NMR (CCl_4) 1.00–2.68 (m, 13 H), 3.57 (t, J = 5.0 Hz, 2 H), 4.01 (s, 1 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.56.

Reaction of 5-Phenyl-1-(phenylselenonyl)-1-penten-3-ol (21) with Lithium Dimethylcuprate. To a suspension of cuprous iodide (953 mg, 5.0 mmol) in 4 mL of ether was added an ethereal solution of methyllithium (16 mL of 0.63 M solution, 10 mmol) at 0 °C. Then, a solution of 5-phenyl-1-(phenylselenonyl)-1-penten-3-ol (**23**, 153 mg) in 5 mL of THF was added to the ice-cooled mixture, which was allowed to stand overnight at room temperature. Usual workup of the reaction mixture followed by separation with TLC afforded 1-phenyl-4-hexen-3-ol (**24**, 44 mg, 50%) as an oil: IR (neat) 3300, 970; NMR (CCl_4) 1.40–2.30 (m, 6 H), 2.63 (t, J = 8.0 Hz, 2 H), 3.74–4.10 (m, 1 H), 5.37–5.60 (m, 2 H), 7.07 (s, 5 H); mass spectrum, m/e (relative intensity) 176 (M^+, 19), 158 (19), 143 (19), 129 (23), 105 (31), 91 (100), 77 (19), 71 (100).

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Registry No. (*E*)-1 (Ar = Ph; R = $(CH_2)_2Ph$), 74824-73-0; (*E*)-1 (Ar = Ph; R = CH_2CO_2Bu-*t*), 88842-03-9; *cis*-**3a**, 74824-84-3; *trans*-**3a**, 74824-85-4; *cis*-**3b**, 74824-88-7; *trans*-**3b**, 74824-89-8; *cis*-**3c**, 74824-90-1; *trans*-**3c**, 74824-91-2; *cis*-**3d**, 74824-86-5; *trans*-**3d**, 74824-87-6; **3e**, 74824-99-0; (*E*)-**4**, 74824-93-4; (*Z*)-**4**, 88842-02-8; **5**, 74835-33-9; **6**, 88842-07-3; **7**, 88841-82-1; **9a**, 88841-83-2; **9b**, 78998-88-6; **9c**, 88841-84-3; **9d**, 88841-85-4; **9e**, 88841-86-5; **10**, 79681-30-4; **12a**, 61882-83-5; **12b**, 79681-48-4; **12c**, 79681-49-5; **13a**, 88841-89-8; **13b**, 88841-91-2; **14a**, 16737-04-5; **14b**, 88842-08-4; **15a**, 88841-90-1; **15b**, 88841-92-3; **16a**, 54625-15-9; **16b**, 88842-09-5; **17a**, 88841-94-5; **17b**, 88841-93-4; **17c**, 88841-95-6; **18**, 88841-96-7; *trans*-**19a**, 88841-98-9; *cis*-**19b**, 88841-97-8; *trans*-**19b**, 88842-10-8; *trans*-**19c**, 88841-99-0; **20**, 88842-00-6; **21**, 88842-01-7; $CH_3(CH_2)_6CH(OH)CH(OCH_3)CH_2SePh$, 74824-96-7; $CH_3(CH_2)_6CH(OH)CH(SePh)CH_2OCH_3$, 74824-97-8; (*Z*)-$CH_3(CH_2)_3C(O)(CH_2)_3CH{=}CHOCH_3$, 79681-32-6; (*E*)-$CH_3(CH_2)_3C(O)(CH_2)_3CH{=}CHOCH_3$, 79681-31-5; (*Z*)-$CH_3(CH_2)_3C(O)(CH_2)_3CH{=}CHOCH_2CH_3$, 79681-37-1; (*E*)-$CH_3(CH_2)_3C(O)(CH_2)_3CH{=}CHOCH_2CH_3$, 79681-36-0; $CH_3(CH_2)_3C(O)(CH_2)_3CH{=}CHSPh$, 79681-38-2; (*Z*)-$CH_3(CH_2)_3C(O)CH_2C(CH_3)_2CH_2CH{=}CHOCH_3$, 79681-40-6; (*E*)-$CH_3(CH_2)_3C(O)CH_2C(CH_3)_2CH_2CH{=}CHOCH_3$, 79681-39-3; $CH_3(CH_2)_3C(O)CH_2C(CH_3)_2CH_2CH{=}CHSPh$, 79681-41-7; (*Z*)-$CH(O)CH_2C(CH_3)_2CH_2CH{=}CHOCH_3$, 79681-43-9; (*E*)-$CH(O)CH_2C(CH_3)_2CH_2CH{=}CHOCH_3$, 79681-42-8; (*Z*)-$CH_3(CH_2)_3C(O)(CH_2)_2CH{=}CHOCH_3$, 79681-45-1; (*E*)-$CH_3(CH_2)_3C(O)(CH_2)_2CH{=}CHOCH_3$, 79681-44-0; (*R**,*S**)-$Ph(CH_2)_2CH(OH)CH(OH)CH(OCH_3)CH_2OTHP$, 88853-99-0; (*R**,*S**)-$Ph(CH_2)_2CH(OH)CH(OCH_3)CH_2OTs$, 88842-06-2; (*Z*)-$PhSeCH{=}CHCHO$, 74824-71-8; (*Z*)-Cl-*p*-$C_6H_4SeCH{=}CHCHO$, 74824-72-9; $CH_3(CH_2)_3CHLiC(O)OBu$-*t*, 88842-12-0; MeONa, 124-41-4; (*R**,*S**)-$Ph(CH_2)_2CH(OH)CH(OH)CH_2OTHP$, 88842-14-2; 1-dodecenyl phenyl selenone, 88841-79-6; 1-dodecenyl phenyl selenide, 88841-80-9; 4-methyl-2-(3-hydroxy-2-methoxy-1-propylidene)-γ-butyrolactone, 74824-94-5; *tert*-butyl 2-butyl-5-hydroxy-4-methoxy-2-pentenoate, 88841-81-0; 2-heptyl-3-methoxyoxetane, 74824-98-9; 5,5-dimethyl-3-(phenylseleno)-2-cyclohexen-1-ol, 78998-82-0; 1-butyl-5,5-dimethyl-3-(phenylseleno)-2-cyclohexen-1-ol, 88841-87-6; 5,5-dimethyl-3-(phenylselenonyl)-2-cyclohexen-1-ol, 79681-34-8; 1-butyl-3-(phenylselenonyl)-2-cyclopenten-1-ol, 79681-35-9; 1-butyl-2-methyl-3-(phenylselenonyl)-2-cyclohexen-1-ol, 79681-46-2; 1-butyl-3-(phenylselenonyl)-2-cycloocten-1-ol, 79681-47-3; 10-(phenylthio)-9-decen-5-one, 79681-38-2; 6,6-dimethyl-10-(phenylthio)-9-decen-5-one, 88841-88-7; 2-hydroxy-5-methyl-4,5-dihydrofuran lithium salt, 88853-98-9; 1,2-dimethoxy-3-decanol, 88842-04-0; ethyl 5-phenyl-2(*E*)-pentenoate, 55282-95-6; ethyl 5-phenyl-2(*Z*)-pentenoate, 88842-13-1; (*E*)-5-phenyl-2-penten-1-ol, 75553-23-0; (*R**,*S**)-2-methoxy-5-phenyl-1,3-pentanediol, 88842-05-1; 1-(phenylseleno)-1-decene, 88842-11-9; (*E*)-3-(phenylseleno)-2-propenal, 74824-70-7; benzeneselenenyl bromide, 34837-55-3; 3-acetoxy-2-cyclohexen-1-one, 57918-73-7; 2-(acetoxymethylidene)-1-cyclohexanone, 15839-56-2; chloromagnesium 3-(chloromagnesio)-propoxide, 68236-10-2; 1-ethoxyethyl 3-lithiopropyl ether, 88842-15-3; benzenethiol sodium salt, 930-69-8; phenethyl chloride, 622-24-2; hexyl chloride, 544-10-5; phenyl chloride, 108-90-7; dodecyl bromide, 143-15-7; phenyllithium, 591-51-5; 3-hydroxy-1-decene, 51100-54-0; ethyl (trimethylsilyl)acetate, 4071-88-9; 3-phenylpropenal, 104-55-2; phenyl trimethylsilyl selenide, 33861-17-5; diphenyl diselenide, 1666-13-3; sodium benzeneselenolate, 23974-72-3; 3-bromo-2-cyclopenten-1-one, 51865-32-8; sodium ethoxide, 141-52-6.

Silicon-Mediated Synthesis of Bibenzyl Systems: Synthesis of Ring and Side-Chain Functionalized Hexestrol Derivatives

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Received September 23, 1983

Derivatives of hexestrol [(3*R**,4*S**)-3,4-bis(4-hydroxyphenyl)hexane], a non-steroidal estrogen, bearing photochemically reactive functional groups or γ-emitting radionuclides, are useful as affinity labeling agents for the estrogen receptor or as imaging agents for receptor positive breast tumors, respectively. We have developed convenient synthetic routes to two side chain functionalized and aromatic ring functionalized hexestrol derivatives, based on a direct benzylic coupling reaction mediated by allylsilanes or silyl ketene acetals. 1-Dehydrohexestrol and various aromatic ring substituted 1-dehydrohexestrol derivatives can be prepared by coupling 3-(trimethylsilyl)-1-(4-methoxyphenyl)propene with various reactive benzylic derivatives, and pentestrol derivatives are prepared by the coupling of the silyl ketene acetal derivative of *p*-methoxyphenyl acetic ester with benzylic derivatives. The *R**,*S** (erythro) and *R**,*R** (threo) diastereomers formed in each case can be separated readily by chromatography and recrystallization. This silicon-mediated approach to functionalized hexestrol derivatives provides a convenient route to many compounds of interest as biochemical probes and receptor-based diagnostic reagents.

Introduction

The estrogen receptor is an intracellular protein thought to play a key role in mediating the effects of estrogens on target tissue cells. We have been interested in developing probes for the estrogen receptor that are designed to label the receptor covalently (affinity labeling reagents)[1,2] or to

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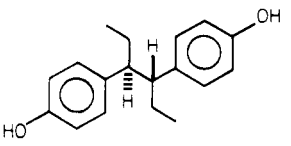
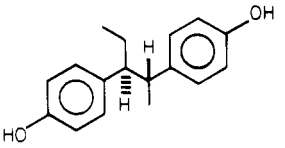
utilize receptor binding to direct specific uptake of a γ-emitting estrogen into target tissues and receptor-containing tumors in vivo (tumor imaging reagents).[3,4] Many of these affinity labeling and tumor imaging agents are non-steroidal estrogens of the hexestrol (1) ((3*R**,4*S**)-



(R*,S*)-Hexestrol (1)

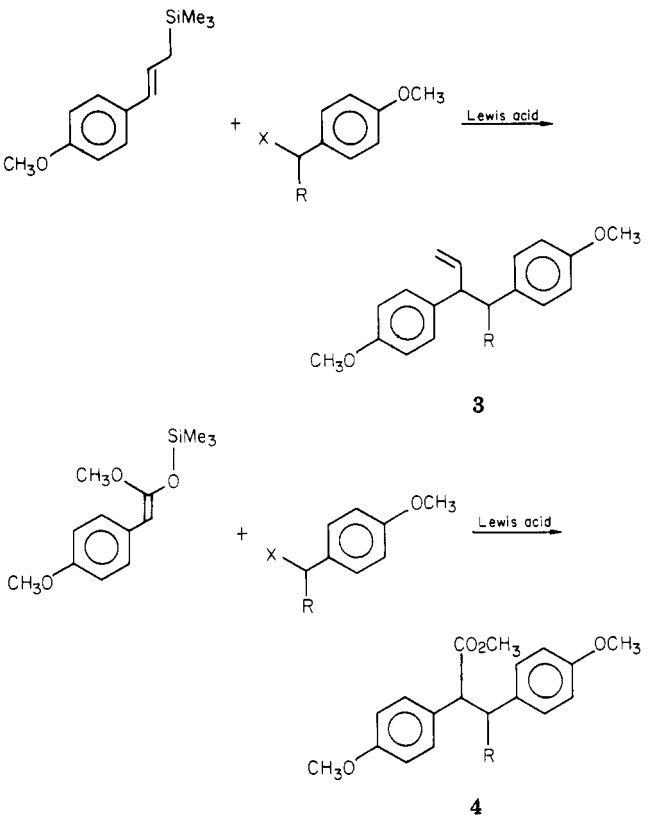


(R*,S*)-Pentestrol or Norhexestrol (2)

3,4-bis(4-hydroxyphenyl)hexane) or the pentestrol (2) ((2*R**,3*S**)-2,3-bis(4-hydroxyphenyl)pentane) type, bearing some functional group either as a substituent on the aromatic rings or on the aliphatic backbone chain. In the past, we have prepared these derivatives either by relatively long sequences involving functionalization of hexestrol itself[5] or by total syntheses that were lengthy and often inefficient.[6]

In this report, we describe the preparation of functionalized hexestrol systems, bearing either aromatic ring functionalization (nitro group) or having side chain functional groups (olefin and carboxylic ester). The approach to these systems is a direct one, involving in all cases a silicon-mediated coupling of two benzylic systems, the first examples involving the reaction of allylic silanes with benzylic electrophiles, the last, the reaction of a silyl ketene acetal with benzylic electrophiles. This new methodology for the synthesis of functionalized hexestrols is efficient and is sufficiently flexible to provide entry into many systems of interest as probes for the estrogen receptor.

Scheme I

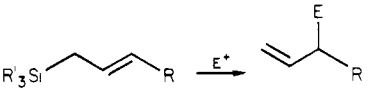


3

4

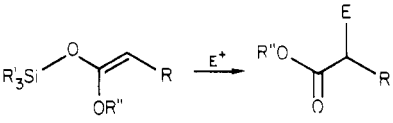
Results and Discussion

General Scheme of Benzylic–Benzylic Coupling. The reaction of allylsilanes with suitable electrophiles in the presence of Lewis acids is known to give coupled products in which the allylic unit has undergone transposition cleanly (eq 1).[7] Closely related to this reaction



(1)

is the α-alkylation of esters achieved by the reaction of electrophiles with silyl ketene acetals in the presence of Lewis acids (eq 2).[8]



(2)

As is shown in Scheme I, we have utilized both of these reactions in the preparation of functionalized hexestrol derivatives. In the case of the allylsilane, reaction of a 1-(4-methoxyphenyl)-3-(trimethylsilyl)propene with a *p*-methoxybenzylic electrophile leads to a 1-dehydrohexestrol methyl ether (3). In addition to the unsaturation in the side chain, additional functionality is tolerated at aromatic ring positions in the allylsilane component. In the case of the silyl ketene acetal, formation of the silane derivative from the enolate of *p*-methoxyphenyl acetic esters followed by Lewis acid mediated coupling with the benzylic electrophile gives a norhexestrol or pentestrol system (4) with the carboxylic ester function as part of the backbone chain. In each case, a mixture of *R**,*S** (erythro) and *R**,*R** (threo) diastereomers is produced.

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(3) For reviews, see: (a) Katzenellenbogen, J. A.; Heiman, D. F.; Carlson, K. E.; Lloyd, J. E. In "Receptor Binding Radiotracers"; Eckelman, W. C., Volume Ed.; CRC Press: Boca Raton, FL, 1982; Vol 1, Chapter 6, pp 93–126. (b) Katzenellenbogen, J. A.; Heiman, D. F.; Senderoff, S. G.; McElvany, K. D.; Landvatter, S. W.; Carlson, K. E.; Goswami, R.; Lloyd, J. E. In "Applications of Nuclear and Radiochemistry"; Morcos, N., Lambrecht, R. M., Eds; Pergamon Press: New York, 1982; pp 311–323. (c) Katzenellenbogen, J. A. In "Radiopharmaceutical Chemistry"; Jones, A. G., Welch, M. J., Eds.; Martinus Nijhoff: The Hague, Netherlands; in press.

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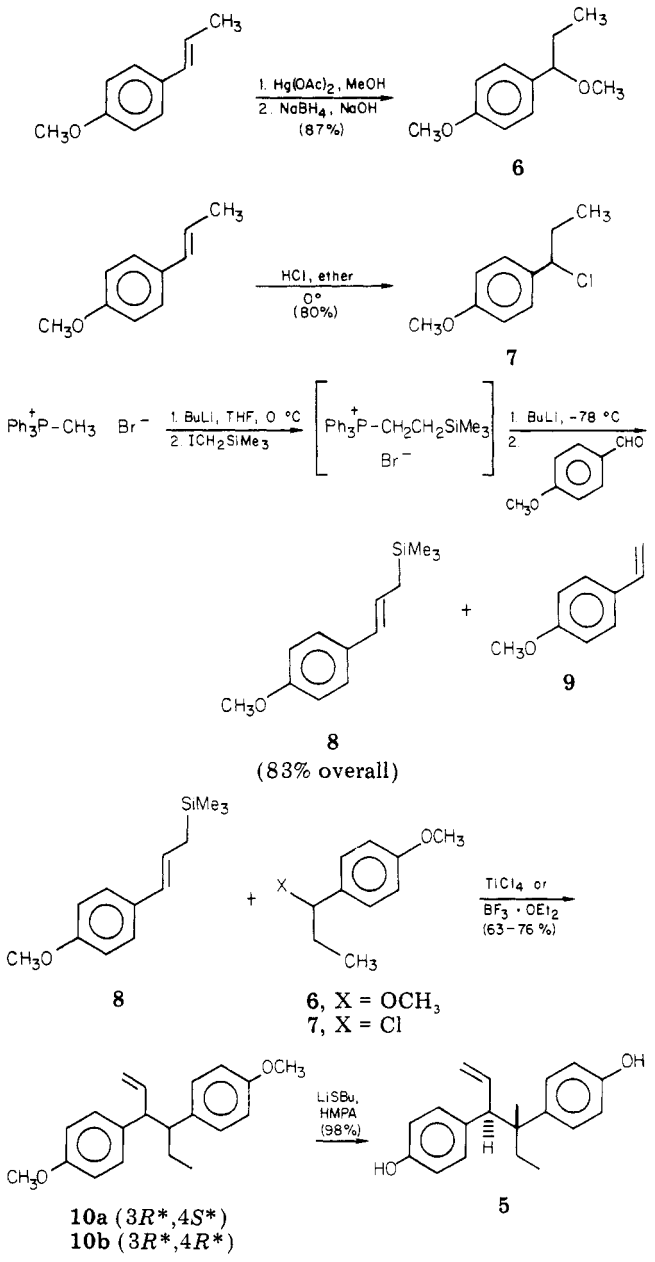
Scheme II



Benzylic Coupling Reactions Utilizing Allylic Silanes. 1-Dehydrohexestrol. We have utilized 1-dehydrohexestrol (**5**) as a precursor for the preparation of tritium-labeled hexestrol and 3′-azidohexestrol,[6a] a photoaffinity labeling agent for the estrogen receptor. 1-Dehydrohexestrol is superior to dienstrol as a precursor for the preparation of ^3H labeled *meso*-hexestrol, since catalytic tritiation of the latter compound produces a mixture of hexestrol diastereomers that must be separated after the radioactivity has been introduced.[9] Our previously described route to 1-dehydrohexestrol[6a] began with α-ethyldesoxyanisoin and involved a Reformatsky addition reaction, a dehydration, and a catalytic hydrogenation, followed by a chromatographic separation of diastereomers, a lithium aluminum hydride reduction, and an elimination.

The silicon-mediated approach to 1-dehydrohexestrol is much more convergent (Scheme II). Two electrophile components were prepared: 1-(4-methoxyphenyl)propyl methyl ether (**6**), by methoxymercuration of anethole followed by demercuration with sodium borohydride,[10] and 1-(4-methoxyphenyl)-1-chloropropane (**7**), by the addition of HCl to anethole.[11] The allylic silane was prepared by the reaction of *p*-anisaldehyde with [2-(trimethylsilyl)-ethylidine]triphenylphosphorane, a reagent described by Seyferth.[12] This reaction produces the desired 1-(4-methoxyphenyl)-3-(trimethylsilyl)propene (**8**), which can be isolated in 83% yield by vacuum distillation. It is shown by NMR to be almost exclusively (>90%) the *E* isomer; a small amount of contaminating 4-methoxystyrene (**9**), formed by the reaction of anisaldehyde with a small amount of methylidinetriphenylphosphorane that is carried over from the preparation of the (silylethylidine)-phosphorane, is cleanly removed during the distillation.

Table I. Reaction of the Allylsilane 8 with Electrophiles in the Presence of Lewis Acids

electrophile	Lewis acid	react time	% yield[a]	isomer ratio[b]
6	$TiCl_4$	30 min	76	1:1
	$BF_3 \cdot OEt_2$	2 h	63	1:1
7	$TiCl_4$	15 min	72	1:1
	$BF_3 \cdot OEt_2$	2 h	70	1:1

[a] Combined isolated yield of both diastereomers after flash chromatography. [b] Determined by GLC.

Reaction of the allylic silane **8** with the benzylic derivatives **6** and **7** was carried out using different Lewis acids (Table I); with both electrophiles, yields exceeding 70% could be obtained within 15–30 min by using titanium tetrachloride. The order of addition of the components is critical. The Lewis acid must be added after the electrophile and allylsilane have been mixed and precooled to −78 °C. Deviation from this procedure led to the formation of polymeric products.

Dehydrohexestrol methyl ether **10** was shown by GLC to be a 1:1 mixture of the *R**,*S** (erythro) isomer (**10a**) and the *R**,*R** (threo) isomer (**10b**). The stereochemistry was assigned by NMR, the *R**,*S** isomer having the resonance of the methyl group terminal on the hexene backbone chain at higher field.[13] The *R**,*S** isomer, being crystalline,[6a] could be isolated from the mixture by fractional crystallization; the *R**,*R** isomer was obtained by Kugelrohr distillation of the mother liquor. (3*R**,4*S**)-1-Dehydrohexestrol (**5**) can be prepared from the *R**,*S** methyl ether (**10a**) by treatment with lithium butanethiolate, as described previously.[6a]

Hexestrol Derivatives Incorporating the Photoreactive *m*-Nitroanisole Moiety. *m*-Nitroanisole undergoes photoassisted nucleophilic substitution when irradiated in the presence of suitable nucleophiles (eq 3).[14] In this process, the methoxy group becomes replaced by the nucleophile. This reaction has been applied to photoaffinity labeling and photoinitiated protein cross-linking by Jelenc.[15]

To utilize photoassisted nucleophilic substitution in photoaffinity labeling of the estrogen receptor we prepared, earlier in our laboratories, a bisnorhexestrol analogue (**12**)

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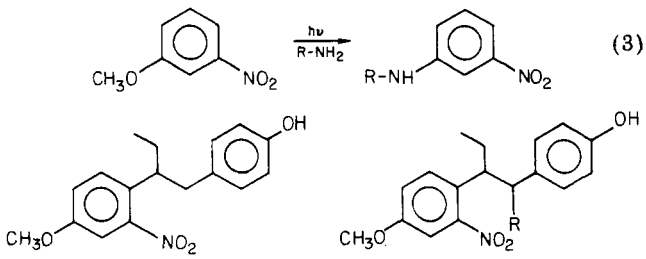


(3)

12

13 (R = CH_3)
14 (R = CH_2CH_3)

that incorporated a *m*-nitroanisole group.[1c,16] Upon irradiation in the presence of a nucleophile, such as butylamine, the methoxy group is replaced by the amine. We also found that this derivative was an efficient, binding-site specific inactivator of the estrogen receptor[1c,16] and thus appeared to have promise as a photoaffinity labeling agent. Its affinity for the estrogen receptor, however, was quite low, being only 2.7% that of estradiol.[16] (Hexestrol has an affinity 300% that of estradiol.)[2c,17]

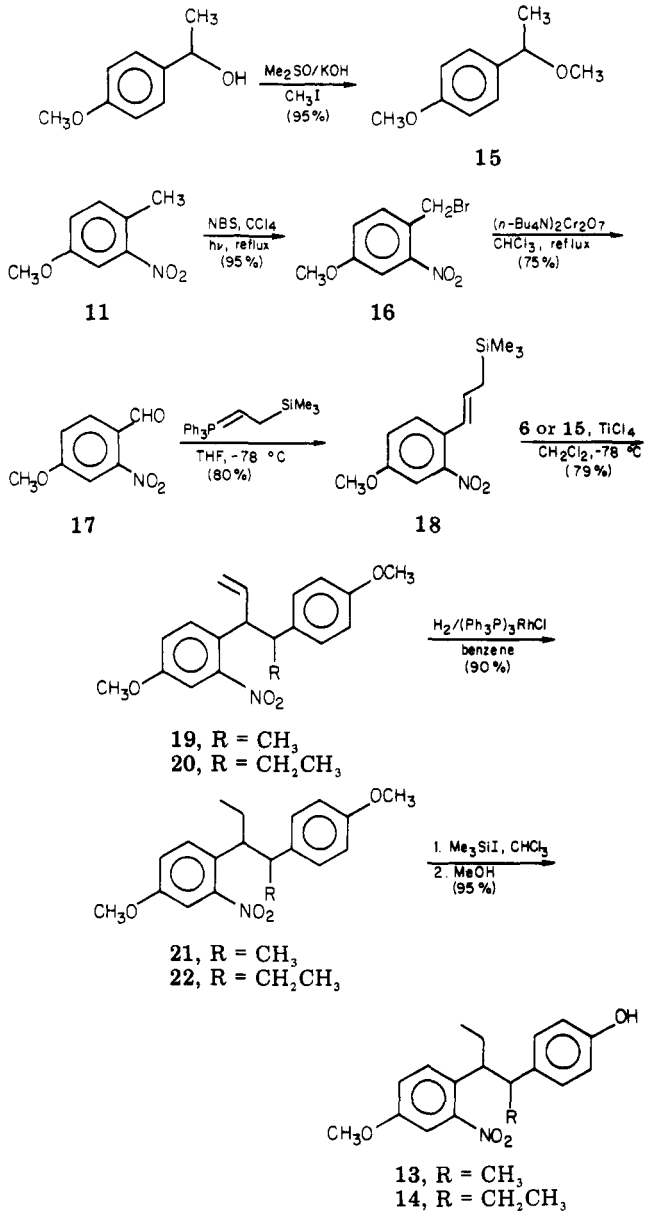
Part of the reduced affinity of compound **12** for the estrogen receptor is due to the presence of the methyl ether group, as methylation of the phenolic function in estradiol or hexestrol is known to reduce the binding affinity significantly.[2c,17] This methyl group, however, is required for the photolytic behavior of the *m*-nitroanisole system. (*m*-Nitrophenols are not expected to be reactive in photoassisted nucleophilic substitutions.)[14]

The lower affinity of this compound could also be attributed to the absence of one of the ethyl groups that is present in hexestrol. As the internal portion of the binding site of the estrogen receptor has a preference for hydrophobic substituents, this reduction in lipophilicity would result in lowered affinity.[6d] In addition, we have shown through calculation of steric energies, that the absence of this ethyl group also has a marked effect on the conformational preferences of this bibenzyl system, reducing considerably the preference for the conformer in which the two aryl groups are disposed in an antiperiplanar arrangement.[6c] Since it appears that the estrogen receptor has a very strong preference for binding hexestrol derivatives in this antiperiplanar conformation,[6c] this change in conformer population would also result in a reduced binding affinity. Therefore, in order to prepare hexestrol derivatives incorporating the photoreactive *m*-nitroanisole function that would have higher affinity for the estrogen receptor, we undertook the preparation of the nitrohexestrol and nitropentestrol methyl ethers (**13** and **14**). These derivatives have the second alkyl substituent on the benzylic centers, and hence the antiperiplanar preference should be restored. They are also more lipophilic than the original derivative.

The synthesis of these analogues was done by an extension of the method used to prepare 1-dehydrohexestrol and involved the preparation of a nitrofunctionalized allylsilane (**18**) and its coupling with the appropriate benzylic electrophiles as outlined in Scheme III.

Benzylic bromination of 2-nitro-4-methoxytoluene (**11**) (N-bromosuccinimide, hν, and radical initiator) afforded **16** in 95% yield, and this material was oxidized directly to the aldehyde **17** in 75% yield by a 10-min exposure to tetrabutylammonium dichromate.[18] The allylsilane **18** was

Scheme III



prepared from **17** in 80% yield, by the Wittig reaction sequence described earlier (Scheme II). Unlike its unsubstituted analogue, **8**, the nitro allylsilane **18** has reasonable stability towards acids; no traces of protonolyzed product are detected after purification by flash chromatography on silica gel. The benzylic electrophile **15** was prepared from 1-(4-methoxyphenyl)ethanol in 95% yield.

Reaction of the nitro allylsilane **18** with the electrophiles **6** and **15** in presence of $TiCl_4$ afforded the desired analogues **19** and **20**, respectively. A 3:1 and 7:1 ratio of *R*,R** to *R*,S** diastereomers was obtained for **19** and **20**, respectively, with the minor product being the desired erythro isomer.

Selective hydrogenation of the olefinic bond in **19** and **20** was effected using Wilkinson's catalyst ($(Ph_3P)_3RhCl$).[19] Hydrogenation was complete within 2 h as monitored by GLC, and no amine formation by reduction of the nitro group could be detected. If hydrogenation was conducted in benzene–ethanol mixtures, isomerization of the double bond to the conjugated position was found to compete with

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(17) Katzenellenbogen, J. A.; Johnson, H. J.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.
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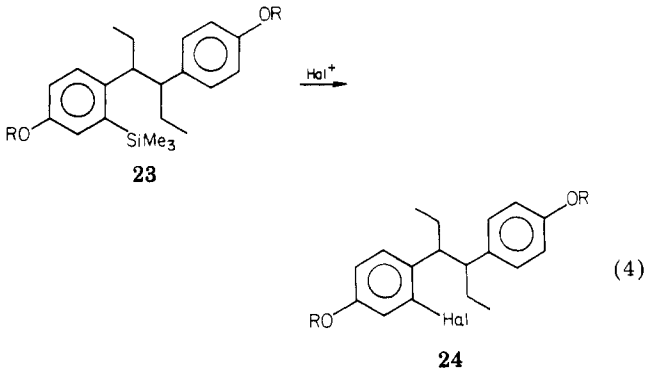
the hydrogenation;[20] this styryl double bond was inert to hydrogenation under these conditions. As described previously,[16] selective cleavage of the methyl ether group on the unsubstituted ring was effected using iodotrimethylsilane, affording the desired monophenolic compounds **13** and **14** in 95% yield. Final purification of the products was done by HPLC.

Hexestrol Derivatives Incorporating Arylsilane Groups: Potential Precursors for Aryl Halogenation. We have been interested in the development of estrogens substituted with γ-emitting halogens that have high binding affinity and selectivity for the estrogen receptor.[3,4] These receptor-binding radiopharmaceutical agents might be useful as imaging agents for estrogen receptor-positive human breast tumors (tumor imaging agents). In earlier work, we have found that the larger halogens (bromine and iodine), while tolerated poorly in terms of receptor binding affinity at positions ortho to the phenolic hydroxyl group in hexestrol, are better tolerated at the meta position (cf. compound **24**).[3a-c,21]

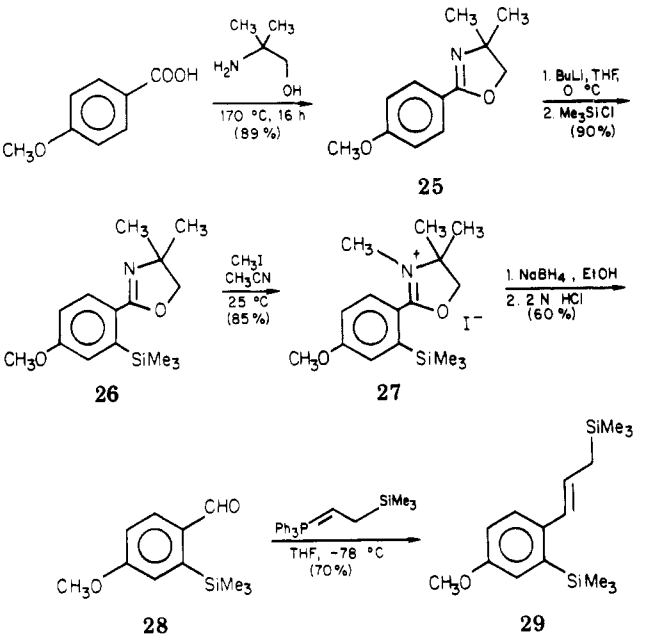
The preparation of meta-substituted halophenols is generally done by a Sandmeyer-type reaction from the corresponding *m*-aminophenol, which itself may be prepared from the *o*-haloanisole by treatment with amide ion (elimination to a benzyne intermediate followed by meta additions of amide ion).[21] While a diazonium decomposition-based procedure for the synthesis of the *m*-halohexestrols could be adapted for the efficient incorporation of short-lived γ-emitting isotopes of bromine and iodine, the direct ipso aromatic halogenation of the corresponding *m*-silylphenol derivatives[22] is a very attractive alternative (eq 4).



The synthesis of a *m*-silyl hexestrol derivatives such as **23** would involve the preparation of an appropriate trimethylsilyl-functionalized aldehyde **28** which could then be transformed into the allylsilane coupling precursor **29** (Scheme IV). We based our approach on the work of Gschwend who has developed a method to convert aryloxazolines directly into their *o*-lithio derivatives which can then react with electrophiles.[23]

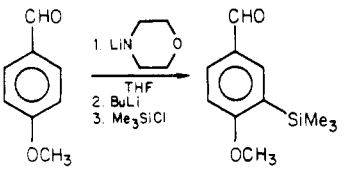
The oxazoline **25**, prepared from *p*-anisic acid and 2-amino-2-methyl-1-propanol,[24] was lithiated at 0 °C in THF with *n*-butyllithium. After 6 h the reaction was quenched with trimethylsilyl chloride, giving the *o*-trimethylsilyl-substituted oxazoline derivative **26**. The oxazolinium salt **27**, prepared by the treatment of **26** with methyl iodide

Scheme IV



in acetonitrile, was reduced to the oxazolidine by using sodium borohydride. Hydrolysis of the oxazolidine was carried out in methanol by warming with 2 N hydrochloric acid. The aldehyde **28** was isolated in 60% yield by Kugelrohr distillation of the crude product. Conversion of the aldehyde **28** to the allylsilane **29** was carried out by using the same Wittig procedure outlined earlier (Scheme II).

In our earlier attempts to develop facile routes to the aldehyde **28** we attempted to utilize the method of Comins,[25] which involves the ortholithiation of aldehydes by the in situ protection of the aldehyde as the amino alkoxide. We found, however, that with a para-substituted aldehyde such as *p*-anisaldehyde, the methoxy group has a stronger directing effect upon the lithiation process than the amino alkoxide; hence, all products isolated contained the silyl group ortho to the methoxy substituent.



Attempts to achieve a benzylic–benzylic coupling between the allylsilane **29** and the electrophiles **6** and **15**, utilizing a variety of Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$) and coupling conditions, resulted in loss of the aryl trimethylsilyl group. Hence, in our hands, this has not been a feasible approach to compounds such as **23**.

Benzylic Coupling Utilizing Silyl Ketene Acetals. Norhexestrol Acids. In a series of studies, we investigated the tolerance of the estrogen receptor for binding hexestrol derivatives containing various functional groups on the hexane chain.[6d] One noteable outcome of this study was that derivatives of norhexestrol acid, that is ones bearing a carbonyl group on what would be carbon 2 of hexestrol (cf. **32**), appeared to have unusually high affinity for the receptor. While in the past, we have prepared norhexestrol acid derivatives by a three-step procedure that is only moderately efficient,[6d] we have found that these derivatives can be prepared in one pot by a silicon-

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(24) Ginos, J.; Allen, P. *J. Org. Chem.* **1963**, *28*, 2759.
(25) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *42*, 4213.

Scheme V

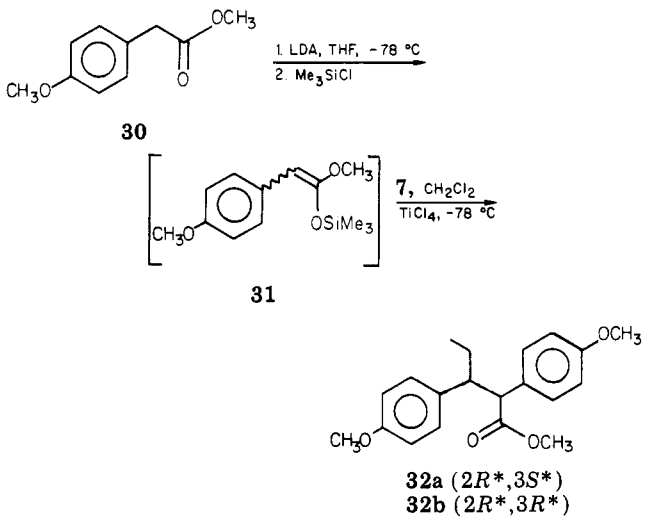

Table II. Reaction of the O-Silylated Ketene Acetal 31 with the Electrophile 7

Lewis acid	reaction time, h	yield[a] of 32a-32b, %	isolated yield[b] of 32a, %
$TiCl_4$	0.5	70	30
$BF_3 \cdot OEt_2$	1.5	68	35
$SnCl_4$	1.5	75	38

[a] Combined yield (GLC) of both isomers. [b] Yield after fractional crystallization.

mediated benzylic coupling (Scheme V).

Methyl (4-methoxyphenyl)acetate (**30**) was converted to the *O*-trimethylsilyl ketene acetal (**31**) by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran, followed by quenching with chlorotrimethylsilane. The coupling of this silyl ketene acetal with the benzylic chloride **7** was investigated with various Lewis acids (Table II). The coupling product, ca. a 1:1 mixture of *R*,S** and *R*,R** diastereomers, was isolated in ca. 70% yield, and the desired *R*,S** (erythro) diastereomer **32a** could be isolated by fractional crystallization.

Conclusion

Various substituted hexestrol derivatives, bearing functional groups at aromatic ring positions or on the aliphatic backbone chain, have proved to be useful as probes for studying the estrogen receptor. While in the past these had been prepared via multistep routes, they can all be synthesized rapidly and conveniently by a convergent approach involving, as the key step, a silicon-mediated benzylic coupling reaction.

Experimental Section

General Procedures. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed with 0.25 mm silica gel coated plastic sheets with fluorescent indicator UV_{254} (Brinkmann Instruments). Preparative layer chromatography was carried out with 2.0 mm Merck Silica Gel 60 F-254 precoated TLC plates. All column chromatography was done using the flash chromatography technique.[26] The column packing was Woelm 32-63 μm silica gel. Analytical gas chromatography was carried out on a Hewlett Packard 5790A series gas chromatograph equipped with a flame ionization detector. The column was a 12.5 m × 0.2 mm capillary column containing crosslinked dimethylsilicone as the stationary phase.

Proton magnetic resonance (^1H NMR) spectra were recorded on Varian EM 390 (90 MHz) or Nicolet NT 360 (360 MHz) spectrometers in the indicated solvents. Chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard (δ scale). Infrared (IR) spectra were obtained with Perkin Elmer Model 137 or Nicolet 7000 FT IR spectrometers and data are presented in cm^{-1} for important diagnostic absorptions. Mass spectra were obtained on a Varian Associates MAT CH-5 spectrometer at 10 or 70 eV. High-resolution mass spectra were obtained on a Varian 731 high-resolution mass spectrometer. Data are presented in the form *m/e* (intensity relative to base peak = 100). Microanalytical data were provided by the Microanalytical Service Laboratory of the University of Illinois.

n-Butyllithium was purchased from Alfa (Ventron) and titrated prior to use.[27] Other reagents and solutions were purchased as analytical reagent grade or purified according to literature procedures as noted. Commercial sources included: Aldrich Chemical Co., Mallinckrodt Inc., Silar Chemical Co., Alfa (Ventron), and Eastman Chemical Co.

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Diisopropylamine was distilled from calcium hydride to ensure dryness as was methylene chloride. All other solvents were used as received.

1-(4-Methoxyphenyl)-1-methoxypropane (6). To a suspension of 15.9 g (50 mmol) of mercuric acetate in 50 mL methanol was added 7.4 g (50 mmol) of anethole. The mixture was stirred vigorously for 30 min, by which time it had become homogeneous. The reduction of the mercurial intermediate was then carried out by adding 50 mL of 3 M aqueous sodium hydroxide and 50 mL of 0.5 M sodium borohydride in 3 M sodium hydroxide. The mixture was stirred for 3 h until the mercury had coagulated. The solution was filtered and extracted with ether (3 × 50 mL). The extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford 8.9 g (94%) of a colorless oil. Distillation (78–79 °C (0.5 mm)) afforded 8.2 g (87%) of the product 6: ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 7.5 Hz), 1.83 (m, 2 H), 3.25 (s, 3 H), 3.82 (s, 3 H), 3.90 (t, 1 H, *J* = 6 Hz), 7.2 (AA'BB', 4 H, *J* = 8.5 Hz, Δν = 0.36 ppm); mass spectrum (70 eV), *m/e* (relative intensity) 180 (M^+, 2.2), 152 (10), 151 (100), 135 (17).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 8.82.

1-(4-Methoxyphenyl)-1-chloropropane (7). Anethole (6 g, 40.5 mmol) was dissolved in 30 mL of ether and cooled to 0 °C. HCl gas was then bubbled through the solution for 6 h at 0 °C. The solution was flushed with nitrogen to remove any dissolved HCl gas. Water (50 mL) was then added, and the organic layer was separated and dried ($MgSO_4$). Removal of the solvent in vacuo afforded 6.5 g (84%) of a colorless oil. Distillation (88–90 °C (0.4 mm)) yielded 6.2 g (80%) of the product 7: ^1H NMR ($CDCl_3$) δ 1.0 (t, *J* = 7.5 Hz, 3 H), 1.8–2.2 (m, 2 H), 3.81 (s, 3 H), 4.75 (t, *J* = 6 Hz, 3 H), 7.05 (AA'BB', 4 H, *J* = 8.5 Hz, Δν = 0.55 ppm); mass spectrum (10 eV), *m/e* (relative intensity) 184 (M^+, 0.5), 149 (100), 130 (6), 95 (17).

Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.08; H, 7.04. Found: C, 65.16; H, 7.16.

General Method for the Preparation of Allylsilanes. *n*-Butyllithium (45 mmol) was added dropwise with stirring over 0.5 h to a suspension of methyltriphenylphosphonium bromide (14.28 g, 40 mmol) in dry tetrahydrofuran (75 mL) at 0 °C under nitrogen. The mixture was warmed to room temperature, stirred for 1 h, and recooled to 0 °C, and (iodomethyl)trimethylsilane (9.1 g, 45 mmol) added over 10 min. The mixture was again allowed to come to room temperature to precipitate the new phosphonium salt. After 1 h the reaction was treated with a second equivalent of *n*-butyllithium (45 mmol) at −78 °C. The mixture was allowed to warm slowly to room temperature and stirred for a further 1.5 h to give the dark red solution of the ylid. The solution was cooled to −78 °C, and a solution of the aldehyde (37.5 mmol) in dry tetrahydrofuran (40 mL) was added dropwise over 15 min under nitrogen. After 0.5 h the mixture was allowed to warm slowly to room temperature and was stirred under nitrogen for 16 h. The reaction was quenched by pouring into

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saturated ammonium chloride solution (100 mL) and extracted with ether (3 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude reaction product was purified according to the procedures noted for the specific allylsilane.

1-(4-Methoxyphenyl)-3-(trimethylsilyl)prop-1-ene (8) was prepared from 5.3 g (3.9 mmol) of 4-methoxybenzaldehyde. Purification by distillation (99 °C (0.5 mm)) afforded 7.2 g (83%) of the allylsilane 8: ^1H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 1.68 (d, 2 H, J = 7.7 Hz), 3.82 (s, 3 H), 6.17 (m, 1 H, —CH=C*H*—CH_2—), 6.24 (d, 1 H, J = 16 Hz, —C*H*=CH—), 7.08 (AA'BB', 4 H, J = 8.7 Hz, $\Delta\nu$ = 0.41 ppm); mass spectrum (10 eV), m/e (relative intensity) 213 (M^+, 0.5), 139 (37), 107 (100).

Anal. Calcd for $C_{13}H_{12}OSi$: C, 70.84; H, 9.09. Found: C, 70.63, H, 8.93.

(3*R,4*S**)- and (3*R**,4*R**)-3,4-Bis(4-methoxyphenyl)-1-hexene (10a and 10b).** To a solution of the allylsilane 8 (0.44 g, 2 mmol) and the electrophile 6 (0.36 g, 2 mmol) in dichloromethane (15 mL) at −78 °C was added a solution of 0.22 mL (2 mmol) of titanium tetrachloride ($TiCl_4$) in 2 mL of dichloromethane dropwise over 5 min. The mixture was stirred at −78 °C for 15 min at which time GC analysis indicated disappearance of the allylsilane. The reaction was quenched with 20 mL of methanol and extracted with ether (3 × 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.45 g of the crude product. Preparative layer chromatography (10% ether–hexane) afforded 0.43 g (72%) of a light yellow oil which was shown (GLC) to be approximately a 1:1 mixture of two isomers. Trituration with hexane afforded 0.21 g (35%) of a white crystalline solid (3*R**,4*S**)-3,4-bis(4-methoxyphenyl)-1-hexene (**10a**): mp 116–118 °C (lit.[28] 117–119 °C); ^1H NMR (CCl_4) δ 0.6 (t, J = 7.4 Hz, 3 H), 1.4 (m, 2 H), 2.6 (dt, J = 6.0, 3.0 Hz, 1 H), 3.25 (t, J = 9 Hz, 1 H), 3.8 (s, 6 H), 4.65 (m, 2 H), 5.7 (m, 1 H), 6.8 (AA'BB', J = 8 Hz, $\Delta\nu$ = 0.41 ppm, 4 H); Kugelrohr distillation of the mother liquor afforded 0.18 g (30%) of a colorless oil (3*R**,4*R**)-3,4-bis(4-methoxyphenyl)-1-hexene (**10b**): ^1H NMR (CCl_4) δ 0.7 (t, J = 7.33 Hz, 3 H), 1.42 (m, 2 H), 2.63 (dt, J = 10, 3 Hz, 1 H), 3.3 (t, J = 9 Hz, 1 H), 3.7 (s, 6 H), 5.0 (m, 2 H), 6.0 (m, 1 H), 6.75 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 0.45 ppm, 4 H); mass spectrum (70 eV), m/e (relative intensity) 296 (M^+, 3.5), 150 (14), 149 (100), 146 (9.2), 121 (35); Anal. (high-resolution mass spectrum) calcd for $C_{20}H_{24}O_2$, 296.1170; found, 296.1165.

1-(4-Methoxyphenyl)-1-methoxyethane (15). Potassium hydroxide (powdered, 4.5 g, 0.13 mmol, 4 mmol/replaceable hydrogen) was stirred in Me_2SO (60 mL) for 5 min. 1-(4-Methoxyphenyl)ethanol (5.0 g, 33 mmol) was then added followed by methyl iodide (9.34 g, 66 mmol), 2 mmol/replaceable hydrogen). After stirring at room temperature for 30 min the solution was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (5 × 200 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo to afford a yellow oil. Distillation under reduced pressure (66 °C (0.4 mm)) afforded 5.6 g of the product 15: ^1H NMR ($CDCl_3$) δ 1.4 (d, J = 7.0 Hz, 3 H), 3.15 (s, 3 H), 3.7 (s, 3 H), 4.2 (q, J = 6 Hz, 1 H), 7.0 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 0.41 ppm, 4 H); mass spectrum (10 eV), m/e (relative intensity) 166 (M^+, 13), 15 (12), 151 (100), 135 (25).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.28; H, 8.65.

α-Bromo-2-nitro-4-methoxytoluene (16). A solution of 2-nitro-4-methoxytoluene (11) (5.0 g, 30.3 mmol), *N*-bromosuccinimide (5.39 g, 30.3 mmol), and benzoyl peroxide (15 mg) in 100 mL of carbon tetrachloride was refluxed under strong illumination using a 400-W General Electric sunlamp. After 6 h the solution was cooled and the solid succinimide removed by filtration. The filtrate was concentrated to yield a brown solid. Recrystallization from methylene chloride–hexane afforded 7.1 g (95%) of the product 16: mp 63–64 °C (lit.[16] 63–64 °C); ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.7 (s, 2 H), 7.03–7.55 (m, 3 H); IR (KBr) 1540, 1536 cm^{-1}.

2-Nitro-4-methoxybenzaldehyde (17). A solution of the benzylic bromide 16 (6.7 g, 27.2 mmol) and bis(tetrabutylammonium) dichromate (10.0 g, 14.2 mmol, 1.5 equiv) in 20 mL $CHCl_3$ was heated under reflux for 10 min. TLC analysis showed the disappearance of the bromide. The reaction was rapidly cooled in an ice bath and filtered through a pad of silica gel (20 g) to eliminate the inorganic and tetrabutylammonium salts; the silica was then washed with diethyl ether (100 mL). Evaporation of the combined organic solvents afforded 4.5 g (95%) of the crude organic product. Purification by flash chromatography (10% ether–hexane) afforded 3.7 g (75%) of the aldehyde 17 as light yellow crystals: mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H, $ArOCH_3$), 7.2 (dd, J = 8.5, 2.5 Hz, 1 H, Ar H), 7.5 (d, J = 2.5 Hz, 1 H, Ar H), 7.95 (d, J = 8.5 Hz, 1 H, Ar H), 10.2 (s, 1 H, ArC*H*O); IR (KBr) 1690, 1535, 1355 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 181 (M^+, 10), 165 (46), 151 (100).

Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.10; H, 3.82; N, 7.36.

1-(2-Nitro-4-methoxyphenyl)-3-(trimethylsilyl)prop-1-ene (18) was prepared from 1.5 g (5.67 mmol) of the aldehyde 17 (see general method for the preparation of allylsilanes). Purification by flash chromatography (5% ether–hexane) afforded 1.76 g (80%) of the allylsilane 18 as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 1.68 (d, J = 7.7 Hz, 2 H), 3.82 (s, 3 H), 6.2–6.35 (m, 1 H, $ArCH_2$—C*H*=CH—), 6.45 (d, J = 17 Hz, 1 H), —CH=C*H*—$SiMe_3$), 6.9 (dd, J = 7.5, 2.5 Hz, 1 H, Ar H), 7.2 (J = 2.5 Hz, 1 H, Ar H), 7.4 (d, J = 7.5 Hz, 1 H, Ar H); IR (neat) 1530, 1350 cm^{-1} (Ar–NO_2); mass spectrum (10 eV), m/e (relative intensity) 265 (M^+, 15), 264 (10), 175 (32), 159 (13), 133 (11), 75 (18), 73 (100).

Anal. Calcd for $C_{13}H_{19}NO_3Si$: C, 58.84; H, 7.22; N, 5.28. Found: C, 58.71; H, 7.26; N, 5.46.

General Method for Coupling the Allylsilane 18 with the Electrophiles. The nitro allylsilane 18 (0.57 g, 2.15 mmol) and the electrophile (2.15 mmol) were dissolved in 15 mL of dichloromethane and cooled to −78 °C under N_2. Titanium tetrachloride (2.15 mmol) in 5 mL of dichloromethane was added dropwise over 5 min. The reaction was stirred at −78 °C for 1 h at which point TLC analysis showed the disappearance of the allylsilane. The reaction was quenched by pouring into 100 mL of saturated ammonium chloride solution and was then extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to afford a reddish brown oil. The products were isolated by flash chromatography on silica gel (5% CH_2Cl_2, 10% ether, 85% hexane).

(3*R,4*S**)- and (3*R**,4*R**)-4-(4-Methoxyphenyl)-3-(2-nitro-4-methoxyphenyl)-1-pentene (19a and 19b)** were isolated in 79% yield (0.56 g) as a 3:1 mixture of diastereomers. Purification by flash chromatography afforded the two diastereomers with the 3*R**,4*R** isomer being the major product.

(3*R**,4*S**)-**19a**: ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 7.5 Hz, 3 H), 2.9–3.3 (m, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 4.0 (t, J = 9.0 Hz, 1 H), 4.65–4.95 (m, 2 H), 5.55–6.0 (m, 1 H), 6.75–7.3 (m, 7 H); IR (neat) 1550, 1335 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 327 (M^+, 3.7), 295 (6), 270 (5), 136 (12), 135 (100).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.69; H, 9.28; N, 4.28. Found: C, 69.52; H, 9.46; N, 4.53.

(3*R**,4*R**)-**19b**: ^1H NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7.5 Hz), 2.9–3.2 (m, 1 H), 3.67 (s, 3 H), 3.71 (s, 3 H), 4.1 (t, J = 9.0 Hz, 1 H), 5.0–5.3 (m, 2 H), 5.8–6.25 (m, 1 H), 6.6–7.3 (m, 7 H); IR (neat) 1550, 1335 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity), 327 (M^+, 2), 136 (9), 135 (100).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.69; H, 9.28; N, 4.28. Found: C, 69.61; H, 9.59; H, 4.01.

(3*R,4*S**)- and (3*R**,4*R**)-3-(2-Nitro-4-methoxyphenyl)-4-(4-methoxyphenyl)-1-hexene (20a and 20b)** were isolated in 70% yield (0.51 g) as a 7:1 mixture of diastereomers. Purification by flash chromatography afforded the two diastereomers with the 3*R**,4*R** isomer being the major product.

(3*R**,4*R**)-**20a**: ^1H NMR ($CDCl_3$) δ 0.56 (t, J = 7.33 Hz, 3 H), 1.2–1.6 (m, 2 H), 2.6–2.8 (m, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 3.9–4.15 (t, J = 6 Hz, 1 H), 4.6–4.9 (m, 2 H), 5.55–5.95 (m, 1 H), 6.65–7.3 (m, 7 H); mass spectrum (10 eV), m/e (relative intensity) 341 (0.7), 150 (13), 149 (100), 121 (17), 84 (6).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.56; H, 6.66; N, 4.15.

(3*R**,4*R**)-**20b**: ^1H NMR ($CDCl_3$) δ 0.65 (t, J = 7.37 Hz, 3 H), 1.1–2.0 (m, 2 H), 2.65 (m, 1 H), 3.60 (s, 3 H), 3.71 (s, 3 H), 4.10 (t, J = 9 Hz, 1 H), 5.0–5.2 (m, 2 H), 5.65–6.10 (m, 1 H), 6.5–7.2 (m, 7 H); mass spectrum (10 eV), m/e (relative intensity) 341 (M^+,

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9), 279 (10), 160 (13), 150 (39), 149 (100).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.32; H, 6.71; N, 4.21.

General Method for the Hydrogenation of the Nitro Olefinic Compounds 19a, 19b, 20a, and 20b. To 0.30 mmol of the olefinic compound in 5 mL benzene was added 10 mg (0.01 mmol) of tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst). The homogeneous solution was hydrogenated for 3 h at 25 °C when TLC analysis showed complete disappearance of the starting material. The solvent was removed in vacuo, and 10 mL of ether was added to precipitate the catalyst. The mixture was filtered through celite and further purified by flash chromatography on silica gel (15% ether–hexane) to afford the hydrogenated product in almost quantitative yield (>95%).

(2*R,3*S**)-2-(4-Methoxyphenyl)-3-(2-nitro-4-methoxyphenyl)pentane (21a)**: ^{1}H NMR ($CDCl_3$) δ 0.55 (t, J = 7.4 Hz, 3 H), 1.05 (d, J = 7.5 Hz, 3 H), 1.2–1.6 (m, 2 H), 2.6–3.2 (m, 2 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 6.8–7.35 (m, 7 H); IR (neat) 1555, 1335 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 329 (M^+, 0.4), 163 (6), 136 (10), 135 (100), 105 (10), 44 (35), 28 (18).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.50; H, 6.97; N, 4.01.

(2*R,3*R**)-2-(4-Methoxyphenyl)-3-(2-nitro-4-methoxyphenyl)pentane (21b)**: ^{1}H NMR ($CDCl_3$) δ 0.68 (t, J = 7.33 Hz, 3 H), 1.3 (d, J = 7.5 Hz, 3 H), 1.5–2.0 (m, 2 H), 1.85–3.1 (m, 1 H), 3.3–3.6 (m, 1 H), 3.7 (s, 3 H), 3.75 (s, 3 H), 6.6–7.2 (m, 7 H); mass spectrum (10 eV), m/e (relative intensity) 329 (M^+, 0.5), 136 (12), 135 (100), 44 (17).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.25; H, 7.12; N, 4.21.

(3*R,4*S**)-3-(2-Nitro-4-methoxyphenyl)-4-(4-methoxyphenyl)hexane (22a)**: ^{1}H NMR ($CDCl_3$) δ 0.5 (t, J = 7 Hz, 3 H), 0.55 (t, J = 7 Hz, 3 H), 1.2–1.5 (m, 4 H), 2.3–2.5 (m, 1 H), 3.0–3.3 (m, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 6.8–7.3 (m, 7 H); IR (neat) 1550, 1335 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 343 (M^+, 0.8), 151 (8), 149 (100), 105 (7).

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.90; H, 7.53; N, 4.23.

(3*R,4*R**)-3-(2-Nitro-4-methoxyphenyl)-4-(4-methoxyphenyl)hexane (22b)**: ^{1}H NMR ($CDCl_3$) δ 0.65 (s, 3 H), 0.72 (s, 3 H), 1.2–2.0 (m, 4 H), 2.4–2.7 (dt, J = 10.0, 3.0 Hz, 1 H), 3.2–3.5 (dt, J = 10.0, 3.0 Hz, 1 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 6.6–7.2 (m, 7 H); mass spectrum (70 eV), m/e (relative intensity) 343 (M^+, 0.3), 172 (17), 150 (8), 149 (100).

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.72; H, 7.03; N, 4.16.

General Method for the Selective Cleavage of the Methyl Ether Group on Compounds 21a, 21b, 22a, 22b. To the dimethyl ether hexestrol and penestrol analogues (0.15 mmol) in 0.5 mL $CDCl_3$ was added 80 mg (0.4 mmol) of iodotrimethylsilane under nitrogen. The reaction was stirred for 9 h at 25 °C. Methanol (25 mL) was then added, and the reaction was stirred for another 12 h at 25 °C. The methanol was removed in vacuo, and the resulting oil was taken up in ethyl acetate (50 mL) and washed with dilute aqueous sodium bisulfite. The organic layer was dried ($MgSO_4$), and the solvent removed in vacuo to yield a brown oil. Flash chromatography on silica gel (50% ether–hexane) afforded the monophenolic product (80–90% yields).

(2*R,3*S**)-2-(4-Hydroxyphenyl)-3-(2-nitro-4-methoxyphenyl)pentane (13a)**: ^{1}H NMR ($CDCl_3$) δ 0.54 (t, 3 H), 0.99 (d, 3 H, J = 7 Hz), 1.2–1.6 (m, 2 H), 2.68–2.75 (m, 1 H), 3.0–3.2 (m, 1 H), 3.86 (s, 3 H), 4.60 (s, 1 H), 6.90 (AA'BB', 4 H, J = 8.5 Hz, $\Delta\nu$ = 0.42 ppm), 7.13 (dd, 1 H, J = 8.80, 2.60 Hz), 7.2 (d, 1 H, J = 2.6 Hz), 7.28 (d, 1 H, J = 8.85 Hz); mass spectrum (10 eV), m/e (relative intensity) 315 (M^+, 0.4), 195 (4), 178 (4), 121 (100); Anal. (high-resolution mass spectrum) calcd for $C_{18}H_{21}NO_4$, 315.1502; found, 315.1486.

(2*R,3*R**)-2-(4-Hydroxyphenyl)-3-(2-nitro-4-methoxyphenyl)pentane (13b)**: ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.3 Hz, 3 H), 1.23 (d, J = 7 Hz, 3 H), 1.6–2.0 (m, 2 H), 2.90 (m, 1 H), 3.25 (dt, J = 10.0, 3.0 Hz, 1 H), 3.78 (s, 3 H), 4.53 (s, 1 H), 6.74 (AA'BB', 4 H, J = 8.5 Hz; $\Delta\nu$ = 0.41 ppm), 6.97 (dd, J = 8.5, 2.70 Hz, 1 H), 7.02 (d, J = 2.64 Hz, 1 H), 7.12 (d, J = 8.86 Hz, 1 H); mass spectrum (10 eV), m/e (relative intensity) 315 (M^+, 0.5), 195 (6), 178 (10), 121 (100); Anal. (high-resolution mass spectrum) calcd for $C_{18}H_{21}NO_4$, 315.1502; found, 315.1500.

(3*R,4*S**)-3-(2-Nitro-4-methoxyphenyl)-4-(4-hydroxyphenyl)hexane (14a)**: ^{1}H NMR ($CDCl_3$) δ 0.55 (t, J = 7 Hz, 3 H), 0.6 (t, J = 7 Hz, 3 H), 1.2–1.8 (m, 4 H), 2.2–2.6 (m, 1 H), 3.0–3.3 (m, 1 H), 3.85 (s, 3 H), 4.3 (s, 1 H), 6.72 (AA'BB', J = 8.54 Hz, $\Delta\nu$ = 0.42 ppm, 4 H), 6.89 (dd, J = 8.60, 2.75 Hz, 1 H), 7.02 (d, J = 2.64 Hz, 1 H), 7.15 (d, J = 8.62 Hz, 1 H); IR (neat) 1550, 1335 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 329 (M^+, 0.6), 178 (4), 150 (6), 149 (100).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.53; H, 7.22; N, 4.10.

(3*R,4*R**)-3-(2-Nitro-4-methoxyphenyl)-4-(4-hydroxyphenyl)hexane (14b)**: ^{1}H NMR ($CDCl_3$) δ 0.62 (t, J = 7 Hz, 3 H), 0.65 (t, J = 7 Hz, 3 H), 1.4–1.6 (m, 2 H), 1.8–2.0 (m, 2 H), 2.45–2.58 (dt, J = 10.0, 3.0 Hz, 1 H), 3.27–3.40 (dt, J = 10.0, 3.0 Hz, 1 H), 3.72 (s, 3 H), 4.42 (s, 1 H), 6.60 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 0.40 ppm, 4 H), 6.84 (dd, J = 8.62, 2.6 Hz, 1 H), 6.91 (d, J = 2.62 Hz, 1 H), 7.0 (d, J = 8.60 Hz, 1 H); mass spectrum (10 eV), m/e (relative intensity) 329 (M^+, 0.4), 190 (8), 178 (6), 151 (8), 150 (12), 149 (100).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.21; H, 7.11; N, 4.50.

2-(4-Methoxyphenyl)-4,4-dimethyl-2-oxazoline (25). *p*-Anisic acid (7.6 g, 0.05 mmol) and 2-amino-2-methyl-1-propanol (4.45 g, 0.05 mmol) were refluxed at 170 °C. Within 2 h the reflux temperature had fallen to 150 °C. The reaction was refluxed for a further 14 h by which time the reflux temperature was 110 °C. Water and some unreacted amine were then removed under aspirator vacuum. The reaction mixture was then distilled (136–138 °C (2 mm)) to afford 9.1 g (89%) of the oxazoline **25**: ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 6 H), 3.8 (s, 3 H), 4.05 (s, 2 H), 6.85 (d, J = 6 Hz, 2 H, Ar H), 7.85 (d, J = 6 Hz, 2 H, Ar H); IR (neat) 1650 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 205 (M^+, 17), 191 (17), 190 (100), 162 (22), 134 (21).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.49; H, 7.11; N, 6.60.

2-(4-Methoxy-2-(trimethylsilyl)phenyl)-4,4-dimethyl-2-oxazoline (26). A solution of the oxazoline **25** (1.0 g, 5 mmol) in THF (20 mL) was cooled under a nitrogen atmosphere in an ice bath. *n*-Butyllithium (3.6 mL of a 1.7 M solution, 6 mmol) was then added dropwise. After the reaction was stirred at ice bath temperature for 6 h, a solution of chlorotrimethylsilane (1.3 g, 12 mmol) in 10 mL THF was added at once, and the reaction was stirred at room temperature for 4 h. After workup (H_2O, brine, Na_2SO_4), the residue was purified by preparative layer chromatography to afford 1.2 g (90%) of the ortho-silylated oxazoline **26**. ^{1}H NMR ($CDCl_3$) δ 0.45 (s, 9 H), 1.45 (s, 6 H), 3.85 (d, J = 2.5 Hz, 1 H, Ar H), 7.95 (d, J = 7.5 Hz, 1 H, Ar H); IR (neat) 1645 cm^{-1}; mass spectrum (10 eV), m/e (relative intensity) 277 (M^+, 6), 263 (24), 262 (100).

Anal. Calcd for $C_{15}H_{23}NO_2Si$: C, 64.94; H, 8.35; N, 5.05. Found: C, 64.77; H, 8.62; N, 5.11.

2-(4-Methoxy-2-(trimethylsilyl)phenyl)-3,4,4-trimethyloxazolinium Iodide (27). A solution of the oxazoline **26** (0.29 g, 1.05 mmol) and methyl iodide (0.225 g, 1.58 mmol) in 10 mL of acetonitrile was refluxed for 12 h. The reaction was then cooled and the solvent removed in vacuo to afford 350 mg (91%) of a colorless oil. Trituration with hexane afforded 329 mg (85%) of white crytals of **27**: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9 H), 1.75 (s, 6 H), 3.5 (s, 3 H), 3.85 (s, 3 H), 5.05 (s, 2 H), 7.0–7.2 (m, 2 H), 8.1 (d, J = 6 Hz, 1 H); mass spectrum (10 eV), m/e (relative intensity) 419 (M^+, 1.3), 404 (14), 292 (21), 276 (15), 262 (23), 222 (38), 207 (100), 142 (21).

Anal. Calcd for $C_{16}H_{12}INO_2Si$: C, 45.82; H, 6.25; N, 3.34. Found: C, 45.82; H, 6.41; N, 3.51.

4-Methoxy-2-(trimethylsilyl)benzaldehyde (28). Sodium borohydride (0.27 g, 7.2 mmol) was added to a solution of the oxazolinium iodide **27** (0.3 g, 0.72 mmol) in 10 mL of ethanol at ice bath temperature over a period of 30 min. The solution was then stirred at 0–5 °C for 2 h. Sodium hydroxide (20 mL of a 5% solution) was added and the solution was extracted with ether (3 × 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to afford 0.32 g of a reddish/brown oil. Hydrochloric acid (10 mL, 5% HCl solution) and 20 mL methanol were then added, and the solution was heated on a steam bath for 30 min. After cooling, the solution was extracted with ether (3 × 50 mL), the extracts were dried ($MgSO_4$), and the solvent

was removed in vacuo. Purification by flash chromatography (10% ether–hexane) afforded 89 mg (60%) of the aldehyde **28**: ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 9 H), 3.89 (s, 3 H), 7.0 (dd, J = 7.5, 2.5 Hz, 1 H), 7.2 (d, J = 2.5 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 10.01 (s, 1 H); IR (neat) 1695 cm^{-1}; mass spectrum (70 eV) m/e (relative intensity) 208 (M^+, 1.3), 195 (16), 194 (56), 193 (100), 178 (20), 134 (34).

Anal. Calcd for $C_{11}H_{16}O_2Si$: C, 63.45; H, 7.68. Found: C, 63.62; H, 7.35.

1-(2-(Trimethylsilyl)-4-methoxyphenyl)-3-(trimethylsilyl)prop-1-ene (29) was prepared from 0.2 g (0.72 mmol) of the aldehyde **28** (see general method for the preparation of allylsilanes). Purification by distillation under reduced pressure (150 °C (0.2 mm)) afforded 0.18 g (85%) of the allylsilane **29**: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 0.3 (s, 9 H), 1.66 (d, J = 7.7 Hz, 2 H), 3.82 (s, 3 H), 5.6–6.1 (m, 1 H), 6.6 (d, J = 16.5 Hz, 1 H), 6.9 (dd, J = 5.6, 2.5 Hz, 1 H), 7.15 (d, J = 2.5 Hz, 1 H), 7.25 (d, J = 8.5 Hz, 1 H); mass spectrum (10 eV), m/e (relative intensity) 292 (M^+, 20), 180 (10), 189 (59), 73 (100); Anal. (high-resolution mass spectrum) calcd for $C_{16}H_{28}OSi_2$, 292.1679; found, 292.1681.

Methyl (4-Methoxyphenyl)acetate (30). To a solution of 4 g (24 mmol) of (4-methoxyphenyl)acetic acid in 100 mL of methanol was added 8.3 mL of a 5 M HCl solution in dioxane (3% HCl). The solution was brought to reflux for 16 h and then extracted into ether (3 × 50 mL). The combined organic extracts were washed with 100 mL saturated sodium carbonate solution and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 4.32 g of the crude product. Flash chromatography over silica gel and elution with 10% ether–hexane afforded 4.2 g (93%) of the methyl ester **30**: ^{1}H NMR (CCl_4) δ 3.55 (s, 2 H), 3.7 (s, 3 H), 3.82 (s, 3 H), 6.95 (AA'BB', J = 8.5 Hz, $\Delta\nu$ = 0.43 ppm, 4 H); bp 113–115 °C (2 mm) (lit.[29] 155–157 °C (23 mm)).

(2*R,3*S**)-Methyl 2,3-Bis(4-methoxyphenyl)pentanoate (32).** To a solution of 0.40 mL (0.29 g, 2 mmol) of diisopropylamine in THF (5 mL) at −30 °C was added an equivalent of n-butyllithium (1 mL of a 2 M solution in hexane, 2 mmol), and the solution was stirred for 0.5 h. The solution was then cooled to −78 °C, and a solution of the methyl ester **30** (0.36 g, 2 mmol) in THF (5 mL) was added dropwise over 10 min. The solution was stirred for 2 h at −78 °C and then quenched with 0.26 mL of chlorotrimethylsilane (0.21 g, 2 mmol). The solution was then allowed to warm slowly to 0 °C and the THF was removed under reduced pressure (1 mm). After all the THF had been removed, the solution was recooled to −78 °C under nitrogen, and the electrophile **7** (0.45 g, 2.5 mmol) in dichloromethane (10 mL) was added dropwise. Titanium tetrachloride (0.45 mL, 4 mmol) in dichloromethane (10 mL) was then added to the reaction mixture dropwise over 10 min. The reaction mixture was stirred at −78 °C for 1 h when GLC analysis showed disappearance of the starting material. The reaction was quenched with methanol (20 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.52 g of the crude product. Preparative thin-layer chromatography (10% ethyl acetate–hexane) afforded 0.47 g (71%) of an oil which was shown by NMR to be a mixture of diastereomers. Fractional crystallization (methylene chloride–hexane) afforded 0.25 g (38%) of the product **32a**, mp 124–126 °C (lit.[6d] 124–125 °C).

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Registry No. **6**, 88932-42-7; **7**, 88932-43-8; **8**, 82482-05-1; **10a**, 78387-60-7; **10b**, 88932-44-9; **11**, 17484-36-5; **13a**, 88932-45-0; **13b**, 88932-46-1; **14a**, 88932-47-2; **14b**, 88932-48-3; **15**, 77525-91-8; **16**, 57559-52-1; **17**, 22996-21-0; **18**, 88932-49-4; **19a**, 88932-50-7; **19b**, 88932-51-8; **20a**, 88932-52-9; **20b**, 88932-53-0; **21a**, 88932-54-1; **21b**, 88932-55-2; **22a**, 88932-56-3; **22b**, 88932-57-4; **25**, 53416-46-9; **26**, 88932-58-5; **27**, 88932-59-6; **28**, 88932-60-9; **29**, 88932-61-0; **30**, 23786-14-3; **32a**, 83303-94-0; **32b**, 88932-62-1; $(CH_3)_3SiCH_2CH{=}PPh_3$, 63922-69-0; anethole, 104-46-1; methyltriphenylphosphonium bromide, 1779-49-3; (iodomethyl)trimethylsilane, 4206-67-1; 4-methoxybenzaldehyde, 123-11-5; 1-(4-methoxyphenyl)ethanol, 3319-15-1; *p*-anisic acid, 100-09-4; 2-amino-2-methyl-1-propanol, 124-68-5; (4-methoxyphenyl)acetic acid, 104-01-8.

Syntheses of Hydroxy Ketones from Lactones

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γ-Hydroxy ketones (**4**, n = 2) are cleanly obtained by the addition of 1.1 equiv of n-butyllithium to γ-lactones dissolved in ether at −90 °C, since in these conditions the formation of diols by double organometallic attack is avoided, especially in the case of substituted lactones. The corresponding reactions performed in tetrahydrofuran are less satisfactory. The method cannot be applied to δ-valerolactone and to ε-caprolactone, as well as to β-lactones, from which extremely complex mixtures are obtained in low yields. Furthermore the reactions of Grignard reagents with lactones in ether or in tetrahydrofuran are quite poor. From those lactones which behave unsatifactorily toward n-butyllithium in ether, the corresponding β-, δ-, and ε-hydroxy ketones (**4**, n = 1, 3, 4) are prepared in two steps. The reactions with α,α-dilithioalkyl phenyl sulfones in tetrahydrofuran at low temperatures afford the ω-hydroxy-β-keto sulfones (**12**), which are successively cleaved with aluminum amalgam to afford **4** in satisfactory overall yields.

Introduction

The reaction of lactones with organometallic reagents is a useful tool for the homologation of a carbon chain. The ring opening can follow different pathways (a and b, Scheme I), depending principally on the ring size and the nature of the organometallic reagent.

The sterically constrained β-lactones (**1**, n = 1) react with organolithium, -magnesium, and -cadmium compounds to give mixtures of β-halopropionic acids (**2**, from Grignard reactions), carboxylic acids (**3**), β-hydroxy ketones (**4**, n = 1), vinyl ketones (**5**), and diols (**7**, n = 1).[1] The use of organocuprates of Grignard reagents under the catalytic

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