, direct lithiation with *tert*-butyllithium was attempted without success. Conversion to stannane 38 could be realized in modest yield when recourse was made to Schlosser's base.[39] Notwithstanding the availability of 38, eventual condensation with 6 did not prove workable in our hands.

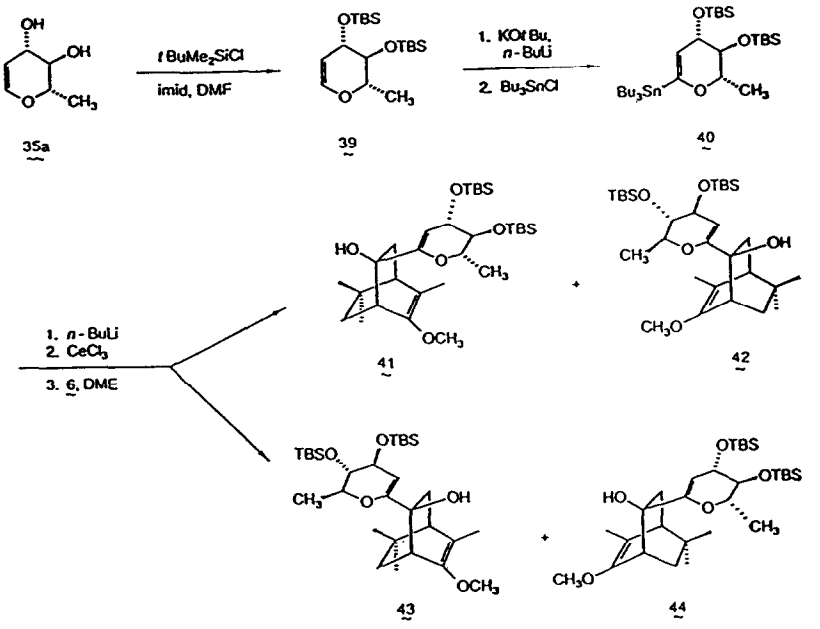


34 35a, R = H; b, R = Bz 36a, R = Bz; b, R = H 37 38

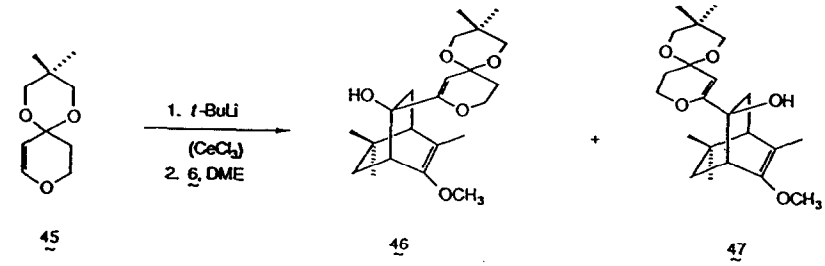
Difficulties paralleling those described above are not unknown.[40] No correlation seemingly exists between the nature and number of substituents present on the glycal and the synthetic utility of the corresponding α-lithio derivative. Nor can we yet offer a satisfactory rationale. In actuality, the observations to follow seemingly becloud the relevant issues further.

Acquisition of Suitable Oxy-Cope Precursors. The pathway to glycal 39 was realized by silylation of diol 35a. The derived vinylstannane 40 was subsequently produced in the predescribed manner. Transmetalation of 40 with *n*-butyllithium, conversion to the dichlorocerium reagent, and addition of 0.5 equiv of 6 at -78 °C provided in 67% yield the four possible diastereomeric alcohols.[41] By means of chromatography, the pair of higher R_f anti alcohols (41 + 42, ratio 1:1, 32%) could be separated from those possessing syn stereochemistry (43 + 44, ratio 2:1, 35%). Exclusion of the $CeCl_3$ afforded the diols in 61% yield and approximately the same ratio (21 and 40%). The preferred direction of attack on 6 in this instance is noteworthy.

In light of the preceding results, it seemed that ketal 45[34f] might be equally responsive to this chemistry. If 46 could be assembled and subsequently engaged successfully in [3,3] sigmatropic rearrangement, some modification of our original plan would be required since 45 is achiral. For the moment, the issue of the prior resolution of 6 is deferred. Lithiation of 45 was effected with *tert*-butyllithium in tetrahydrofuran as



solvent at -78 °C, with eventual warming to 0 °C where the vinyllithium species was stable for short periods of time. This consideration is not inconsequential, since any excess *tert*-butyllithium is effectively destroyed by reaction with the solvent at this temperature and is not available to promote the enolization of 6. Following addition of the tricyclic ketone, there resulted a 1:1 mixture of 46 and 47. These alchols proved readily separable by silica gel chromatography. The more mobile stereoisomer was assigned the anti alcohol

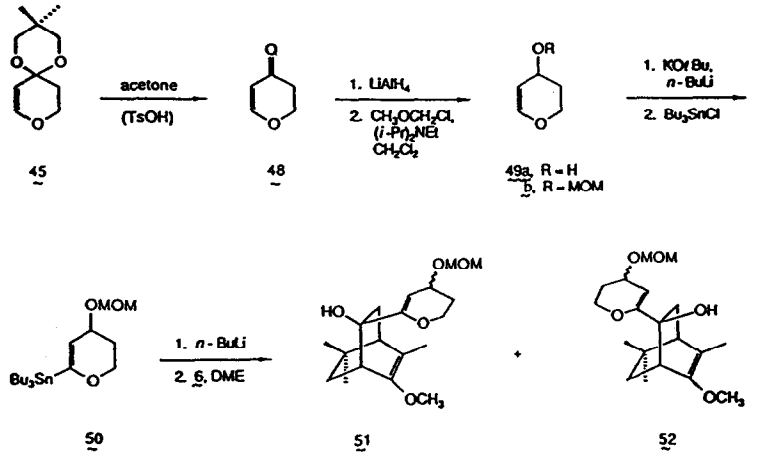


45 46 47

configuration 46 by analogy to the polarity and spectral properties of 16, 17, and 41-44. More specifically, the gem-dimethyl resonances for 46 are characterized by a typically larger chemical shift separation than are those in 47, while the vinyl proton signal in 47 appears downfield of that in 46.

The yield of this coupling reaction could be improved to 60% by preforming the dichlorocerium reagent prior to exposure to 6. More interesting was the attendant increase in the relative proportion of 46 when cerium(III) serves as the counterion. Product ratios were more variable under these circumstances, but the relative distribution of 46:47 peaked at approximately 4.6:1.

In light of the reputed stability of MOM ethers to strong deprotonation conditions,[42] the substituted dihydropyran 49b was prepared as shown in the scheme.[43,44] The *tert*-butyl-



dimethylsilyl[45] and *tert*-butyldiphenylsilyl[46] ethers were also synthesized, but deprotonation problems were subsequently encountered with both of these systems. Similarly, attempts to lithiate 49b directly with *tert*-butyllithium failed to provide for carbinol formation after trapping with benzaldehyde. However, the combination of Schlosser's base and tri-*n*-butyltin chloride once again proved effective and provided for the acquisition of 50 in moderate purity. As with all compounds related to 50, we were forced to forego extensive purification because of rapid degradation of these vinyltin intermediates in the presence of adsorbents. Transmetalation of 50 at -78 °C followed by exposure to 6 proceeded well to make 51 (27%) and 52 (34%) conveniently available.

Attempts to Realize Oxyanionic Cope Rearrangement. The feasibility of achieving [3,3] sigmatropic rearrangement within the potassium alkoxide of 17 was earlier shown to require the presence of 18-crown-6 and somewhat forcing conditions (refluxing tetrahydrofuran). The root cause of the kinetic retardation may be the vinylic methyl and methoxyl groups present on the bicyclo[2.2.2]octene substructure. To what extent would additional substituents on the dihydropyran component impede symmetry-allowed electrocyclization? Whereas some additional kinetic retardation was anticipated, a total shutdown of the rearrangement was certainly not expected.

Alcohols 41/42, 46, and 51 were in turn subjected to a substantial number of varied conditions deemed favorable for conversion to tricyclic enolate ions typified by 18 and 19. These included heating with potassium hexamethyldisilazide or potassium hydride in either tetrahydrofuran (25 → 70 °C) or diglyme (25 → 140 °C) containing 18-crown-6. Pretreatment of the KH with iodine[47] offered no particular advantage. In every instance, only starting material was recovered in varying amounts.[48] The efficiency of the recovery was related directly to the duration of reaction and in particular to the harshness of the conditions employed. However, under no circumstances was ketone formation evident. The degradation products, when present, were complex and non-characterizable.

In summary, we have shown that certain 2-lithiodihydropyrans can be prepared and utilized with resonable efficiency to construct relatively complex alcohols. Unfortunately, even minimal substitution of the dihydropyran ring precludes operation of the oxy-Cope rearrangement that would make available the tricyclic forskolin framework. The greater steric demands imparted by these pendant groups on the transition state for [3,3] sigmatropic shift appear to be sufficient to give structural degradation the kinetic advantage. The additional oxygenated groups could also be exerting electronic effects of a deleterious nature. As the sophistication of [3,3] sigmatropy continues to grow, constructive delineation of these effects should prove feasible.

Experimental Section

2,4,4-Trimethyl-2-cyclohexenone (8). A magnetically stirred solution of 81 mL (0.89 mol) of isobutyraldehyde and 50 g (0.594 mol) of ethyl vinyl ketone was treated in three portions with 1.5 mL of concentrated sulfuric acid over a 1-h period. Occasional cooling in an ice bath was necessary to maintain a temperature below 50 °C. The mixture was stirred for 5 h before the reaction flask was fitted with a reflux condenser and Dean-Stark trap and heated for 12 h so as to collect 14 mL of water. The volatiles were removed at 15 Torr and 25 °C, at which point the remaining liquid was vacuum distilled to give 8 as a clear, colorless oil, bp 38-40 °C at 0.5 Torr; 51.5 g (63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 2.25 (t, J = 6.8 Hz, 2 H), 1.64 (t, J = 6.8 Hz, 2 H), 1.53 (s, 3 H), 0.95 (s, 6 H); MS m/z (M^+) calcd 138.1045, obsd 138.1045.

3-Allyl-2,4,4-trimethylcyclohexanone (9). To a cold (-78 °C), magnetically stirred solution of 10 g (72.4 mmol) of 8 in 125 mL of dichloromethane was added dropwise over 30 min 108 mL (108 mmol, 1.5 eq) of 1.0 M titanium tetrachloride in dichloromethane. The mixture was stirred an additional 15 min, allyltrimethylsilane was added neat in dropwise fashion over 15 min, and the contents were stirred at -78 °C for 3 h. Progress of the reaction was noted by observing the disappearance of UV-active 8. The reaction mixture was quenched with water (125 mL) while still cold and the organic phase was washed with 100 mL of water prior to drying and solvent evaporation. The residue was purified by silica gel chromatography (elution with 5-20% ether/petroleum ether) to give 11.55 g (89%) of 9 as a mobile, colorless oil; IR (neat, cm^{-1}) 3070, 2955, 2860, 1700, 1627, 1457, 1382, 1360, 1237, 1143, 1003, 905, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1 H), 4.93 (m, 2 H), 2.8-1.1 (series of m, 8 H), 1.05-0.85 (m, 9 H); MS m/z (M^+) calcd 180.1514, obsd 180.1514.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.67; H, 11.20.

Oxidation of 9. To a magnetically stirred solution of 565 mg (3.14 mmol) of 9 in 6 mL of acetonitrile and 6 mL of carbon tetrachloride was added 10 mL of water and 2.75 g (12.9 mmol) of sodium periodate. The resulting biphasic mixture was treated with ca 20 mg of ruthenium trichloride trihydrate. The blackened mixture was vigorously stirred at 25 °C for several hours, diluted with dichloromethane, filtered through a short plug of Celite, and extracted three times with additional dichloromethane. The combined extracts were dried and concentrated, and the residual oil was purified by silica gel chromatography (elution with 20% ether in petroleum ether containing 1% acetic acid). There was isolated 565 mg (92%) of 10 as a white crystalline solid, mp 138-144 °C; IR ($CHCl_3$, cm^{-1}) 3600-2500 (broad), 2980, 1705, 1460, 1410, 1388, 1368, 1293, 1130 (broad); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.6-2.4 (m, 2 H), 2.4-2.1 (m, 3 H), 1.95 (m, 1 H), 1.70 (m, 1 H), 1.0 (m, 9 H); MS m/z (M^+) calcd 198.1282, obsd 198.1257.

An analytical sample was prepared by recrystallization from ether-petroleum ether, mp 138-144 °C.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.40; H, 9.15. Found: C, 66.65; H, 9.20.

exo-3,8,8-Trimethylbicyclo[2.2.2]octane-2,6-dione (11). To a magnetically stirred solution containing 3.70 g (18.66 mmol) of 10 in 80 mL of glacial acetic acid was added 30 g of polyphosphoric acid (prepared by adding 200 g of phosphorus pentoxide in several portions to 100 mL of 85% phosphoric acid and heating at 190 °C for 2 h). The mixture was heated to 100 °C at which point stirring was initiated. After 17 h, the dark-colored solution was poured into brine (200 mL) and extracted with benzene (6 x 50 mL). The combined benzene extracts were washed with saturated sodium bicarbonate solution, dried, and concentrated. The resulting brown oil was purified by silica gel chromatography (elution with 20% ether in petroleum ether) to give 3.07 g (91%) of oily 11, which slowly crystallized upon standing at room temperature; IR ($CHCl_3$, cm^{-1}) 2970, 2965, 2875, 1740, 1715, 1458, 1420, 1398, 1381, 1325, 1158, 1102, 1090, 1060, 1020, 992, 897; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (t, J = 2.9 Hz, 1 H), 2.88 (m, 1 H), 2.66 (ddd, J = 19.54, 3.61, 2.58 Hz, 1 H), 3.34 (dd, J = 9.57, 2.22 Hz, 1 H), 1.87 (m, 2 H), 1.19 (s, 3 H), 1.17 (d, J = 7.3 Hz, 3 H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.65, 206.99, 64.98, 44.87, 42.00, 38.31, 36.47, 31.65, 29.41, 29.00, 13.82; MS m/z (M^+) calcd 180.1150, obsd 180.1150.

An analytically pure sample, mp 63-66 °C, was prepared by recrystallization from petroleum ether.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C. 73.22; H, 8.99.

O-Methylation of 11. To a cold (-23 °C), magnetically stirred solution of 520 mg (2.88 mmol) of 11 and 1.0 mL (5.76 mmol) of HMPA in 10 mL of dry 1,2-dimethoxyethane was added dropwise 2.47 mL (3.46 mmol) of 1.4 M potassium hexamethyldisilazide solution in the same solvent. The resulting orange solution was stirred at -23 °C for 30 min, treated dropwise over 1 min with 0.49 mL of methyl triflate, stirred at -20 °C for 10 min before warming to 25 °C over 20 min and quenching with 10 mL of saturated ammonium chloride solution. The mixture was diluted with ether (20 mL) and extracted further with this solvent (3 x 10 mL). The combined extracts were dried and concentrated, and the crude oil was purified by silica gel chromatography (elution with 5, 10, and finally 50% ether-petroleum ether). There was isolated 312 mg (55%) of 6 and 40 mg (7.2%) of 12.

For 6: colorless oil; IR (neat, cm^{-1}) 2935, 2865, 1725, 1676, 1455, 1409, 1375, 1360, 1338, 1308, 1275, 1255, 1203, 1170, 1140, 1106, 1072, 1020, 912, 900, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3 H), 3.08 (t, J = 2.8 Hz, 1 H), 2.35 (dd, J = 18.6, 2.3 Hz, 1 H), 2.12 (t, J = 2.7 Hz, 1 H), 2.0 (dd, J = 18.6, 3.1 Hz, 1 H), 1.78 (s, 3 H), 1.60 (m, 2 H), 1.09 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.52, 146.47, 121.31, 57.34, 50.46, 49.45, 39.31, 37.01, 34.48, 31.00, 28.59, 15.16; MS m/z (M^+) calcd 194.1307, obsd 194.1302.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.95; H, 9.44.

For 12: colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (dd, J = 7.1, 2.2 Hz, 1 H), 3.56 (s, 3 H), 2.88 (m, 1 H), 2.46 (ddd, J = 14.1, 7.1, 2.1 Hz, 1 H), 2.18 (dd, J = 7.1, 2.1 Hz, 1 H), 1.57 (d, J = 2.7 Hz, 3 H), 1.13 (s, 3 H), 1.08 (d, J = 7.05 Hz, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.96, 154.17, 97.28, 55.09, 53.73, 49.78, 40.39, 38.22, 35.38, 31.64, 28.75, 17.67.

Addition of Vinylmagnesium Bromide to 6. A cold (-78 °C), magnetically stirred solution of 60 mg (0.31 mmol) of 6 in 5 mL of dry tetrahydrofuran was treated dropwise with 0.62 mL (0.62 mmol) of a 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran. The cold bath was removed and the reaction mixture was allowed to warm to 25 °C during 1 h. Following the addition of saturated ammonium chloride solution and ether, the aqueous phase was extracted with ether (3 x 10 mL). The combined organic phases were dried and concentrated, and the residual oil was purified by silica gel chromatography (elution with 10-20% ether in petroleum ether). There was obtained 20 mg (29%) of oily 14 and 35 mg (51%) of crystalline 13 (80% overall yield).

For 13: IR ($CHCl_3$, cm^{-1}) 3570, 2940, 2860, 1678, 1450, 1440, 1412, 1378, 1360, 1310, 1272, 1220, 1148, 1107, 1053, 1025, 1000, 930; ^1H NMR (300 MHz, $CDCl_3$) δ 6.1 (dd, J = 17.2, 10.7 Hz, 1 H), 5.4 (dd, J = 17.3, 1.4 Hz, 1 H), 5.16 (dd, J = 10.7, 1.3 Hz, 1 H), 3.59 (s, 3 H), 2.48 (dd, J = 3.45, 2.3 Hz, 1 H), 2.21 (dd, J = 14.4, 2.2 Hz, 1 H), 1.83 (m, 1 H), 1.77 (s, 3 H), 1.43 (dd, J = 13.4, 2.14 Hz, 1 H), 1.2 (m, 2 H), 1.01 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 150.0, 142.68, 117.50, 113.54, 75.88, 56.55, 49.45, 45.53, 38.51, 37.13, 33.55, 31.34, 28.25, 14.98; MS m/z (M^+) calcd 222.1620, obsd 222.1628.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.24, H, 10.08.

For 14: IR (film, cm^{-1}) 3455, 2945, 2868, 1721, 1687, 1447, 1384, 1366, 1348, 1294, 1226, 1209, 1151, 1116, 1053, 1006, 924; ^1H NMR (80 MHz, $CDCl_3$) δ 5.97 (dd, J = 10.5, 17.3 Hz, 1 H), 5.12 (dd, J = 17.1, 1.4 Hz, 1 H), 4.97 (dd, J = 10.4, 1.4 Hz, 1 H), 3.53 (s, 3 H), 2.35 (t, J = 2.8 Hz, 1 H), 2.2-1.0 (m, 5 H), 1.70 (s, 3 H), 1.16 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.02, 147.13, 117.23, 110.12, 75.72, 56.81, 49.46, 44.73, 37.66, 36.19, 33.33, 31.64, 28.06, 14.83; MS m/z (M^+) calcd 222.1620, obsd 222.1620.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.77; H, 10.05.

Cope Rearrangement of 14. To a 0 °C stirred solution of 15 mg (0.067 mmol) of 14 and 26 mg (0.10 mmol) of 18-crown-6 in 2 mL of dry tetrahydrofuran was added 0.071 mL (0.10 mmol) of 1.4 M potassium hexamethyldisilazide in 1,2-dimethoxyethane solution. The cold bath was removed and the reaction mixture was allowed to warm to 25 °C over 3 h, quenched with saturated ammonium chloride solution and extracted several times with ether. The combined extracts were dried and concentrated, and the residual oil was purified by silica gel chromatography (elution with 5% ether/petroleum ether). There was isolated 10 mg (66%) of 15 as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3010, 2960, 2920, 2870, 1701, 1660, 1460, 1410, 1386, 1363, 1350, 1332, 1220, 1170, 1140, 1128, 1058, 1040, 1015, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 4.50 (t, J = 4.3 Hz, 1 H), 3.50 (s, 3 H), 2.51-2.18 (m, 4 H), 2.00 (m, 2 H), 1.90 (d, J = 4.3 Hz, 2 H), 1.77 (m, 1 H), 1.31 (s, 3 H), 1.02 (s, 3 H), 0.91 (s, 3 H).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.58; H, 9.93.

Addition of 2-Lithiodihydropyran to 6. To a cold (-78 °C), magnetically stirred solution of dihydropyran (84.2 mg, 1.0 mmol) in 0.3 mL of dry tetrahydrofuran was added 0.65 mL (1.1 mmol) of 1.7 M *tert*-butyllithium in pentane. The yellow mixture was warmed to 0 °C and stirred for 60 min. This solution (almost colorless at this point) was added to a cold (-78 °C), magnetically stirred solution of 80 mg (0.412 mmol) of 6 in 4 mL of dry 1,2-dimethoxyethane. The reaction mixture was allowed to reach ambient temperature (25 °C) very gradually during 1 h, quenched with saturated ammonium chloride solution, and extracted with ether (3x). The combined extracts were dried and concentrated. The residue was purified by silica gel chromatography (elution with 10-30% ether in petroleum ether) to give 62 mg (54%) of 17 and 40 mg (35%) of 16, both as colorless oils.

For 16: IR (film, cm^{-1}) 3464, 2929, 2864, 1691, 1664, 1464, 1449, 1384, 1364, 1346, 1286, 1227, 1208, 1154, 1142, 1109, 1069, 1014, 932, 916, 766; ^1H NMR (300 MHz, $CDCl_3$) δ 5.05 (t, J = 3.87 Hz, 1 H), 4.01 (m, 2 H), 3.58 (s, 3 H), 2.87 (dd, J = 3.8, 2.05 Hz, 1 H), 2.36 (dd, J = 14.5, 2.4 Hz, 1 H), 2.08 (m, 2 H), 1.86-1.75 (m, 3 H), 1.74 (s, 3 H), 1.30 (dd, J = 13.2, 2.0 Hz, 1 H), 1.20 (dd, J = 14.5, 3.5 Hz, 1 H), 1.08 (dd, J = 13.1, 3.85 Hz, 1 H), 0.98 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 154.78, 149.41, 116.72,

97.60, 77.52, 66.37, 56.55, 48.94, 41.93, 37.01, 34.35, 33.66, 31.23, 28.69, 22.18, 20.36, 14.99; MS *m/z* (M^+) calcd 278.1882, obsd 278.1893.

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: 73.05; H, 9.55.

For 17: IR ($CHCl_3$, cm^{-1}) 3566, 2955, 2870, 1687, 1672, 1450, 1383, 1348, 1315, 1285, 1253, 1225, 1180, 1155, 1131, 1113, 1094, 1070, 1048, 975, 963, 923; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (t, J = 3.85 Hz, 1 H), 4.0 (m, 2 H), 3.50 (s, 3 H), 2.67 (t, J = 2.8 Hz, 1 H), 2.57 (s, 1 H), 2.02 (m, 3 H), 1.76 (m, 4 H), 1.67 (s, 3 H), 1.15 (s, 3 H), 1.0 (m, 1 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.49, 150.26, 116.21, 96.39, 75.99, 66.38, 56.38, 49.19, 42.41, 35.80, 34.18, 33.70, 31.68, 27.90, 22.11, 20.17, 14.92; MS *m/z* (M^+) calcd 278.1882, obsd 278.1875.

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.43; H, 9.51.

Rearrangement-Protonation of 17. To 17 mg (0.424 mmol) of dry, oil-free potassium hydride was added a solution of 24 mg (0.086 mmol) of 17 in 2 mL of dry tetrahydrofuran. The suspension was stirred at 25 °C for 60 min. To this was added 112 mg of 18-crown-6 and the resulting mixture was heated to 70 °C for 20 min, cooled to 0 °C, and quenched with 2 mL of saturated ammonium chloride solution. The aqueous phase was extracted three times with ether and the combined organic phases were dried and concentrated. The crude product, purified by silica gel chromatography (elution with 15% ether in petroleum ether) afforded 17 mg (68%) of 20; IR ($CHCl_3$, cm^{-1}) 3020, 2930, 1720, 1664, 1520, 1470, 1442, 1390, 1370, 1230, 1162, 1096, 1064, 1050, 1021, 936, 917, 792; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (dd, J = 6.3, 2.2 Hz, 1 H), 4.44 (d, J = 4.9 Hz, 1 H), 3.73-3.67 (m, 1 H), 3.56 (m, 1 H), 3.50 (s, 3 H), 2.51 (dd, J = 18.0, 4.8 Hz, 1 H), 2.27 (dd, J = 17.9, 13.3 Hz, 1 H), 2.16-2.02 (m, 2 H), 1.75-1.48 (m, 5 H), 1.43 (s, 3 H), 1.09 (s, 3 H), 1.07-0.95 (m, 1 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.88, 156.43, 92.90, 63.01, 53.75, 47.41, 47.15, 41.43, 39.94, 33.58, 32.83, 30.03, 29.69, 28.89, 28.15, 27.03, 25.21; MS *m/z* (M^+) calcd 222.1620, obsd 222.1636.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.58; H, 9.93.

Rearrangement-Silylation of 17. To 32 mg (0.8 mmol) of dry, oil-free potassium hydride in a flame-dried, 2-necked 10 mL round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and reflux condenser was added a solution of 68 mg (0.244 mmol) of 17 in 3 mL of anhydrous tetrahydrofuran via canula. The resulting suspension was stirred at 25 °C under nitrogen for 40 min and 211 mg (0.8 mmol) of 18-crown-6 was introduced. The mixture was heated to 75 °C for 20 min before being cooled to -78 °C and treated with a solution of 150 mg (1 mmol) of *tert*-butyldimethylchlorosilane and 0.28 mL (2 mmol) of triethylamine in 2 mL of tetrahydrofuran (the amine hydrochloride was first removed via centrifugation). The reaction mixture was warmed to 25 °C over 20 min and quenched with water. The aqueous phase was extracted with ether (2 x 10 mL) and the combined organic phases were dried and concentrated. The residual yellow oil was purified by silica gel chromatography (elution with 5% ether in petroleum ether) to give 78.2 mg (82%) of 21 as a clear colorless oil; IR ($CHCl_3$, cm^{-1}) 2995, 2965, 2930, 2860, 2830, 1662, 1468, 1460, 1388, 1375, 1360, 1300, 1282, 1255, 1220, 1180, 1141, 1129, 1092, 1062, 1032, 1010, 950, 922, 910, 893, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (dd, J = 3.2, 2.3 Hz, 1 H), 4.54 (dd, J = 7.25, 1.75 Hz, 1 H), 4.34 (t, J = 2.6 Hz, 1 H), 3.60 (m, 1 H), 3.48 (s, 3 H), 3.34 (dt, J = 11.0, 3.35 Hz, 1 H), 2.13 (m, 1 H), 1.95 (m, 2 H), 1.79 (dd, J = 15.4, 7.3 Hz, 1 H), 1.58-1.34 (m, 4H), 1.17 (s, 3 H), 1.01 (s, 3 H), 0.97 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.03, 148.16, 105.62, 91.88, 70.42, 63.20, 54.20, 52.56, 40.41, 40.15, 38.75, 33.59, 31.51, 30.83, 26.53, 25.80, 24.65, 24.18, 18.34, -4.45, -4.50; MS *m/z* (M^+) calcd 392.2747, obsd 392.2713.

Rearrangement-Selenenylation of 17. The oxyanionic Cope rearrangement was performed on 17 (25 mg, 0.09 mmol) exactly as described above. Following cooling of the reaction mixture to -78 °C, 34.5 mg (0.18 mmol) of phenylselenenyl chloride was added as a solution in 1 mL of tetrahydrofuran. The temperature was maintained at -78 °C with stirring for 1 h, the cold bath was removed, and the reaction mixture was quenched with saturated ammonium chloride solution. The aqueous phase was extracted with ether and the combined organic phases were dried and concentrated. The resulting crude oil was purified by silica gel chromatography (elution with 20% ether in petroleum ether) to give 31 mg (79%) of 22, homogeneous by TLC and spectroscopic analysis. Recrystallization from ether-petroleum ether afforded yellow cubic-shaped crystals, mp 139-141 °C; IR ($CHCl_3$, cm^{-1}) 3000, 2955, 2930, 1700, 1668, 1432, 1462, 1448, 1437, 1391, 1380, 1369, 1350, 1258, 1215, 1144, 1118, 1092, 1065, 1040, 1000, 942, 910, 882, 840, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2 H), 7.32 (m, 3 H), 5.49 (J = 6.0 Hz, 1 H), 4.57 (dd, J = 6.9, 1.8 Hz, 1 H), 3.94 (m, 1 H), 3.86 (d, J = 0.85 Hz, 1 H), 3.65 (dm, J = 15 Hz, 1 H), 3.50 (s, 3 H), 2.51 (m, 1 H), 2.25 (s, 1 H), 2.05 (d, J = 15.6 Hz, 1 H), 1.84 (dd, J = 15.9, 7.0 Hz, 1 H), 1.65 (s, 3 H), 1.59-1.51 (m, 3 H), 1.25-1.1 (m, 1 H), 1.10 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.12, 157.90, 135.40, 129.98, 129.28, 128.96, 92.15, 72.71, 63.55, 59.68, 54.22, 48.10, 47.72, 42.00, 39.05, 34.62, 32.95, 30.60, 27.75, 24.72, 23.27; MS *m/z* (M^+) calcd 434.1360, obsd 434.1405.

Oxidation-Elimination of 22. To a magnetically stirred solution of 22 in 7 mL of absolute methanol and 1.5 mL of water was added 189 mg (2.25 mmol) of sodium bicarbonate followed by 482 mg (2.25 mmol) of sodium periodate. The mixture was stirred at 25 °C for 1 h, the precipitated solids were removed by filtration, and the filtrate was concentrated. The crude product was taken up in ether and washed with saturated ammonium chloride solution. The aqueous layer was extracted several times with ether, and the combined organic phases were dried and concentrated. The crude product was purified by silica gel chromatography (elution with 40% ether in petroleum ether) to provide 113 mg of 23 as a white solid. Recrystallization from petroleum ether gave colorless plates, mp 98-100 °C; IR ($CHCl_3$,cm^{-1}) 3005, 2960, 2940, 2870, 2835, 1660, 1605, 1462, 1448, 1385, 1352, 1270, 1210, 1170, 1145, 1126, 1100, 1064, 1048, 1010, 950, 928, 905; ^1H NMR (300 MHz, $CDCl_3$) δ

5.95 (s, 1 H), 4.68 (dd, J = 5.9, 2.65 Hz, 1 H), 4.61 (d, J = 5.1 Hz, 1 H), 3.71 (m, 1 H), 3.55 (s, 3 H), 3.38 (m, 1 H), 2.56 (ddd, J = 12.5, 5.2, 3.7 Hz, 1 H), 2.02 (m, 2 H), 1.69-1.42 (m, 4 H), 1.55 (s, 3 H), 1.23 (s, 3 H), 1.17 (s, 3 H), 1.2-1.04 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.88, 173.41, 154.94, 122.10, 91.95, 75.65, 63.25, 54.58, 46.94, 45.54, 37.55, 36.41, 28.58, 27.77, 25.80, 25.61, 21.71; MS m/z (M^+) calcd 276.1725, obsd 276.1724.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.91; H, 8.72.

Methylation of 23. A cold (0 °C), magnetically stirred solution of diisopropylamine (117 μL, 0.84 mmol) in 3 mL of tetrahydrofuran was treated with 0.49 mL (0.80 mmol) of 1.6 M *n*-butyllithium in hexanes. This solution was stirred at 0 °C for 20 min and cooled to -78 °C whereupon 110 mg (0.398 mmol) of **23** was added as a solution in 3 mL of tetrahydrofuran. The reaction mixture was warmed to 0 °C, stirred for 40 min before 1.4 mL of HMPA was added, recooled to -78 °C (5 mL more tetrahydrofuran was added to allow stirring), and treated with 124 μL (4.0 mmol) of methyl iodide. The mixture was warmed to 25 °C over 20 min, stirred at ambient temperature for 2 h, and quenched with 25 mL of saturated ammonium chloride solution and 5 mL of water. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic layers were dried and concentrated. The residue was purified by silica gel chromatography to give 44.6 mg (39%) of **24** as an oil and 60.3 mg (52%) of **25** as a white solid.

For **24**: IR ($CHCl_3$, cm^{-1}) 3060, 2930, 2830, 1720, 1670, 1605, 1460, 1379, 1368, 1353, 1338, 1312, 1293, 1270, 1232, 1202, 1155, 1140, 1125, 1060, 1042, 1013, 980, 950, 925, 897, 787, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1 H), 4.62 (dd, J = 6.6, 1.27 Hz, 1 H), 4.16 (dt, J = 10.5, 4.0 Hz, 1 H), 3.70 (d, J = 0.64 Hz, 3 H), 3.65 (dt, J = 10.76, 3.17 Hz, 1 H), 3.48 (s, 3 H), 2.23 (dd, J = 12.0, 4.2 Hz, 1 H), 1.97 (d, J = 14.25 Hz, 1 H), 1.94-1.75 (m, 2 H), 1.64 (m, 1 H), 1.32 (s, 3 H), 1.35-1.16 (m, 2 H), 1.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.21, 144.77, 139.96, 135.69, 113.81, 92.44, 72.26, 58.80, 53.87, 47.33, 42.64, 38.74, 34.60, 28.75, 28.15, 26.68, 24.97, 23.77; MS m/z (M^+) calcd 290.1882, obsd 290.1875.

For **25**: IR ($CHCl_3$, cm^{-1}) 3000, 2960, 2870, 2835, 1667, 1608, 1463, 1449, 1439, 1379, 1349, 1263, 1216, 1168, 1142, 1122, 1103, 1095, 1062, 989, 890, 830; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (s, 1 H), 4.57 (dd, J = 5.6, 3.0 Hz, 1 H), 3.70 (m, 1 H), 3.51 (s, 3 H), 3.26 (dt, J = 12.0, 3.0 Hz, 1 H), 2.16 (dd, J = 12.3, 3.9 Hz, 1 H), 1.98 (m, 2 H), 1.63 (s, 3 H), 1.59-1.43 (m, 3 H), 1.46 (s, 3 H), 1.3-0.8 (m, 1 H), 1.21 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.47, 172.0, 156.77, 121.42, 90.79, 78.89, 63.67, 54.47, 51.89, 46.15, 38.07, 36.57, 30.48, 29.25, 28.83, 27.66, 25.63, 24.33; MS m/z (M^+) calcd 290.1880, obsd 290.1905. An analytical sample was prepared by recrystallization from petroleum ether, mp 124-126 °C.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.54; H, 9.11.

Acidic Hydrolysis of 24. To a magnetically stirred solution containing 80 mg (0.276 mmol) of **24** in 3 mL of tetrahydrofuran was added 0.5 mL of 10% hydrochloric acid. The reaction mixture was stirred for 2 h at 25 °C, then diluted with 10 mL of ether and 5 mL of water. The aqueous phase was extracted with ether (3x), the combined organic layers were dried and concentrated, and the product was purified by silica gel chromatography (elution with 20% ether in petroleum ether) to deliver **23** in quantitative yield.

Hydride Reduction of 25. To a cold (0 °C), magnetically stirred solution of 55 mg (0.19 mmol) of **25** in 1 mL of dichloromethane was added 0.284 mL (0.284 mmol, 1.5 equiv) of diisobutylaluminum hydride in hexanes (1.0 M). The reaction mixture was stirred with warming to 25 °C over 25 min before being quenched with a solution of sodium potassium tartrate in water. The aqueous phase (after dilution with ether) was extracted several times with ether, the combined organic phases were dried and concentrated, and the residual oil was purified by silica gel chromatography (gradient elution with 10-50% ether in petroleum ether). There was obtained 49 mg (88%) of **27a** as an oil, which solidified to a white solid upon prolonged storage at 25 °C, mp 93-94 °C; IR ($CHCl_3$, cm^{-1}) 3520, 3000, 2960, 2875, 2832, 1668, 1645, 1462, 1448, 1405, 1371, 1352, 1238, 1172, 1150, 1133, 1092, 1056, 1038, 1000, 987, 900, 868, 852; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (d, J = 1.8 Hz, 1 H), 4.64 (dd, J = 6.8, 2.0 Hz, 1 H), 4.12 (dd, J = 9.35, 1.8 Hz, 1 H), 3.74 (m, 1 H), 3.60 (m, 1 H), 3.50 (s, 3 H), 3.29 (d, J = 9.4 Hz, 1 H), 1.90 (AB of ABX, $\Delta\nu$ = 47 Hz, J_{AB} = 15.6 Hz, J_{AX} = 1.7 Hz, J_{BX} = 6.8 Hz), 1.75-1.61 (m, 2 H), 1.47-1.32 (m, 2 H), 1.42 (s, 3 H), 1.21 (s, 3 H), 1.13 (s, 3 H), 1.08 (s, 3 H), 1.01-0.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.11, 149.01, 123.21, 92.18, 75.59, 72.45, 58.79, 54.09, 50.26, 43.55, 37.28, 34.32, 29.10, 28.39, 27.05, 23.39, 22.41, 22.05; MS m/z (M^+) calcd 292.2038, obsd 292.2072.

Sulfenylation of 27a. To a magnetically stirred solution of 25 mg (0.086 mmol) of **27a** in 1 mL of anhydrous (distilled from calcium hydride) 1,2-dichloroethane was added 2.6 mL (0.26 mmol) of a 0.1 M solution of 2,4-dinitrobenzenesulfenyl chloride in the same solvent, followed by 72 μL (0.52 mmol) of triethylamine. The reaction mixture was stirred at 25 °C for 30 min, diluted with pentane, filtered to remove the solids, and concentrated. The crude product was purified by silica gel chromatography (elution with 5-20% ether in petroleum ether) to give 25.7 mg (61%) of yellow oily **27b**, which solidified upon evaporative crystallization; IR ($CHCl_3$, cm^{-1}) 2990, 2970, 2930, 2870, 1718, 1592, 1585, 1510, 1492, 1380, 1340, 1300, 1220, 1135, 1110, 1052, 1023, 970, 918, 900, 867, 832; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 2.35 Hz, 1 H), 8.50 (dd, J = 9.2, 2.34 Hz, 1 H), 8.35 (d, J = 9.2 Hz, 1 H), 5.67 (d, J = 2.3 Hz, 1 H), 4.64 (dd, J = 6.73, 1.85 Hz, 1 H), 4.31 (d, J = 2.29 Hz, 1 H), 3.82 (m, 2 H), 3.52 (s, 3 H), 1.99-1.83 (m, 2 H), 1.80 (dd, J = 11.4, 4.3 Hz, 1 H), 1.61-1.45 (m, 3 H), 1.52 (s, 3 H), 1.28 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 0.85-0.78 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.07, 155.76, 152.87, 144.36, 138.99, 127.56, 124.56, 120.99, 117.26, 91.77, 88.77, 75.61, 61.97, 54.27, 48.96, 44.23, 37.50, 35.06, 31.14, 28.68, 26.92, 24.00, 22.83.

Catalytic Hydrogenation of 25. To a rapidly stirred suspension of 85 mg of 10%

palladium on carbon in 1 mL of 0.3 N potassium hydroxide in ethanol was added 35 mg (0.121 mmol) of **25** as a solution in 2 mL of ethanol. The suspension was stirred vigorously under 1 atmosphere of hydrogen for 48 h, diluted with ether (5 mL), and filtered through a plug of Celite. The crude product was purified by silica gel chromatography (elution with 15% ether in petroleum ether) to give 29 mg (82%) of **26** as a white crystalline solid, mp 108-110 °C (from petroleum ether); IR ($CHCl_3$, cm^{-1}) 3000, 2920, 2850, 1708, 1660, 1460, 1408, 1385, 1365, 1352, 1286, 1263, 1205, 1160, 1138, 1098, 1060, 1035, 1012, 990, 972, 920, 872, 839, 828; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (dd, J = 7.3, 1.7 Hz, 1 H), 3.73-3.67 (m, 1 H), 3.49 (s, 3 H), 3.38 (dt, J = 12.0, 3.35 Hz, 1 H), 2.55 (dd, J = 18.3, 4.7 Hz, 1 H), 2.29 (dd, J = 18.4, 4.3 Hz, 1 H), 2.09 (d, J = 16.5 Hz, 1 H), 1.85-1.43 (series of m, 6 H), 1.54 (s, 3 H), 1.46 (s, 3 H), 1.12 (s, 3 H), 1.01-0.86 (m, 1 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.93, 157.56, 92.71, 81.12, 63.48, 53.66, 52.08, 47.64, 42.34, 40.25, 33.14, 32.80, 31.06, 30.00, 29.58, 27.22, 26.89, 26.75; MS m/z (M^+) calcd 292.2038, obsd 292.2025.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.08; H, 9.74.

***L*-Rhamnal 3-Benzoate (35b).** To a magnetically stirred solution of 15 g (70 mmol) of *L*-rhamnal diacetate in 150 mL of absolute methanol was added several drops of 2 M sodium methoxide solution in methanol. An additional 0.5 mL of methoxide solution was added after 30 min and stirring was continued for 6 h. The reaction mixture was concentrated, diluted with benzene, and concentrated to leave the diol as a yellow solid. This material was taken up in 150 mL of anhydrous pyridine, cooled to -35 °C, and treated dropwise with 8.71 mL (75 mmol) of benzoyl chloride over 5 min. The reaction mixture was maintained at -35 °C for 2 h, warmed to 25 °C for 12h, diluted with 300 mL of diethyl ether, and washed with water (2 x 100 mL) and copper(II) sulfate solution (2 x 100 mL). The aqueous solutions were extracted with ether and the combined organic phases were dried and concentrated. The resulting oily residue was purified by silica gel chromatography (elution with 5-50% ether in petroleum ether) to give 2.9 g of bis-benzoate, 11.79 g (72%) of **35a**, and 1.5 g of a mixture of **35a** and lower R_f impurities. Rechromatography of the impure material provided an additional 750 mg of **35b** (total yield 76.5%) isolated as a clear, colorless oil which slowly crystallized upon prolonged standing, mp 64-65 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3440, 3060, 3020, 2990, 2985, 2915, 2880, 1690, 1640, 1595, 1580, 1445, 1385, 1333, 1312, 1262, 1173, 1140, 1095, 1060, 1022, 942; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09-8.00 (m, 2 H), 7.67-7.52 (m, 1 H), 7.49-7.31 (m, 2 H), 6.50 (dd, J = 6.1, 1.4 Hz, 1 H), 5.54-5.40 (m, 1 H), 4.82 (dd, J = 6.1, 2.6 Hz, 1 H), 4.12-3.85 (m, 1 H), 3.83-3.73 (m, 1 H), 3.47 (br s, 1 H), 1.45 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.02, 146.74, 133.38, 129.80, 129.68, 128.43, 98.79, 74.85, 74.32, 72.71, 17.11; MS m/z (M^+-H_2O) calcd 216.0786, obsd 216.0803; $[\alpha]_D^{25}$ +113.04° (*c* 1.02, $CHCl_3$).

Conversion of 35b to its Xanthante. To a magnetically stirred suspension of 1.80 g (72.4 mmol) of 97% sodium hydride in 20 mL of carbon disulfide (freshly filtered through neutral alumina) was added 11.3 g (48.2 mmol) of **35b** as a solution in 150 mL of carbon disulfide over a period of 15 min. While the mixture was stirred for 30 min, there was produced a greenish-yellow colored appearance with an amorphous, gummy solid. To this was added 30 mL of methyl iodide over a 20 min period. The reaction mixture was stirred at 25 °C for 16 h before being cooled to 0 °C and carefully quenched with 20 mL of ammonium chloride solution. After dilution with 300 mL of ether, the aqueous phase was extracted with ether (3 x 100 mL) and the combined organic phases were dried and concentrated. Silica gel chromatography of the residue (elution with 5-20% ether in petroleum ether) yielded 14.88 g (98%) of a yellow viscous oil. Peak shaving techniques provided a colorless oil for spectroscopic and combustion analysis; IR (neat, cm^{-1}) 3060, 2970, 2940, 2860, 1710, 1639, 1595, 1580, 1485, 1445, 1405, 1335, 1310, 1265, 1240, 1205, 1155, 1105, 1060, 1020, 960, 860, 840, 800, 750, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2 H), 7.59-7.52 (m, 1 H), 7.46-7.40 (m, 2 H), 6.51 (dd, J = 7.15, 1.0 Hz, 1 H), 6.17 (dd, J = 7.0, 5.3 Hz, 1 H), 5.66 (t, J = 4.3 Hz, 1 H), 5.00 (dd, J = 6.15, 3.3 Hz, 1 H), 4.46-4.36 (m, 1 H), 2.55 (s, 3 H), 1.45 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.40, 165.66, 145.98, 133.05, 129.77, 129.67, 128.31, 98.30, 79.21, 72.06, 67.95, 19.19, 16.32; MS m/z (M^+-OC(S)SMe) calcd 217.0865, obsd 217.0878; $[\alpha]_D^{25}$ +176.06° (*c* 0.685, $CHCl_3$).

Anal. Calcd for $C_{15}H_{16}O_4S_2$: C, 55.54; H, 4.97. Found: C, 55.81; H, 5.14.

(+)-(2*S*,4*R*)-2-Methyl-4-hydroxy-3,4-dihydro-2*H*-pyran (36b). To a warm (80 °C), magnetically stirred solution of 440 mg (1.41 mmol) of **35b** and 15 mg of AIBN in 5 mL of benzene was added 1.52 mL (5.6 mmol) of neat tri-*n*-butyltin hydride via syringe. The reaction mixture was rapidly stirred at the reflux temperature for 20 min before being cooled, concentrated, and rapidly purified by silica gel chromatography (deactivated with 5% triethylamine; elution with petroleum ether containing 5% trimethylamine, followed by petroleum ether containing a trace of ether). There was isolated 370 mg of unstable deoxygenated benzoate. This oil was immediately dissolved into 10 mL of methanol and treated with 0.5 mL of 2 M methanolic sodium methoxide solution. After 3 h, an additional 1 mL of the methoxide solution was added and stirring was maintained for a total of 16 h. The solution was concentrated and 10 mL of ammonium chloride solution was added. The aqueous phase was extracted twice with ether, the organic layers were dried and concentrated, and the oily residue was purified by silica gel chromatography (elution with 50% ether in petroleum ether). There was isolated 99 mg (61%) of **36a** as a clear, colorless oil; IR (neat, cm^{-1}) 3350, 3060, 2970, 2910, 2865, 1633, 1442, 1380, 1230, 1150, 1135, 1090, 1062, 1025, 912, 828, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, J = 6.1 Hz, 1 H), 4.71 (dt, J = 6.9, 1.9 Hz, 1 H), 4.45-4.37 (m, 1 H), 4.09-3.98 (m, 1 H), 2.17-2.08 (m, 1 H), 2.01 (br s, 1 H), 1.59-1.51 (m, 1 H), 1.27 (d, J = 6.35 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.05, 105.26, 71.18, 63.04, 39.82, 20.89; MS m/z (M^+) calcd 114.0681, obsd 114.0682; $[\alpha]_D^{25}$ +20.65° (*c* 0.615, $CHCl_3$).

Methoxymethyl Ether 37. To a cold (0 °C), magnetically stirred solution of **36b** (290 mg, 2.54 mmol) and diisopropylethylamine (1.77 mL, 10.2 mmol) in dichloromethane (10 mL) was added 0.39 mL (5.1 mmol) of chloromethyl methyl ether. The reaction mixture was gradually warmed to 25 °C over 1 h and maintained as such for 18 h. After being quenched

with sodium bicarbonate solution, the reaction mixture was diluted with ether, and the organic phase was washed with copper(II) sulfate solution, dried, and concentrated. The oily residue was purified by silica gel chromatography (elution with 20% ether in petroleum ether) to give 269 mg (67%) of 37 as a clear, colorless oil; IR (neat, cm^{-1}) 3050, 2920, 2870, 1628, 1430, 1375, 1226, 1135, 1025, 908, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (dd, J = 6.3, 1.0 Hz, 1 H), 4.75-4.71 (m, 1 H), 4.66 (s, 2 H), 4.34-4.27 (m, 1 H), 4.09-3.98 (m, 1 H), 3.35 (s, 3 H), 2.18-2.09 (m, 1 H), 1.72-1.60 (m, 1 H), 1.27 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.38, 102.73, 95.17, 70.97, 68.48, 55.23, 36.80, 20.98; MS m/z (M^+) calcd 158.0943, obsd 158.0987; $[\alpha]_D^{25}$ +52.63° (c 1.845, $CHCl_3$).

Bissilylation of *L*-Rhamnal. To a magnetically stirred solution of 5.0 g (23.34 mmol) of *L*-rhamnal diacetate in 55 mL of anhydrous methanol was added several drops of methanolic 2 M sodium methoxide solution. After 3 h, the reaction mixture was concentrated, diluted with benzene (100 mL), and reconcentrated to leave the diol as a white solid. This diol was taken up in 40 mL of dimethylformamide and treated with 7.62 g (0.112 mol) of imidazole followed by 8.44 g (56 mmol) of *tert*-butyldimethylchlorosilane. The resulting solution was stirred at 25 °C for 16 h, diluted with 200 mL of ether, and washed with water (1 x 100 mL) and copper(II) sulfate solution (2 x 100 mL). The aqueous phases were back extracted once with ether, then the combined organic layers were dried and concentrated. The crude product was purified by silica gel chromatography (elution with 1-2% ether in petroleum ether) to furnish 8.03 g (96%) of 39 as a clear, homogeneous, colorless oil; IR (neat, cm^{-1}) 3060, 2950, 2920, 2880, 2850, 1640, 1468, 1459, 1405, 1385, 1357, 1247, 1165, 1110, 1070, 1042, 1002, 975, 938, 890, 870, 835, 775; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J = 6.25, 0.9 Hz, 1 H), 4.66 (dd, J = 6.2, 3.2 Hz, 1 H), 4.07 (m, 1 H), 3.93 (m, 1 H), 3.57 (dd, J = 6.4, 5.0 Hz, 1 H), 1.31 (d, J = 6.7 Hz, 3 H), 0.91 (s, 12 H), 0.12, 0.10, 0.096 (3s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.08, 102.75, 75.19, 74.79, 69.29, 26.05, 25.97, 18.16, 18.10, 17.17, -3.68, -3.90, -4.11, -4.24; MS m/z (M^+-CH_3) calcd 343.2080, obsd 343.2130; $[\alpha]_D^{25}$ +54.87° (c 1.56, $CDCl_3$). An analytical sample was prepared by silica gel chromatography.

Anal. Calcd for $C_{18}H_{38}O_3Si_2$: C, 60.28; H, 10.69. Found: C, 60.44; H, 10.71.

Condensation of 40 with 6. A cold (-78 °C), magnetically stirred solution of 1.38 g (12.3 mmol) of potassium *tert*-butoxide in 40 mL of anhydrous tetrahydrofuran was treated with 8.7 mL (13.9 mmol) of 1.6 M *n*-butyllithium in hexanes. After 15 min, 2.75 g (7.7 mmol) of 39 was added as a solution in 5 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred for 60 min before 6.3 mL (23.1 mmol) of neat tri-*n*-butyltin chloride was introduced via syringe. The solution was gradually warmed to 25 °C over 1 h and recooled to 0 °C before being quenched with saturated ammonium chloride solution. The organic phase was dried and concentrated to leave 40 as a yellow oil, which was decolorized by rapid elution through a short column of silica gel (deactivated with triethylamine; elution with 2% triethylamine in petroleum ether) and utilized as such.

A cold (-78 °C), magnetically stirred solution of 1.3 g (2 mmol) of 40 in 2 mL of anhydrous tetrahydrofuran was treated with 1.25 mL (2 mmol) of 1.6 M *n*-butyllithium in hexanes. After 40 min of stirring at -78 °C, 194 mg (1 mmol) of 6 was introduced as a solution in 2 mL of anhydrous 1,2-dimethoxyethane. The reaction mixture was stirred at -78 °C for 15 min before being warmed to 25 °C over 15 min, quenched with ammonium chloride solution (10 mL), and extracted with ether. The combined organic phases were dried and concentrated to leave a crude product which was purified by silica gel chromatography (elution with 10% ether-petroleum ether). There was isolated 115.7 mg (21%) of a 1:1 mixture of diastereomers 41/42 and 224 mg (40%) of a 2:1 mixture of 43/44.

The same products were similarly prepared through the intermediacy of the dichlorocerium reagent. Thus, the vinyl anion, prepared as above, was added via canula at -78 °C to a stirred suspension (-78 °C) of anhydrous cerium(III) chloride (from 745 mg of cerium trichloride heptahydrate, dried at 1 Torr and 135 °C for 2 h in 1 mL of anhydrous tetrahydrofuran. The cerate was stirred for 60 min at -78 °C before 194 mg (1 mmol) of 6 was introduced. The higher R_f mixture 41/42 (1:1) was isolated as an oil (177.9 mg, 32%). The less mobile mixture 43/44 (2:1) was also isolated as an oil (195.8 mg, 35%).

For 41/42: The following signals were culled from the relatively complex 300 MHz ^1H NMR spectrum in $CDCl_3$: δ 4.60 (d, J = 3.05 Hz) and 4.68 (d, J = 3.05 Hz) - vinylic, 3.52 (s) and 3.47 (s) - methoxyl, 1.67 (s) and 1.64 (s) - vinylic methyl, 1.30 (d, J = 6.6 Hz, 3 H) - pyran ring methyl - overlapping for the two diastereomers, 1.15 (s, 3 H) - gem-dimethyl, 0.89 (s, 3 H) - gem-dimethyl, 0.90 (s, 9 H), - *tert*-butyl, 0.88 (s, 9 H) - *tert*-butyl, 0.09, 0.084, 0.078, 0.069 singlets for silyl-methyls: ^{13}C NMR (75 MHz, $CDCl_3$) ppm (156.33, 155.74), 150.18, 116.46, (99.82, 99.04), 75.90, 75.74, 75.51, 75.46, 74.85, (70.78, 70.47), 56.47, (49.34, 49.21), (42.83, 42.51), (35.99, 35.82), (35.21, 35.07), (33.75, 33.64), (31.80, 31.70), 27.88, (15.13, 14.90) (Si-C not included).

For 43/44: ^1H NMR (300 MHz, $CDCl_3$) δ 5.00-4.97 (1 H, vinylic), 3.59 and 3.58 (s, 3 H, methoxyls), 1.75 (s, 3 H, vinylic methyl), 1.32 and 1.31 (d, 3 H, J = 6.75 Hz, pyran methyl), 1.00 and 0.99 (s, 3 H, gem-dimethyl), 0.86 and 0.855 (s, 3 H, gem-dimethyl), 0.10, 0.09, 0.088, 0.080 (s, 3 H each, methyl of silyl groups); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (154.55, 153.82), (149.65, 149.59), 116.77, (99.44, 98.88) - vinyl carbons; 77.13, (75.55, 75.32), (74.16, 73.93), (69.88, 69.18), 56.80, 49.14, (43.11, 42.69), (37.81, 36.75), (34.56, 34.30), (33.63, 33.56), (31.35, 31.31), (28.52, 28.48), 15.09 (Si-C not included).

Condensation of 45 with 6. To a cold (-78 °C), magnetically stirred solution of 373 mg (2.02 mmol) of 45 in 1.5 mL of tetrahydrofuran was added 1.76 mL (3.0 mmol) of 1.76 M *tert*-butyllithium in pentane. The temperature was raised to 0 °C and maintained as such with stirring for 60 min. This greenish-colored solution was added to a cold (-78 °C) stirred suspension of anhydrous cerium (III) chloride in 3 mL of tetrahydrofuran (from 782 mg $CeCl_3 \cdot 7H_2O$, dried at 140 °C and 0.5 Torr for 2.5 h, then stirred in tetrahydrofuran at 25 °C for 2 h) via canula. The resulting suspension (orange-brown colored) was stirred at

-78 °C for 60 min. To this was added 245 mg (1.26 mmol) of **6** as a solution in 2 mL of 1,2-dimethoxyethane. After 2 h at -78 °C, the mixture was warmed to 25 °C during 1 h prior to quenching with 10 mL of ammonium chloride solution. Hydrochloric acid (1.0 M) was carefully added to break the resulting emulsion but not to lower the pH below 6. The aqueous phase was extracted several times with ether and the combined organic layers were dried and concentrated. The resulting oily product was purified by silica gel chromatography (elution with 20-80% ether in petroleum ether). There was isolated 210 mg of **46** as a clear, colorless oil, 48.7 mg of impure **47**, 64 mg of impure **46**, and 113 mg of unreacted **45**. Rechromatography of the impure fractions gave 230 mg (48%) of pure **46** and 50 mg (11%) of pure **47**, both as clear, colorless oils.

For **46**: IR ($CHCl_3$, cm^{-1}) 3560, 3430, 3290, 2940, 2850, 1670, 1650, 1595, 1540, 1455, 1356, 1338, 1250, 1215, 1170, 1145, 1100, 1075, 958, 908, 870, 715; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (s, 1 H), 4.14 (t, J = 5.8 Hz, 2 H), 3.70 (dd, J = 11.5, 4.45 Hz, 2 H), 3.50 (s, 3 H), 3.38 (d, J = 11.6 Hz, 2 H), 2.64 (t, J = 2.8 Hz, 1 H), 2.4 (s, 1 H), 2.07-1.71 (m, 6 H), 1.70 (s, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.09-0.91 (m, 1 H), 0.88 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.58, 149.99, 115.78, 93.94, 93.11, 76.02, 70.37 (2C), 64.53, 56.26, 49.30, 42.71, 35.77, 35.49, 33.82, 33.68, 31.70, 30.07, 27.91, 23.09, 22.36, 15.01; MS m/z (M^+-$C(CH_3)_3CH_2OH$) calcd 292.1674, obsd 292.1709.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.95; H, 9.34.

For **47**: IR ($CHCl_3$, cm^{-1}) 3560, 2950, 2860, 2240, 1680, 1650, 1458, 1360, 1342, 1322, 1309, 1257, 1220, 1200, 1175, 1150, 1130, 1112, 1101, 1080, 1052, 1010, 973, 873, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (s, 1 H), 4.16-4.11 (m, 2 H), 3.66 (dd, J = 11.6, 4.9 Hz, 2 H), 3.57 (s, 3 H), 3.48-3.44 (m, 2 H), 3.44-3.39 (m, 1 H), 2.82-2.40 (m, 1 H), 2.15 (br s, 1 H), 2.07-1.94 (m, 2 H), 1.81 (t, J = 2.75 Hz, 1 H), 1.74 (s, 3 H), 1.36-1.00 (m, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.90 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.46, 149.43, 116.77, 95.79, 93.32, 76.57, 70.55, 70.46, 64.28, 56.64, 49.05, 43.13, 36.74, 34.85, 33.55, 33.01, 31.29, 30.09, 28.31, 22.89, 22.38, 14.99; MS m/z (M^+) calcd 378.2406, obsd 378.2396.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.71; H, 9.03.

Methoxymethyl Ether of 4-Hydroxy-3,4-dihydro-2*H*-pyran (49b). To a magnetically stirred solution of 16.5 g (90 mmol) of **45** in 50 mL of acetone was added 50 mg of *p*-toluenesulfonic acid. The solution was stirred at 25 °C for 30 min before 10 mg of additional acid catalyst was added. After a further 60 min, the reaction mixture was concentrated at 25 °C and 50 Torr and the residue was taken up in ether and washed with sodium bicarbonate solution (50 mL). After extraction twice with ether, the combined organic phases were dried and concentrated (25 °C at 50 Torr). The residual oil was purified by silica gel chromatography to give 6.8 g (77%) of **48** as a sensitive, clear, colorless oil which was reduced immediately without characterization.

To a cold (0 °C), magnetically stirred suspension of 194 mg (5.10 mmol) of lithium aluminum hydride in 10 mL of ether was added dropwise a solution of 500 mg (5.1 mmol) of **48** in 10 mL of ether over a 10 min time interval. The reaction mixture was stirred for 15 min at 25 °C, then cooled to 0 °C prior to careful quenching with 0.2 mL of water, 0.2 mL of 15% sodium hydroxide solution, and 0.6 mL of water. Anhydrous magnesium sulfate was added, the solids were filtered, and the filtrate was concentrated (ambient temperature, 50 Torr). The residual oil was purified by silica gel chromatography (elution with 50% ether in petroleum ether) to give 374 mg (73%) of **49a** as a clear, colorless oil which was carried directly forward.

A cold (0 °C), magnetically stirred solution of 370 mg (3.7 mmol) of **49a** in 5 mL of anhydrous dichloromethane and 1.22 mL (7.0 mmol) of diisopropylethylamine was treated dropwise with 0.42 mL (5.55 mmol) of neat chloromethyl methyl ether via syringe. The solution was stirred for 2 h at 0 °C before being warmed to 25 °C, where it was maintained for 16 h. Following dilution with ether (15 mL), the reaction mixture was quenched with sodium bicarbonate solution, washed twice with copper(II) sulfate solution, dried, and concentrated at 25 °C. The product was purified by silica gel chromatography (elution with 20% ether in petroleum ether) which yielded 347 mg (65%) of **49b**; ^1H NMR (80 MHz, $CDCl_3$) δ 6.45 (d, J = 6.2 Hz, 1 H), 4.95-4.80 (m, 1 H), 4.66 (ABq, $\Delta\nu$ = 7.8 Hz, J_{AB} = 7.4 Hz, 2H), 4.07-3.89 (m, 3 H), 3.33 (s, 3 H), 1.98-1.79 (m, 2 H); MS m/z (M^+) calcd 144.0831, obsd 144.0781.

Condensation of 50 with 6. To a cold (-78 °C), magnetically stirred suspension of 280 mg (2.5 mmol) of sublimed potassium *tert*-butoxide in 2 mL of anhydrous tetrahydrofuran was added 1.74 mL (2.78 mmol) of 1.6 M *n*-butyllithium in hexanes. After 10 min, 200 mg (1.39 mmol) of **49b** was added as a solution in 1 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred for 60 min at -78 °C before being treated with 1.13 mL (4.17 mmol) of neat tri-*n*-butyltin chloride via syringe. The solution was warmed to 25 °C and stirred for 60 min before being quenched with ammonium chloride solution and diluted with ether. The organic phase was washed with water, dried, and concentrated to leave an orange-colored oil. This material was very rapidly purified by elution through a short column of silica gel pretreated with triethylamine (elution with 3% triethylamine in petroleum ether containing a trace of ether). There was obtained 560 mg of slightly impure **50** as a clear, colorless oil, which was used directly without further purification.

To a cold (-78 °C), magnetically stirred solution of **50** (340 mg, 0.79 mmol) in 2 mL of anhydrous tetrahydrofuran was added 0.42 mL (0.667 mmol) of 1.6 M *n*-butyllithium in hexanes. The solution was stirred at -78 °C for 60 min, at which time 59 mg (0.30 mmol) of **6** was added as a solution of 2 mL of anhydrous 1,2-dimethoxyethane. After 15 min at -78 °C, the reaction mixture was warmed to 25 °C during 30 min and quenched with ammonium chloride solution (3 mL). The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic layers were dried and concentrated to leave an oily residue. This

material was purified by silica gel chromatography (elution with 5-80% ether in petroleum ether) to provide 27 mg (27%) of less polar, clear, colorless, oily 51 as a 1:1 mixture of diastereomers (^{1}H NMR), 34 mg (34%) of 52 as a clear, colorless, oily 1:1 mixture of diastereomers, and 10 mg (10%) of a mixture of 51, 52, and a third unidentified by-product.

For 51: IR ($CHCl_3$, cm^{-1}) 3560, 3000, 2920, 1680, 1650, 1455, 1440, 1375, 1360, 1340, 1308, 1210, 1148, 1090, 1030, 980, 960, 940, 915, 875; ^{1}H NMR (300 MHz, $CDCl_3$) vinylic protons (δ 4.90-4.86), methyl enol ether singlets (3.50, 3.44), methyl ether singlets (3.36, 3.35) vinyl methyl singlet (1.66), gem-dimethyl singlets (1.14, 0.86); MS *m/z* (M^+) calcd 338.2093, obsd 338.2106.

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.78; H. 9.01.

For 52: IR (neat, cm^{-1}) 3450, 2920, 1770, 1680, 1645, 1450, 1375, 1365, 1340, 1285, 1250, 1210, 1145, 1090, 1030, 915, 862, 730; ^{1}H NMR (300 MHz, $CDCl_3$) vinylic (δ 5.28, 5.27), methyl enol ether singlets (3.584, 3.582), methyl ether singlets (3.38, 3.37), vinyl methyl (1.75 overlapping), gem-dimethyl singlets [(1.00, 0.99), 0.86]; ^{13}C NMR (75 MHz, $CDCl_3$) ppm (158.76), 158.28), 149.33, (116.92, 116.69), (98.09, 97.51), (94.50, 94.45), (77.58, 77.37), (65.42, 65.02), (63.01, 62.85), 56.63, 55.31, 48.98, (42.73, 42.40), (36.92, 36.85), (34.77, 34.49), 33.60, 31.24, 29.00, (28.59, 28.48), 15.01; MS *m/z* (M^+) calcd 338.2093, obsd 338.2086.

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