Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Bruker Aspect 3000 spectrometer operating at 400 and 100.5 MHz, respectively, using deuteriochloroform as solvent. Assignments were confirmed by double irradiation. Chemical shifts are reported relative to internal $SiMe_4$. Infrared spectra were recorded on a Perkin-Elmer PE 580 spectrometer. TLC was performed on silica gel (Merck 60 F_{254}). Column chromatography was conducted on silica gel (Merck 60, 70-230 mesh). Elemental analyses were performed by the Service Central de Microanalyse du CNRS at Vernaison (France).

General Procedure. Method A. A solution of 317 mg (1.05 mmol) of *N*-(phenylseleno)phthalimide (NPSP) dissolved in methylene chloride (2 mL) was cooled to -78 °C and treated with $SnCl_4$ (0.22 mL, 1.1 mmol). After 2 min of stirring, a methylene chloride solution (5 mL) of the unsaturated substrates (1 mmol) was added, and the mixture was stirred 1 h at -78 °C and then 3 h (48 h in the case of substrates **6** and **7**) at room temperature. The reaction mixture was diluted with methylene chloride (150 mL) and washed with a saturated $NaHCO_3$ solution and with water. In the case of compounds **6** and **7**, the precipitate was filtered off, diluted in aqueous 2 M sodium hydroxide (5 mL), and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Products were purified by column chromatography.

Method B. A solution of 317 mg (1.05 mmol) of NPSP dissolved in methylene chloride (2 mL) was treated with $SnCl_4$ (1 mL of a 10 mM methylene chloride solution). Amide **1** (205 mg, 1 mmol) dissolved in methylene chloride (5 mL) was added, and the reaction mixture was stirred 72 h at room temperature. The mixture was worked up as described in method A.

Method C. This method was like method A, but 0.2 mL of trimethylsilyl triflate (TMSOTf) was used instead of $SnCl_4$.

Method D. This method was like method B, but 1 mL of a 10 mM methylene chloride solution of TMSOTf was used instead of $SnCl_4$.

Method E. A solution of 317 mg (1.05 mmol) of NPSP dissolved in methylene chloride (2 mL) was cooled to -78 °C and treated with 2 mmol of BF_3 (as a stock solution of CH_3NO_2). After 2 min of stirring, **1** (205 mg, 1 mmol) was added and the mixture was then stirred for 1 h at room temperature. The mixture was worked up as described in method A.

Method F. A solution of 317 mg (1.05 mmol) of NPSP dissolved in nitromethane (2 mL) was treated with 4 mmol of BF_3 (as a stock solution in CH_3NO_2). The unsaturated derivative (1 mmol) was added and the mixture was stirred 15 days at room temperature under argon. The mixture was worked up as described in method A.

2-(3,4-(Methylenedioxy)phenyl)-4-((phenylseleno)methyl)-2-oxazoline (8): ^1H NMR ($CDCl_3$) δ 3.03 (1 H, dd, J = 12.5 Hz, J = 7.5 Hz, C*H*-Se-Ph), 3.26 (1 H, dd, J = 5.5 Hz, C*H*-Se-Ph), 3.79 (1 H, dd, $J_{5',5}$ = 15 Hz, $J_{4,5}$ = 7 Hz, H5), 4.12 (1 H, dd, $J_{5',4}$ = 9.5 Hz, H5'), 4.86 (1 H, m, H4), 6.00 (2 H, s, O-CH_2-O), 6.79 (1 H, d, J = 8 Hz), 7.27 (3 H, m, Se-Ph), 7.31 (1 H, d, J = 1.25 Hz), 7.39 (1 H, dd), 7.57 (2 H, m, Se-Ph); ^{13}C NMR ($CDCl_3$) δ 31.92 (*C*-Se-Ph), 60.13 (C5), 78.95 (C4), 101.50 (O-CH_2-O), 107.99, 108.32, 121.61, 123.17, 147.59, 150.23 (*C* arom, piperonyl), 123.38, 127.47, 128.97, 129.05, 133.35, 134.05 (Se-Ph), 163.27 (C2). Anal. Calcd for $C_{17}H_{15}NO_3Se$: C, 56.68; H, 4.20; N, 3.89; Se, 21.92. Found: C, 56.82; H, 4.28; N, 3.86; Se, 21.88.

2-(3,4-Dimethoxyphenyl)-4-((phenylseleno)methyl)-2-oxazoline (9): ^1H NMR ($CDCl_3$) δ 3.05 (1 H, dd, J = 12.5 Hz, J = 7.5 Hz, C*H*-Se-Ph), 3.29 (1 H, dd, J = 5 Hz, C*H*-Se-Ph), 3.82 (1 H, dd, $J_{5,5'}$ = 15 Hz, $J_{4,5}$ = 6.5 Hz, H5), 3.92 (6 H, s, 2OCH_3), 4.15 (1 H, dd, $J_{4,5'}$ = 9.5 Hz, H5'), 4.87 (1 H, m, H4), 6.85 (2 H, m), 7.22 (3 H, m), 7.44 (2 H, m), 7.56 (1 H, m). Anal. Calcd for $C_{18}H_{19}NO_3Se$: C, 57.45; H, 5.09; N, 3.72; Se, 20.98. Found: C, 57.82; H, 5.13; N, 3.63; Se, 21.04.

2-(2,3,4-Trimethoxyphenyl)-4-((phenylseleno)methyl)-2-oxazoline (10): ^1H NMR ($CDCl_3$) δ 3.03 (1 H, dd, J = 12.5 Hz, J = 7.5 Hz, C*H*-Se-Ph), 3.29 (1 H, dd, J = 5.5 Hz, C*H*-Se-Ph), 3.83 (1 H, dd, $J_{5,5'}$ = 15 Hz, $J_{5,4}$ = 6.5 Hz, H5), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 4.16 (1 H, dd, $J_{4,5'}$ = 9.5 Hz, H5'), 4.82 (1 H, m, H4), 6.66 (1 H, d, J = 9 Hz), 7.27 (s H, m, Se-Ph), 7.44 (1 H, d), 7.57 (2 H, m, Se-Ph). Anal. Calcd for $C_{19}H_{21}NO_4Se$: C, 56.16; H, 5.21; N, 3.45; Se, 19.43. Found: C, 55.83; H, 5.33; N, 3.30; Se, 19.47.

***N*-Methyl-*N*-(2-acetoxy-3-(phenylseleno)propyl)piperonylamide (12):** IR (film) cm^{-1} 1675 (C=O), 1735 (CH_3O-C=O); ^1H NMR ($CDCl_3$) δ 1.95 (3 H, s, CH_3), 2.99 (3 H, s, OAc), 3.09 (2 H, m), 3.60 (1 H, m), 3.90 (1 H, m), 5.34 (1 H, m), 6.00 (2 H, s, O-CH_2-O), 6.84 (3 H, m), 7.27 (3 H, m, Se-Ph), 7.53 (2 H, m, Se-Ph). Anal. Calcd for $C_{19}H_{19}NO_5Se$: C, 54.29; H, 4.56; N, 3.33; Se, 18.79. Found: C, 54.10; H, 4.53; N, 3.06; Se, 18.75.

3-Acetoxy-4-(phenylseleno)butyl 3,4-(Methylenedioxy)phenyl Ketone (14): IR (film) cm^{-1} 1635 (C=O), 1735 (CH_3O-C=O); ^1H NMR ($CDCl_3$) δ 1.92 (3 H, s, OAc), 2.08 (1 H, m, H2), 2.19 (1 H, m, H2'), 2.81 (2 H, t, J = 7.5 Hz, H1, H1'), 3.09 (1 H, dd, $J_{4,4'}$ = 12 Hz, $J_{3,4'}$ = 6 Hz, *H4'*), 3.14 (1 H, dd, $J_{3,4}$ = 6 Hz, H4), 5.10 (1 H, m, H3), 6.04 (2 H, s, O-C*H*$_2$-O), 6.84 (1 H, d, J = 8 Hz), 7.28 (3 H, m, Se-Ph), 7.40 (1 H, d, J = 1.25 Hz), 7.51 (1 H, dd), 7.55 (2 H, m, Se-Ph). Anal. Calcd for $C_{20}H_{20}O_5Se$: C, 57.29; H, 4.81; Se, 18.83. Found: C, 57.12; H, 4.87; Se, 18.75.

6,7-(Methylenedioxy)-4-((phenylseleno)methyl)-1,2,3,4-tetrahydroisoquinoline (15): ^1H NMR ($CDCl_3$) δ 2.39 (1 H, s, NH), 2.85 (1 H, m, H4), 3.06 (1 H, dd, J = 12.5 Hz, J = 4.5 Hz, C*H*-Se-Ph), 3.21 (2 H, m, H3, H3'), 3.34 (1 H, dd, J = 3 Hz, C*H*-Se-Ph), 3.85 (2 H, s, H1, H1'), 5.88 (2 H, s, O-C*H*$_2$-O), 6.47 (1 H, s), 6.55 (1 H, s), 7.26 (3 H, m, Se-Ph), 7.54 (2 H, m, Se-Ph). Anal. Calcd for $C_{17}H_{17}NO_2Se$: C, 58.96; H, 4.95; N, 4.04; Se,22.80. Found: C, 59.03; H, 4.83; N, 3.97; Se, 22.62.

2-Methyl-6,7-(methylenedioxy)-4-((phenylseleno)methyl)-1,2,3,4-tetrahydroisoquinoline (16): ^1H NMR ($CDCl_3$) δ 2.33 (3 H, s, NCH_3), 2.45 (1 H, dd, $J_{3,3'}$ = 11.5 Hz, $J_{3',4}$ = 4 Hz, H3'), 2.89 (1 H, m, H4), 2.99 (1 H, dd, $J_{3,4}$ = 3 Hz, H3), 3.20 (1 H, d, $J_{1,1'}$ = 15 Hz, H1), 3.21 (1 H, dd, J = 12 Hz, J = 3 Hz, C*H*-Se-Ph), 3.29 (1 H, dd, J = 10.5 Hz, C*H*-Se-Ph), 3.63 (1 H, d, H1'), 5.89 (2 H, br s, O-CH_2-O), 6.48 (1 H, s, H5), 6.55 (1 H, s, H8), 7.28 (3 H, m, Se-Ph), 7.57 (2 H, m, Se-Ph). Anal. Calcd for $C_{18}H_{18}NO_2Se$: C, 60.17; H, 5.05; N, 3.90; Se, 21.98. Found: C, 59.91; H, 5.17; N, 3.83; Se, 22.04.

2-(3,4-(Methylenedioxy)phenyl)-4-methyl-2-oxazoline (17): ^1H NMR ($CDCl_3$) δ 1.41 (3 H, d, J = 6 Hz, CH_3), 3.57 (1 H, dd, $J_{5,5'}$ = 15 Hz, $J_{4,5}$ = 7 Hz, H5), 4.11 (1 H, dd, $J_{4,5'}$ = 9.5 Hz, H5'), 4.82 (1 H, m, H4), 6.00 (2 H, s, O-CH_2-O), 6.82 (1 H, d, J = 8 Hz, H arom), 7.40 (1 H, d, J = 1.5 Hz, H arom), 7.49 (1 H, dd, H arom); ^{13}C NMR ($CDCl_3$) δ 21.05 (CH_3), 61.52 (C5), 76.27 (C4), 101.45 (O-CH_2-O), 107.97, 108.31, 122.13, 123.02, 147.60, 150.09 (C arom), 163.42 (C2). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.57; H, 5.22; N, 6.64.

Registry No. **1**, 64654-11-1; **2**, 114908-28-0; **3**, 73664-69-4; **4**, 114908-29-1; **5**, 114908-30-4; **6**, 68291-57-6; **7**, 114908-31-5; **8**, 114908-32-6; **9**, 114908-33-7; **10**, 114908-34-8; **11**, 114908-35-9; **12**, 114908-36-0; **13**, 114908-37-1; **14**, 114908-38-2; **15**, 114908-39-3; **16**, 114908-40-6; **17**, 114908-41-7; NPSP, 71098-88-9.

Organocuprate Conjugate Addition to 2,3-Dihydro-4*H*-pyran-4-ones[1]

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The scope and utility of organocopper-mediated conjugate addition methodologies have been amply illustrated during the past 15 years with numerous reviews[2-8] and at least one monograph[9] appearing on the subject. A variety of organocuprate reagents have been developed utilizing stoichiometric (Gilman),[10] mixed ligand (heterocuprate),[11] catalytic,[12] and "higher order" (copper(I) cyanide)[13] cuprate

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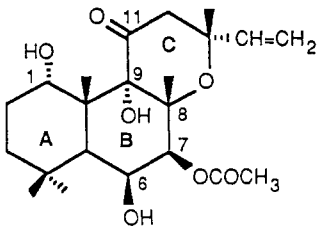
Table I. Organocuprate Conjugate Additions

			substrate					
			6, % yield[a]			7, % yield		
	reagents	solvents	GC[b]	isol[c]	1,2-add.[d]	GC	isol	1,2-add.
A	CH_2=CHMgBr	THF	88	78	10	57	40	29
	Me_2SCuBr	ether	88	72	6	37	26	22
B	CH_2=CHMgBr	THF	84	79	5	44	39	19
	CuI	ether	90	86	6	50	37	11
C	CH_2=CHMgBr	THF	92	88	7	80	72	19
	CuCN	ether	86	84	14	83	75	17
D	CH_2=CHLi	THF	71	64	16	65	60	8
	CuCN	ether	99	92	0[e]	95	84	0[e]

[a] Material balance was starting material. [b] Capillary GC analysis. [c] Isolated yields of 1,4-adduct following workup. [d] Yield of 1,2-addition product by GC. [e] None detected by GC.

procedures to effect conjugate addition. Many different solvents,[14] solubilizing agents,[15] Lewis acids,[16-18] and reactivity enhancing additives[19-21] have also been investigated in order to optimize conjugate ligand delivery. With such a plethora of synthetic options, it is not immediately clear which technique is most applicable to a particular synthetic objective. Choosing an appropriate reagent in the correct solvent at a favorable temperature in a cost effective manner can present a synthetic challenge.

This laboratory is involved in the preparation of partial derivatives of forskolin (**1**), a biologically active di-



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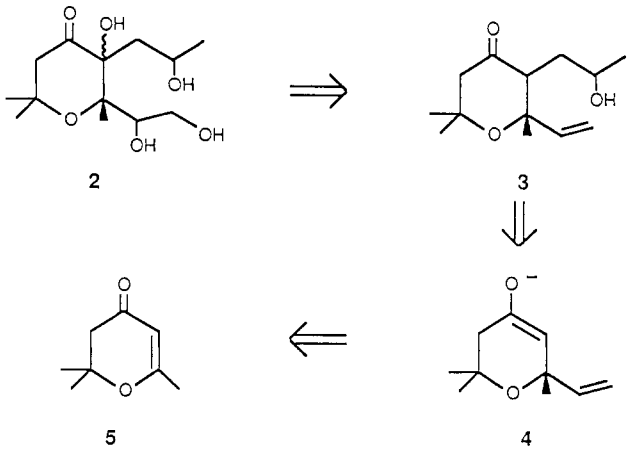
terpene.[22,23] To elucidate the essential pharmacophore and thereby design therapeutic agents with a simplified molecular structure, our attention was initially focused on the C-ring portion of the molecule. Compound **2** (Scheme I), a promising partial derivative, preserves all the polar

Scheme I



functionalities of forskolin in a single structure. Retrosynthetic disconnection of the α-hydroxy moiety adjacent to the ketone and the two hydroxyl groups of the ethanediol portion of **2** reveals the vinyl ketone **3** as a reasonable intermediate. This product was envisioned as arising from a tandem conjugate addition/alkylation sequence delivering a vinyl ligand to pyran-4-one **5**, affording the intermediate **4**, followed by in situ trapping with propylene oxide to yield **3**. Once **3** was available, an appropriate hydroxylation procedure could provide **2**. Pyran-4-one **5** is easily prepared by the de-ethoxycarbonylation of pyran-4-one ester **6** which in turn is readily constructed by acylation of ethyl acetoacetate with 3,3-dimethylacryoyl chloride followed by cyclization.[24]

Hashimoto et al.[25] have reported the successful conjugate addition of a vinyl ligand via $(CH_2$=$CH)_2Cu(CN)Li_2$ to the 2,3-dihydropyran-4-one C ring of a trideoxy forskolin analogue, but Saksena et al.[26] were unable to achieve the same transformation with a 1,9-carbonate blocked forskolin precursor. Recently, the Crimmins group was able to add a vinyl moiety to a spiro ketal pyran-4-one using an organocuprate derived from vinylmagnesium bromide with $(Bu)_3P$ as an additive.[27] A study of conjugate addition methods for the introduction of a vinyl group to pyran-4-one **5** was undertaken to facilitate the preparation of

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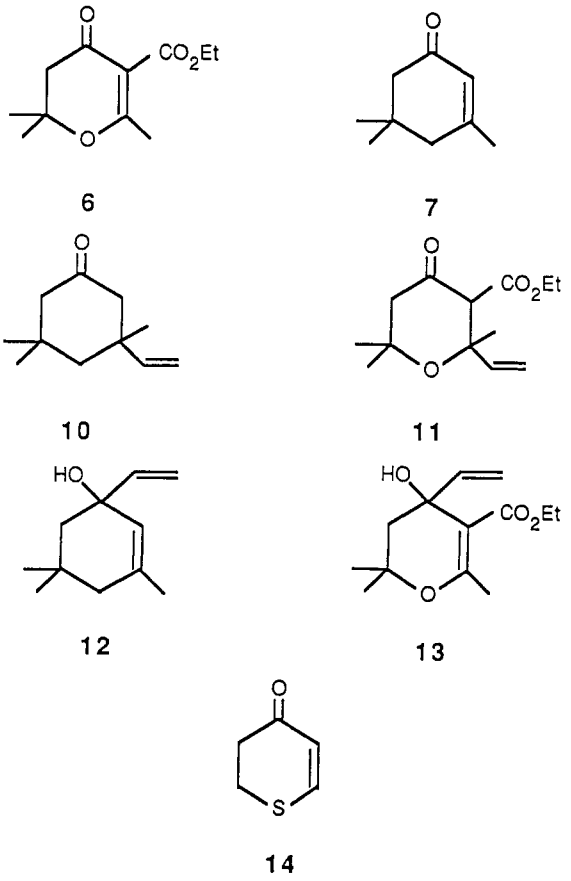
Chart I



partial forskolin derivative **2**. The carbocyclic analogue of **5** is inexpensively accessible as isophorone (**7**) and could serve as a well-studied,[13,28] convenient model system for contrasting various organocuprate reactivity differences. In addition, **6** would represent a related substrate for 1,4-conjugate addition. For the purposes of this study, **5**, **6**, and **7** (Chart I) were chosen as substrates to examine several literature cited methodologies for appending the requisite vinyl moiety for subsequent elaboration into our desired target nucleus **2**.

Results and Discussion

Expected 1,4-addition products **10**, from isophorone, and **11**, from **6**, are obtained following workup, utilizing reagents A–D, and yields are shown in Table I. 1,2-Addition is also observed to give minor products **12** and **13**, respectively, in amounts dependent upon the reagent used. Vinylmagnesium bromide was effective for conjugate addition with Me_2S·CuBr (reagent A), CuI (reagent B), and CuCN (reagent C) while vinyllithium was effective only with CuCN (reagent D). The Grignard reagent methods produced more 1,2-addition, which was most pronounced in tetrahydrofuran (THF). Diethyl ether appeared to be the solvent of choice both for yield and product distribution reasons.

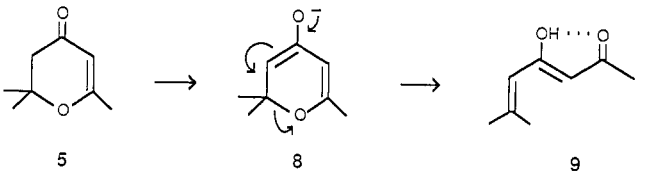
Some reports have appeared detailing organocuprate conjugate additions to pyranones,[29-31] all of which employed a 2:1 ratio of an organometallic reagent with copper(I) iodide. Attempts to apply this procedure to the enones listed in Table I using vinyllithium and CuI or Me_2S·CuBr gave disappointing results. Only the corresponding 1,2-addition products **12** and **13** could be detected by GC analysis.

Table II. Calculated Charge[a] and ^{13}C NMR Shifts of the β-Carbons of Enones 5, 6, and 7

enone	charge	^{13}C shift
5	0.1258	172.190
6	0.1968	175.167
7	−0.0326	159.700

[a] Calculations performed on a MicroVAX II running VMS version 4.4 using the MOPAC program with the AM1 Hamiltonian. (Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902).

Scheme II



Ester **6** consistently afforded higher yields of conjugate product than **7**, indicating the greater electronic activation of the β-carbon in **6** toward conjugate addition. House and Wilkins[14] have reported that the reduction potential of enones correlates directly with their ability to function as conjugate acceptors, thereby implicating electronic factors in organocuprate ligand delivery. Intuitively, the double activation seen in **6** should result in more efficient ligand transfer. This electronic activation is supported quantitatively by the MOPAC[32] calculated atomic charges and ^{13}C NMR shifts of the β-carbons of enones **5**, **6**, and **7** (Table II). The most electron-poor β-carbon of the enones examined resides in **6**. Direct yield comparison of **6** with the related compound **5** was not possible however due to proton loss with **5** leading to **9** (Scheme II).

Theoretically from Table II, **5** would be predicted to undergo conjugate addition, but no procedure examined could effect 1,2- or 1,4-addition to **5**. The ring does open however, presumably by proton abstraction through intermediate **8** to form compound **9** (Scheme II). The amount of this product varies with reaction time and can form almost quantitatively at room temperature over a 24-h period. The β-diketone **9** can be easily separated from **5** via column chromatography and was identified on the basis of ^1H NMR, ^{13}C NMR, IR, and mass spectral data. Our initial concern was that the organocuprate reagent was not forming properly and some undesirable organometallic species was effecting proton removal. This hypothesis was discounted however by an experiment in which **5** and **7** were added in equimolar quantities to $(CH_2{=}CH)_2Cu(CN)Li_2$ in diethyl ether. Gas chromatographic analysis of the resulting reaction mixture indicated that in addition to starting materials, only conjugate delivery of a vinyl moiety to **7** and ring opening of **5** had occurred. It may be inferred from this experiment that the organocopper conjugate addition reagent was present and promoting formation of the ring-opened product.

Several factors may be responsible for the failure of **5** to undergo 1,2- or 1,4-addition. The constitution of an organocuprate reagent is complex and dependent upon the copper salt used, the stoichiometry of preparation, the

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(32) MOPAC 3.13, A General Molecular Orbital Package by J.J.P. Stewart, F.J. Seiler Research Laboratory, U.S. Air Force, Colorado Springs, CO 80840.

ligand and metal counterion employed, and the solvent used. From ^{7}Li and ^{1}H NMR studies[33,34] on the solution composition of organocuprates, an intricate and dynamic equilibrium between several species is apparent in THF, but a homogenous reagent is formed in ether. One of the species present in THF with the preparation of Me_2CuLi is "free" methyllithium. This "free" organolithium in the analogous vinylcopper reagents may be impairing the conjugate process by increasing the product of proton abstraction, i.e. **9**. In addition, the byproduct lithio or magnesio salts formed via metathesis during cuprate preparation may be adversely affecting the reaction course by chelation stabilization of the ring-opened product. The lack of 1,4-addition may reflect steric inhibition by the *gem*-dimethyls of **5** and/or a subtle electronic effect due to the pyran-4-one oxygen adjacent to the conjugate addition site. The absence of 1,2-addition may be associated with through-space donation of electrons by the pyran-4-one ring oxygen to the carbonyl of **5**, diminishing its ability to function as an electrophilic center. These deleterious influences are overcome by **6** through the overwhelming electronic activation afforded by the ester moiety. In any event, the only significant process occurring is proton abstraction to yield **9**.

Recent reports[16-18] have recommended the use of $BF_3{\cdot}Et_2O$ or chlorotrimethylsilane (TMSCl) as an activating reagent to enhance organocuprate conjugate additions to difficult enones. TMSCl may be used alone or with tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA). TMSCl and $BF_3{\cdot}Et_2O$ alone were employed in our optimum addition procedure, reagent D (a "higher order" cuprate), but neither of these methods afforded detectable amounts of 1,4-conjugate delivery to **5** and only starting material was recovered. The TMEDA/TMSCl procedure of Johnson and Marren[19] and the TMSCl/HMPA method of Nakamura and co-workers[20] using $(CH_2{=}CH)MgBr$ were also tried unsuccessfully. These reagents are considered to be less basic, but again, only starting material with no detectable 1,2- or 1,4-addition was observed. Gelin and Gelin[24] have also noted ring scission of **5** into the acyclic **9** with sodium ethoxide and the Taylor group[35-37] has observed ring opening in their studies of organocuprate additions to the analogous thian-4-one **14**. In contrast to our observations, all ring-opened products in Taylor's work resulted from initial 1,4-conjugate addition of $(CH_3)_2CuLi_2$ to **14**, with consequent expulsion of thiolate and ultimately formation of a disulfide.

Since the preparation of **11** was straightforward, we thought to amend our synthetic strategy by C-alkylation of **11** followed by decarboxylation to afford our target. Unfortunately, all attempts to alkylate **11** with benzyl bromide as a model electrophile resulted in O-alkylation. Apparently the considerable steric congestion in **11** impedes the electrophile approach onto carbon and only O-alkylation is observed.

Of the copper salts investigated, copper(I) cyanide proved superior. The following benefits are noted: (1) no rigorous purification is necessary; (2) it is neither light sensitive nor hygroscopic; (3) the use of noxious additives such as dimethyl sulfide is avoided; (4) the derived organocuprates are thermally stable up to 0 °C and may be prepared from either the Grignard reagent or organolithium; and (5) it is considerably less expensive than other copper(I) salts.

In summary, organocuprate conjugate addition to 2,3-dihydro-4*H*-pyran-4-ones is substrate dependent, with substituents that favor the least electron density at the β position being favored for reaction. The reaction is solvent dependent with diethyl ether being the solvent of choice. For manipulative ease, the "higher order" cuprates obtained by use of copper(I) cyanide are clearly unsurpassed. The pyran-4-one **5**, however, does not function adequately for 1,4- or 1,2-addition under the conditions employed due to proton abstraction with concomitant ring cleavage. Other work on forskolin partial derivatives is being conducted and will be reported.

Experimental Section

General. Microanalytical data were supplied by Atlantic Microlab, Inc., of Atlanta, GA. Infrared spectra were taken as thin films on a Perkin-Elmer 281B spectrophotometer calibrated with a polystyrene film. Proton magnetic spectra were recorded on either a Varian EM 390 spectrometer at 90 MHz or a Varian VXR 300 spectrometer at 300 MHz. Carbon magnetic spectra were recorded on the Varian VXR 300 spectrometer at 75 MHz and all signals are reported with tetramethylsilane as the internal standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and exch. = exchangeable. Mass spectral results were provided by a Finnegan 3221-F200 spectrometer, with an ionization voltage of 70 eV. Gas chromatographs were recorded on a Hewlett-Packard 5890A capillary chromatograph using a 30-m DB-5 column run isothermally at the indicated temperature using helium as the carrier at a flow rate of 1 mL/min. Chart speed was at 0.5 in./min and retention times (t_R) are given in minutes. GC yields were determined by addition of total peak heights of all products. No internal standard was used. Isophorone, $CH_2{=}CHMgBr$, and all copper(I) salts were purchased from Aldrich Chemical Co. and used without further purification. Vinyllithium was purchased from Organometallics, Inc. Diethyl ether was purified and dried by distillation over lithium aluminum hydride and THF was purified and dried by distillation from potassium metal using benzophenone ketyl as indicator. Chromatographic purification of the reaction products were performed using silica gel 60 open column chromatography or a Harrison and Harrison Research Inc. Chromatotron centrifically accelerated thin-layer device with 4.0-mm plates of Kieselgel 60 PF_{254}. Analytical samples were prepared by medium pressure column chromatography using silica gel 60 (230–400 mesh).

General Preparation of 1,2-Addition Compounds. To a stirred solution of 5 mmol of the requisite enone under argon at 0–5 °C in 25 mL of dry THF was slowly added 5 mL of a 1 M solution of vinylmagnesium bromide in THF. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with aqueous saturated ammonium chloride and extracted with two 50-mL portions of ether. The extracts were combined and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The residue containing **13** was chromatographed on silica gel with hexane:ethyl acetate (9:1) as eluent. The residue containing **12** was unstable for chromatography and was distilled under reduced pressure (35 °C oil bath temperature at 0.25 Torr) for purification. No attempt was made to optimize yield as these compounds were to be used only for identification of peaks in the gas chromatograms of the 1,4-addition protocols. Complete spectral and elemental analyses confirmed the structure of the products.

General Preparation of 1,4-Addition Compounds. To a stirred suspension of 5 mmol of the specified copper(I) salt in 30 mL of dry ether or THF, cooled to −70 °C (dry ice/acetone) under argon, was slowly added 10 mmol of either vinylmagnesium bromide or vinyllithium each contained in THF. This was stirred at −70 °C for 30 min and 5 mmol of enone was slowly added neat. This was allowed to gradually warm to room temperature and

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stirred overnight. The reaction was quenched with a saturated ammonium chloride/ammonium hydroxide solution (9/1) and extracted with two 50-mL portions of ether. The extracts were combined and dried over $MgSO_4$, and GC analysis was performed after concentration in vacuo. Isolation of the product was performed on a Chromatotron on a 4-mm plate of Kieselgel 60 PF_{254}, using hexane/ether (9/1) as the eluent. Complete spectral and elemental analyses confirmed the structure of the products. Yields are listed in Table I.

Simultaneous Addition of 5 and 7 to $(CH_2{=}CH)_2Cu(CN)Li_2$. To a well-stirred grey suspension of 5 mmol of $(CH_2{=}CH)_2Cu(CN)Li_2$ prepared by the aforementioned general procedure, contained in 30 mL of dry ether under argon at −70 °C, were added 5 mmol of **5** and **7** simultaneously via syringe. This was allowed to warm to room temperature and stir overnight. Workup in the usual manner afforded the residue which was submitted to gas chromatographic analysis. From the chromatogram, 1,4-conjugate addition to isophorone yielding **10** and ring cleavage of **5** to afford **9** had occurred (peaks were verified by coinjection with authentic specimens). Starting materials **5** and **7** were also present.

Addition of 5 to $(CH_2{=}CH)_2Cu(CN)Li_2$ with Added $(CH_3)_3SiCl$ or $BF_3{\cdot}Et_2O$. To a well-stirred grey suspension of 5 mmol of $(CH_2{=}CH)_2Cu(CN)Li_2$ prepared by the general procedure, contained in 30 mL of dry ether under argon at −70 °C, was added 1 equiv of $(CH)_3SiCl$ or $BF_3{\cdot}Et_2O$. This was permitted to stir for 15 min and 5 mmol of **5** was added neat. This was allowed to warm to room temperature and stir for 3 h, whereupon the reaction was quenched and worked up in the usual manner to afford the residue for gas chromatographic analysis. The gas chromatogram evidenced only starting materials.

2,2,6-Trimethyl-2,3-dihydro-4*H*-pyran-4-one (5):[24] GC 130 °C, 2.00 min; IR (cm^{-1}) 2960, 1660, 1600, 1390, 1150; ^1H NMR ($CDCl_3$) δ 5.30 (s, 1 H), 2.46 (s, 2 H), 2.00 (s, 3 H), 1.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 192.455, 172.190, 103.123, 80.852, 46.952, 26.162, 21.487; MS, *m/e* (relative abundance) 140 (2.01), 139 (23.41), 125 (2.13), 96 (7.27), 83 (100.00), 78 (2.58), 68 (4.34).

5-Carbethoxy-2,2,6-trimethyl-2,3-dihydro-4*H*-pyran-4-one (6):[24] GC 180 °C, 2.75 min; IR (cm^{-1}) 2980, 1720, 1670, 1590, 1390, 1080; ^1H NMR ($CDCl_3$) δ 4.28 (q, 2 H), 2.50 (s, 2 H), 2.15 (s, 3 H), 1.40 (s, 6 H), 1.30 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.074, 175.167, 165.665, 110.846, 81.537, 60.775, 47.083, 26.109, 20.777, 14.207.

4-Hydroxy-6-methyl-3,5-heptadien-2-one (9):[24] GC 130 °C, 2.38 min; IR (cm^{-1}) 3450, 1650, 1600, 1250, 1155; ^1H NMR ($CDCl_3$) δ 12.30 (exch.), 5.80 (m, 1 H), 5.50 (s, 1 H), 3.70 (s, exch.), 2.30 (s, 3 H), 2.10 (s, 3 H), 1.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.290, 183.413, 153.208, 121.631, 101.229, 28.003, 27.678, 25.534, 20.856; MS, *m/e* (relative abundance) 140 (16.85), 125 (100.00), 83 (37.60), 69 (41.87), 54 (41.20).

1-Hydroxy-3,5,5-trimethyl-1-vinyl-2-cyclohexen-1-ol (12): GC 160 °C, 2.25 min; IR (cm^{-1}) 3420, 1660; ^1H NMR ($CDCl_3$) δ 6.20–5.80, 5.40–4.90 (m, 4 H), 1.75 (s, 2 H), 1.70 (s, 3 H), 1.60 (s, 2 H), 1.25 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.985, 136.233, 124.225, 111.324, 71.892, 48.433, 44.310, 30.259, 28.284, 24.004; MS, *m/e* (relative abundance) 166 (14.54), 151 (72.58), 133 (75.40), 110 (80.75), 95 (100.00). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.31; H, 10.85.

5-Carbethoxy-4-hydroxy-2,2,6-trimethyl-4-vinyl-2,3-dihydro-4*H*-pyran (13): GC 180 °C, 4.25 min; IR (cm^{-1}) 3500, 1710, 1600; ^1H NMR ($CDCl_3$) δ 6.10–5.80 (m, 1 H), 5.40–5.00 (m, 2 H), 4.25 (q, 2 H), 4.05 (s, 1 H), 2.20 (s, 3 H), 1.20–1.45 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 170.281, 168.891, 163.686, 145.582, 112.195, 76.100, 69.354, 60.066, 46.267, 29.341, 25.071, 21.060, 14.319. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.88; H, 8.42.

3,5,5-Trimethyl-3-vinylcyclohexanone (10):[28] GC 160 °C, 3.00 min; IR (cm^{-1}) 1710, 1635; ^1H NMR ($CDCl_3$) δ 5.95–5.60, 5.10–4.85 (m, 3 H), 2.58, 2.14 (AB dd, J = 15 Hz, 2 H), 2.15 (s, 2 H), 1.67 (s, 2 H), 1.14 (s, 3 H), 1.07 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.409, 147.015, 111.700, 54.238, 50.702, 49.708, 41.405, 36.174, 32.882, 31.419, 29.171; MS, *m/e* (relative abundance) 166 (72.59), 151 (44.08), 124 (16.37), 110 (48.28), 95 (60.67), 83 (90.08), 67 (100.00).

3-Carbethoxy-2,6,6-trimethyl-2-vinyltetrahydropyran-4-one (11): GC 180 °C, 0.79 min; IR (cm^{-1}) 1740, 1640, 1610; ^1H NMR ($CDCl_3$) δ 13.20 (exch.), 6.40–6.10 (m, 1 H), 5.40–5.00 (m, 2 H), 4.35 (q, 2 H), 2.35 (s, 2 H), 1.63 (s, 3 H), 1.40 (s, 6 H), 1.35 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.443, 170.943, 144.134, 112.385, 101.393, 74.109, 70.812, 60.595, 41.234, 29.523, 29.295, 28.912, 14.078; MS, *m/e* (relative abundance) 240 (2.54), 225 (40.56), 179 (84.48), 167 (62.80), 83 (100.00). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.07; H, 8.40.

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Synthesis of New Amino Acids Mimicking Sulfated and Phosphorylated Tyrosine Residues

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Introduction

The presence of a sulfated tyrosine residue was first detected in fibrinopeptide B,[1] then on fibrinogens,[2] gastrin,[3] and cholecystokinin,[4] and more recently in several secretory proteins such as immunoglobin G[5] and fibronectin,[6] and in an insect neuropeptide designated leucosulfakinin.[7] Presumably, the *O*-sulfate ester group is introduced at a posttranslational stage of the biosynthesis but very little is known about the enzyme(s) responsible for this modification.[8] The ester bond of tyrosine *O*-sulfate is remarkably acid labile[1] and is therefore likely to be hydrolyzed in some of the common protein-chemical procedures.[9] The low chemical stability of ester sulfate groups has thus prevented the widespread use of natural compounds containing tyrosine *O*-sulfate residues for pharmacological investigations. Another posttranslational covalent modification of proteins that has been recognized as an important cell-regulation process and therefore extensively studied[10,11] is protein phosphorylation. The occurrence of phosphorylated tyrosine as a protein modification implies the existence of enzymes called tyrosine kinases capable of phosphorylating tyrosine.[12] The role of these tyrosine kinases is of great interest since tyrosine phosphorylation has been implicated in regulatory events such as cell transformation and hormone-induced cell growth.[13-15]

In order to elucidate the mechanisms of such phenomena that have not been clearly established yet, it appears to be essential to use analogues that cannot be hydrolyzed as substrates or inhibitors of sulfo-transferase or as substitutes of the Tyr(SO_3H) group in active peptides.

In order to enhance the chemical stability of compounds containing tyrosine *O*-sulfate and tyrosine *O*-phosphate residues, we have synthesized new amino acids related to sulfated and phosphorylated tyrosine residues, in which

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