Regio- and Stereoselectivity of the Reaction between Cyanocuprates and Cyclopentene Epoxides. Application to the Total Synthesis of Prostaglandins

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A systematic study of the reaction between cyclopentene epoxides and alkyl-, alkenyl-, and arylcyanocuprates is described. Alkylcyanocuprates react with complete regio- and stereoselectivity to provide *trans*-4-alkylcyclopent-2-enols in excellent yields. Vinyl-, allyl-, and phenylcyanocuprates, on the other hand, afford mixtures of 1,2- and 1,4-adducts. Hydroxy-directed epoxidation of the 4-alkylcyclopentenols, followed by oxidation and enol ether formation, sets the stage for a second conjugate addition, from which *cis*-2,3-dialkyl-*trans*-4-hydroxycyclopentanones are obtained in high yield. The application of this methodology to the total synthesis of 2-decarboxy-2-(hydroxymethyl)-PGE_1, PGE_1, $PGF_{1\alpha}$, and $PGF_{2\alpha}$ is described.

During the past several years we have been developing the highly regio- and stereoselective addition of mixed cyanocuprates to cyclic epoxyalkenes. Most of our previous work has focused on the use of cyclohexene epoxides.[1,2]

In this context, we have shown that cyanocuprates react with 1,3-cyclohexadiene monoepoxide **1** in a conjugate manner and with complete stereoselectivity to afford *trans*-4-substituted-cyclohex-2-enols **2** in high yield. A simple manipulation of these allylic alcohols, on the other hand, sets the stage for a second conjugate addition of a cyanocuprate reagent, from which highly functionalized cyclohexane systems are obtained with complete stereocontrol (Scheme I).[3]

The distinctive advantages of the stereoselective tandem 1,4-opening of cyclohexene epoxides with cyanocuprate reagents prompted us to investigate the scope and stereochemical consequences of the reaction with cyclopentene epoxides. It was envisioned that this methodology could provide a unique route for the stereocontrolled introduction of substituents onto a cyclopentane ring, in a manner heretofore not possible by alkylation of enolates or 1,4-addition to enones.

Our study included those cyanocuprates that could be easily prepared from commercially available alkyllithium compounds, as well as the cuprates derived from vinyllithium, vinylmagnesium bromide, allyllithium, allylmagnesium bromide, phenyllithium, and phenylmagnesium bromide. In addition, some cyanocuprates were prepared from the corresponding iodides by metal–halogen exchange with an alkyllithium reagent followed by treatment with copper(I) cyanide.

Reaction of Cyanocuprates with Cyclopentadiene Monoepoxide. The initial stage of our investigation was carried out on the readily available cyclopentadiene monoepoxide **10**.[4] The results of the addition of several cyanocuprates to this cyclopentene epoxide are summarized in Table I.

As shown in Table I, alkylcyanocuprates (entries 1–5) reacted with complete regio- and stereoselectivity to produce the *trans*-4-alkylcyclopent-2-enols **11–15**, usually in high yield. Entries 4 and 5, however, deserve some comment. Previous attempts in our laboratory to introduce a β-functionalized two-carbon piece onto cyclopentadiene monoepoxide in a conjugate manner by using the cuprate derived from the lithium enolate of *tert*-butyl acetate had not been successful. It was considered that a less hindered ester enolate could achieve satisfactory results and, as shown in entry 4, the cuprate derived from the lithium enolate of ethyl acetate and copper(I) cyanide did react exclusively in a conjugate fashion, albeit in a low yield. Copper species of this kind have been utilized for the S_N2 displacement of allyl halides;[5] to our knowledge, however, this is the first example of a conjugate addition of a cuprate of this nature. Similarly, the cyanocuprate prepared from the lithium salt of (tributylmethyl)tin[6] (entry 5) also reacted in a conjugate manner but in a disappointingly low yield. A nonpolar material, presumably $(n\text{-}Bu_3SnCH_2)_2$ arising from oxidative coupling of the cuprate, was the major product isolated from the reaction mixture.

In clear contrast with the high regioselectivity displayed by alkylcyanocuprates, sp^2-hybridized cyanocuprates afforded mixtures of trans-1,2- and trans-1,4-adducts. The examples given in entries 6 and 7 indicate, however, that the degree of regioselectivity is highly dependent on the substitution pattern of the vinylic moiety attached to copper. Thus, while vinylcyanocuprate (entry 6) showed a complete lack of regioselectivity, the cuprate derived from (1*E*)-1-iodo-3-[(*tert*-butyldimethylsilyl)oxy]-1-octene[7] (entry 7) provided a 1:4 mixture of 1,2- and 1,4-adducts, respectively.

The reaction of phenylcyanocuprate with cyclopentadiene monoepoxide (entry 8) was devoid of the high regioselectivity observed with cyclohexadiene monoepoxide.[1a] Indeed, while the reaction with the latter afforded exclusively the 1,4-adduct, the addition to the five-membered ring analogue provided both regioisomers in a surprisingly low ratio.

The stereochemical elucidation of the addition products was based on the analysis of their ^1H NMR spectra. Thus, the chemical shift of the carbinol proton allowed for a conclusive assignment of regioisomers owing to its allylic character in the 1,4-adducts. The trans stereochemistry of these adducts, on the other hand, is supported by the relative values of the chemical shifts of the two homoallylic ($H_{5\alpha}$ and $H_{5\beta}$) protons. Table II summarizes the spectroscopic data obtained for representative products.

(1) (a) Marino, J. P.; Hatanaka, H. *J. Org. Chem.* **1979**, *44*, 4467. (b) Marino, J. P.; Abe, H. *Synthesis* **1980**, *11*, 872. (c) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379. (d) Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

(2) For previous reports involving cycloheptene and cyclopentene epoxides, see: (a) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675. (b) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907. (c) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389. (d) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1984**, *49*, 5279.

(3) For a related methodology involving homocuprates, see: Wender, P. A.; Erhart, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

(4) Korach, M.; Nielsen, D. R.; Rideout, W. H. *Organic Syntheses*; John Wiley and Sons: New York, 1973; Collect. Vol. I, p 414.

(5) Kuwajima, I.; Doi, Y. *Tetrahedron Lett.* **1972**, 1163.

(6) Kauffmann, T.; Kriegesmann, R. *Chem. Ber.* **1982**, *115*, 1810.

(7) Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

0022-3263/87/1952-4898$01.50/0

Scheme I

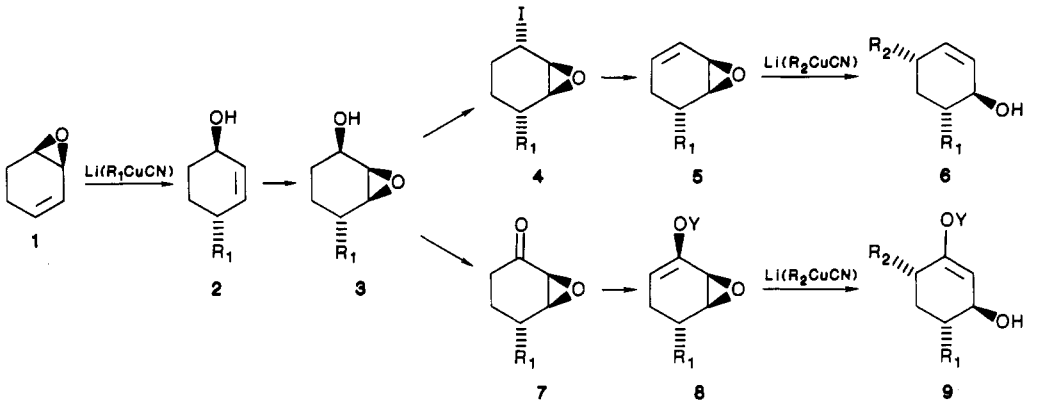
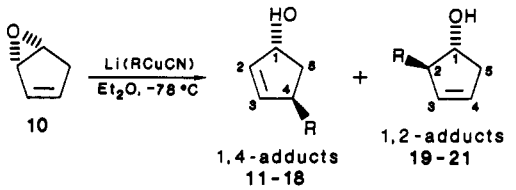


Table I. Reaction of Cyanocuprates with Cyclopentadiene Monoepoxide



entry	cyanocuprate (R)	product(s) 1,4-adduct	1,2-adduct	ratio 1,4/1,2	yield (%)[a]
1	Me	11			78
2	*n*-Bu	12			95
3	*t*-Bu	13			88
4	EtO_2CCH_2	14			17
5	$(n\text{-Bu})_3SnCH_2$	15			5
6	$CH_2{=}CH$	16	19	1:1	75
7	(*E*)-$C_5H_{11}CH(OTBDMS)CH{=}CH$[b]	17	20	4:1	80
8	Ph	18	21	2:1	50

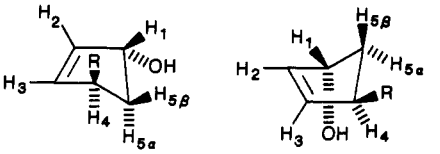
[a] Yields refer to pure compound(s) isolated by column chromatography or distillation. [b] TBDMS = *tert*-butyldimethylsilyl.

It is a general observation that *cis*-1,4-disubstituted-cyclopentenes present large differences, often in the range of 1 ppm, in the chemical shifts of their H_5-protons; normally, the upfield proton is assigned as being syn to both substituents. Alternatively, this difference does not usually exceed 0.3 ppm for the trans isomers.[8,9] As shown in Table II, the observed difference between the chemical shifts of $H_{5\alpha}$ and $H_{5\beta}$ in adducts **11** and **13** is smaller than 0.3 ppm.

The certainty of the trans asignment for the 1,4-adducts is reinforced by the observed upfield shift of $H_{5\alpha}$ and downfield shift of $H_{5\beta}$ with increasing steric bulk of the R group. This is consistent with an increase in the relative population of conformation A and/or an increase of the torsional angle that brings $H_{5\beta}$ closer to being coplanar with C_1 and C_2. As a consequence, $H_{5\beta}$ is placed in the deshielding cone of the double bond, while $H_{5\alpha}$ is forced into the shielding region of the double bond.

Reaction of Cyanocuprates with Epoxy Enol Phosphates and Epoxy Silyl Enol Ethers. The second phase of our study of the reaction between cyanocuprates and cyclopentene epoxides was aimed at introducing another carbon substituent onto the cyclopentene ring system in a regioselective and stereocontrolled manner. For this purpose, the *trans*-4-substituted-cyclopent-2-enols **11**, **12**, **17**, and **18** were first transformed into the required cyclopentene epoxides by using the protocol previously reported for the cyclohexenyl system.[1d] Thus, hydroxy-directed epoxidation[10] of these allylic alcohols with *tert*-butyl hydroperoxide and vanadyl acetylacetonate provided the *cis*-epoxycyclopentanols **22–25**, which were subsequently oxidized with Collins reagent[11] to afford the corresponding

Table II. Conformations and ^1H NMR Spectral Data for Some *trans*-1,4-Substituted Cyclopent-2-enols



A B

proton	11 (R = Me) δ	11 (R = Me) *J* (Hz)	13 (R = *t*-Bu) δ	13 (R = *t*-Bu) *J* (Hz)
H_1	4.86	$J_{1,5\alpha}$ = 2.6	4.81	$J_{1,5\alpha}$ = 2.9
H_2	5.77	$J_{4,5\alpha}$ = 7.5	5.84	$J_{4,5\alpha}$ = 8.0
H_3	5.88	$J_{1,5\beta}$ = 7.1	5.94	$J_{4,5\beta}$ = 7.2
H_4	2.94	$J_{4,5\beta}$ = 5.2	2.72	$J_{4,5\beta}$ = 5.4
$H_{5\alpha}$	1.94	$J_{1,4}$ = 2.1	1.68	$J_{1,4}$ = 2.2
$H_{5\beta}$	1.69		1.95	

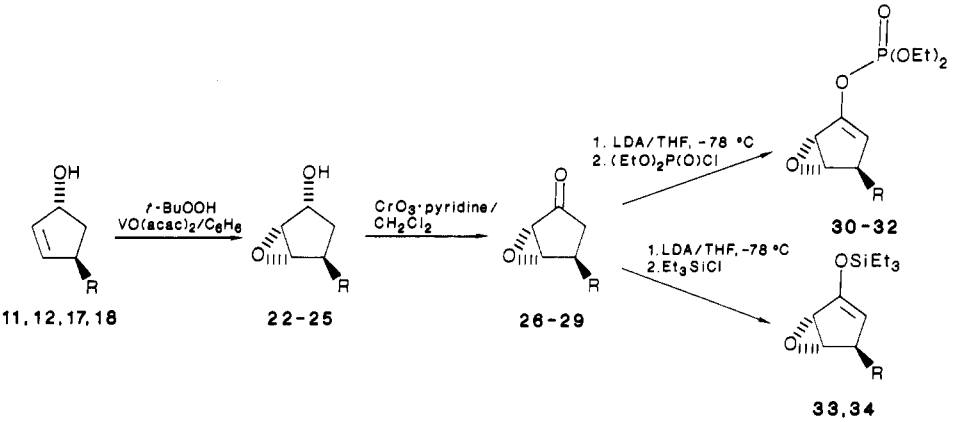
(8) (a) Anteunis, M.; Danneels, D. *Org. Magn. Reson.* **1975**, *7*, 345. (b) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 1969; p 287. (c) Fay, C. K.; Grutzner, J. B.; Johnson, L. F.; Sternhell, S.; Wasterman, P. *J. Org. Chem.* **1973**, *38*, 3122. (d) Gaudemer, A. *Spectroscopic Methods in Stereochemistry: Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1, p 77 ff and p 89 ff.

(9) (a) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternak, T. *Helv. Chim. Acta* **1970**, *53*, 739. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (c) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (d) DeClerq, P.; Van Haver, D.; Tavernier, D.; Vandervalle, M. *Tetrahedron* **1974**, *30*, 55.

(10) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Terahishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

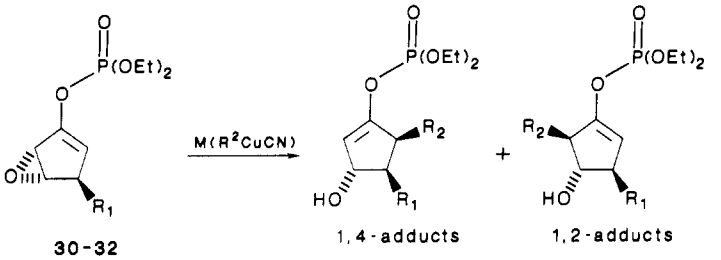
(11) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

Scheme II



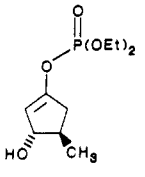
entry	substr (R)	products (% yield)			
1	11 (Me)	22 (95)	26 (75)	30 (94)	
2	12 (*n*-Bu)	23 (100)	27 (80)	31 (90)	33 (100)
3	17 [(*E*)-C_5H_{11}CH(OTBDMS)CH=CH]	24 (98)	28 (82)	32 (85)	34 (100)
4	18 (Ph)	25 (90)	29 (79)		

Table III. Reaction of Cyanocuprates with Cyclopentenyl Epoxy Enol Phosphates



entry	substr[a]	M	R^2	product(s) 1,4-adduct	1,2-adduct	Ratio 1,4/1,2	yield[b] (%)
1	30	Li	Me	35			90
2	30	Li	*n*-Bu	36			95
3	31	Li	*n*-Bu	37			85
4	32	Li	*n*-Bu	38			58
5	32	Li	$TMSO(CH_2)_6CH_2$	39			60
6	32	Li	*t*-Bu	40			61
7	30	Li	*t*-Bu	41	42	2:3	50[c]
8	30	MgBr	CH_2=CH		44		98
9	30	Li, MgBr	CH_2=$CHCH_2$		45		99
10	30	Li	Ph	46	47	1:2	80
11	30	MgBr	Ph	46	47	1:6	75

[a] **30**, R^1 = Me; **31**, R^1 = *n*-Bu; **32**, R^1 = (*E*)-C_5H_{11}CH(OTBDMS)CH=CH. [b] Yields refer to pure isolated product(s). [c] A 10% yield of **43** was also isolated from this reaction.



43

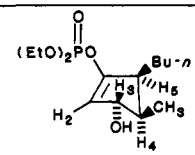
ketones **26–29**. Enolate formation with lithium diisopropylamide in tetrahydrofuran at −78 °C, followed by trapping of the enolates with diethyl chlorophosphate or triethylsilyl chloride, then provided the epoxy enol phosphates **30–32** or epoxy silyl enol ethers **33–34**, respectively, in high overall yield (Scheme II).

The substitution pattern of the enol phosphates and silyl enol ethers thus obtained posed a challenge to the regioselectivity, and mainly the stereoselectivity of the cuprate reaction. A trans conjugate addition onto these systems would place the incoming group cis and in a 1,2-relationship with the R group already present in the five-membered ring, thus affording the thermodynamically less stable *cis*-4,5-disubstituted-cyclopent-2-enols. Previous examples from our laboratories[2c] had indicated that the addition does proceed in a 1,4-fashion; however, the stereochemistry of the products could not be definitely confirmed. A more thorough examination of this reaction was necessary to conclusively assess both the extent of its regioselectivity and the stereochemistry of the resulting adducts.

The results of the addition of several cyanocuprates to epoxy enol phosphates **30–32** are summarized in Table III.

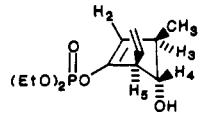
Simple alkylcyanocuprates, with the exception shown

Table IV. Conformations and ^1H NMR Spectral Data for Adducts 37 and 44



37

proton	δ	^3J (Hz)
H_2	5.36	$J_{2,3}$ = 2.0
H_3	4.31	$J_{3,4}$ = 5.1
H_4	2.15	$J_{3,5}$ = 1.0
H_5	2.75	$J_{4,5}$ = 7.3



44

proton	δ	^3J (Hz)
H_2	5.18	$J_{2,3}$ = 1.9
H_3	2.54	$J_{3,4}$ = 5.3
H_4	3.60	($J_{3,5}$ = 0)
H_5	3.21	$J_{4,5}$ = 5.3

in entry 7, reacted with complete regio- and stereoselectivity to afford the corresponding trans-1,4-adducts in good to excellent yields. *tert*-Butylcyanocuprate, on the other hand, displayed an apparent capricious behavior. While this cuprate reacted with enol phosphate **30** (entry 7) to give a mixture of regioisomers, it added regioselectivity to **32** (entry 6), which contained a larger R^1 group. These results must involve factors other than steric hindrance.

The reaction between epoxy enol phosphate **30** (R^1 = CH_3) and vinylcuprate (entry 8) or allylcyanocuprate (entry 9) afforded exclusively the corresponding 1,2-adducts in essentially quantitative yield. We have reported that the regiochemistry of the reaction between cyclohexenyl epoxy enol ethers and vinylcyanocuprate is highly dependent on the specific substrate used and particularly its substitution pattern.[1d] The results obtained in the present study, however, are insufficient to assess such an influence in the case of cyclopentenyl epoxy enol phosphates.

On the other hand, it had been previously found that the outcome of the reaction between cyclohexenyl epoxy enol ethers and vinylcyanocuprate is independent of the use of vinyllithium or vinylmagnesium bromide as the precursor for the cuprate reagent.[1d] Similarly, no significant difference was observed this time in the reaction between epoxy enol phosphate **30** and allylcyanocuprate prepared from allyllithium or allylmagnesium bromide (entry 9). Phenylcyanocuprate, on the other hand, displayed a marked dependency on the nature of the counterion (Li vs. MgBr), as shown in Table III entries 10 and 11. The replacement of lithium by MgBr resulted in a threefold increase in the amount of 1,2-adduct formed.

The ^1H NMR data obtained for representative 1,4- and 1,2-adducts are summarized in Table IV. The regiochemical assignment was made in a straightforward manner by examination of the chemical shift of the carbinol proton. Due to its allylic nature in the 1,4-adducts, this proton showed a distinctive downfield shift with respect to that of the corresponding 1,2-isomer.

The stereochemical assignment, on the other hand, followed the postulated mechanism of formation of these compounds and the analysis of their preferred conformations. Thus, a 1,2-opening of the epoxy ring should afford a *cis*-3,5-disubstituted-*trans*-4-hydroxycyclopentenyl phosphate (cf. **44**), whose preferred conformation would be the one that minimizes the allylic strain between the bulky phosphate moiety and the new substituent (i.e., the vinyl group in **44**). For this to occur, the incoming group should adopt a pseudoaxial disposition. The spectral evidence corroborates these assumptions: H_4 in compound **44** is unusually shielded (δ = 3.60 ppm) for a cyclopentyl carbinol proton, which is consistent with an upfield shift caused by two cis substituents. Furthermore, H_4 shows relatively small and equal couplings with H_3 and H_5, in agreement with a trans arrangement with these two protons, while no homoallylic coupling was detected between H_3 and H_5.

A conjugate addition onto the allylic epoxy system, on the other hand, should provide a *cis*-4,5-disubstituted-*trans*-3-hydroxycyclopentenyl phosphate (cf. **37**), whose preferred conformation, by the same reasoning as for the 1,2-adduct, should be the one depicted in Table IV. The ^1H NMR spectrum of compound **37** shows a homoallylic coupling between H_3 and H_5, typical of a trans-1,4-disposition. Moreover, H_4 in **37** presents two different coupling constants (J = 7.3 and 5.1 Hz), consistent with a cis and a trans coupling, respectively.

The stereochemistry of the other adducts was assigned by correlation of their ^1H NMR spectra with those of compounds **37** and **44**. In the case of adducts **38**, **39**, and **40**, however, the complexity of their spectra (due to the presence of diastereoisomers) did not allow for conclusive assignments.

The synthetic utility of the 1,4-addition of cyanocuprates to epoxy enol ethers lies primarily in the opportunity to perform a subsequent restoration of the carbonyl group. To this purpose, it seemed ideal to utilize silyl enol ethers, since these derivatives are both easy to prepare and cleave under very mild conditions.[12] Our selection of triethylsilyl enol ethers, as opposed to the more traditionally used trimethylsilyl enol ethers, was dictated by the greater stability of the former compounds. Thus, while the trimethylsilyl enol ethers could be easily obtained from the corresponding epoxycyclopentanones and underwent conjugate addition with several cyanocuprates, the instability of both the parent enol ether and the 1,4-adduct made these compounds impractical for synthetic purposes. The epoxy triethylsilyl enol ethers, on the other hand, were stable for a few months when stored at −10 °C under nitrogen, and their 1,4-adducts could be isolated from the reaction mixtures provided that no heat was applied during the concentration of the crude extracts. Purification of these adducts by flash column chromatography or vacuum distillation, however, led to extensive decomposition to the corresponding 4,5-disubstituted-cyclopentenones. Consequently, the 1,4-adducts were usually not characterized but immediately subjected to mild hydrolysis with potassium fluoride in pH 7 phosphate buffer/ethanol, to afford the desired β-hydroxycyclopentanones.

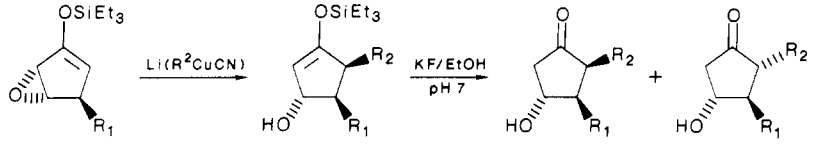
The results of the reaction of silyl enol ethers **33** and **34** with several alkylcyanocuprates are summarized in Table V.

As illustrated, all the cases examined proceeded with complete regiochemical control. Indeed, fluoride-induced hydrolysis of the initially formed 1,4-adducts **48–53** provided exclusively the 2,3-dialkyl-4-hydroxycyclopentanones **54–63**, thus confirming the higher selectivity of epoxy silyl enol ethers relative to their enol phosphate analogues. The stereochemical outcome of some of these two-step sequences, on the other hand, required a more in-depth analysis.

The reaction of epoxy silyl enol ether **33** with *n*-butylcyanocuprate (entry 1) afforded the 1,4-adduct **48**, which was subsequently hydrolyzed, as indicated above, to give β-hydroxycyclopentanone **54** in 85% overall yield. The trans relationship between the C_5-butyl group and the C_3-hydroxyl group in adduct **48** is strongly supported by the spectroscopic data. Indeed, the ^1H NMR spectrum of this compound shows a large coupling constant (J = 7.3 Hz) between H_4 and H_5 and a smaller coupling constant (J = 5.4 Hz) between H_3 and H_4, as well as a fairly large

(12) Reviews: (a) Rasmussen, J. K. *Synthesis* **1977**, 91. (b) Fleming, I. *Chimia* **1980**, *34*, 265.

Table V. Reaction of Alkylcyanocuprates with Cyclopentenyl Epoxy Silyl Enol Ethers



33, 34 48-53 54-59 60-63

entry	substr[a]	cyanocuprate (R)	1,4-adduct	hydrolysis product(s)	ratio cis/trans	yield[b] (%)
1	33	*n*-Bu	48	54		85
2	33	$TMSO(CH_2)_6CH_2$	49	55[c] + 60[c]	1:7	78
3	34	$TMSO(CH_2)_6CH_2$	50	56[c] + 61[c]	1:8	80
4	34	*t*-Bu	51	57		65
5	34	$CH_3(CH_2)_5CH_2$	52	58 + 62	1:4	70
6	33	$CH_3(CH_2)_5CH_2$	53	59 + 63	2:1	60[d]

[a] **33**, R^1 = *n*-Bu; **34**, R^1 = (*E*)-$C_5H_{11}CH(OTBDMS)CH{=}CH$. [b] Yields refer to isolated 4-hydroxycyclopentanones. [c] Fluoride treatment also removed the TMS group. [d] Reaction quenched before completion; see text.

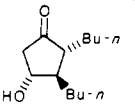


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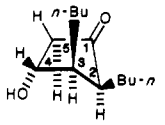
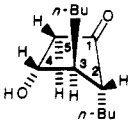
Table VI. ^1H NMR Spectral Data for Compounds 54 and 64



54



64

proton	54 δ	54 *J* (Hz)	64 δ	64 *J* (Hz)
H_2	2.61	$J_{2,3}$ = 7.0	1.86–1.88	$J_{2,3}$ = ---
H_3	2.17–2.21	$J_{2,5\alpha}$ = 1.7	1.86–1.88	$J_{2,5\beta}$ = 1.0
H_4	4.36	$J_{3,4}$ = 2.3	4.13	$J_{3,4} \simeq$ 6.8
$H_{5\alpha}$	2.20	$J_{4,5\alpha}$ = 0.0	2.20	$J_{4,5\alpha}$ = 6.8
$H_{5\beta}$	2.43	$J_{4,5\beta}$ = 5.9	2.65	$J_{4,5\beta}$ = 6.8

homoallylic coupling (J = 2.0 Hz) between H_3 and H_5. These data are consistent with a cis arrangement of H_4 and H_5 and a trans arrangement of H_3 with both H_4 and H_5. The stereochemistry of cyclopentanone **54**, on the other hand, was rigorously established by carrying forward its epimerization with potassium acetate in ethanol,[13] to afford the thermodynamically more stable trans isomer **64**. Table VI summarizes the ^1H NMR data obtained for the C_2-epimeric cyclopentanones **54** and **64**.

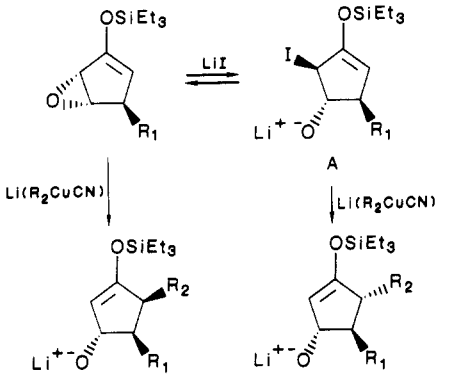
Particularly noticeable are the upfield shifts of H_2 and H_3 observed in the spectrum of the trans isomer **64**, which are consistent with a shielding effect due to a *cis*-alkyl group.

Treatment of epoxy silyl enol ether **33** with the mixed cyanocuprate derived from 1-iodo-7-[(trimethylsilyl)-oxy]heptane[14] (entry 2, Table V), followed by immediate hydrolysis with potassium fluoride, provided a 1:7 mixture of *cis*- and *trans*-hydroxycyclopentanones **55** and **60**, respectively, in 78% combined yield. Essentially the same results were obtained when the above reaction was carried out on the epoxy silyl enol ether **34** (entry 3). Whether unexpected or not, these stereochemical results were unequivocally confirmed by comparison of the ^1H NMR spectra of the *cis*- and *trans*-hydroxycyclopentanones thus obtained with that of compounds **54** and **64**, respectively.

(13) Pike, J. C.; Lincoln, F. H.; Schneider, W. P. *J. Org. Chem.* **1969**, *34*, 3552.

(14) Prepared from commercially available cycloheptanone in the following manner: (i) MCPBA, CH_2Cl_2 (80%); (ii) TMSCl, NaI, CH_3CN; (iii) BH_3·THF; (iv) hexamethyldisilazene, TMSCl, diethyl ether (66% overall).

Scheme III



In particular, the signal of the carbinol proton was especially useful in determining the ratio of cis and trans isomers in the crude reaction mixtures.

At first sight, a major difference between entry 1 and entries 2 and 3 that could account for the observed stereoselectivity of these reactions was the steric bulk of the R^2 group. It should be recalled that this factor was crucial in determining the degree of regioselectivity in the addition of cyanocuprates to enol phosphates; it was considered that it was now affecting the stereoselectivity of the reaction with silyl enol ethers. To test this hypothesis, epoxy silyl enol ether **34** was reacted with *tert*-butylcyanocuprate. If the steric compression between the incoming cuprate and the R^1 group already present in the substrate was indeed determining the stereochemistry of the cuprate addition, then the *tert*-butyl group should provide predominantly the trans isomer. Hydrolysis of the initial adduct, however, gave exclusively the *cis*-2,3-dialkylhydroxycyclopentanone **57** in 65% yield (entry 4).

The exact nature of the cuprate reagent employed was next taken into consideration. Indeed, the reactions depicted in entries 1 and 4 involved cuprates generated directly from alkyllithium reagents and copper(I) cyanide, while those in entries 2 and 3 required prior metal–halogen exchange of the parent iodo compound. Therefore, these last two additions were actually performed in the presence of a significant amount of lithium iodide, which is quite soluble in ether, even at −78 °C. The presence of lithium iodide suggests an alternative mechanism for the 1,4-trans-cuprate addition. Indeed, the lithium iodide could

open the epoxy ring to give the allylic iodide intermediate A, in equilibrium with the starting epoxy enol ether (Scheme III). A trans conjugate addition of the cyanocuprate reagent onto this new intermediate would lead to the formation of the 4,5-*trans*-disubstituted-cyclopentene system.[15] Such an addition would be more favored in those cases where the steric hindrance between the incoming cuprate and the R^1 group already present in the molecule makes the direct 1,4-epoxide opening slower.

The above hypothesis is supported by the following additional observations. The reaction of epoxy enol ether **34** with the cuprate generated from *n*-heptyllithium, itself prepared in situ by metal–halogen exchange of 1-iodoheptane with *tert*-butyllithium, provided a 1:4 mixture of *cis*- and *trans*-2,3-cyclopentanones **58** and **62**, respectively, after fluoride treatment (entry 5). Conversely, the reaction of the sterically less demanding epoxy enol ether **33** with the same cuprate afforded a 2:1 mixture of *cis*- and *trans*-2,3-cyclopentanones **59** and **63**, respectively, after hydrolysis (entry 6). These results are consistent with a preferential addition to intermediate A in the first case and to the parent epoxy enol ether in the second case.

The conditions used to effect the hydrolysis of the 1,4-adducts to the hydroxycyclopentanones did not cause epimerization. This was demonstrated by subjecting pure *cis*-2,3-dialkylcyclopentanone **58** to the fluoride treatment. No sign of epimerization was detected by ^1H NMR after several days.

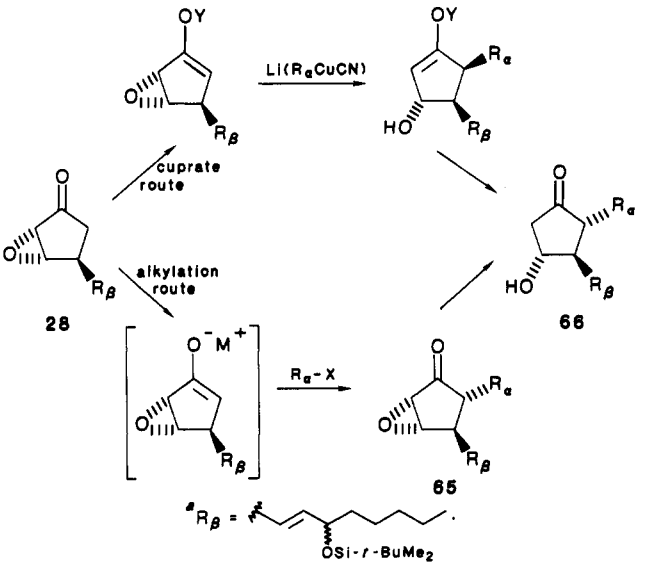
Under salt-free conditions, then, the addition of alkylcyanocuprates to epoxy silyl enol ethers proceeds in good yields and is completely regio- and stereoselective, even in sterically demanding situations (entries 1 and 4). The synthesis of β-hydroxycyclopentanone **57**, with its 1,2-cis arrangement of a *tert*-butyl group and a substituted prostaglandin β-chain, clearly illustrates the contra-thermodynamic outcome of our methodology.

Total Synthesis of Prostaglandins. The successful application of the regio- and stereoselective addition of cyanocuprates to the total synthesis of prostaglandins has been the subject of previous communications from our laboratory.[2c,d] We present herein a detailed account of the more recent approach, which provided a new entry into prostaglandins of the E and F types.

For some time now, the readily available epoxy ketone **28** was considered to be a useful intermediate for the synthesis of prostanoids. Regiospecific alkylation of the enolate of **28** with a reactive electrophile, or addition of a cyanocuprate reagent onto a suitable enol ether derivative of **28**, would allow for the preparation of differently α-substituted prostaglandin analogues (Scheme IV). The alkylation route would be best suited for reactive halides such as allylic propargylic ones, and also for aldehydes (aldol reactions). Successful alkylation would provide epoxy-PGA derivatives **65** which, in turn, could be converted into the corresponding PGE analogues **66**.[16] The cuprate route, on the other hand, reverses the electronics of the addition and, therefore, would be more appropriate for the introduction of saturated α-chains.[17]

The cuprate route had already led to a highly convergent synthesis of (±)-PGA_1 and (±)-PGB_1.[2c] Indeed, the reaction of enol phosphate **32** with the cyanocuprate derived from 1-lithio-7-[(trimethylsilyl)oxy]heptane gave exclusively the 1,4-regioisomer **39** (Table III, entry 5). Subsequent hydrolysis under two different sets of basic conditions, followed by oxidation of the C_1-hydroxy group and deprotection of the allylic alcohol, afforded PGA_1 or PGB_1. The extension of the above methodology to the synthesis of PGE_1, however, proved to be more elusive. Several attempts were made in order to effect the hydrolysis of the enol phosphate **39** with retention of the 3-hydroxy group. Unfortunately, the elimination to give the more stable cyclopentenone systems could not be avoided.

Scheme IV[a]



It became apparent that a different protecting group had to be employed. In this respect, the triethylsilyl enol ether **34** proved to be a rather convenient one. It could be prepared with the same efficiency as its trimethylsilyl analogue and exhibited a greater stability toward hydrolysis.

Treatment of triethylsilyl enol ether **34** with the cuprate derived from 1-iodo-7-[(trimethylsilyl)oxy]heptane, followed by fluoride-induced hydrolysis as already described, afforded a 1:8 mixture of hydroxycyclopentanones **56** and **61**, respectively, in 80% overall yield from **34** (Table V, entry 3). It should be noted that the conditions employed to effect the hydrolysis of the triethylsilyl enol ether also removed the C_1-trimethylsilyl protecting group of the α-chain but did not affect the *tert*-butyldimethylsilyl group. High-pressure liquid chromatography of the above mixture then provided diastereomerically pure **61a**, which was successfully converted into the bronchodilator (±)-2-decarboxy-2-(hydroxymethyl)-PGE_1 **67**,[18] and into PGE_1 and $PGF_{1\alpha}$, as shown in Scheme V.

Thus, removal of the *tert*-butyldimethylsilyl protecting group from **61a** with hydrofluoric acid in acetonitrile[19] afforded **67** in 90% yield. Alternatively, selective oxidation of the primary alcohol of **61a** with oxygen and platinum[20] gave the carboxylic acid **68**, which was subsequently deprotected, as described before, to afford (±)-PGE_1. To our knowledge, this is the first example in which an oxidation of the primary alcohol of the α-chain has been successfully

(15) This mechanism was suggested by one of the referees. For a similar anti addition of a cuprate reagent to an allylic bromide, see: Chapleo, C. B.; Finch, M. A. W.; Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans 1* **1980**, 2084.

(16) (a) Bundy, G. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 76. (b) Corey, E. J.; Ensley, H. E. *J. Org. Chem.* **1973**, *38*, 3187.

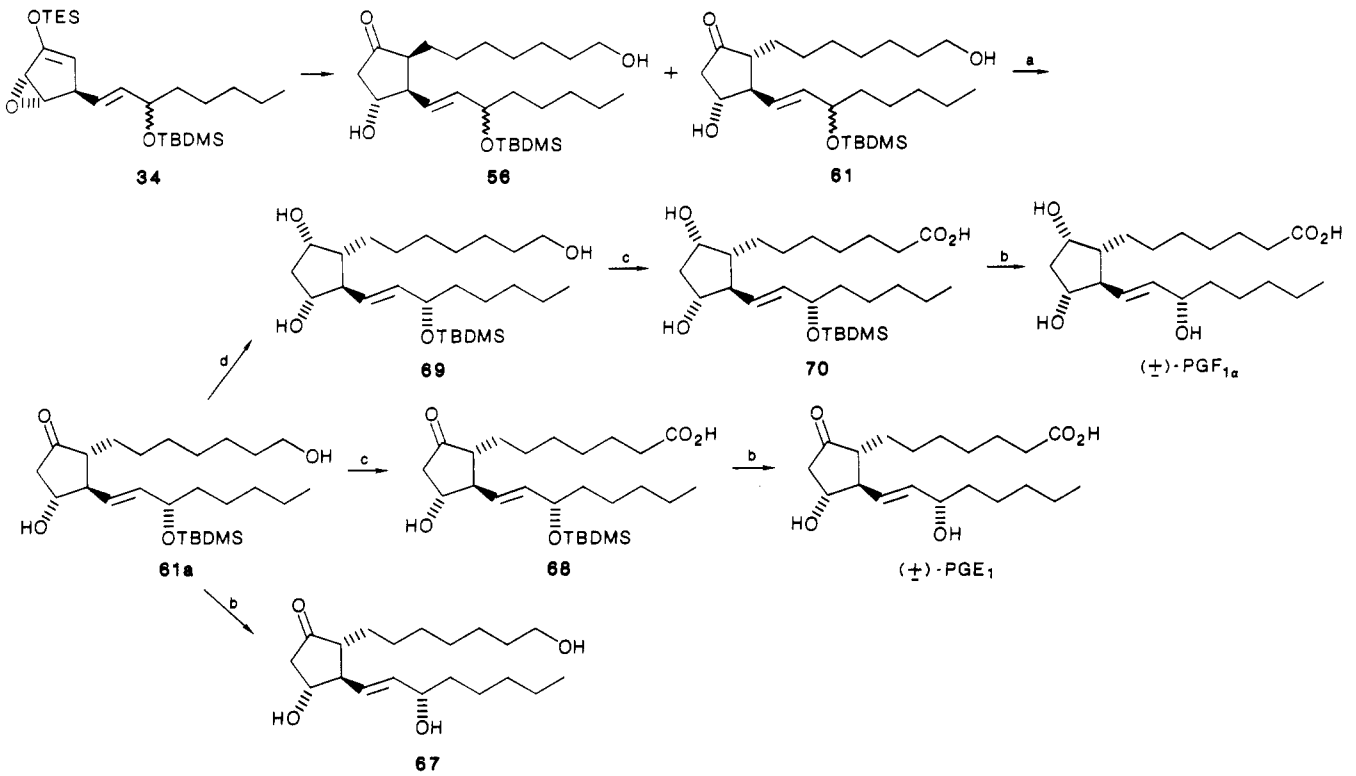
(17) For related approaches to prostaglandins involving organocuprates, see: (a) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. (b) Suzuki, M.; Wawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.

(18) (a) Kluender, H. C.; Peruzzotti, G. P. *Tetrahedron Lett.* **1977**, *24*, 2063. (b) Nizankowska, E.; Sheridan, A. Q.; Maile, M. H.; Cross, C. J.; Nizankowski, R.; Prochowska, K.; Szczeklik, A. *Prostaglandins* **1985**, *29*, 349.

(19) Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, 3981.

(20) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

Scheme V[a]



[a] Reagents: (a) HPLC; (b) HF, CH_3CN; (c) O_2, PtO_2, H_2O–acetone; (d) L-Selectride, THF, 0 °C.

carried out on a PGE system. Finally, stereoselective reduction of the carbonyl group of **61a** with L-selectride,[21] followed by oxidation of the primary alcohol and removal of the silyl protecting group, provided (±)-$PGF_{1\alpha}$. Our synthetic prostaglandins showed spectral characteristics (IR, ^1H NMR, and ^{13}C NMR) identical with those of authentic samples.[22]

The alkylation route, as mentioned before, was considered a better approach toward the synthesis of prostaglandins of the 2-series. Indeed, the preliminary reactions of the lithium enolate of **28** with allyl bromide or formaldehyde provided fairly good yields of alkylated products; it was later found, however, that our initial results could not be systematically reproduced. Moreover, when the reaction was performed with alkylating agents more suited to our purposes, such as methyl 7-iodo-5-heptynoate[23] or methyl 7-oxoheptanoate,[24] no alkylation could be achieved. Either the parent epoxy ketone **28** was recovered from the reaction mixtures or, more often, extensive decomposition of its enolate was observed. It should be mentioned that essentially the same results were obtained when this enolate was regiospecifically generated from the triethylsilyl enol ether **34**.[25]

Our lack of success in carrying forward the alkylation of epoxy ketone **28** or its triethylsilyl enol ether **34** was probably due to the presence of the oxirane ring. Indeed, the incoming electrophile must approach the cyclopentane nucleus from the α-face, as opposed to the more sterically demanding β-face; such an approach was partially hindered by the epoxy ring. In addition, this ring introduced a high degree of strain and an inductive effect that had to render a less reactive enolate anion.

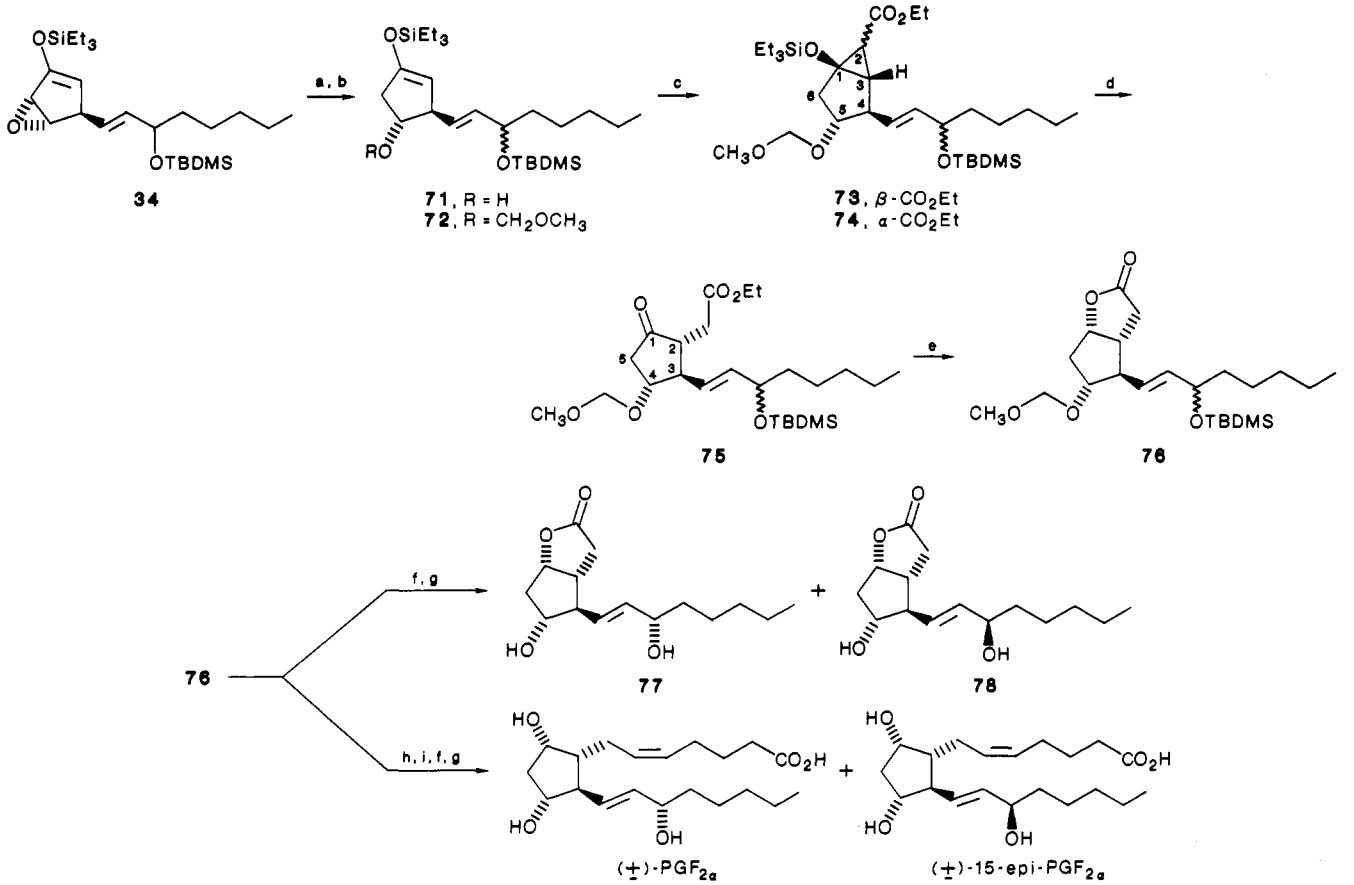
It was then considered that a regiospecific reductive opening of the oxirane ring in **34**, followed by protection of the resulting hydroxy group, would facilitate the subsequent alkylation step while maintaining its regiospecificity. A closer examination, however, revealed that such an approach would pose a new problem, intrinsically associated with the alkylation of enolates generated from 4-hydroxy-protected cyclopentanones.[26] These enolates are known to undergo rapid equilibration and subsequent β-elimination of the protected hydroxy group, owing to the greater acidity of the C_5-hydrogens. It should be mentioned that, although we did perform attempts in this direction, they served only to confirm the above observation.

Consequently, a chemoselective carbene addition onto the C_1–C_2 double bond of an epoxy ring-opened derivative of **34** was envisioned as an alternative route to alkylation. Such a reaction would render a silyloxy-substituted cyclopropane that could then be fragmented to generate the corresponding α-alkylated cyclopentanone.[27,28] Examination of molecular models suggested that the carbene addition would preferentially take place from the less hindered α-side of the molecule, thus setting up the correct stereochemistry at C_2.

Treatment of an ethereal solution of epoxy silyl enol ether **34** with lithium aluminum hydride selectively provided alcohol **71**, which was subsequently protected as a

(21) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.
(22) We thank Dr. Douglas R. Morton of the Upjohn Company for providing us with samples of pure 2-decarboxy-2-(hydroxymethyl)-PGE_1, PGE_1, $PGF_{1\alpha}$, and $PGF_{2\alpha}$.
(23) Corey, E. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 8483.
(24) Suzuki, M.; Wawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.
(25) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; The Benjamin/Cummings Publishing Co.: Menlo Park, CA, 1972; p 492. (b) D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.
(26) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755.
(27) Reviews: (a) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (b) Conia, J. M. *Pure Appl. Chem.* **1975**, *43*, 317. (c) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 588.
(28) Reissig, H.-U.; Hirsh, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 813.

Scheme VI[a]



[a] Reagents: (a) $LiAlH_4$, Et_2O, 0 °C; (b) CH_3OCH_2Cl, *i*-Pr_2EtN, CH_2Cl_2; (c) CO_2EtCHN_2, $CuSO_4$(cat), PhH, Δ; (d) Et_3NHF, THF; (e) PBPH, THF, −78 °C → r.t.; (f) aq. HF, CH_3CN; (g) 5% HCl, THF–H_2O; (h) DiBAL-H, CH_2Cl_2, −78 °C; (i) $Na[Ph_3P{=}CH(CH_2)_3CO_2^-]$, PhH–$Me_2SO$, 75 °C.

methoxymethyl ether, affording **72** in 90% overall yield. Reaction of **72** with 1.5 equiv of ethyl diazoacetate in the presence of a catalytic amount of anhydrous copper sulfate gave a 4:1 mixture of *exo*- and *endo*-(silyloxy)cyclopropane carboxylate esters **73** and **74**, respectively, in 70% combined yield (Scheme VI).

The trans stereochemistry between H_3 and H_4 in both **73** and **74** was supported by the ^1H NMR data obtained for each isomer. Thus, these two protons exhibit a very small coupling with each other (J = 0 Hz in **73** and 1.6 Hz in **74**), consistent with a trans arrangement. Unequivocal confirmation of this assignment was later obtained by independent conversion of each isomer into lactone **76**.

The stereochemistry of the carbethoxy group, on the other hand, was assigned on the basis of the relative values of the coupling between H_2 and H_3. Indeed, vicinal protons in cyclopropanes usually present smaller coupling constants when they are trans than when they are cis oriented.[8d] The observed coupling constants between H_2 and H_3 are J = 4.0 Hz in **73** and 9.8 Hz in **74**, indicating a trans and a cis relationship, respectively. It should also be mentioned that the preponderance of isomer **73** is well in agreement with the reported anti selectivity of carbethoxy carbenes.[29]

Treatment of the mixture of **73** and **74** with triethylammonium fluoride effected selective desilylation of the triethylsilyl group and regiospecific opening of the cyclopropane ring to afford γ-keto ester **75**, in 95% yield.[28] Stereoselective reduction of the cyclopentanone carbonyl from the β-face of the molecule with lithium *cis,cis,trans*-perhydro-9b-boraphenalyl hydride (PBPH)[30] in tetrahydrofuran at −78 °C, followed by gradual warming of the reaction mixture, resulted in the isolation of lactone **76** in 80% yield (Scheme VI).

Conclusive proofs of the structure of lactone **76** were obtained by its conversion into the known[31] prostaglandin precursor **77** and into (±)-$PGF_{2\alpha}$. Thus, removal of the *tert*-butyldimethylsilyl group with aqueous hydrofluoric acid in acetonitrile,[19] followed by hydrolysis of the methoxymethylene group with 5% hydrochloric acid in aqueous tetrahydrofuran, afforded lactone **77** and its C_{15}-epimer in 30–40% overall yield from epoxy ketone **28**. It should be mentioned that simultaneous removal of the protecting groups could be achieved with 24% aqueous hydrobromic acid in dimethoxyethane,[32] albeit in a lower yield. Alternatively, lactone **76** was reduced with diisobutylaluminum hydride in dichloromethane at −78 °C, and the resulting mixture of isomeric lactols was reacted with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide.[33] Removal of the protecting groups as described before, followed by chromatographic purification, provided

(29) Reviews: (a) Moss, R. A. "Steric Selectivity in the Addition of Carbenes to Olefins", In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, p 35. (b) Closs, G. L. *Structures of Carbenes and the Stereochemistry of Carbenes Additions*; Eliel, E. L., Allinger, N. L., Eds.; Interscience Publishers: New York, 1968; Vol. 3, p 193.

(30) Brown, H. C.; Dickason, W. C. *J. Am. Chem. Soc.* **1970**, *92*, 709.

(31) Corey, E. J.; Weinshenker, N. M.; Schaff, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(32) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.

(33) Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Young, S. N. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2789.

(±)-$PGF_{2\alpha}$ and (±)-15-epi-$PGF_{2\alpha}$ (Scheme VI).[22]

Conclusions. The tandem 1,4-opening of cyclopentene epoxides with cyanocuprate reagents provides a new entry for the stereocontrolled synthesis of polyfunctionalized cyclopentane ring systems. The reaction is completely regio- and stereoselective for alkylcyanocuprates generated directly from alkyllithium reagents. Alkenyl- and arylcyanocuprates, on the other hand, react with different degree of selectivity, depending upon the specific substrate and reagent used. The presence of inorganic salts in the reaction medium has a dramatic effect on the stereoselectivity of the reaction, probably by providing a different mechanistic pathway for the cuprate addition.

Experimental Section

General Methods. Oxygen- and/or moisture-sensitive reactions were carried out in flame-dried glassware equipped with tight-fitting rubber serum septa and under a positive pressure of dry nitrogen. Reagents and solvents were handled by using standard syringe techniques. Diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride; *N,N*-diisopropylamine, triethylamine, and pyridine from barium oxide; dichloromethane, acetonitrile, and dimethyl sulfoxide from calcium hydride; and benzene from sodium metal. Commercial methyllithium (low halide solution in ether), *n*-butyllithium (solution in hexane), and *tert*-butyllithium (solution in hexane) were purchased from Alfa Chemicals and titrated[34] prior to use. Technical-grade copper cyanide was purchased from J. T. Baker and was employed without further purification. Flash chromatography was performed by the procedure of Still et al.,[35] using Baker 40-μm particle diameter silica gel. High-pressure liquid chromatography was carried out on a Waters 590 instrument having a Waters 481 LC spectrophotometer and a Waters R401 differential refractometer. Melting points were determined in a Thomas-Hoover oil immersion capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on either a Perkin-Elmer 727B or 457 grating spectrophotometer. ^{1}H NMR spectra were recorded on a Varian T-60A, Brüker AM-300, or Brüker WM-360 instrument. ^{13}C NMR spectra were obtained on a JEOL-FX90Q, Brüker AM-300, or Brüker WM-360 spectrometer and are completely decoupled. Mass spectra were recorded on a Finnigan 4021 GCMS/DS instrument at 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN.

Reaction of Cyclopentadiene Monoepoxide with Cyanocuprates. Most cuprates were prepared by reaction of commercially available organolithium or organomagnesium compounds with copper(I) cyanide in diethyl ether. In other cases, the alkyllithium compound was generated in situ by reaction of a suitable precursor with *n*-BuLi, *t*-BuLi, or LDA.

Typically, to a suspension of 1.5 equiv of copper(I) cyanide in 125 mL of anhydrous ether/0.1 mol of copper salt, at −40 °C, was added 1.3 equiv of a solution of organolithium (or organomagnesium) reagent. After the mixture was stirred at −40 °C for 1 h, it was cooled to −78 °C, and a 5 M solution of freshly distilled cyclopentadiene monoepoxide in anhydrous ether was added dropwise. The mixture was allowed to warm up to room temperature overnight and then quenched with saturated NH_4Cl solution. The organic layer was separated, washed with saturated NaCl solution, and dried over anhydrous $MgSO_4$. Evaporation of the ether afforded the corresponding substituted cyclopentenols.

***trans*-4-Methylcyclopent-2-enol (11).** From 27.0 g (0.33 mol) of cyclopentadiene monoepoxide and Li(MeCuCN) was isolated 25.2 g (78%) of the title compound as a light yellow liquid. Distillation provided an analytically pure sample, bp 70–72 °C (30 mmHg): IR (neat) 3350, 1615, 1190, 1090, 1020, 980, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 7.1 Hz), 1.51–1.54 (m, 1 H), 1.69 (ddd, 1 H, J = 14.0, 7.1, 5.2 Hz), 1.94 (ddd, 1 H, J = 14.0, 7.5, 2.6 Hz), 2.94 (m, 1 H), 4.86 (dqd, 1 H, J = 7.1, 2.1, 0.5 Hz), 5.77 (dt, 1 H, J = 5.5, 2.2 Hz), 5.88 (ddd, 1 H, J = 5.5, 2.1, 0.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.91, 38.41, 42.42, 77.20, 132.07, 141.50; mass spectrum, m/e 90 (M), 81 (base). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.43.

***trans*-4-Butylcyclopent-2-enol (12).** From 20.5 g (0.25 mol) of cyclopentadiene monoepoxide and Li(*n*-BuCuCN) was isolated 58.2 g (95%) of **12** as a light yellow oil. An analytically pure sample could be obtained by distillation, bp 84 °C (2.5 mmHg), or flash chromatography (hexane–ethyl acetate, 5:1; R_f 0.21): IR (neat) 750, 1030, 1120, 1620, 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.21–1.37 (m, 6 H), 1.58–1.65 (m, 1 H), 1.74 (ddd, 1 H, J = 14.0, 7.5, 2.7 Hz), 2.80–2.84 (m, 1 H), 4.82 (dqd, 1 H, J = 7.1, 2.1, 0.7 Hz), 5.78 (dt, 1 H, J = 5.6, 2.2 Hz), 5.92 (ddd, 1 H, J = 5.6, 2.0, 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.72, 22.56, 29.92, 35.39, 40.22, 43.86, 76.35, 132.76, 139.98; mass spectrum, m/e 140 (M), 123 (base). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.12; H, 11.57.

***trans*-4-*tert*-Butylcyclopent-2-enol (13).** From 820 mg (10 mmol) of cyclopentadiene monoepoxide and Li(*t*-BuCuCN) was isolated 1.23 g (88%) of **13** as a light yellow oil. An analytically pure sample could be obtained by distillation, bp 70–71 °C (1.6 mmHg), or flash chromatography (hexane–ethyl acetate, 5:1; R_f 0.20): IR (neat) 820, 875, 1165, 1500, 1510, 3370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 9 H), 1.51–1.54 (m, 1 H), 1.68 (ddd, 1 H, J = 14.2, 8.0, 2.9 Hz), 1.95 (ddd, 1 H, J = 14.2, 7.3, 5.4 Hz), 2.72 (ddq, 1 H, J = 8.0, 5.4, 2.2 Hz), 4.81 (dqd, 1 H, J = 7.2, 2.2, 0.9 Hz), 5.84 (dt, 1 H, J = 5.7, 2.3 Hz), 5.94 (ddd, 1 H, J = 5.7, 2.1, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.43, 29.12, 35.98, 55.54, 77.10, 133.82, 137.29; mass spectrum, m/e 140 (M), 123 (base). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.20; H, 11.51.

***trans*-4-(Carbethoxymethyl)cyclopent-2-enol (14).** *n*-Butyllithium (4.4 mL of 1.8 M solution, 8 mmol) was added to a solution of dry *N,N*-diisopropylamine (1.12 mL, 8 mmol) in THF (10 mL) at 0 °C. After 30 min, the solution of LDA was cooled to −78 °C and then transferred under nitrogen onto a well-stirred suspension of copper(I) cyanide (1.61 g, 18 mmol) and dry ethyl acetate (700 mg, 8 mmol) in anhydrous THF (30 mL) at −100 °C. The mixture was allowed to warm up slowly to −30 °C and then cooled down to −78 °C. Freshly distilled cyclopentadiene monoepoxide (328 mg, 4.0 mmol) was added dropwise, and the mixture allowed to warm up to room temperature over 4 h. Workup as described in the general procedure, followed by flash chromatography (hexane–ether, 1:1; R_f 0.25), provided **14** (115 mg, 17%) as a light yellow liquid: IR (neat) 770, 1035, 1075, 1730, 3065, 3200–3600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.1 Hz), 1.35 (dt, 1 H, J = 13.9, 4.8 Hz), 2.37 (dd, 1 H, J = 15.7, 7.4 Hz), 2.45 (dd, 1 H, J = 15.7, 6.5 Hz), 2.53 (dt, 1 H, J = 13.9, 8.0 Hz), 2.89–2.95 (m, 1 H), 4.09 (q, 2 H, J = 7.1 Hz), 4.76 (dd, 1 H, J = 8.0, 4.8 Hz), 5.78–5.82 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.21, 39.78, 40.43, 40.65, 60.37, 77.00, 134.32, 136.70, 172.62; mass spectrum, m/e 170 (M), 152, 125, 107, 95, 82, 79 (base). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.56; H, 8.31.

***trans*-4-[(Tributylstannyl)methyl]cyclopent-2-enol (15).** *n*-Butyllithium (0.38 mL of 2.63 M solution, 1 mmol) was added to a solution of (tri-*n*-butylstannyl)methyl iodide[36] (431 mg, 1 mmol) in ether (5 mL) at −50 °C. After 1 h, the solution was transferred under nitrogen onto a well-stirred suspension of copper(I) cyanide (134 mg, 1.5 mmol) in anhydrous ether (5 mL) at −40 °C. The mixture was stirred at −40 °C for 1 h and then cooled down to −78 °C. Freshly distilled cyclopentadiene monoepoxide (123 mg, 1.5 mmol) was added dropwise, and the mixture allowed to warm up to room temperature overnight. Workup as described in the general procedure, followed by flash chromatography (hexane–ether, 3:1; R_f 0.36), provided **15** (19 mg, 5%) as a light yellow oil: IR ($CDCl_3$) 1030–1050, 3600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–1.65 (m, 31 H), 1.99 (dd, 1 H, J = 14.2, 7.6 Hz), 3.03–3.11 (m, 1 H), 4.82–4.89 (m, 1 H), 5.74–5.75 (m, 1 H), 5.85–5.86 (m, 1 H). Anal. Calcd for $C_{18}H_{36}OSn$: C, 55.85; H, 9.37. Found: C, 55.62; H, 9.26.

***trans*-4-Vinylcyclopent-2-enol (16) and *trans*-2-Vinylcyclopent-3-enol (19).** From the reaction of 12.3 g (150 mmol) of cyclopentadiene monoepoxide and Li(vinyl-CuCN), according to the general procedure, there was obtained 12.4 g (75%) of a

(34) Watson, S. C.; Eastham, J. E. *J. Organomet. Chem.* **1967**, *9*, 165.
(35) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(36) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151. (b) Seyferth, D.; Andrews, S. B.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1972**, *37*, 69.

pale yellow liquid consisting of a 1:1 mixture of **16** and **19**, as determined by ^1H NMR. The adducts could not be separated by distillation or chromatography.

16 (in the mixture): IR (neat) 795, 915, 1000, 1035, 1645, 3060, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80–2.21 (m, 2 H), 3.42–3.63 (m, 1 H), 4.75–5.30 (m, 4 H), 5.75–5.95 (m, 2 H). Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.08. Found: C, 76.05; H, 9.43.

19:[37] IR (neat) 820, 850, 915, 990, 1040, 1640, 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.65 (m, 2 H), 3.12–3.43 (m, 1 H), 4.10–4.42 (m, 1 H), 4.83–5.21 (m, 3 H), 5.50–5.83 (m, 2 H). Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.08. Found: C, 76.22; H, 9.15.

***trans*-4-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]cyclopent-2-enol (17) and *trans*-2-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]cyclopent-3-enol (20).** *tert*-Butyllithium (62 mL of 1.84 M solution, 114 mmol) was added dropwise to a solution of (1*E*)-1-iodo-3-[(*tert*-butyldimethylsilyl)oxy]-1-octene (20.0 g, 54.3 mmol) in anhydrous ether (215 mL) at −78 °C. After 3 h at −78 °C, the solution was transferred under nitrogen onto a mechanically stirred suspension of copper(II) cyanide (10.2 g, 114 mmol) in anhydrous ether (215 mL) at −40 °C. The mixture was stirred at −40 °C for 1.5 h,[38] and then freshly distilled cyclopentadiene monoepoxide (9.4 g, 114 mmol) was added dropwise. The resulting mixture was stirred between −40 °C and −30 °C for 2 h and then allowed to warm up to room temperature over 5 h. Workup as described in the general procedure, followed by column chromatography (hexane–ethyl acetate, 5:1), provided 14.1 g (80%) of a 4:1 mixture of adducts **17** and **20**, respectively. A second chromatography afforded analytically pure samples of each regioisomer.

17 (R_f 0.30 in hexane–ethyl acetate, 5:1): IR (neat) 770, 840, 970, 1080, 1260, 1405, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 and 0.01 (2 × s, 6 H), 0.81–0.88 (m, 3 H), 0.86 (s, 9 H), 1.24–1.48 (m, 8 H), 1.87 (dddd, 1 H, J = 13.9, 6.8, 5.1, 2.9 Hz), 1.95 (ddt, 1 H, J = 13.9, 7.6, 2.9 Hz), 3.48–3.50 (m, 1 H), 3.99 (dt, 1 H, J = 5.8, 5.5, 6.6 Hz), 4.85–4.89 (m, 1 H), 5.33 (ddd, 1 H, J = 15.4, 7.0, 1.0 Hz), 5.41 (ddd, 1 H, J = 15.4, 5.9, 1.3 Hz), 5.81–5.87 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.00, −3.50, 14.70, 23.30, 25.70, 26.60, 28.00, 32.50, 39.00, 41.60, 47.40, 74.20, 77.50, 133.30, 134.00, 134.30, 138.90. Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18. Found: C, 70.21; H, 11.15.

20 (R_f 0.35 in hexane–ethyl acetate, 5:1): IR (neat) 770, 840, 965, 1080, 1255, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.81–0.90 (m, 3 H), 0.86 (s, 9 H), 1.24–1.48 (m, 8 H), 2.26 (m, 1 H), 2.67 (dtd, 1 H, J = 17.0, 4.0, 2.0 Hz), 3.14–3.15 (m, 1 H), 4.01–4.03 (m, 1 H), 4.12–4.14 (m, 1 H), 5.41–5.46 (m, 2 H), 5.59–5.62 (m, 1 H), 5.71–5.74 (m, 1 H).

***trans*-4-Phenylcyclopent-2-enol (18) and *trans*-2-Phenylcyclopent-3-enol (21).** From 1.0 g (12.2 mmol) of cyclopentadiene monoepoxide and Li(PhCuCN) there were obtained 650 mg of **18** and 320 mg of **21** (50% combined yield) as light yellow oils after chromatography (hexane–ether, 1:1).

18 (R_f 0.20 in hexane–ether, 1:1): IR (neat) 690, 740, 1021, 1600, 3345 cm^{-1}; ^1H NMR (CCl_4) δ 1.95–2.34 (m, 2 H), 3.86–3.97 (br s, 1 H), 3.96–4.28 (m, 1 H), 4.82–5.15 (m, 1 H), 5.94–6.02 (m, 2 H), 7.19–7.22 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 44.00, 50.20, 77.00, 126.40, 127.20, 128.70, 134.30, 138.70, 145.10; mass spectrum, m/e 160 (M), 142, 115 (base), 104, 91, 77. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.35; H, 7.61.

21 (R_f 0.42 in hexane–ether, 1:1): IR (neat) 690, 745, 1045, 3350 cm^{-1}; ^1H NMR (CCl_4) δ 2.20–2.60 (m, 2 H), 2.78–2.90 (br s, 1 H), 3.48–3.70 (m, 1 H), 3.90–4.25 (m, 1 H), 5.60–5.78 (m, 2 H), 7.02–7.20 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 41.20, 60.50, 80.60, 126.40, 127.30, 128.40, 129.30, 132.20, 142.70; mass spectrum, m/e 160 (M), 142 (base), 115, 104, 91, 77. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.35; H, 7.35.

Synthesis of *cis*-2,3-Epoxycyclopentanols. General Procedure. Epoxy alcohols **22–25** were all synthesized from the corresponding *trans*-4-substituted-cyclopent-2-enols by reaction with *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl acetylacetonate. In those cases where the starting material consisted of a mixture of 1,2- and 1,4-adducts, only the latter was epoxidized, thus allowing for an easier chromatographic separation.

In a typical run, 90% *t*-BuOOH (27.4 g, 0.27 mol, 1.3 equiv) was added dropwise to a stirred solution of allylic alcohol **11** (20.9 g, 0.21 mol) and $VO(acac)_2$ (363 mg, 1.34 mmol) in dry benzene (500 mL). The resulting light orange solution was stirred at 40 °C for 24 h. The solvent was removed under reduced pressure, and the residue was taken up into ether and filtered through a short pad of Florisil. Concentration of the filtrate afforded 22.8 g (95%) of epoxy alcohol **22** as an orange oil. Column chromatography (hexane–ethyl acetate, 1:2; R_f 0.57) provided an analytically pure sample of the product.

***cis*-2,3-Epoxy-*trans*-4-methylcyclopentanol (22):** IR (neat) 810, 830, 850, 930, 980, 1065, 1080, 1230, 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 7.4 Hz), 1.38 (dt, 1 H, J = 13.0, 7.9 Hz), 1.62 (dd, 1 H, J = 13.0, 7.9 Hz), 2.36 (quintet, 2 H, J = 7.4 Hz and OH-broad), 3.24 (d, 1 H, J = 2.7 Hz), 3.46 (td, 1 H, J = 8.1, 1.4 Hz). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.76.

***trans*-4-Butyl-*cis*-2,3-epoxycyclopentanol (23).** From 120.3 g (0.86 mol) of **12** there was obtained 134.3 g (100%) of epoxy alcohol **23** as an orange oil. Column chromatography (hexane–ethyl acetate, 3:1; R_f 0.24) provided an analytically pure sample: IR (neat) 850, 870, 1070, 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (dist. t, 3 H, J = 6.4 Hz), 1.05–1.23 (m, 6 H), 1.30 (dt, 1 H, J = 13.2, 8.0 Hz), 1.65 (dd, 1 H, J = 13.2, 8.0 Hz), 2.18 (dist. q, 1 H, J = 7.5 Hz), 2.80–2.90 (m, 1 H), 3.23 (d, 1 H, J = 2.7 Hz), 3.41 (dist. dd, 1 H, J = 2.7, 1.2 Hz), 4.23 (td, 1 H, J = 8.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.78, 22.56, 29.44, 31.22, 33.17, 38.32, 58.53, 59.77, 72.23; mass spectrum, m/e 156 (M), 138, 109, 95, 83, 71, 57, 41 (base). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.23; H, 10.21.

***trans*-4-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-*cis*-2,3-epoxycyclopentanol (24).** From 40.7 g of a 4:1 mixture of 1,4- and 1,2-adducts **17** and **20**, respectively, there was obtained 6.0 g of **20** and 23.1 g (98%) of epoxy alcohol **24**, as light yellow oils, after chromatography (hexane–ethyl acetate, 5:1).

24: R_f 0.29 hexane–ethyl acetate, 4:1); IR (neat) 780, 815, 840, 970, 1080, 1255, 3430 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 to 0.02 (4 × s, two of them collapsed, 6 H), 0.82–0.91 (m, 3 H), 0.85–0.86 (2 × s, 9 H), 1.22–1.51 (m, 9 H), 1.81 (ddd, 1 H, J = 13.0, 10.3, 9.0 Hz), 1.87–1.92 (m, 1 H, OH), 2.94 (t, 1 H, J = 7.7 Hz), 3.32 (dd, 1 H, J = 5.3, 2.7 Hz), 3.49–3.51 (m, 1 H), 4.00 (dist. q, 1 H, J = 5.8 Hz), 4.32 (br t, 1 H, J = 7.9 Hz), 5.36 (dd, 1 H, J = 15.6, 7.6 Hz), 5.48 (dd, 1 H, J = 15.6, 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.21, 13.94, 18.27, 22.61, 24.94, 25.91, 31.82, 34.20, 38.32, 40.81, 58.47, 58.91, 72.56, 73.26, 128.14, 135.61.

***cis*-2,3-Epoxy-*trans*-4-phenylcyclopentanol (25).** From 328 mg (2.0 mmol) of **18** there was obtained 325 mg (90%) of epoxy alcohol **25** as an orange oil. Column chromatography (hexane–ethyl acetate, 3:1) gave an analytically pure sample of the product: IR (neat) 698, 760, 850, 972, 1165, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42–2.16 (m, 2 H), 3.35–3.66 (m, 4 H), 4.34–4.70 (t, 1 H, J = 8.0 Hz), 6.92–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.15, 44.44, 59.56, 60.10, 72.88, 126.84, 127.16, 128.79, 141.40; mass spectrum, m/e 176 (M), 158, 115, 104 (base), 91, 77. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.68; H, 6.88.

Synthesis of 2,3-Epoxycyclopentanones. General Procedure. Epoxy ketones **26–29** were all synthesized from the corresponding epoxy alcohols by oxidation with 6–10 equiv of chromium trioxide–pyridine complex. Optimum yields were achieved when the reagent was prepared in situ and the reaction was carried out under fairly dilute conditions (ca. 0.01 M in substrate).

In a typical run, vacuum-dried CrO_3 (17.7 g, 177 mmol) was added in small portions to a solution of dry pyridine (28.0 g, 354 mmol) in anhydrous CH_2Cl_2 (1.5 L) at 0 °C. The resulting burgundy solution was stirred at 10–15 °C for 15 min and then cooled down to 0 °C. Crude epoxy alcohol **24** (6.0 g, 17.6 mmol) was dissolved in CH_2Cl_2 (100 mL) and slowly added to the oxidizing mixture, which was stirred at room temperature for an additional 2 h. The solution was then decanted from a gummy residue, which was rinsed exhaustively with CH_2Cl_2. The combined organic solution was successively washed with ice-cold 5%

(37) A pure sample of compound **19** was prepared by reaction of cyclopentadiene monoepoxide with vinylmagnesium bromide–CuI in THF.

(38) The complete formation of the cuprate reagent was determined by a negative Gilman's test for organometallics: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, John Wiley and Sons: New York, 1957; Vol. I, p 417.

HCl, saturated $NaHCO_3$, and NaCl solution and finally dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1) to yield 4.90 g (82%) of epoxy ketone **28** as a light yellow oil.

***trans*-2,3-Epoxy-4-methylcyclopentanone (26).** From 4.7 g (41 mmol) of epoxy alcohol **22** there was obtained 3.5 g (75%) of the title compound as a yellow liquid: IR (neat) 800, 845, 990, 1180, 1215, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7.2 Hz), 1.63 (d, 1 H, J = 17.7 Hz), 2.48 (dd, 1 H, J = 17.7, 7.8 Hz), 2.63 (quintet, 1 H, J = 7.2 Hz), 3.26 (d, 1 H, J = 2.4 Hz), 3.66 (d, 1 H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 17.08, 29.65, 38.97, 54.03, 62.32, 209.73. Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.24.

***trans*-4-Butyl-2,3-epoxycyclopentanone (27).** From 7.8 g (50 mmol) of epoxy alcohol **23** there was obtained 6.2 g (80%) of **27** as a light yellow oil: R_f 0.60 (hexane–ethyl acetate, 5:1); IR (neat) 735, 805, 905, 995, 1130, 1180, 1205, 1295, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–0.90 (m, 3 H), 1.28–1.46 (m, 6 H), 1.75 (d, 1 H, J = 17.9 Hz), 2.43 (dd, 1 H, J = 17.9, 8.0 Hz), 2.51–2.57 (m, 1 H), 3.28 (d, 1 H, J = 2.4 Hz), 3.72 (d, 1 H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.83, 22.65, 28.85, 31.65, 35.23, 37.49, 54.35, 61.57, 209.89. Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.10; H, 9.02.

***trans*-4-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-2,3-epoxycyclopentanone (28)**: IR (neat) 780, 830, 970, 1060–1090, 1255, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.03 to 0.01 (4 × s, 6H), 0.83–0.89 (m, 3 H), 0.84–0.85 (2 × s, 9 H), 1.17–1.43 (m, 8 H), 1.85 (dd, 1 H, J = 18.0, 6.7 Hz), 2.55 (dd, 1 H, J = 18.1, 8.1 Hz), 3.21 (t, 1 H, J = 8.1 Hz), 3.32 (d, 1 H, J = 1.9 Hz), 3.73 (d, 1 H, J = 2.0 Hz), 4.03 (dist. q, 1 H, J = 6.1 Hz), 5.41 (ddt, 1 H, J = 15.6, 8.1, 1.4 Hz), 5.58 (ddd, 1 H, J = 15.6, 6.1, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ −3.39, −2.91, 15.35, 19.58, 23.91, 26.19, 27.21, 33.07, 38.97, 39.51, 55.55, 62.21, 74.04, 128.03, 138.22, 210.27. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12. Found: C, 67.53; H, 10.12.

***trans*-2,3-Epoxy-4-phenylcyclopentanone (29).** From 238 mg (1.35 mmol) of epoxy alcohol **25** there was obtained 186 mg (79%) of **29** as a pale yellow oil: IR (neat) 700, 760, 787, 845, 1175, 1750 cm^{-1}; ^1H NMR (CCl_4) δ 2.01 (dd, 1 H, J = 18.0, 2.0 Hz), 2.71 (dd, 1 H, J = 18.0, 8.0 Hz), 3.35 (d, 1 H, J = 2.0 Hz), 3.57–3.82 (m, 2 H), 6.94–7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 39.10, 40.60, 54.60, 61.79, 126.88, 127.38, 129.06, 209.17; mass spectrum, m/e 174 (M), 157, 131, 117 (base), 77. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.66; H, 5.85.

Synthesis of Epoxy Enol Ethers. General Procedure. Epoxy enol ethers **30–34** were all synthesized from the corresponding 2,3-epoxycyclopentanones by formation of the enolate with LDA in THF at −78 °C, followed by trapping of the enolate with diethyl chlorophosphate or triethylsilyl chloride. In most cases, the crude epoxy enol ethers were pure enough for further reaction with cyanocuprates.

In a typical run, *n*-BuLi (15.2 mL of 1.58 M, 24 mmol) was added dropwise to a solution of dry *N*,*N*-diisopropylamine (3.64 mL, 26 mmol) in anhydrous THF (300 mL) at 0 °C. After being stirred at 0 °C for 30 min, the solution was cooled to −78 °C and *trans*-4-methyl-2,3-epoxycyclopentanone (**26**) (2.24 g, 20 mmol), dissolved in anhydrous THF (30 mL), was added dropwise. About 1 h was allowed for enolate formation, and then freshly distilled diethyl chlorophosphate (3.47 mL, 24 mmol) was added dropwise. The reaction mixture was allowed to warm up from −78 °C to room temperature over 5–6 h and then quenched by addition of saturated NH_4Cl (75 mL). The organic layer was decanted, the aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic solution and extracts were dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave a crude product, which was purified by distillation to afford 4.66 g (94%) of epoxy enol phosphate **30** as a pale yellow liquid, bp 100–110 °C (bath temperature) at 0.025 mmHg.

In the case of triethylsilyl enol ethers, a nonaqueous workup was performed, which consisted in removing the solvent under reduced pressure, taking the residue up into petroleum ether, filtering the salts through a short pad of Florisil, and concentrating the filtrate to give the crude product.

Diethyl *trans*-4,5-epoxy-3-methylcyclopent-1-enyl phosphate (30): IR (neat) 825, 1000, 1180, 1280, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 7.3 Hz), 1.26–1.31 (m, 6 H), 2.72–2.74 (m, 1 H), 3.55 (t, 1 H, J = 2.8 Hz), 3.78 (dd, 1 H, J = 2.8, 2.2 Hz), 4.11–4.17 (m, 4 H), 5.33–5.34 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.73, 16.05, 17.19, 37.61, 56.20, 56.52, 59.82, 64.43, 64.70, 118.23, 118.44, 151.06. Anal. Calcd for $C_{10}H_{17}O_5P$: C, 48.39; H, 6.90. Found: C, 48.36; H, 6.80.

Diethyl *trans*-4,5-Epoxy-3-butylcyclopent-1-enyl Phosphate (31). From 3.08 g (20 mmol) of epoxy ketone **27** there was obtained 5.22 g (90%) of enol phosphate **31** as a light yellow oil: IR (neat) 820, 1000, 1170, 1280, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70–1.10 (m, 3 H), 1.10–1.60 (m, 12 H), 2.50–2.90 (m, 1 H), 3.50–3.70 (m, 1 H), 3.70–3.90 (m, 1 H), 4.00–4.40 (m, 4 H), 5.20–5.40 (m, 1 H).

Diethyl *trans*-3-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-oct-1-enyl]-4,5-epoxycyclopent-1-enyl Phosphate (32). From 340 mg (1 mmol) of epoxy ketone **28** there was obtained 430 mg (85%) of enol phosphate **32**, as a yellow-orange oil: IR (neat) 780, 840, 970, 1040, 1190, 1260, 1285, 1635 cm^{-1}; ^1H NMR (CCl_4) δ 0.00 (s, 6 H), 0.80–0.90 (m, 12 H), 1.05–1.50 (m, 14 H), 3.15–3.30 (m, 1 H), 3.50–3.60 (m, 1 H), 3.60–3.70 (m, 1 H), 3.80–4.40 (m, 5 H), 5.10–5.25 (m, 1 H), 5.30–5.55 (m, 2 H).

***trans*-3-*n*-Butyl-4,5-epoxy-1-[(triethylsilyl)oxy]cyclopentene (33).** From 1.54 g (10 mmol) of epoxy ketone **27** there was obtained 2.70 g (100%) of silyl enol ether **33** as a light orange oil: IR (neat) 1010, 1210, 1250, 1350, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (q, 6 H, J = 7.9 Hz), 0.88–1.01 (m, 12 H), 1.28–1.32 (m, 6 H), 2.60–2.66 (m, 1 H), 3.53 (t, 1 H, J = 2.0 Hz), 3.56 (t, 1 H, J = 2.4 Hz), 4.73 (dd, 1 H, J = 4.8, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 4.57, 6.30, 13.23, 22.66, 28.46, 32.63, 42.82, 57.93, 59.12, 109.77, 155.82.

***trans*-4,5-Epoxy-3-[(1*E*)-3-[(*tert*-butyldimethylsilyl)-oxy]oct-1-enyl]-1-[(triethylsilyl)oxy]cyclopentene (34).** From 3.40 g (10 mmol) of epoxy ketone **28** there was obtained 4.60 g (100%) of silyl enol ether **34** as a light orange oil: IR (neat) 830, 970, 1080, 1200, 1255, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 to 0.02 (4 × s, 6 H), 0.70 (q, 6 H, J = 7.9 Hz), 0.84–0.89 (m, 12 H), 0.98 (t, 9 H, J = 7.9 Hz), 1.17–1.33 (m, 6 H), 1.34–1.47 (m, 2 H), 3.29 (dist. dd, 1 H, J = 7.6, 2.7 Hz), 3.55–3.59 (m, 2 H), 4.02–4.05 (m, 1 H), 4.63–4.67 (m, 1 H), 5.37 (ddd, 1 H, J = 15.5, 7.6, 1.0 Hz), 5.49–5.57 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.70, −4.16, −4.66, 6.44, 13.95, 18.24, 22.59, 24.92, 25.93, 31.83, 38.23, 45.48, 58.29, 58.88, 73.19, 108.05, 128.37, 136.41, 156.43.

Reaction of Epoxy Enol Ethers with Cyanocuprates. The generation of the cuprate was performed as described before. Usually, 3–4 equiv of cuprate reagent were employed. In those cases where the alkyllithium precursor was prepared in situ by metal–halogen exchange from the corresponding alkyl iodide, longer reaction times and higher temperatures were necessary to drive the reaction to completion.

In general, yields were higher when the ethereal solutions of the resulting adducts were thoroughly dried with anhydrous magnesium sulfate and concentrated in vacuo with no external heat. The adducts resulting from the reaction with epoxy enol phosphates were sufficiently stable to stand chromatographic purification, but those obtained from epoxy silyl enol ethers were not. Consequently, the latter were usually subjected to immediate hydrolysis (see below).

A Typical Run. To a solution of 1-iodo-7-[(trimethylsilyl)-oxy]heptane (3.92 g, 12.45 mmol) in anhydrous ether (100 mL), at −78 °C, was added *t*-BuLi (11.58 mL of 2.15 M, 24.92 mmol). The mixture was stirred at −78 °C for 4 h and then transferred via a double-tipped needle to a suspension of copper(I) cyanide (2.45 g, 27.40 mmol) in anhydrous ether (170 mL) at −40 °C. After 1.5 h at −40 °C,[38] the mixture was cooled down to −78 °C and a solution of epoxy silyl enol ether **34** (1.41 g, 3.11 mmol) in ether (20 mL) was added dropwise. The resulting suspension was stirred at −78 °C for 5 h and at −35 °C for an additional 2 h, after which time the reaction was still incomplete, as determined by TLC. The vessel was sealed with Parafilm and kept at −10 °C (freezer) overnight. The reaction was then quenched with saturated NH_4Cl solution (50 mL) and filtered through a short pad of Celite. The organic layer was decanted, washed with saturated NaCl solution (25 mL), and dried over anhydrous magnesium sulfate. Removal of the solvent on a rotary evaporator whose water bath was kept at room temperature then afforded adduct **50**.

The reactions involving cyanocuprates prepared from commercially available organolithium compounds were usually com-

plete after stirring the mixture at −78 °C for 4 h and at room temperature for an additional 4 h.

Diethyl 4β,5β-Dimethyl-3α-hydroxycyclopent-1-enyl Phosphate (35). From 2.73 g (11 mmol) of epoxy enol phosphate **30** and Li(MeCuCN) there was obtained 2.62 g (90%) of the title compound as a pale yellow oil after chromatography (100% ethyl acetate, R_f 0.20): IR (neat) 1010, 1260, 1445, 1650, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 7.2 Hz), 1.00 (d, 3 H, J = 7.2 Hz), 1.30–1.34 (m, 6 H), 2.11 (quintet d, 1 H, J = 7.2, 5.2 Hz), 2.38–2.46 (m, 1 H), 2.78 (dist. quintet, 1 H, J = 7.2 Hz), 4.09–4.18 (m, 4 H), 4.31 (ddd, 1 H, J = 5.2, 3.0, 1.0 Hz), 5.29 (dd, 1 H, J = 3.0, 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.80, 13.29, 15.84, 16.16, 40.38, 40.65, 44.28, 64.38, 64.65, 80.36, 110.48, 110.64, 156.47. Anal. Calcd for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01. Found: C, 48.25; H, 7.85.

Diethyl 5β-*n*-Butyl-3α-hydroxy-4β-methylcyclopent-1-enyl Phosphate (36). From 4.72 g (19 mmol) of **30** and Li(*n*-BuCuCN) there was obtained 5.53 g (95%) of hydroxy enol phosphate **36** as a pale yellow oil after chromatography (100% ethyl acetate; R_f 0.33); IR (neat) 1030, 1275, 1650, 3430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.02 (d, 3 H, J = 7.3 Hz), 1.21–1.47 (m, 12 H), 1.81–1.89 (m, 1 H), 2.15 (quintet d, 1 H, J = 7.3, 5.1 Hz), 2.75 (dist. q, 1 H, J = 7.3 Hz), 4.11–4.19 (m, 4 H), 4.31 (ddd, 1 H, J = 5.1, 2.0, 1.0 Hz), 5.36 (br s, 1 H, $W_{1/2}$ = 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.24, 13.94, 15.89, 16.16, 22.93, 27.05, 29.76, 44.44, 45.53, 64.32, 64.59, 80.30, 110.86, 155.98. Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88. Found: C, 55.06; H, 8.84.

Diethyl 4β,5β-Di-*n*-butyl-3α-hydroxycyclopent-1-enyl Phosphate (37). From 5.80 g (20 mmol) of epoxy enol phosphate **31** and Li(*n*-BuCuCN) there was obtained 5.92 g (85%) of 1,4-adduct **37** as a light brown oil: R_f 0.43 (100% ethyl acetate); IR (neat) 1020, 1170, 1270, 1650, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–1.10 (m, 6 H), 1.10–1.70 (m, 18 H), 1.85–2.10 (m, 1 H), 2.70–3.00 (m, 1 H), 4.00–4.70 (m, 5 H), 5.50–5.60 (br s, 1 H, $W_{1/2}$ = 4.0 Hz).

Diethyl 5β-*n*-Butyl-4β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-enyl]-3α-hydroxycyclopent-1-enyl Phosphate (38). From 470 mg (1 mmol) of epoxy enol phosphate **32** and Li(*n*-BuCuCN) there was obtained 309 mg (58%) of compound **38** as a light yellow oil after chromatography (100% ether; R_f 0.53): IR (neat) 780, 840, 880, 980, 1040, 1180, 1260, 1655, 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00–0.03 (4 × s, 6 H), 0.83–0.92 (m, 15 H), 1.19–1.44 (m, 20 H), 2.70–2.72 (m, 1 H), 2.84–2.86 (m, 1 H), 4.06–4.12 (m, 1 H), 4.13–4.21 (m, 4 H), 4.47–4.52 (m, 1 H), 5.40–5.41 (br s, 1 H), 5.49–5.60 (m, 2 H).

Diethyl 5-[7-[(trimethylsilyl)oxy]heptyl]-4β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-enyl]-3α-hydroxycyclopent-1-enyl Phosphate (39). The reaction of 470 mg (1 mmol) of **32** with the cyanocuprate prepared from 1-iodo-7-[(trimethylsilyl)oxy]heptane provided 398 mg (60%) of the title compound as a light yellow oil after chromatography (100% ether): IR (neat) 780, 840, 970, 1040, 1100, 1260, 1660, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (4 × s, 6 H), 0.09 (s, 9 H), 0.84–0.93 (m, 12 H), 1.17–1.60 (m, 26 H), 2.69–2.72 (m, 1 H), 2.85 (m, 1 H), 3.52–3.62 (t, 2 H, J = 6.6 Hz), 4.06–4.13 (m, 1 H), 4.14–4.22 (m, 4 H), 4.48–4.52 (m, 1 H), 5.40 (br s, 1 H), 5.47–5.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.50, −4.30, 14.09, 16.02, 18.10, 22.38, 24.72, 25.81, 27.29, 28.20, 29.17, 29.52, 31.80, 32.72, 38.61, 46.39, 53.50, 62.11, 64.48, 73.12, 78.43, 111.38, 127.07, 136.50, 152.23.

Diethyl 5β-*tert*-Butyl-4β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-enyl]-3α-hydroxycyclopent-1-enyl Phosphate (40). From 470 mg (1 mmol) of **32** and Li(*t*-BuCuCN) there was obtained 324 mg (61%) of 1,4-adduct **40** as a pale yellow oil after chromatography (100% ether, R_f 0.49): IR (neat) 840, 960, 1040, 1170, 1260, 1650, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (2 × s, 6 H), 0.80–0.90 (m, 12 H), 0.95 (s, 9 H), 1.10–1.60 (m, 14 H), 2.55–2.80 (m, 2 H), 3.80–4.30 (m, 6 H), 5.35–5.60 (m, 3 H).

Diethyl 5β-*tert*-Butyl-3α-hydroxy-4β-methylcyclopent-1-enyl Phosphate (41), Diethyl 5β-*tert*-Butyl-4α-hydroxy-3β-methylcyclopent-1-enyl Phosphate (42), and Diethyl *trans*-3-Hydroxy-4-methylcyclopent-1-enyl Phosphate (43). From 496 mg (2 mmol) of epoxy enol phosphate **30** and Li(*t*-BuCuCN) there were obtained 120 mg (20%) of the 1,4-adduct **41**, 180 mg (30%) of the 1,2-adduct **42**, and 50 mg (10%) of the reduced product **43**, as pale yellow oils after chromatography (100% ethyl acetate).

41: R_f 0.35 (100% ethyl acetate); IR (neat) 855, 1040, 1275, 1650, 3430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9 H), 1.15 (d, 3 H, J = 7.3 Hz), 1.26–1.30 (m, 6 H), 2.15–2.22 (m, 1 H), 2.52 (d, 1 H, J = 7.3 Hz), 4.05–4.11 (m, 4 H), 4.27 (br d, 1 H, J = 5.7 Hz), 5.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.86, 15.95, 16.11, 29.27, 34.09, 48.02, 56.20, 64.22, 64.49, 78.95, 114.00, 154.96, 155.39. Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89;; H, 8.88. Found: C, 54.62; H, 8.75.

42: R_f 0.41 (100% ethyl acetate); IR (neat) 755, 855, 910, 975, 1030, 1270, 1655, 3430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9 H), 0.99 (d, 3 H, J = 7.0 Hz), 1.22–1.26 (m, 6 H), 2.32–2.38 (m, 2 H), 3.10–3.30 (m, 1 H), 3.51–3.53 (m, 1 H), 4.01–4.07 (m, 4 H), 5.12 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.73, 16.00, 19.20, 27.86, 31.87, 44.23, 62.75, 63.02, 64.00, 64.27, 79.71, 113.51, 113.68, 147.64, 148.08. Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88. Found: C, 54.78; H, 8.90.

43: R_f 0.27 (100% ethyl acetate); IR (neat) 755, 850, 960, 1030, 1170, 1270, 1660, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3 H, J = 7.1 Hz), 1.30–1.37 (m, 6 H), 1.98 (ddd, 1 H, J = 16.3, 6.1, 1.2 Hz), 2.06–2.14 (m, 1 H), 2.27–2.41 (m, 1 H), 2.76 (ddd, 1 H, J = 16.3, 8.2, 2.0 Hz), 4.09–4.18 (m, 4 H), 4.28–429 (m, 1 H), 5.29 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.84, 16.11, 19.20, 38.48, 38.70, 40.87, 64.32, 64.59, 81.60, 111.62, 111.83, 152.35, 152.73. Anal. Calcd for $C_{10}H_{19}O_5P$: C, 47.99; H, 7.65. Found: C, 48.08; H, 7.78.

Diethyl 4α-Hydroxy-3β-methyl-5β-vinylcyclopent-1-enyl Phosphate (44). From 496 mg (2 mmol) of epoxy enol phosphate **30** and MgBr(vinyl CuCN) there was obtained 540 mg (98%) of the title compound as a light brown oil. Column chromatography (100% ether; R_f 0.24) provided an analytically pure sample: IR (neat) 850, 915, 980, 1030, 1270, 1655, 3090, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3 H, J = 7.0 Hz), 1.28–1.36 (m, 6 H), 2.54 (qdd, 1 H, J = 7.0, 5.3, 1.9 Hz), 2.60–2.80 (m, 1 H), 3.19–3.23 (m, 1 H), 3.60 (t, 1 H, J = 5.3o Hz), 4.07–4.15 (m, 4 H), 5.12 (ddd, 1 H, J = 10.1, 1.6, 0.8 Hz), 5.18 (ddd, 1 H, J = 17.1, 2.1, 1.1 Hz), 5.18 (q, 1 H, J = 1.9 Hz), 5.71 (ddd, 1 H, J = 17.1, 10.1, 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 15.78, 16.05, 18.98, 44.17, 57.23, 57.50, 64.32, 64.59, 83.23, 112, 92, 113.13, 117.63, 136.70, 146.50, 146.94. Anal. Calcd for $C_{12}H_{21}O_5P$: C, 52.17; H, 7.66. Found: C, 51.96; H, 7.61.

Diethyl 5β-Allyl-4α-hydroxy-3β-methylcyclopent-1-enyl Phosphate (45). The reaction of 496 mg (2 mmol) of epoxy enol phosphate **30** with either Li(C_3H_5CuCN) or MgBr(C_3H_5CuCN) afforded 570 mg (99%) of the 1,2-adduct **45** as a light brown oil. An analytically pure sample of this compound was obtained by chromatography on silica gel (100% ether; R_f 0.20): IR (neat) 890, 1035, 1270, 1650, 3090, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3 H, J = 7.0 Hz), 1.28–1.32 (m, 6 H), 2.10 (dtd, 1 H, J = 14.2, 7.1, 1.1 Hz), 2.42–2.52 (m, 3 H), 2.63–2.66 (m, 1 H), 3.54 (t, 1 H, J = 5.4 Hz), 4.07–4.16 (m, 4 H), 5.01–5.11 (m, 3 H), 5.79 (ddt, 1 H, J = 17.2, 10.2, 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 15.78, 16.11, 19.20, 35.23, 44.28, 52.08, 52.35, 64.27, 64.49, 82.42, 112.21, 112.32, 116.71, 135.83, 147.70, 148.13. Anal. Calcd for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.99. Found: C, 53.66; H, 8.00.

Diethyl 3α-Hydroxy-4β-methyl-5β-phenylcyclopent-1-enyl Phosphate (46) and Diethyl 4α-Hydroxy-3β-methyl-5β-phenylcyclopent-1-enyl Phosphate (47). From 496 mg (2 mmol) of epoxy enol phosphate **30** and Li(PhCuCN) there were obtained 172 mg (26%) of 1,4-adduct **46** and 350 mg (54%) of 1,2-adduct **47**, as pale yellow oils after chromatography (100% ethyl acetate).

46: R_f 0.21 (100% ethyl acetate); IR (neat) 705, 735, 860, 965, 1035, 1270, 1655, 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3 H, J = 7.0 Hz), 1.19–1.28 (m, 6 H), 2.40–2.51 (m, 2 H), 3.92–4.02 (m, 5 H), 4.52 (br d, 1 H, J = 3.9 Hz), 5.67 (br s, 1 H, $W_{1/2}$ = 3.0 Hz), 7.08–7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.43, 15.73, 16.00, 46.39, 54.08, 128.25, 128.90, 137.62, 153.38. Anal. Calcd for $C_{16}H_{23}O_5P$: C, 58.89; H, 7.10. Found: C, 58.75; H, 7.05.

47: R_f 0.41 (100% ethyl acetate); IR (neat) 705, 760, 875, 970, 1020, 1265, 1655, 3410 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3 H, J = 7.0 Hz), 1.19–1.23 (m, 6 H), 2.65–2.69 (m, 1 H), 2.83–3.05 (m, 1 H), 3.75 (t, 1 H, J = 5.6 Hz), 3.84 (dd, 1 H, J = 5.6, 1.5 Hz), 3.89–3.98 (m, 4 H), 5.37 (d, 1 H, J = 1.5 Hz), 7.20–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.68, 15.95, 19.03, 44.12, 59.83, 64.16, 64.43, 86.97, 114.33, 126.84, 128.19, 128.41, 140.22, 146.45, 146.88. Anal. Calcd for $C_{16}H_{23}O_5P$: C, 58.89; H, 7.10. Found: C, 58.65; H, 7.00.

4β,5β-Dibutyl-3α-hydroxy-1-[(triethylsilyl)oxy]cyclopentene (48). From 1.34 g (5 mmol) of epoxy silyl enol ether **33** and Li(*n*-BuCuCN) there was obtained 1.65 g (100%) of 1,4-ad-

duct **48** as a light yellow oil: R_f 0.28 (hexane–ether, 9:1); IR (neat) 735, 750, 1010–1020, 1245, 1640, 3150–3600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64–0.71 (m, 6 H), 0.84–0.97 (m, 15 H), 1.23–1.39 (m, 12 H), 1.85 (qd, 1 H, J = 7.3, 5.4 Hz), 2.56 (dist. q, 1 H, J = 7.3 Hz), 4.33–4.36 (m, 1 H), 4.63 (dist. dd, 1 H, J = 2.5, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 4.68, 6.52, 13.94, 23.04, 27.76, 28.03, 29.81, 30.79, 45.96, 50.89, 79.65, 104.03, 161.73.

4β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-3α-hydroxy-5-[7-[(trimethylsilyl)oxy]heptyl]-1-[(triethylsilyl)oxy]cyclopentene (50). The reaction of 1.41 g (3.11 mmol) of epoxy silyl enol ether **34** with the cuprate prepared from 1-iodo-7-[(trimethylsilyl)oxy]heptane provided 3.80 g of crude adduct **50**. An aliquot of this material was purified by flash chromatography on silica gel (hexane–ether, 3:1), affording fairly pure compound **50**: R_f 0.38 (hexane–ether, 5:1); IR (neat) 750, 840, 1095, 1250, 1645, 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01–0.02 (4 × s, 6 H), 0.08 (s, 9 H), 0.66–0.72 (m, 6 H), 0.80–0.84 (m, 12 H), 0.85–0.96 (m, 9 H), 1.23–1.61 (m, 20 H), 2.15–2.19 (m, 1 H), 2.60–2.73 (m, 1 H), 3.51–3.58 (m, 2 H), 4.00–4.06 (m, 1 H), 4.31–4.42 (m, 1 H), 4.62–4.70 (m, 1 H), 5.40–5.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.10, −0.41, 4.79, 6.57, 14.05, 18.28, 22.66, 25.05, 25.91, 27.05, 29.44, 30.03, 31.87, 32.85, 38.84, 50.29, 55.87, 62.75, 73.64, 79.82, 103.27, 131.82, 134.26, 160.48.

General Procedure for the Hydrolysis of 3-Hydroxy-1-[(triethylsilyl)oxy]cyclopentenes. The 1,4-adducts from the cuprate addition to epoxy silyl enol ethers were usually subjected to immediate hydrolysis to afford the corresponding β-hydroxycyclopentanones, which could be purified by column chromatography.

A Typical Run. A solution of crude adduct **50** (ca. 3.1 mmol) in ethanol (90 mL) was added to a solution of potassium fluoride (3.06 g, 52.7 mmol) in pH 7 phosphate buffer (60 mL), and the mixture was stirred at room temperature for 3 h. The ethanol was removed in vacuo, and the remaining aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were washed with saturated NaCl solution and dried over anhydrous magnesium sulfate. Concentration under reduced pressure and chromatography of the residue, eluting with 100% ether, gave 1.13 g (80%) of a light yellow oil consisting of a 1:8 mixture of **56** and **61**, respectively.

2β,3β-Dibutyl-4α-hydroxycyclopentanone (54). Hydrolysis of adduct **48** according to the procedure described above afforded compound **54** in 85% yield after chromatography (hexane–ether, 1:1; R_f 0.21): IR (neat) 735, 915, 1745, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.89 (m, 6 H), 1.15–1.62 (m, 12 H), 1.90–1.97 (m, 1 H), 2.17–2.21 (m, 1 H), 2.20 (dd, 1 H, J = 19.4, 1.7 Hz), 2.43 (dd, 1 H, J = 19.4, 5.9 Hz), 2.61 (dist. q, 1 H, J = 7.0 Hz), 4.36 (dt, 1 H, J = 5.9, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.77, 22.71, 23.79, 26.59, 29.15, 29.80, 44.70, 47.26, 50.12, 70.56, 218.35; mass spectrum, m/e 212 (M), 194, 155, 99 (base). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. found: C, 73.31; H, 11.21.

2α,3β-Dibutyl-4α-hydroxycyclopentanone (64). Treatment of **54** with 80 equiv of potassium acetate in ethanol at room temperature for 100 h provided a 4:7 mixture of the starting **54** and its C_2-epimer **64**, respectively, along with variable amounts of the corresponding cyclopentenones. Column chromatography on silica gel (hexane–ether, 2:1) allowed for an easy separation of the β-hydroxy ketones from the enones; however, **54** and **64** could not be separated from each other.

64 (in the mixture with **54**): ^1H NMR ($CDCl_3$) δ 0.83–0.92 (m, 6 H), 1.20–1.80 (m, 12 H), 1.86–1.88 (m, 2 H), 2.20 (dd, 1 H, J = 18.3, 6.8 Hz), 2.65 (ddd, 1 H, J = 18.3, 6.8, 1.0 Hz), 4.13 (dist. q, 1 H, J = 6.8 Hz).

3β-Butyl-2α-(7-hydroxyheptyl)-4α-hydroxycyclopentanone (60). Crude adduct **49**, obtained from the reaction of epoxy silyl enol ether **33** (470 mg, 1.75 mmol) with 4 equiv of the cuprate derived from 1-iodo-7-[(trimethylsilyl)oxy]heptane, was hydrolyzed with KF (1.7 g, 30 mmol) in pH 7 phosphate buffer (35 mL)/ethanol (52 mL). Column chromatography (hexane–ether, 1:4) provided 368 mg (78%) of a 1:7 mixture of **55** and **60**, respectively. These two epimers could not be separated and, therefore, spectral data for the minor isomer could not be clearly ascertained.

60: R_f 0.18 (hexane–ether, 1:4); IR (neat) 845, 965, 1080, 1735, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7.1 Hz), 1.19–1.57 (m, 18 H), 1.80–1.89 (m, 2 H), 2.16 (dd, 1 H, J = 18.3, 6.6 Hz), 2.60 (ddd, 1 H, J = 18.3, 6.6, 0.8 Hz), 3.57 (t, 2 H, J = 6.6 Hz), 4.07 (dist. q, 1 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.89, 23.01, 25.57, 26.82, 29.09, 29.21, 29.33, 29.57, 32.31, 32.60, 47.15, 49.05, 53.94, 62.82, 72.89, 217.93; mass spectrum, m/e 270 (M), 253, 156, 138, 99 (base). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.96; H, 11.06.

3β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-2α-(7-hydroxyheptyl)-4α-hydroxycyclopentanone (61). Crude adduct **50** was hydrolyzed as described in the general procedure to afford 1.13 g (80%) of a 1:8 mixture of **56** and **61**, respectively. This mixture was subjected to hplc separation (ca. 2 mg per run, Porasil 8 mm × 10 cm analytical column, hexane–ethyl acetate, 3:1, 4 mL/min) to afford diastereomerically pure compound **61a** (R_f 0.28 in 100% ether); an analytically pure sample of either diastereoisomer of **56**, however, could not be obtained by this technique.

61a: IR (neat) 780, 835, 1075, 1255, 1745, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03–0.05 (2 × s, 6 H), 0.71–0.88 (m, 12 H), 1.20–1.70 (m, 20 H), 1.97 (dist. dt, 1 H, J = 11.1, 5.5 Hz), 2.21 (dd, 1 H, J = 18.3, 9.5 Hz), 2.34 (dt, 1 H, J = 11.9, 8.7 Hz), 2.72 (ddd, 1 H, J = 18.3, 7.4, 0.9 Hz), 3.61 (t, 2 H, J = 6.6 Hz), 4.02 (dist. q, 1 H, J = 8.6 Hz), 4.10 (dist. q, 1 H, J = 6.0 Hz), 5.48 (ddd, 1 H, J = 15.4, 8.6, 0.7 Hz), 5.67 (dd, 1 H, J = 15.4, 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.22, 14.01, 18.30, 22.65, 24.98, 25.93, 26.71, 27.72, 29.15, 29.74, 31.83, 32.78, 38.44, 46.13, 54.71, 63.00, 72.29, 72.95, 128.67, 138.02, 214.60; mass spectrum, m/e 397, 379, 253, 95, 75 (base). Anal. Calcd for $C_{26}H_{50}O_4Si$: C, 68.67; H, 11.08. Found: C, 68.35; H, 10.94.

2β-*tert*-Butyl-3β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]-oct-1-enyl]-4α-hydroxycyclopentanone (57). Crude adduct **51**, obtained from the reaction of epoxy silyl enol ether **34** (225 mg, 0.5 mmol) with 4 equiv of Li(*t*-BuCuCN), was hydrolyzed with KF (490 mg, 8.4 mmol) in pH 7 phosphate buffer (10 mL)/ethanol (15 mL). Column chromatography (hexane–ether, 2:1) provided 129 mg (65%) of diastereomeric hydroxy ketones **57**.

For the less polar isomer: R_f 0.20 (hexane–ether, 2:1); IR (neat) 780, 840, 1250, 1745, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.04 and 0.01 (2 × s, 6 H), 0.81–0.85 (m, 12 H), 0.99 (s, 9 H), 1.22–1.42 (m, 8 H), 2.23 (br d, 1 H, J = 19.2 Hz), 2.40 (dd, 1 H, J = 19.2, 5.4 Hz), 2.68 (br d, 1 H, J = 7.0 Hz); 3.02–3.06 (m, 1 H), 4.01 (dist. q, 1 H, J = 6.4 Hz), 4.15 (br d, 1 H, J = 5.4 Hz), 5.20 (dd, 1 H, J = 15.2, 10.7 Hz), 5.57 (dd, 1 H, J = 15.2, 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ −4.58, −4.22, 13.89, 18.12, 22.59, 24.74, 25.87, 28.55, 31.65, 38.09, 45.48, 52.75, 58.82, 72.17, 73.31, 128.07, 136.77, 215.55; mass spectrum, m/e 339, 325, 295, 253, 75 (base). Anal. Calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18. Found: C, 69.35; H, 11.19.

For the more polar isomer: R_f 0.14 (hexane–ether, 2:1); IR (neat) 780, 840, 1255, 1745, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05 and −0.01 (2 × s, 6 H), 0.83–0.87 (m, 12 H), 1.01 (s, 9 H), 1.23–1.43 (m, 8 H), 2.22 (br d, 1 H, J = 19.1 Hz), 2.39 (dd, 1 H, J = 19.1, 5.4 Hz), 2.67 (br d, 1 H, J = 7.0 Hz), 3.02–3.07 (m, 1 H), 4.02–4.07 (m, 1 H), 4.10 (br d, 1 H, J = 5.3 Hz), 5.28 (ddd, 1 H, J = 15.2, 10.7, 1.0 Hz), 5.61 (dd, 1 H, J = 15.2, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ −4.76, −4.52, 13.95, 18.12, 22.59, 24.86, 25.81, 28.61, 31.77, 38.27, 45.48, 52.81, 58.82, 72.35, 72.77, 127.12, 136.53, 215.31; mass spectrum, m/e 399, 325, 295, 253, 75, 57 (base). Anal. Calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18. Found: C, 69.42; H, 11.26.

3β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-2β-*n*-heptyl-4α-hydroxycyclopentanone (58) and 3β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-2α-*n*-heptyl-4α-hydroxycyclopentanone (62). Epoxy silyl enol ether **34** (452 mg, 1.0 mmol) was treated with 4 equiv of the cuprate prepared from 1-iodoheptane (0.66 mL), *t*-BuLi (3.8 mL of 2.1 M solution), and copper(I) cyanide (716 mg, 8 mmol) in ether (88 mL). Standard workup gave the crude adduct **52**, which was hydrolyzed with KF (990 mg, 17 mmol) in pH 7 phosphate buffer (20 mL)/ethanol (30 mL). Column chromatography (hexane–ether, 2:1) provided 302 mg (70%) of a 1:4 mixture of **58** and **62**, respectively.

58 (one diastereoisomer): IR (neat) 780, 840, 970, 1075, 1255, 1740, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 and 0.01 (2 × s, 6 H), 0.83–0.87 (m, 15 H), 1.23–1.69 (m, 21 H), 2.28 (dd, 1 H, J = 19.2, 1.5 Hz), 2.47 (dd, 1 H, J = 19.2, 5.6 Hz), 2.59–2.65 (m, 1 H), 2.94 (br t, 1 H, J = 8.8 Hz), 4.01 (q, 1 H, J = 6.2 Hz), 4.31 (dist. d, 1 H, J = 5.6 Hz), 5.13 (ddd, 1 H, J = 15.3, 10.0, 0.9 Hz), 5.60 (dd, 1 H, J = 15.3, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.28, 14.07, 18.24, 22.65, 24.86, 25.22, 25.87, 27.48, 29.21, 29.63, 31.89, 38.39,

44.82, 50.12, 51.61, 72.35, 73.25, 125.33, 138.14, 217.52.

62 (mixture of diastereoisomers): IR (neat) 780, 840, 970, 1075, 1255, 1740, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01–0.04 (4 × s, 6 H), 0.82–0.87 (m, 15 H), 1.10–1.62 (m, 20 H), 2.09–2.13 (m, 1 H), 2.10–2.20 (m, 1 H), 2.20 (dd, 1 H, J = 18.4, 9.4 Hz), 2.34 (dt, 1 H, J = 11.6, 8.6 Hz), 2.70 (dd, 1 H, J = 18.4, 7.4 Hz), 4.01 (dist. q, 1 H, j = 8.7 Hz), 4.10 (dist. q, 1 H, J = 5.8 Hz), 5.46 (dd, 1 H, J = 15.3, 8.6 Hz), 5.66 (dd, 1 H, J = 15.3, 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ −4.70, −4.28, 14.01, 18.24, 22.65, 24.98, 25.87, 26.82, 27.84, 29.09, 29.80, 31.83, 38.39, 46.19, 54.12, 54.30, 54.71, 72.29, 72.95, 128.67, 137.90, 214.89; mass spectrum, m/e 381, 363, 349, 337, 241, 75 (base). Anal. Calcd for $C_{26}H_{50}O_3Si$: C, 71.17; H, 11.49. Found: C, 71.05; H, 11.41.

3β-*n*-Butyl-2β-*n*-heptyl-4α-hydroxycyclopentanone (59) and 3β-*n*-Butyl-2α-*n*-heptyl-4α-hydroxycyclopentanone (63). Epoxy silyl enol ether **33** (270 mg, 1.0 mmol) was treated with 4 equiv of the cuprate prepared from 1-iodoheptane (0.66 mL), *t*-BuLi (3.8 mL of 2.1 M solution), and copper(I) cyanide (716 mg, 8 mmol) in ether (88 mL). The reaction was quenched after 5 h at −78 °C and 30 min at −40 °C. Thin layer chromatography of the mixture still showed a significant amount of **33**. Standard workup gave crude adduct **53**, which was hydrolyzed with KF (990 mg, 17 mmol) in pH 7 phosphate buffer (20 mL)/ethanol (30 mL). Column chromatography (hexane–ether, 2:1) provided 150 mg (60%) of a 2:1 mixture of **59** and **63**, respectively. These compounds could not be separated; however, their spectral characteristics were easily obtained from the spectrum of the mixture.

59 (in the mixture with **63**): IR (neat) 1080, 1740, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.91 (m, 6 H), 1.23–1.61 (m, 18 H), 2.20 (dd, 1 H, J = 19.3, 1.2 Hz), 2.15–2.23 (m, 1 H), 2.43 (dd, 1 H, J = 19.3, 5.9 Hz), 2.58–2.64 (m, 1 H), 4.35–4.36 (m, 1 H). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.53; H, 11.94.

63 (in the mixture with **59**): ^1H NMR ($CDCl_3$) δ 0.82–0.91 (m, 6 H), 1.23–1.61 (m, 18 H), 1.84–1.87 (m, 2 H), 2.21 (dd, 1 H, J = 18.3, 6.8 Hz), 2.63 (ddd, 1 H, J = 18.3, 6.8, 1.0 Hz), 4.11 (dist. q, 1 H, J = 6.8 Hz).

(±)-2-Decarboxy-2-(hydroxymethyl)prostaglandin E_1 (67). To a solution of **61a** (340 mg, 0.75 mmol) in acetonitrile (10 mL) was added 47–52% aqueous HF (1.1 mL). The mixture was stirred at room temperature for 1 h, after which it was diluted with ethyl acetate (50 mL) and successively washed with 5% aqueous $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with 100% ethyl acetate and then with ethyl acetate–acetone, 1:1, to afford 230 mg (90%) of the title compound as a white solid, mp 96–98 °C: IR (neat) 975, 1075, 1745, 3420, 3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.7 Hz), 1.23–1.60 (m, 20 H), 1.97 (dist. dt, 1 H, J = 12.0, 6.0 Hz), 2.19 (dd, 1 H, J = 18.4, 9.9 Hz), 2.32 (dt, 1 H, J = 12.0, 8.7 Hz), 2.70 (ddd, 1 H, J = 18.4, 7.4, 0.8 Hz), 3.59 (t, 2 H, J = 6.5 Hz), 3.97–4.03 (m, 1 H), 4.04–4.09 (m, 1 H), 5.50 (dd, 1 H, J = 15.2, 8.7 Hz), 5.63 (dd, 1 H, J = 15.2, 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.59, 25.16, 25.63, 26.65, 27.72, 29.03, 29.57, 31.71, 32.72, 37.43, 46.01, 54.53, 54.71, 62.94, 71.99, 73.01, 131.53, 136.89, 214.60; mass spectrum, m/e 323, 305, 269, 208, 95, 55, 43 (base). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.64; H, 10.60.

3β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-2α-(6-carboxyhexyl)-4α-hydroxycyclopentanone (68). A suspension of platinum oxide (10 mg) in water (7 mL) was hydrogenated on a Parr apparatus at 30 psi for 30 min. The catalyst was then transferred to a solution of ketol **61a** (8 mg) in acetone (10 mL) at 40 °C, and oxygen was bubbled through the suspension for 4 h. The solution was decanted and concentrated in vacuo. The resulting aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent, followed by chromatography (100% ethyl acetate and then 2% methanol/ethyl acetate) provided 5.7 mg (70%) of **68**: R_f 0.33 (acetone–methanol, 9:1); IR (neat) 778, 835, 1075, 1715, 1740, 3100–3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01–0.04 (2 × s, 6 H), 0.80–0.88 (m, 12 H), 1.21–1.55 (m, 18 H), 1.97–2.01 (m, 1 H), 2.20 (dd, 1 H, J = 18.5, 9.1 Hz), 2.31 (dist. t, 2 H, J = 7.3 Hz), 2.34–2.40 (m, 1 H), 2.71 (ddd, 1 H, J = 18.5, 7.2, 0.9 Hz), 4.01 (dist. q, 1 H, J = 8.4 Hz), 4.10 (dist. q, 1 H, J = 6.5 Hz), 5.48 (ddd, 1 H, J = 15.2, 8.3, 0.9 Hz), 5.67 (dd, 1 H, J = 15.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.22, 14.01, 18.30, 22.65, 24.92, 25.93, 27.66, 28.85, 29.27, 31.83, 38.39, 46.25, 53.94, 54.59, 72.35, 73.01, 128.67, 137.90, 215.19; mass spectrum, m/e 411, 393, 301, 75 (base). Anal. Calcd for $C_{26}H_{48}O_5Si$: C, 66.62; H, 10.32. Found: C, 66.45; H, 10.18.

(±)-Prostaglandin E_1. Treatment of 5.3 mg (0.011 mmol) of **68** with 0.1 mL of 47–52% aqueous HF as described before for compound **67** afforded 3.2 mg (80%) of (±)-PGE_1 after chromatography (100% ethyl acetate, followed successively by 2%, 6%, and 10% methanol/ethyl acetate): ^1H NMR (acetone-d_6, 360 MHz) δ 0.91 (t, 3 H, J = 6.0 Hz), 1.26-1.68 (m, 18 H), 2.02-2.14 (m, 2 H), 2.29 (t, 2 H, J = 7.1 Hz), 2.31-2.38 (m, 1 H), 2.59 (ddd, 1 H, J = 18.4, 7.1, 0.7 Hz), 4.03–4.12 (m, 2 H), 5.61–5.67 (m, 2 H).

2β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-3α-(7-hydroxyheptyl)-1α,4α-dihydroxycyclopentane (69). L-Selectride (1.75 mL of 1 M solution in THF) was added dropwise to a stirred solution of ketol **61a** (111 mg, 0.24 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was allowed to warm up to room temperature over 6 h and then quenched by sequential addition of water (1 mL), ethanol (2 mL), 3 M aqueous NaOH (3 mL), and 30% hydrogen peroxide (3 mL). After stirring for 30 min, the aqueous layer was saturated with $NaCO_3$, decanted, and extracted with ether. The combined organic layer and extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (100% ether, followed by 100% ethyl acetate) to afford 94.1 mg (84%) of **69** as a colorless oil: R_f 0.21 (100% ethyl acetate); IR (neat) 775, 835, 970, 1065, 1255, 3100–3600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00–0.03 (2 × s, 6 H), 0.84–0.89 (m, 12 H), 1.25–1.60 (m, 22 H), 1.79 (ddd, 1 H, J = 14.6, 2.0, 1.1 Hz), 2.06 (ddd, 1 H, J = 14.6, 7.0, 4.6 Hz), 2.24 (dist. td, 1 H, J = 8.8, 4.1 Hz), 3.61 (t, 2 H, J = 6.5 Hz), 3.92–3.97 (m, 1 H), 4.03 (dist. q, 1 H, J = 6.1 Hz), 4.20–4.21 (m, 1 H), 5.37 (dd, 1 H, J = 15.3, 8.5 Hz), 5.47 (dd, 1 H, J = 15.3, 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ −4.69, −4.21, 14.00, 18.28, 22.61, 25.05, 25.64, 25.91, 28.03, 29.22, 29.81, 31.82, 32.69, 38.43, 42.98, 50.83, 56.36, 62.91, 73.48, 73.75, 78.68, 78.84, 131.07, 135.02; mass spectrum, m/e 399, 381, 363, 289, 75 (base). Anal. Calcd for $C_{26}H_{52}O_4Si$: C, 68.36; H, 11.47. Found: C, 68.10; H, 11.17.

2β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-3α-(6-carboxyhexyl)-1α,4α-dihydroxycyclopentane (70). Triol **69** (6.6 mg) was oxidized according to the procedure described for the preparation of compound **68** to give 5.1 mg (75%) of hydroxy acid **70** as a colorless oil after chromatography (100% ethyl acetate, followed by 5%, 10%, and 20% methanol/ethyl acetate, respectively): R_f 0.18 (ethyl acetate–methanol, 9:1); IR (neat) 775, 835, 970, 1075, 1255, 1710, 3150–3600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01–0.03 (2 × s, 6 H), 0.85–0.92 (m, 12 H), 1.19–1.61 (m, 21 H), 1.81 (ddd, 1 H, J = 15.0, 2.0, 1.1 Hz), 2.05 (ddd, 1 H, J = 15.0, 7.5, 5.0 Hz), 2.23–2.25 (m, 1 H), 2.32 (dist. t, 2 H, J = 7.4 Hz), 3.94–3.96 (m, 1 H), 4.03 (dist. q, 1 H, J = 6.1 Hz), 4.20–4.21 (m, 1 H), 5.38 (dd, 1 H, J = 15.4, 8.7 Hz), 5.48 (dd, 1 H, J = 15.4, 6.1 Hz); mass spectrum, m/e 395, 377, 351, 303, 187, 75 (base). Anal. Calcd for $C_{26}H_{50}O_5Si$: C, 66.34; H, 10.71. Found: C, 66.49; H, 10.84.

(±)-Prostaglandin $F_{1\alpha}$. Treatment of **70** (5.1 mg) with aqueous HF in acetonitrile according to the procedure described for compound **67** provided 3.5 mg (90%) of (±)-$PGF_{1\alpha}$ after chromatography (100% ethyl acetate, followed by 10% and 20% methanol/ethyl acetate, respectively). The chromatographic and spectral characteristics of the product were identical with those of an authentic sample:[19] ^1H NMR (acetone-d_6, 360 MHz) δ 0.87 (t, 3 H, J = 6.8 Hz), 1.23–1.65 (m, 20 H), 2.15–2.21 (m, 2 H), 2.25 (t, 2 H, J = 7.4 Hz), 3.82 (ddd, 1 H, J = 6.9, 6.0, 4.4 Hz), 3.96 (dist. q, 1 H, J = 6.2 Hz), 4.10–4.13 (m, 1 H), 5.38–5.50 (m, 2 H).

***trans*-3-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-4-hydroxy-1-[(triethylsilyl)oxy]cyclopentene (71).** A solution of epoxy silyl enol ether **34** (2.80 g, 6.2 mmol) in anhydrous ether (10 mL) was added dropwise to a stirred suspension of 95% lithium aluminum hydride (285 mg, 7.5 mmol) in anhydrous ether (250 mL) at 0 °C. The cooling bath was removed and the suspension stirred at room temperature for 2 h, after which time it was poured onto ice-cold saturated NH_4SO_4 solution (50 mL) that had been acidified to pH 3 with 10% sulfuric acid. The aqueous layer was decanted and extracted with ether (3 × 15 mL). The combined organic layer and extracts were successively washed with saturated $NaHCO_3$ and NaCl solutions and then dried over

anhydrous potassium carbonate. Concentration in vacuo afforded 2.80 g (99%) of the title compound as a pale yellow oil: IR (neat) 775, 835, 970, 1010, 1100, 1255, 1645, 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 to 0.01 (4 × s, 6 H), 0.66 (q, 6 H, J = 7.9 Hz), 0.83–0.86 (m, 3 H), 0.85 and 0.86 (2 × s, 9 H), 0.95 (t, 9 H, J = 7.9 Hz), 1.18–1.47 (m, 8 H), 1.87 (br s, 1 H), 2.21 (ddd, 1 H, J = 16.3, 4.0, 1.3 Hz), 2.62 (dd, 1 H, J = 16.3, 6.8 Hz), 3.03–3.05 (m, 1 H), 4.01 (dt, 2 H, J = 5.7, 5.7 Hz), 4.48 (dd, 1 H, J = 6.6, 1.7 Hz), 5.38–5.52 (m, 2 H); mass spectrum m/e 455 (M + 1), 437, 397, 283, 215, 115, 87, 75 (base).

***trans*-3-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-4-(methoxymethoxy)-1-[(triethylsilyl)oxy]cyclopentene (72).** Freshly distilled chloromethyl methyl ether (0.56 mL, 7.3 mmol) was added dropwise to a solution of hydroxy silyl enol ether **71** (2.80 g, 6.1 mmol) and dry *N,N*-diisopropylethylamine (1.39 mL, 7.9 mmol) in dichloromethane (250 mL). The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the residue was taken up in petroleum ether and filtered through a short pad of Florisil. Concentration of the filtrate, followed by (hexane–ethyl acetate, 20:1), provided 2.80 g (91%) of **72** as a colorless oil: IR (neat) 775, 840, 920, 970, 1050, 1155, 1255, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 to 0.02 (4 × s, 6 H), 0.67 (q, 6 H, J = 7.6 Hz), 0.81–0.89 (m, 3 H), 0.86 (2 × s, 9 H), 0.96 (t, 9 H, J = 7.9 Hz), 1.19–1.48 (m, 8 H), 2.32 (ddd, 1 H, J = 16.1, 5.0, 1.1 Hz), 2.58 (ddd, 1 H, J = 16.1, 7.5, 1.6 Hz), 3.19–3.21 (m, 1 H), 3.33 (2 × s, 3 H), 3.91–3.97 (m, 1 H), 4.01 (dt, 1 H, J = 6.0, 6.1 Hz), 4.45 (dd, 1 H, J = 6.4, 1.8 Hz), 4.62 (AB, 2 H, J_{AB} = 6.8 Hz), 5.39–5.53 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.15, 4.95, 6.52, 13.94, 18.27, 22.61, 24.94, 25.97, 31.87, 38.48, 40.43, 51.70, 55.28, 73.48 and 73.64, 80.79 and 80.95, 95.64, 103.06, 132.04 and 132.15, 133.72, 152.36; mass spectrum, m/e 436 (M + 1 − CH_3OCH_2OH), 365, 279, 215, 115, 89 (base), 75.

1α,3α-2β(α)-Carbethoxy-5α-(methoxymethoxy)-4β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-enyl]-1β-[(triethylsilyl)oxy]bicyclo[3.1.0]hexanes (73 and 74). A solution of ethyl diazoacetate (1.10 g, 9.6 mmol) in dry benzene (5 mL) was added dropwise, over a 3-h period, to a suspension of anhydrous copper(II) sulfate (10 mg, 0.06 mmol) in **72** (3.20 g, 6.4 mmol) kept at 90 °C. After the addition was complete, the mixture was stirred at room temperature for an additional 12 h. The solvent was removed in vacuo, and the residue was taken up in petroleum ether and filtered through 20 g of neutral alumina (activity grade III). Concentration of the filtrate under reduced pressure, followed by chromatography of the residue (hexane–ether, 25:1), provided 2.10 g (56%) of **73** and 0.50 g (13%) of **74** as colorless oils.

73: R_f 0.30 (hexane–ether, 12:1); IR ($CDCl_3$) 975, 1040, 1100, 1150, 1250, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 to 0.02 (4 × s two of them collapsed, 6 H), 0.61 (q, 6 H, J = 7.9 Hz), 0.84–0.86 (m, 3 H), 0.86 (2 × s, 9 H), 0.93 (t, 9 H, J = 7.9 Hz), 1.23–1.42 (m, 8 H), 1.25 (t, 3 H, J = 7.1 Hz), 2.13 (t, 1 H, J = 3.1 Hz), 2.19–2.23 (m, 2 H), 2.27–2.30 (m, 1 H), 2.56–2.57 (m, 1 H), 3.29 (2 × s, 3 H), 3.79 (t, 1 H, J = 6.9 Hz), 4.01–4.04 (m, 1 H), 4.11 (q, 2 H, J = 7.1 Hz), 4.52 (AB, 2 H, J_{AB} = 6.9 hz), 5.51–5.56 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.10, 5.60, 6.74, 13.94, 14.38, 18.28, 22.61, 24.94, 25.97, 31.87, 32.20, 35.45, 38.43, 40.97, 50.18, 55.38, 60.15, 71.04, 73.15 and 73.53, 81.23, 95.36, 129.55, and 129.82, 134.69 and 134.80, 169.53; mass spectrum, m/e 452, 328, 317, 215, 115, 87, 73, 45 (base). Anal. Calcd for $C_{31}H_{60}O_2Si_2$: C, 63.65; H, 10.34. Found: C, 63.65; H, 10.27.

74: R_f 0.17 (hexane–ether, 12:1); IR ($CDCl_3$) 975, 1045, 1100, 1150, 1165, 1255, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 to 0.03 (4 × s, 6 H), 0.61 (q, 6 H, J = 7.9 Hz), 0.83–0.88 (m, 3 H), 0.86 and 0.87 (2 × s, 9 H), 0.92 (t, 9 H, J = 7.9 Hz), 1.12–1.50 (m, 8 H), 1.26 (t, 3 H, J = 7.1 Hz), 1.68 (td, 1 H, J = 10.2, 1.6 Hz), 2.08 (d, 1 H, J = 9.8 Hz), 2.34 (dd, 1 H, J = 14.0, 8.5 Hz), 2.47 (ddd, 1 H, J = 14.0, 7.5, 2.3 Hz), 2.84 (br t, 1 H, J = 7.5 Hz), 3.29 (2 × s, 3 H), 4.03 (dt collapsed to a q, 1 H, J = 6.1 Hz), 4.09–4.20 (m, 3 H), 4.54 (AB, 2 H, J_{AB} = 6.7 Hz), 5.52 (ddd, 1 H, J = 15.5, 6.1, 3.1 Hz), 5.63 (dd, 1 H, J = 15.5, 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.10, 5.33, 6.63, 13.94, 14.38, 18.28, 22.66, 24.94, 25.97, 31.93, 35.23, 36.10, 38.58, 38.92, 46.18, 55.28, 60.04, 68.49, 73.37, 85.51, 95.85, 130.96, 134.80, 169.69; mass specturm, m/e 452, 390, 328, 317, 215, 129 (base), 115, 87, 73, 45. Anal. Calcd for $C_{31}H_{60}O_2Si_2$: C, 63.65; H, 10.34. Found: C, 63.67; H, 10.25.

2α-(Carbethoxymethyl)-3β-[(1*E*)-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-enyl]-4α-(methoxymethoxy)cyclopentanone (75). A solution of triethylammonium fluoride (183 mg, 1.5 mmol) in dry THF (2 mL) was added dropwise to a solution of (silyloxy)cyclopropane esters **73** and **74** (760 mg, 1.3 mmol) in dry THF (10 mL). The mixture was stirred at room temperature for 3 h, after which time it was quenched with 5% aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was decanted and extracted with ether (3 × 5 mL). The combined organic layer and extracts were washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. Concentration under reduced pressure (temperature of water bath <30 °C) afforded 580 mg (95%) of γ-keto ester **75** as a slightly yellow oil: IR ($CDCl_3$) 970, 1050, 1100, 1150, 1255, 1730, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 to 0.04 (4 × s, 6 H), 0.80–0.90 (m, 12 H), 1.17–1.50 (m and t, 11 H, J = 7.1 Hz), 2.27–2.70 (m, 5 H), 2.80 (dd, 1 H, J = 18.4, 7.4 Hz), 3.33 (2 × s, 3 H), 3.96–4.02 (m, 1 H), 4.07–4.14 (m, 3 H), 4.60–4.67 (AB, 2 H, J_{AB} = 6.8 Hz), 5.50 (dd, 1 H, J = 15.5, 7.3 Hz), 5.61 (ddd, 1 H, J = 15.5, 6.0, 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ −4.70, −4.28, 14.01, 14.31, 18.24, 22.65, 24.92, 25.87, 31.47, 31.83, 38.33, 44.46, 50.48, 50.90, 55.55, 60.73, 72.95, 96.31, 128.13, 137.78, 171.33, 212.87 (one carbon unaccounted for); mass spectrum, m/e 413, 337, 277, 203, 181, 149, 89, 75, 45 (base).

3aα,6aα-4β-[(1*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]oct-1-enyl]-5α-(methoxymethoxy)perhydropenta[*b*]furan-2-one (76). To a solution of γ-keto ester **75** (565 mg, 1.2 mmol) in dry THF (10 mL) at −78 °C was added lithium perhydro-9b-boraphenalyl hydride (3 mL of 0.5 M solution in THF, 1.5 mmol). The mixture was stirred at −78 °C for 30 min, and at room temperature for 12 h, and then was quenched with 5% aqueous HCl (2 mL). The aqueous layer was decanted and extracted with ether. The combined organic layer and extracts were successively washed with 5% aqueous $NaHCO_3$ and saturated NaCl solutions and then dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by chromatography of the residue (hexane–ether, 5:1), provided 410 mg (80%) of lactone **76** as a colorless oil that solidified upon cooling to −10 °C: IR ($CDCl_3$) 970, 990, 1040, 1150, 1255, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.03 and 0.00 (2 × s, 6 H), 0.79–0.88 (m, 3 H), 0.82 and 0.85 (2 × s, 9 H), 1.17–1.44 (m, 8 H), 2.03 (dtd, 1 H, J = 14.9, 6.0, 2.5 Hz), 2.35 (ddd, 1 H, J = 15.1, 6.4, 1.8 Hz), 2.43 (dd, 1 H, J = 17.8, 1.8 Hz), 2.43–2.50 (m, 1 H), 2.56–2.63 (m, 1 H), 2.71 (dd, 1 H, J = 17.8, 9.9 Hz), 3.30 and 3.31 (2 × s, 3 H), 3.84 (dt, 1 H, J = 12.7, 6.2, 6.5 Hz), 4.02 (dt, 1 H, J = 11.2, 5.7, 5.6 Hz), 4.57 (2 × s, AB collapsed to A^2, 2 H), 4.90 (tt, 1 H, J = 6.9, 2.3 Hz), 5.34–5.42 (m, 1 H), 5.50 (ddd, 1 H, J = 15.5, 5.9, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.75, −4.31, 13.94, 18.17, 22.55, 24.83, 25.86, 31.71, 34.47, 37.94, 38.27, 42.38, 54.08, 55.44, 72.94, 82.04, 82.09, 95.74, 128.14, 136.32, 176.63; mass spectrum, m/e 381, 339, 293, 149, 119, 75, 57, 45 (base). Anal. Calcd for $C_{23}H_{42}O_5Si$: C, 64.74; H, 9.92. Found: C, 64.67; H, 9.82.

(3aα,6aα)-5α-Hydroxy-4β-[(1*E*)-3-hydroxyoct-1-enyl]perhydrocyclopenta[*b*]furan-2-ones (77 and 78). A solution of lactone **76** (43 mg, 0.1 mmol) and 0.2 mL of 50% aqueous HF in acetonitrile was stirred at room temperature for 30 min. The mixture was diluted with dichloromethane (10 mL) and washed with 10% aqueous $NaHCO_3$ solution (2 × 5 mL). The aqueous layer was decanted and extracted with dichloromethane (2 × 5 mL). The combined organic layer and extracts were washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. Concentration under reduced pressure afforded a pale yellow oil which was dissolved in THF (7 mL). To this solution was added 5% aqueous HCl (0.6 mL) and the resulting mixture was refluxed for 20 h. Upon cooling, the mixture was diluted with dichloromethane (10 mL), washed with 10% aqueous $NahCO_3$ solution, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo, and column chromatography of the residue (100% ether), afforded the epimeric hydroxy lactones **77** and **78** (20 mg, 72% overall).

78: R_f 0.31 (100% ethyl acetate); IR ($CDCl_3$) 975, 1100, 1200, 1770, 3250–3600 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.88 (t, 3 H, J = 6.7 Hz), 1.24–1.56 (m, 8 H), 1.96 (ddd, 1 H, J = 14.8, 7.3, 2.8 Hz), 2.31 (dt collapsed to a q, 1 H, J = 7.9 Hz), 2.44 (dd, 1 H, J = 17.9, 1.8 Hz), 2.51–2.63 (m, 2 H), 2.73 (dd, 1 H, J = 17.9, 9.6 Hz), 3.99 (dt collapsed to a q, 1 H, J = 7.2 Hz), 4.09 (dist. q, 1 H, J = 6.4 Hz), 4.90 (td, 1 H, J = 7.0, 3.0 Hz), 5.48 (dd, 1 H, J

= 15.5, 8.0 Hz), 5.63 (dd, 1 H, J = 15.5, 6.0 Hz); mass spectrum, m/e 269 (M + 1), 268, 250, 179, 151, 133, 119, 99, 71, 43 (base).

77: R_f 0.25 (100% ethyl acetate); IR ($CDCl_3$) 975, 1100, 1200, 1770, 3240–3560, 3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.7 Hz), 1.24–1.55 (m, 8 H), 1.97 (ddd, 1 H, J = 14.8, 7.0, 2.9 Hz), 2.33 (q, 1 H, J = 7.8 Hz), 2.47 (dd, 1 H, J = 17.9, 1.7 Hz), 2.45–2.66 (m, 2 H), 2.75 (dd, 1 H, J = 17.9, 9.7 Hz), 3.99 (q, 1 H, J = 7.0 Hz), 4.11 (q, 1 H, J = 6.1 Hz), 4.91 (td, 1 H, J = 7.0, 2.9 Hz), 5.49 (ddd, 1 H, J = 15.5, 8.1, 0.9 Hz), 5.64 (dd, 1 H, J = 15.5, 5.9 Hz). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.12; H, 8.98.

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Preorganized Macrocyclic Ligands: A Novel Approach to Functionalized Hemispherands via Aromatization

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Reaction of the 1,3-diaryl-2-propanone moiety in the flexible 18-membered macrocycle **2b** with nitromalonodialdehyde to yield the hemispherand **1f** represents a novel method for the synthesis of partly preorganized macrocyclic ligands. The O–O repulsion in the macrocyclic cavity is compensated for by the energetically favorable formation of an aromatic ring. The macrocycle **2b** was synthesized in five steps from **3a**. The carbonyl group of **3a** was protected via ketalization. Subsequent lithiation, reaction with dimethylformamide, reduction, and cyclization with diethylene glycol ditosylate gave the macrocycle **2a** in a yield of 68%. The X-ray crystal structure of **2a** shows that the methoxy groups are located at opposite faces of the macroring and the macrocyclic cavity is filled by the methoxy methyl groups. The binding free energies ($\Delta G°$) of **2a** and **2b**, determined by the picrate extraction method showed that they are poor ligands for alkali cations with the highest values measured for K^+ [8.5 (**2a**) and 7.6 (**2b**) kcal·mol^{-1}]. An alternative synthesis of functionalized hemispherands **1b–e** involved the synthesis of 5′-functionalized *m*-teranisyls and the subsequent introduction of the polyethyleneoxy bridge via the corresponding 3,3″-bis(hydroxymethyl) derivatives. Compound **3c** was synthesized in three steps from **8a** and converted into **4c** by reaction with nitromalonodialdehyde. The terphenyl **4c** was converted into *m*-teranisyls with different functional groups at the 5′-position. Depending on the functional group present at the 5′-position, an aldehyde group at the 3- and 3″-positions was introduced by either bromo to lithium exchange and reaction with dimethylformamide (**7a,e**) or by reaction of the 3,3″-unsubstituted *m*-teranisyls **4d** and **9b** with hexamethylenetetramine in trifluoroacetic acid. The hemispherands **1b–e** were obtained after reduction of the dialdehydes and macrocyclization of the bis(hydroxymethyl) derivatives with diethylene glycol ditosylate in 35–40% yields.

Introduction

The selective complexation of metal and organic cations has been studied mainly with flexible macrocyclic polyether hosts.[1] Complexation of a guest cation by a host molecule can be optimized by variation of the geometrical relationship between host and guest, and with polyfunctional cations such as guanidinium[2] or uronium[3] this approach has been proven successful.

An alternative way to increase the stability of a host–guest complex was introduced by Cram et al.[4] who demonstrated that preorganization of binding sites in a rigid molecular framework may lead to very stable complexes. This principle was experimentally demonstrated with the synthesis of the spherands and their complexes with Li^+ and Na^+ cations.[5] The very high negative values for the free energy of complexation can be attributed to three factors. First, because of the rigid molecular framework the host hardly undergoes the conformational changes upon complexation that generally lower the stability of complexes with flexible macrocyclic hosts. Second, as a consequence of the preorganization of the rigid host, repulsive forces between electronegative binding sites cannot be minimized by conformational changes in the uncomplexed host. Upon complexation of an electron-deficient guest, these repulsive forces are converted into attractive forces between host and guest. Third, the methoxy groups prevent solvent molecules from entering the cavity. Therefore the binding sites do not have to be desolvated during complexation.

In addition to the spherands, Cram et al. have synthesized compounds in which at least half of the binding

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