Scope and Stereochemical Course of the Addition of (Trimethylsilyl)allenes to Ketones and Aldehydes. A Regiocontrolled Synthesis of Homopropargylic Alcohols

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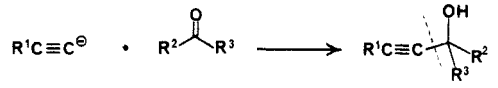
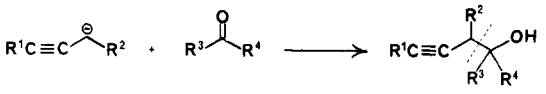
The reaction of (trimethylsilyl)allenes with aldehydes and ketones in the presence of titanium tetrachloride provides a regiocontrolled route to homopropargylic alcohols of a variety of substitution types. The addition of 1-alkyl-substituted (trimethylsilyl)allenes to carbonyl compounds furnishes the desired acetylenes directly, while reactions involving allenylsilanes **6**, **7**, and **9** initially produce mixtures of acetylenes and (trimethylsilyl)vinyl chloride derivatives. Exposure of these mixtures to the action of potassium fluoride in dimethyl sulfoxide then generates the desired homopropargylic alcohols. The addition of the chiral allenylsilane **9** to achiral aldehydes has been found to proceed with modest (3–4:1) diastereoselectivity to produce mainly syn (erythro) homopropargylic alcohols.

In recent years chemists have devised many important synthetic reactions exploiting the unique and versatile chemistry of the carbon–carbon triple bond.[2] The semihydrogenation of alkynes, for example, constitutes a popular stereoselective approach to disubstituted olefins. A widely employed route to trisubstituted olefins employs stereoselective "reductive alkylation" methods involving alkenylaluminum, -boron, -silicon, -tin, -mercury, -zirconium, and -copper intermediates. Acetylene derivatives also participate in a variety of useful ring-forming processes, including 1,3-dipolar cycloadditions, Diels–Alder reactions, and cobalt-mediated [2 + 2 + 2] cyclotrimerizations.

The acetylenic intermediates employed in these synthetic methods are frequently assembled by the reaction of organometallic derivatives of terminal acetylenes (or acetylene itself) with organic electrophiles. Equation 1



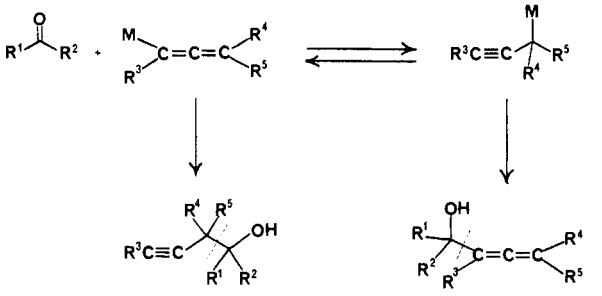
(1)



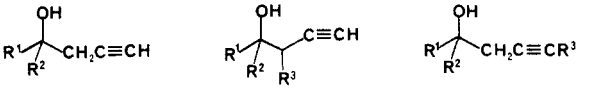
(2)

illustrates this popular approach as applied to the synthesis of propargylic alcohols. A second general strategy for the synthesis of alkynes involves substitution and addition reactions of propargylic anion equivalents;[3] this alternative approach is particularly well-suited for the preparation of certain α-branched and β-functionalized acetylenes such as *homo*propargylic alcohols (eq 2). Unfortunately, the utility of this methodology is limited by the tendency of propargylic metal derivatives to combine with carbonyl compounds (and other electrophiles) to produce both allenic and acetylenic products. This regiochemical ambiguity arises from the fact that these species generally exist as an equilibrating mixture of allenic and propargylic organometallic derivatives (Scheme I), which combine with carbonyl compounds via S_E2' (or S_Ei) pathways to afford homopropargylic and allenic alcohols (respectively).[3] The product distribution in these reactions is consequently determined by the position of the equilibrium between the two organometallic intermediates, as well as by their relative rates of addition to carbonyl compounds. Both the steric bulk of the electrophile and the substitution pattern on the organometallic species have thus been found to influence the regiochemical outcome of these reactions.

Scheme I



Despite these complications, considerable progress has recently been recorded toward the development of useful "propargylic anion equivalents". Type I homopropargylic alcohols, for example, can be prepared by the addition of allenylboronate esters to aldehydes (though not to ketones).[4] Although allenyllithium unfortunately combines



I II III

with carbonyl compounds to afford mixtures of allenic and acetylenic alcohols,[5] allenylmagnesium bromide reacts with many carbonyl derivatives to furnish the desired type I products.[3] Alternatively, triisopropylsilyl derivatives of these acetylenes can be prepared by the reaction of the lithium derivative of 1-(triisopropylsilyl)propyne with ketones and aldehydes by using the procedure described by Corey and Rücker.[6]

(1) Fellow of the Alfred P. Sloan Foundation, 1981–1985.

(2) For reviews, see: (a) Viehe, H. G., Ed. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969. (b) Patai, S., Ed. *The Chemistry of the Carbon–Carbon Triple Bond*; Wiley: New York, 1978.

(3) For reviews of the chemistry of propargylic anion equivalents, see: (a) Epsztein, R. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Part B, pp 107–176. (b) Moreau, J.-L. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; pp 363–413. (c) Klein, J. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; p 343–381.

(4) (a) Favre, E.; Gaudemar, M. *J. Organomet. Chem.* **1974**, *76*, 297. (b) Favre, E.; Gaudemar, M. *Ibid.* **1974**, *76*, 305. (c) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667.

(5) For example, see: Clinet, J.-C.; Linstrumelle, G. *Synthesis* **1981**, 875.

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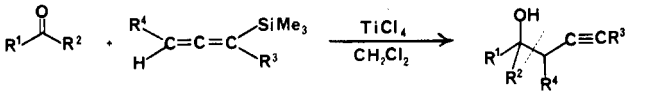
Very recently several methods have been developed for the synthesis of homopropargylic alcohols with the substitution pattern represented in structure II. These methods employ 3-alkyl-substituted allenyltitanium,[9] -alanate,[10] and -zinc compounds[11] and unfortunately are not also applicable to the synthesis of type III products. In fact, prior to our studies no *general* propargylic anion equivalent was available for the synthesis of type III alcohols.[12]

Allenylsilanes are readily available organometallic compounds which (under normal conditions) are not subject to the dynamic equilibrium outlined in Scheme I. Research in our laboratory has previously demonstrated the utility of allenylsilanes as valuable three-carbon units in [3 + 2] annulation routes to five-membered carbocycles and heterocycles.[14] In 1980 we reported that these organosilicon derivatives can also function as general propargylic anion equivalents in reactions with carbonyl compounds and acetals.[15] As formulated in eq 3, homo-



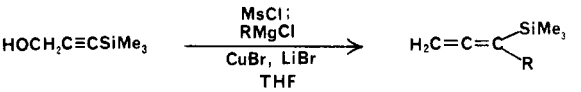
(3)

propargylic alcohols of *all three types* (I, II, and III) were found to be readily available via the regiospecific addition of (trimethylsilyl)allenes to ketones and aldehydes in the presence of titanium tetrachloride. In this paper we now provide full details of our investigation of the scope of this reaction. Further examples of the method are described, including several new cases involving chiral allenes which define the stereochemical course of the reaction.

Results

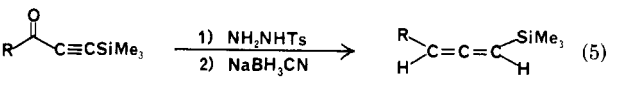
Preparation of Allenylsilanes. A variety of general synthetic approaches to allenylsilanes have recently been developed,[16,17] and a number of specialized routes to various specific functionalized derivatives[18] are available as well. The five allenylsilanes (**2**, **3**, **6**, **7**, and **9**) required for this investigation were all conveniently prepared in one or two steps beginning with known compounds.

The general method of Westmijze and Vermeer[16a] provided access to the 1-substituted (trimethylsilyl)allenes **2** and **3**. Reaction of the mesylate derivative (generated in



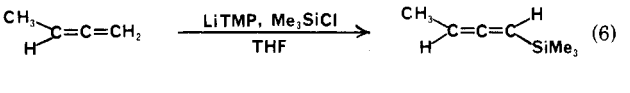
(4)

situ) of 3-(trimethylsilyl)-2-propyn-1-ol (**1**)[19] with a mixture of methylmagnesium chloride, cuprous bromide, and lithium bromide in THF (−70 → 25 °C) gave 1-methyl-1-(trimethylsilyl)allene (**2**) in 83% yield on a 25-g scale.[21] The preparation of the isopropyl derivative **3** was carried out in a similar fashion, as previously reported by Westmijze and Vermeer.[16a] (Trimethylsilyl)allene itself (**6**) and the 3-substituted derivative **7** were conveniently synthesized by using our previously described reductive deoxygenation strategy (eq 5).[14b,15] Finally, 3-methyl-1-



(5)

(trimethylsilyl)allene (**9**) was prepared by the direct silylation of the lithium derivative of 1,2-butadiene. Thus, sequential treatment of a THF solution of **8** with 1.0 equiv of lithium tetramethylpiperidide (−78 °C, 3 h) and 1.05 equiv of trimethylsilyl chloride (−78 → 25 °C, 12 h) afforded the desired allenylsilane in 41% yield after distillation.



(6)

Synthesis of Homopropargylic Alcohols: Scope of

(6) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719. By contrast, the lithium derivative of 1-(trimethylsilyl)propyne[7] reacts with aldehydes to afford both allenic and acetylenic adducts, although the corresponding Reformatsky reagent provides homopropargylic alcohols regiospecifically.[8]

(7) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, 5041.

(8) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579.

(9) (a) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768. (b) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.

(10) Hahn, G.; Zweifel, G. *Synthesis* **1983**, 883.

(11) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.

(12) Allenic products (or mixtures) are produced by the reaction of ketones and aldehydes with organometallic derivatives (Scheme I) in which R^3 = alkyl and $R^4 = R^5 = H$.[3,9,13a] Recently, Zweifel has shown that allenyldialkylboranes (generated via the reaction of lithium chloropropargylide with trialkylboranes) combine with aldehydes (but not ketones) to yield type III homopropargylic alcohols.[13b]

(13) (a) Pearson, N. R.; Hahn, G.; Zweifel, G. *J. Org. Chem.* **1982**, *47*, 3364. (b) Zweifel, G.; Backlund, S. J.; Leung, T. *J. Am. Chem. Soc.* **1978**, *100*, 5561.

(14) (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (c) Danheiser, R. L.; Fink, D. M. *Tetrahedron Lett.* **1985**, *26*, 2513. (d) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233.

(15) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925.

(16) (a) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390. See also: (b) Tanigawa, Y.; Murahashi, S.-I. *J. Org. Chem.* **1980**, *45*, 4536. (c) Montury, M.; Psaume, B.; Gore, J. *Tetrahedron Lett.* **1980**, *21*, 163.

(17) (a) Patrick, T. B.; Haynie, E. C.; Probst, W. J. *J. Org. Chem.* **1972**, *37*, 1553. (b) Beard, C. D.; Craig, J. C. *J. Am. Chem. Soc.* **1974**, *96*, 7950. (c) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632. (d) Yogo, T.; Koshino, J.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 1781. (e) Montury, M.; Gore, J. *Tetrahedron Lett.* **1980**, *21*, 51. (f) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (g) Clinet, J.-C.; Linstrumelle, G. *Synthesis* **1981**, 875. (h) Wenkert, E.; Leftin, M. H.; Michelotti, E. L. *J. Org. Chem.* **1985**, *50*, 1122.

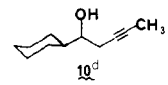
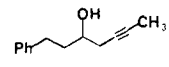
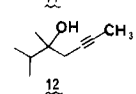
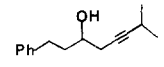
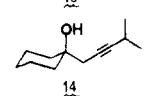
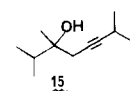
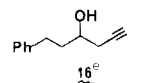
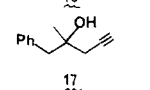
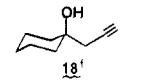
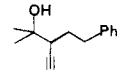
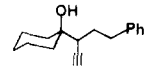
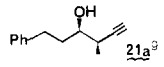
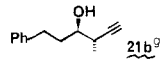
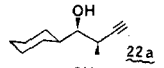
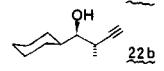
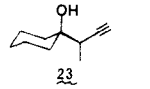
(18) (a) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607. (b) Ganem, B. *Tetrahedron Lett.* **1974**, 4467. (c) Orlov, V. Y.; Lebedev, S. A.; Ponomarev, S. V.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1975**, *45*, 708. (d) Shen, C. C.; Ainsworth, C. *Tetrahedron Lett.* **1979**, 83, 87, 89, 93. (e) Bertrand, M.; Dulcere, J.-P.; Gil, G. *Tetrahedron Lett.* **1980**, *21*, 1945. (f) Clinet, J.-C.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 3987. (g) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621. (h) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579. (i) Visser, R. G.; Brandsma, L.; Bos, H. J. T. *Tetrahedron Lett.* **1981**, *22*, 2827. (j) Dulcere, J.-P.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3179. (k) Pillot, J.-P.; Bennetau, B.; Dunogues, J.; Calas, R. *Tetrahedron Lett.* **1981**, *22*, 3401. (l) Fleming, I.; Perry, D. A. *Tetrahedron* **1981**, *37*, 4027. (m) Kruithof, K. J. H.; Klumpp, G. W. *Tetrahedron Lett.* **1982**, *23*, 3101. (n) Pornet, J.; Mesnard, D.; Miginiac, L. *Tetrahedron Lett.* **1982**, *23*, 4083. (o) Parker, K. A.; Petraitis, J. J.; Kosley, R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389. (p) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225. (q) Verkruijsse, H. D.; Verboom, W.; Van Rijn, P. E.; Brandsma, L. *J. Organomet. Chem.* **1982**, *232*, C1. (r) Van Rign, P. E.; Brandsma, L. *J. Organomet. Chem.* **1982**, *233*, C25. (s) Barton, T. J.; Hussmann, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6316. (t) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (u) Cutting, I.; Parson, P. J. *Tetrahedron Lett.* **1983**, *24*, 4463. (v) Bridges, A. J.; Fedij, V.; Turowski, E. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1093. (w) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.

(19) This compound can be purchased from Petrarch Systems, Inc., or, alternatively, can be prepared by the silylation of 2-propyn-1-ol.[20]

(20) Komarov, N. V.; Shostakovskii, M. F. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1960**, 1300.

(21) Danheiser, R. L.; Tsai, Y.-M.; Fink, D. M. *Org. Synth.*, submitted for publication.

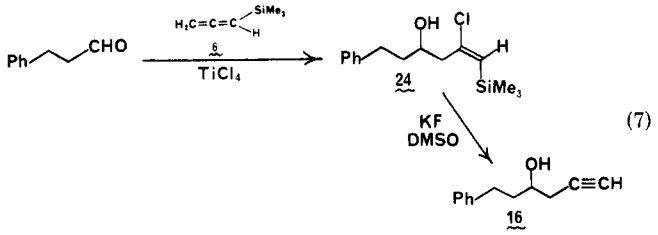
Table I. Regiocontrolled Synthesis of Homopropargylic Alcohols

entry	carbonyl compound	allenylsilane	method[a]	product(s)	% yield[b,c]
1	cyclohexanecarboxaldehyde	2	A	 **10**[d]	68
2	$PhCH_2CH_2CHO$	2	A	 **11**	85
3	*i*-$PrCOCH_3$	2	A	 **12**	86
4	$PhCH_2CH_2CHO$	3	A	 **13**	89
5	cyclohexanone	3	A	 **14**	84
6	*i*-$PrCOCH_3$	3	A	 **15**	51
7	$PhCH_2CH_2CHO$	6	B	 **16**[e]	84
8	$PhCH_2COCH_3$	6	B	 **17**	72
9	cyclohexanone	6	B	 **18**[f]	89
10	CH_3COCH_3	7	B	 **19**	38
11	cyclohexanone	7	B	 **20**	49
12	$PhCH_2CH_2CHO$	9	B	 **21a**[g]  **21b**[g]	89 (3.1:1)
13	cyclohexanecarboxaldehyde	9	B	 **22a**  **22b**	81 (4.1:1)
14	cyclohexanone	9	B	 **23**	77

[a] Method A: reaction of carbonyl compound with 1.1–1.5 equiv each of allene and $TiCl_4$ in CH_2Cl_2 at −78 °C or −78 → 25 °C (for details see text). Method B: reaction as in method A, then treatment with 2.0–2.5 equiv of KF in Me_2SO (25 °C, 4–24 h). [b] Isolated yields of compounds purified by distillation, recrystallization, or chromatography. [c] Ratios were determined by gas chromatographic analysis. [d] Reference 11. [e] Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, *5*, 621. [f] Lauger, P.; Prost, M.; Charlier, R. *Helv. Chim. Acta* **1959**, *42*, 2379. [g] Widler, L.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1085.

the Reaction. Table I delineates the scope of the regiocontrolled synthesis of homopropargylic alcohols via allenylsilanes. A typical procedure for the reaction of 1-substituted allenylsilanes (e.g., **2** and **3**) involves the addition of 1.1 equiv of the allene to a methylene chloride solution of the preformed complex of carbonyl compound and titanium tetrachloride at −78 °C. These reactions lead directly to the formation of the desired homopropargylic alcohols. While aldehydes generally undergo reaction at −78 °C, additions to ketones often require warming to 0 °C or room temperature for complete reaction; in these cases it is also advisable to employ excess (1.5 equiv) Lewis acid. In no case have we detected the formation of isomeric allenic alcohols as byproducts.

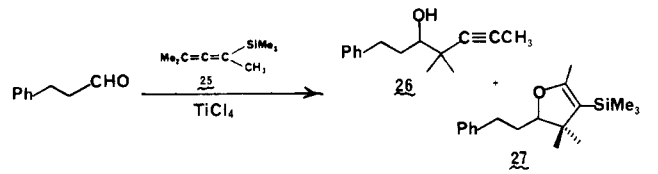
In contrast to the behavior of allenylsilanes **2** and **3**, allenes lacking alkyl substituents at C-1 follow a different course in their reactions with carbonyl compounds. For example, addition of (trimethylsilyl)allene (**6**) to hydrocinnamaldehyde (CH_2Cl_2, −78 °C, 1 h) gave a mixture of the desired homopropargylic alcohol **16** and (predominantly) the (*E*)-(trimethylsilyl)vinyl chloride derivative **24**. Fortunately, the unexpected product could be easily transformed to the desired acetylene by employing the method of Cunico and Dexheimer.[22] Thus, exposure of



(7)

the crude mixture of allenylsilane adducts to 2.5 equiv of potassium fluoride in Me_2SO at 25 °C for 4 h furnished the homopropargylic alcohol **16** in 84% overall yield. The facility of this elimination reaction also serves to confirm the stereochemistry assigned to **24**, since the corresponding (*Z*)-(trimethylsilyl)vinyl chloride would be inert to the action of fluoride ion under these conditions.[22]

One significant limitation of this methodology has been identified: 3,3-disubstituted allenylsilanes react with carbonyl compounds to produce mixtures of the desired homopropargylic alcohols and 4,5-dihydrofurans. For example, addition of **25**[14b] to hydrocinnamaldehyde gave the acetylene **26** and the dihydrofuran annulation product **27** in 27% and 54% yield, respectively. Cleavage of **27** to **26** with fluoride could not be accomplished under a variety of conditions. The mechanistic implications of this observation are considered in detail in the discussion section of this paper.

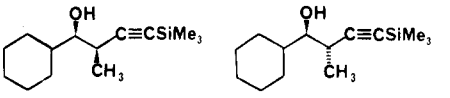


(8)

Synthesis of Homopropargylic Alcohols: Stereochemical Course of the Reaction. Reactions of aldehydes with the chiral allenylsilane **9** proceed with modest diastereoselection to generate predominantly syn ("erythro") homopropargylic alcohols. For example, addition of **9** to hydrocinnamaldehyde under our usual conditions produced the expected acetylenic product in 89% yield as a 3.1:1 mixture of diastereomers. The identity of the major product as the syn isomer was established by chemical correlation with the previously reported acetonide derivative **31**.[23] As outlined in Scheme II, the diastereomeric homopropargylic alcohols were first converted to the corresponding (trimethylsilyl)acetylene derivatives **28a** and **28b** to facilitate chromatographic separation. Desilylation of the separated major isomer then gave a pure homopropargylic alcohol, which was transformed to an acetonide derivative via the four-step sequence summarized in Scheme II. Comparison of ^1H NMR data[23] established the structure of this compound as **31**. In a similar fashion, cyclohexanecarboxaldehyde combined with the chiral allene **9** to produce the syn and anti homopropargylic alcohols **22a** and **22b** in a 4.1:1 ratio (Table I, entry 13). ^1H NMR analysis of the trimethylsilyl derivatives (**32a** and **32b**) of these acetylenes[24] confirmed the assignment of syn stereochemistry to the major diastereomer.

Discussion

Scheme III outlines the general mechanistic course of the addition of (trimethylsilyl)allenes to carbonyl compounds. In the interest of clarity, this scheme presents the addition of an aldehyde to a simple 1-substituted allenylsilane as a representative example of the reaction. The initial step in the process most likely involves the regiospecific electrophilic substitution of an aldehyde–Lewis acid complex at C-3 of the allenylsilane;[25] the resulting vinyl cation A receives stabilization through hyperconjugative interaction with the adjacent carbon–silicon bond. Based on our earlier observations,[14] we propose that this intermediate cation is then subject to a rapid 1,2-trimethylsilyl shift[26,27] (even at −78 °C), thus establishing an equilibrium with an isomeric vinyl cation B. Desilylation of either A or B serves to generate the acetylenic product (D).



32a **32b**

The scheme outlined here can also accommodate the anomalous course of reactions involving allenylsilanes such as **6**, **7**, and **9** which lack 1-alkyl substituents. It will be recalled that the addition of these allenes to ketones and aldehydes leads to the formation of (trimethylsilyl)vinyl chloride products (C) as well as the usual homopropargylic alcohols. Apparently when R^2 = H in intermediate A, substitution by chloride ion can compete with desilylation, resulting in the formation of product C. This is not the case when R^2 = alkyl: strong nonbonded steric interactions hinder attack of chloride on both intermediate cations A (repulsion by R^2) and B (repulsion by $-CH_2C(OTiL_n)R'$).

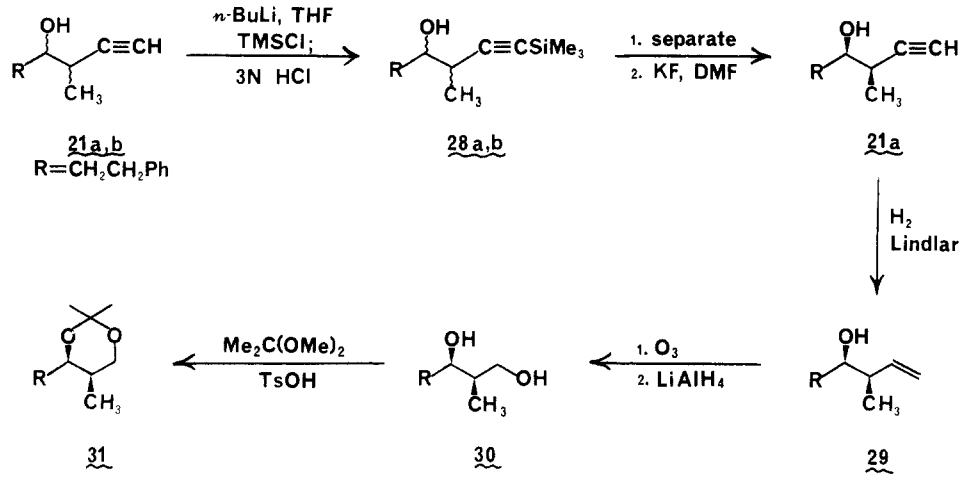
Alternative explanations for the absence of type C products when R^2 = alkyl can be formulated within the context of Scheme III. For example, it is conceivable that if formed, tetrasubstituted vinyl chlorides (i.e., product C with R^2 = alkyl) undergo very rapid elimination of Me_3SiCl in order to relieve steric congestion. Althernatively, desilylation of B (or a derived vinyl chloride) to the acetylene D may take place with the assistance of the titanium alkoxide moiety as nucleophile. Note that the trimethylsilyl group is accessible to the titanium alkoxy group (or associated chloride ion) in intermediate B but not in intermediate A. This internal desilylation pathway would therefore be mose likely when R^2 = alkyl, since when R^2 = H the *secondary* vinyl cation A predominates over the *primary* carbocation B.

Scheme III also accounts for the formation of the dihydrofuran product from the reaction of hydrocinnamaldehyde with 1,3,3-trimethyl-1-(trimethylsilyl)allene (**25**). In this case steric hindrance by the methyl groups derived from C-3 of the allene retards the rate of desilylation, permitting cyclization to the oxygen heterocycle to take place as well. In support of this hypothesis we have found that these reactions can be directed to produce exclusively the dihydrofuran annulation products simply by employing allenylsilanes that incorporate bulky trialkylsilyl groups.[14d]

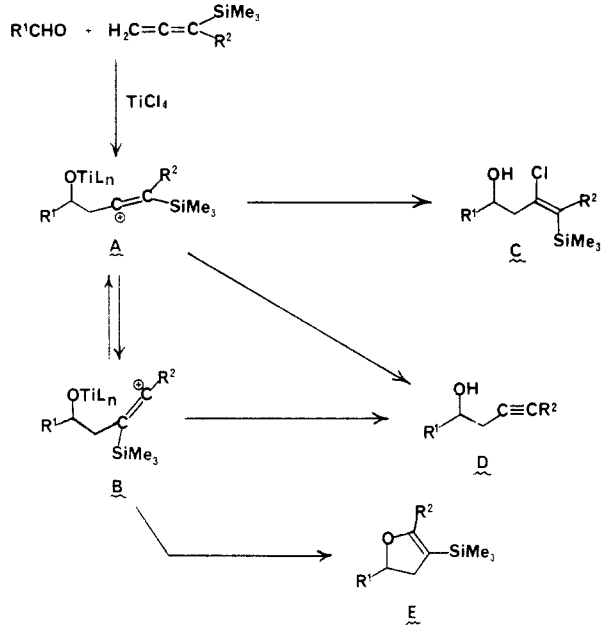
As detailed in the results section, achiral aldehydes combine with the chiral allenylsilane 3-methyl-1-(tri-

(22) Cunico, R. F.; Dexheimer, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 2868.
(23) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641.
(24) We thank Professor Hisashi Yamamoto for furnishing us with spectroscopic and gas chromatographic data for the homopropargylic alcohols **32a** and **32b**.
(25) For other examples of electrophilic substitution reactions involving allenylsilanes, see ref 14, 15, and: (a) Bourgeois, P. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1974**, *278*, 969. (b) Bourgeois, P.; Calas, R.; Merault, G. *J. Organomet. Chem.* **1977**, *141*, 23. (c) Jellal, A.; Santelli, M. *Tetrahedron Lett.* **1980**, *21*, 4487. (d) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153.
(26) For a review of 1,2-cationic rearrangements in organosilicon compounds, see: Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. II, pp 190–192.
(27) For a review of migration across the double bond of vinyl cations, see: Stang, P. J.; Rappaport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*; Academic Press: New York, 1979; pp 459–483.

Scheme II



Scheme III



methylsilyl)allene to yield predominantly syn (erythro) homopropargylic alcohols. The stereochemical outcome of these reactions can be rationalized on the basis of either of two alternative transition-state models. Hayashi and Kumada have proposed that the transition-state geometry for the addition of β-substituted allylsilanes to aldehydes involves an antiperiplanar orientation of the reacting double bonds.[28] This process generates mainly syn homoallylic alcohols and mechanistically is closely related to our allenylsilane substitution reactions. Scheme IV compares the two alternative antiperiplanar transition-state structures for the addition of the chiral allene **9** to an aldehyde.[29] In this model steric repulsion between the allene methyl and aldehyde R groups destabilizes transition state **34**, and consequently **33** (leading to the syn product) is predicted to be favored.

Denmark and Weber have recently provided evidence that aldehyde–allylsilane condensations can (at least in certain intramolecular cases) proceed via transition-state structures involving an alternative *synclinal* orientation of double bonds.[30] Scheme V compares the synclinal geometries for our allenylsilane substitution reactions. In this case the predominant formation of syn homopropargylic alcohol diastereomers would be predicted provided that the dominant steric interaction in these structures is the steric repulsion between the allene methyl group and the Lewis acid which is complexed to the aldehyde carbonyl.[31] At this time our data unfortunately does not allow us to distinguish between these two alternative transition-state geometries.

Summary

The $TiCl_4$-promoted addition of allenylsilanes to aldehydes and ketones provides a general, regiocontrolled synthetic route to homopropargylic alcohols of a variety of substitution types. Reactions involving chiral allenes proceed with a preference for the formation of the syn (erythro) diastereomers, complementing the reactions of other propargylic anion equivalents which combine with aldehydes to generate mainly anti (threo) homopropargylic alcohols.[3,9b,11]

Experimental Section

Instrumentation. Infrared (IR) spectra were obtained on Perkin-Elmer 283B and 397 grating spectrophotometers. ^1H NMR spectra were measured with Varian T-60 (60 MHz) and Bruker WM-250 (250 MHz) spectrometers. ^{13}C NMR spectra were determined on JEOL FX-90Q (22.5 MHz) and Bruker WM-270 (67.9 MHz) spectrometers. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as an internal standard. Low resolution mass spectra (MS) were measured with Varian MAT 44 and Finnegan MAT 8200 instruments; high resolution mass spectra (HRMS) were determined on a Finnegan MAT 8200 spectrometer. Gas chromatography was performed on a Hewlett-Packard 5790 instrument. Ozonolyses were conducted by using a Welsbach T-23 ozonator. Elemental analyses were performed by Robertson Laboratory, Inc., of Florham Park, NJ. Melting points and boiling points are uncorrected.

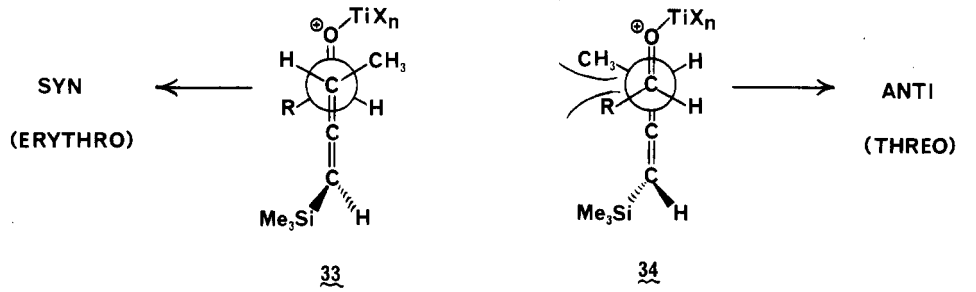
(28) (a) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963.

(29) Several recent studies support our assumption of an anti alignment of the new C–C bond and breaking C–Si bond in this S_E2' reaction. For example, see ref 25d and: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962. (b) Wetter, H.; Scherer, P. *Helv. Chim. Acta* **1983**, *66*, 118. (c) Young, D.; Kitching, W.; Wickham, G. *Tetrahedron Lett.* **1983**, *24*, 5789 and references cited therein.

(30) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655. For a related study on the stereochemical course of allylstannane–aldehyde condensations, see: Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.

(31) Denmark and co-workers have invoked similar arguments to rationalize the stereochemical course of related allylmetal–aldehyde condensations: S. E. Denmark, private communication.

Scheme IV



33 34

Scheme V

35 36

Materials. Methylene chloride, triethylamine, chlorotrimethylsilane, dimethylformamide, tetramethylpiperidine, and dimethyl sulfoxide were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Titanium tetrachloride, methanesulfonyl chloride, and all aldehydes and ketones were distilled before use. Potassium fluoride was dried at 100 °C (0.1 mmHg) for 15 h.

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Büchi rotary evaporator at 15–20 mmHg. Column chromatography was performed on E. Merck silica gel 60 (230–400 mesh). Hexane was distilled prior to use as an eluant. Preparative radial thin-layer chromatography was carried out by employing a Harrison Research Inc. Chromatotron on plates coated with E. Merck PF-254 silica gel 60 ($CaSO_4 \cdot {}^1/_2H_2O$ binder).

3-Methyl-1-(trimethylsilyl)allene (9). To a solution of 2,2,6,6-tetramethylpiperidine (25.9 g, 0.183 mmol) in 110 mL of THF at 0 °C was added *n*-butyllithium solution (2.62 M in hexane, 70 mL, 183 mmol) dropwise over 30 min. The reaction mixture was stirred for 10 min at 0 °C, cooled to −78 °C, and then transferred over 1 h via cannula into a solution of 1,2-butadiene (9.9 g, 183 mmol) in 285 mL of THF at −78 °C (the rate of addition was controlled so that the internal temperature remained below −75 °C). The resulting mixture was stirred at −78 °C for 3 h and then treated dropwise over 45 min with a solution of chlorotrimethylsilane (20.9 g, 192 mmol) in 25 mL of THF. The resulting solution was allowed to warm to room temperature over 12 h and was then poured into an ice-cold mixture of pentane and 1 M aqueous HCl. The organic phase was separated and washed with ten 500-mL portions of water, dried over $MgSO_4$, filtered, and concentrated by atmospheric distillation through a 29-cm Vigreux column. Spinning-band distillation of the residual liquid provided 9.50 g (41%) of **9** as a colorless oil: bp 107–110 °C; IR (film) 2970, 2910, 2880, 1945, 1370, 1250, 1200, 850, 765, 700, and 645 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.60 (dd, 3 H, J = 4.0, 7.0 Hz), 4.70 (dq, 1 H, J = 7.0, 7.0 Hz), 4.84 (dq, 1 H, J = 4.0, 7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 211.1, 81.9, 77.7, 13.1, −1.0; MS, m/e 126 (M^+).

General Procedure for the Synthesis of Homopropargylic Alcohols: Method A. 1-Cyclohexyl-3-pentyn-1-ol (10). A solution of cyclohexanecarboxaldehyde (1.35 g, 12.0 mmol) and titanium tetrachloride (2.50 g, 13.2 mmol) in 50 mL of methylene chloride was stirred for 10 min at −78 °C and then treated dropwise over 4 min with 1-methyl-1-(trimethylsilyl)allene (1.82 g, ca. 93% purity, 13.4 mmol). The resulting clear, burgundy-colored solution was stirred at −78 °C for 2 h and then poured into a rapidly stirred mixture of 225 mL of ether and 225 mL of 3 N HCl. The resulting mixture was vigorously stirred for 20 min, and the aqueous phase was then separated and extracted with three 100-mL portions of ether. The combined organic phases were washed with 200 mL of saturated $NaHCO_3$ solution and 200 mL of saturated NaCl solution, dried over Na_2SO_4, and filtered through anhydrous magnesium sulfate. Triethylamine (5 mL) was added, and the methylene chloride and ether solvents were removed by rotary evaporation at 20 mmHg to give 3.6 g of a mixture of **10** and Et_3N as a yellow oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) followed by Kugelrohr distillation (oven temperature 125 °C, 41 mmHg) furnished 1.36 g (68%) of 1-cyclohexyl-3-pentyn-1-ol (**10**) as a colorless oil which crystallized upon standing: mp 53–54 °C; IR (film) 3430, 2930, 2860, 1450, 1260, 1200, 1080, 1030, 980, 885, 830 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91–1.93 (m, 11 H), 1.81 (t, 3 H, J = 2.6 Hz), 2.08 (br s, 1 H), 2.17–2.45 (m, 2 H), 3.38–3.45 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 78.1, 75.6, 74.2, 42.5, 29.0, 28.2, 26.4, 26.1, 26.0, 24.9, 3.4; MS, m/e 166 (M^+).

For reactions involving $\lesssim$1 g of carbonyl compounds the following isolation procedure was employed (see text for discussion): the cold reaction mixture was diluted with aqueous sodium bicarbonate solution, allowed to warm to ca. 0 °C, and then extracted with methylene chloride. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated.

1-Phenyl-5-heptyn-3-ol (11). Reaction of 3-phenylpropionaldehyde (0.067 g, 0.50 mmol) with titanium tetrachloride (0.105 g, 0.55 mmol) and 1-methyl-1-(trimethylsilyl)allene (0.076 g, ca. 93% purity, 0.56 mmol) in 2 mL of methylene chloride at −78 °C for 1 h according to general procedure A gave 0.146 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) furnished 0.080 g (85%) of 1-phenyl-5-heptyn-3-ol (**11**) as a colorless oil: IR (film) 3400, 3080, 3060, 3030, 2920, 2860, 1605, 1495, 1455, 1050, 1030, 745, 695 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.6–1.9 (m, 5 H), 1.95–2.05 (m, 1 H), 2.15–2.45 (m, 2 H), 2.55–2.9 (m, 2 H), 3.65 (quin, 1 H, J = 7 Hz), 7.12 (br s, 5 H); MS, m/e 188 (M^+).

2,3-Dimethyl-5-heptyn-3-ol (12). Reaction of 3-methyl-2-butanone (0.043 g, 0.50 mmol) with titanium tetrachloride (0.143 g, 0.75 mmol) and 1-methyl-1-(trimethylsilyl)allene (0.076 g, ca. 93% purity, 0.56 mmol) in 2 mL of methylene chloride at −78 °C to 25 °C over 1 h and then at 25 °C for 0.5 h according to general procedure A furnished 0.120 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) yielded 0.060 g (86%) of 2,3-dimethyl-5-heptyn-3-ol (**12**) as a colorless oil: IR (film) 3460, 2965, 2920, 2880, 1465, 1450, 1385, 1370, 1140, 1085, 1035, 930, and 850 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz), 1.12 (s, 3 H), 1.6–2.1 (m, 5 H), 2.30 (q, 2 H, J = 2 Hz); MS, m/e 125 ($M^+ - 15$).

7-Methyl-1-phenyl-5-octyn-3-ol (13). Reaction of 3-

phenylpropionaldehyde (0.067 g, 0.50 mmol) with titanium tetrachloride (0.100 g, 0.53 mmol) and 1-isopropyl-1-(trimethylsilyl)allene (0.085 g, 0.55 mmol) in 2 mL of methylene chloride at −78 °C for 1 h according to general procedure A gave 0.116 g of a yellow oil. Preparative thin-layer chromatography on silica gel (elution with tetrahydrofuran–hexane) afforded 0.096 g (89%) of 7-methyl-1-phenyl-5-octyn-3-ol (**13**) as a colorless oil: IR (film) 3390, 3085, 3065, 3030, 2970, 2930, 2875, 1605, 1500, 1455, 1385, 1365, 1320, 1080, 1055, 1030, 930, 850, 745, 695 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.18 (d, 6 H, J = 7 Hz), 1.6–2.2 (m, 2 H), 2.2–2.45 (m, 4 H), 2.5–3.0 (m, 2 H), 3.74 (quin, 1 H, J = 6 Hz), 7.30 (s, 5 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 141.8, 128.3, 125.7, 89.0, 75.0, 69.3, 37.7, 31.8, 27.7, 23.2, 20.4; MS, m/e 198 (M^+ − 18).

1-(4-Methyl-2-pentynyl)-1-cyclohexanol (14). Reaction of cyclohexanone (0.049 g, 0.50 mmol) with titanium tetrachloride (0.143 g, 0.75 mmol) and 1-isopropyl-1-(trimethylsilyl)allene (0.085 g, 0.55 mmol) in 2 mL of methylene chloride at −78 °C for 2 h and then at −78 °C to 25 °C over 2 h according to general procedure A furnished 0.102 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) yielded 0.076 g (84%) of 1-(4-methyl-2-pentynyl)-1-cyclohexanol (**14**) as a colorless oil: IR (film) 3430, 2965, 2935, 2860, 1465, 1450, 1380, 1360, 1350, 1320, 1265, 1250, 1170, 1150, 1075, 1060, 1035, 980, 960, 920, 910, 870, 850, 830, 730 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.18 (d, 6 H, J = 7 Hz), 1.56 (br s, 10 H), 1.90 (s, 1 H), 2.33 (d, 2 H, J = 2 Hz), 2.3–2.9 (m, 1 H); MS, m/e 165 (M^+ − 15).

2,3,7-Trimethyl-5-octyn-3-ol (15). Reaction of 3-methyl-2-butanone (0.043 g, 0.50 mmol) with titanium tetrachloride (0.143 g, 0.75 mmol) and 1-isopropyl-1-(trimethylsilyl)allene (0.085 g, 0.55 mmol) in 2 mL of methylene chloride at −78 °C to 0 °C over 1.5 h and then at 0 °C for 1 h according to general procedure A furnished 0.081 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) provided 0.043 g (51%) of 2,3,7-trimethyl-5-octyn-3-ol (**15**) as a colorless oil: IR (film) 3450, 3220, 2970, 2940, 2880, 1465, 1385, 1320, 1190, 1090, 1035, 930, and 845 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.88 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.17 (d, 6 H, J = 7 Hz), 1.5–2.0 (m, 2 H), 2.2–2.8 (m, 3 H); MS, m/e 125 (M^+ − 43).

General Procedure for the Synthesis of Homopropargylic Alcohols: Method B. 1-Phenyl-5-hexyn-2-ol (16). A solution of 3-phenylpropionaldehyde (1.01 g, 7.50 mmol) and titanium tetrachloride (1.57 g, 8.25 mmol) in 30 mL of methylene chloride was stirred at −78 °C for 5 min and then treated over 1 min with (trimethylsilyl)allene (1.01 g, 9.0 mmol). After 1 h at −78 °C, the dark red mixture was diluted with aqueous sodium bicarbonate solution, allowed to warm to ca. 0 °C, and extracted with methylene chloride. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 2.08 g of a yellow oil. A solution of this material and anhydrous potassium fluoride (1.10 g, 18.4 mmol) in 25 mL of dimethyl sulfoxide was stirred at 25 °C for 4 h, then diluted with water, and extracted with ether. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography on silica gel (elution with ethyl acetate–hexane) yielded 1.10 g (84%) of 1-phenyl-5-hexyn-3-ol (**16**) as a colorless oil: IR (film) 3545, 3400, 3295, 3080, 3060, 3025, 2930, 2860, 2120, 1600, 1495, 1455, 1075, 1050, 1030, 745, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.78–1.87 (m, 2 H), 2.02 (t, 1 H, J = 2.7 Hz), 2.34 (dd, J = 2.7, 6.2 Hz, 2 H), 2.58–2.83 (m, 3 H), 3.72 (br quin, 1 H, J = 6.2 Hz), 7.11–7.28 (m, 5 H); MS, m/e 156 (M^+ − 18).

2-Methyl-1-phenyl-4-pentyn-2-ol (17). Reaction of 1-phenyl-2-propanone (0.067 g, 0.50 mmol) with titanium tetrachloride (0.143 g, 0.75 mmol) and (trimethylsilyl)allene (0.084 g, 0.75 mmol) in 2 mL of methylene chloride at −78 °C for 2 h according to general procedure B gave 0.131 g of a yellow oil. Subsequent reaction of this material with anhydrous potassium fluoride (0.067 g, 1.16 mmol) in 1.5 mL of Me_2SO at 25 °C for 15 h then afforded 0.093 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) furnished 0.063 g (72%) of 2-methyl-1-phenyl-4-pentyn-2-ol (**17**) as a colorless oil: IR (film) 3545, 3450, 3290, 3085, 3060, 3030, 2975, 2925, 2120, 1600, 1495, 1450, 1375, 1360, 1280, 1250, 1210, 1150, 1110, 1095, 1030, 955, 935, 890, 780, 725, 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (s, 3 H), 1.88 (br s, 1 H), 2.10 (t, 1 H, J = 2.5 Hz), 2.28 (d, 2 H, J = 2.5 Hz), 2.87 (s, 2 H), 7.30 (s, 5 H); MS, m/e 174 (M^+).

1-(2-Propynyl)-1-cyclohexanol (18). Reaction of cyclohexanone (0.098 g, 1.00 mmol) with titanium tetrachloride (0.285 g, 1.50 mmol) and (trimethylsilyl)allene (0.168 g, 1.50 mmol) in 4 mL of methylene chloride at −78 °C to 25 °C over 2 h according to general procedure B furnished 0.256 g of a yellow oil. Further reaction of this material and anhydrous potassium fluoride (0.150 g, 2.60 mmol) in 3 mL of Me_2SO at 25 °C for 16 h then afforded 0.180 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) provided 0.124 g (89%) of 1-(2-propynyl)-1-cyclohexanol (**18**) as a colorless oil: IR (film) 3430, 3305, 2930, 2860, 2115, 1445, 1265, 1170, 1150, 1075, 1060, 1035, 975, 940, 870 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.55 (br s, 10 H), 1.98 (s, 1 H), 2.06 (t, 1 H, J = 2.5 Hz), 2.35 (d, 2 H, J = 2.5 Hz); MS, m/e 99 (M^+ − 39).

2-Methyl-3-(2-phenylethyl)-4-pentyn-2-ol (19). To a solution of acetone (0.054 g, 0.93 mmol) and 1-(2-phenylethyl)-3-(trimethylsilyl)allene (0.184 g, 0.85 mmol) in 3.5 mL of methylene chloride at −78 °C was added titanium tetrachloride (0.241 g, 1.27 mmol), and the resulting mixture was stirred at −78 °C for 0.5 h and then allowed to warm to 0 °C over 1.5 h. Isolation according to general procedure B gave 0.176 g of a brown oil. Subsequent reaction of this material and anhydrous potassium fluoride (0.093 g, 1.60 mmol) in 2 mL of Me_2SO at 25 °C for 14 h provided 0.147 g of a brown oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) afforded 0.065 g (38%) of 2-methyl-3-(2-phenylethyl)-4-pentyn-2-ol (**19**) as a colorless oil: IR (film) 3550, 3425, 3300, 3085, 3060, 3025, 2975, 2930, 2865, 2110, 1605, 1500, 1455, 1375, 1345, 1155, 1125, 1030, 915, 825, 770, 750, 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 1.7–3.1 (m, 7 H), 7.17 (br s, 5 H); MS, m/e 169 (M^+ − 33).

1-[1-(2-Phenylethyl)-2-propynyl]-1-cyclohexanol (20). To a solution of cyclohexanone (0.098 g, 1.0 mmol) and 1-(2-phenylethyl)-3-(trimethylsilyl)allene (0.216 g, 1.0 mmol) in 4 mL of methylene chloride at −78 °C was added titanium tetrachloride (0.285 g, 1.5 mmol), and the resulting mixture was then allowed to warm to 25 °C over 2 h. Isolation according to general procedure B gave 0.331 g of a brown oil. Further reaction of this material with anhydrous potassium fluoride (0.137 g, 2.35 mmol) in 3 mL of Me_2SO at 25 °C for 16 h furnished 0.276 g of a yellow oil. Column chromatography on silica gel (elution with tetrahydrofuran–hexane) provided 0.119 g (49%) of the homopropargylic alcohol **20** as a colorless oil: IR (film) 3560, 3460, 3300, 3085, 3060, 3025, 2935, 2860, 2110, 1605, 1500, 1450, 1380, 1350, 1260, 1150, 1030, 970, 745, 695 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.2–2.1 (m, 12 H), 2.2–2.55 (m, 3 H), 2.65–3.2 (m, 2 H), 7.10 (br s, 5 H); MS, m/e 242 (M^+).

4-Methyl-1-phenyl-5-hexyn-3-ol (21). Reaction of 3-phenylpropionaldehyde (0.214 g, 1.59 mmol) with titanium tetrachloride (0.332 g, 1.75 mmol) and 3-methyl-1-(trimethylsilyl)-allene (0.241 g, 1.91 mmol) in 8 mL of methylene chloride at −78 °C for 25 min according to general procedure B gave 0.459 g of a yellow oil. Further reaction of this material with anhydrous potassium fluoride (0.739 g, 12.7 mmol) in 8 mL of Me_2SO at 25 °C for 10 h provided 0.313 g of a yellow oil. Gas chromatographic analysis (12.5 m × 0.2 mm crosslinked dimethyl silicone fused silica capillary column; program, 125 °C for 3 min and then 125–300 °C at 15°/min) indicated that this material consisted of a 3.1:1 mixture of syn and anti diastereomers. A portion of this material (0.294 g) was purified by preparative radial thin layer chromatography on silica gel (elution with ethyl acetate–hexane) followed by Kugelrohr distillation to yield 0.253 g (90%) of **21**: bp oven temp 120 °C (11 mmHg); IR (film) 3430, 3300, 3090, 3070, 3030, 2980, 2940, 2110, 1605, 1500, 1455, 1380, 1090, 1040, 945, 750, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, 3 H, J = 6.9 Hz, syn isomer), 1.23 (d, 3 H, J = 7.1 Hz, anti isomer), 1.74–2.00 (m, 3 H), 2.12 (d, 1 H, J = 2.4 Hz, syn isomer), 2.15 (d, 1 H, J = 2.4 Hz, anti isomer), 2.52–2.76 (m, 2 H), 2.79–2.95 (m, 1 H), 3.44–3.48 (m, 1 H, anti isomer), 3.57–3.61 (m, 1 H, syn isomer), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 141.8, 128.4, 125.8, 85.9, 73.4, 70.5, 35.1, 32.8, 32.1, 15.8; in addition, peaks for the anti diastereomer were observed at 71.1, 36.8, 32.9, 17.3; MS, m/e 170 (M^+ − 18). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.62; H, 8.48.

4-Methyl-1-phenyl-6-(trimethylsilyl)-5-hexyn-3-ol (28). To a solution of the mixture of diastereomeric homopropargylic

alcohols **21a** and **21b** (0.181 g, 0.961 mmol) in 5 mL of THF at −78 °C was added *n*-butyllithium solution (2.44 M in hexane, 0.98 mL, 2.40 mmol) in one portion. After 30 min, the reaction mixture was treated with chlorotrimethylsilane (0.261 g, 2.40 mmol) in one portion, stirred at −78 °C for 0.5 h, and then allowed to warm to 25 °C over 0.5 h. Hydrochloric acid (3 N, 30 mL) was then added, and the resulting solution was stirred at room temperature for 1.5 h and then diluted with ether. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.259 g of a pale yellow oil. Partial separation of the diastereomeric alcohols was accomplished by using preparative radial thin-layer chromatography on silica gel (elution with ethyl acetate–hexane), which provided 0.046 g of the anti diastereomer, 0.141 g of the syn diastereomer, and 0.044 g of a 2.6:1 syn:anti mixture of isomers (92% combined yield). Anti diastereomer: IR (film) 3440, 3100, 3070, 3040, 2970, 2910, 2170, 1610, 1500, 1460, 1410, 1375, 1250, 1130, 1050, 1000, 920, 845, 760, 700, 650, 635 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.19 (d, 3 H, J = 6.9 Hz), 1.79–1.89 (m, 3 H), 2.56 (dq, 1 H, J = 6.9, 4.9 Hz), 2.64–2.90 (m, 2 H), 3.41 (br s, 1 H), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.0, 128.4, 125.8, 107.5, 87.7, 73.5, 36.7, 34.4, 32.1, 17.3, 0.1. Syn diastereomer: IR (film) 3400, 3100, 3070, 3040, 2970, 2910, 2170, 1610, 1500, 1460, 1410, 1380, 1250, 1050, 965, 920, 845, 760, 700, 650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.16 (d, 3 H, J = 7.0 Hz), 1.73–1.95 (m, 3 H), 2.56–2.74 (m, 2 H), 2.83–2.94 (m, 1 H), 3.53–3.59 (m, 1 H), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.0, 128.4, 128.3, 125.8, 108.6, 86.8, 73.4, 35.3, 34.0, 32.0, 15.8, 0.1.

4-Methyl-1-phenyl-5-hexen-3-ol (29). A solution of *syn*-(trimethylsilyl)homopropargylic alcohol **28a** (0.209 g, 0.802 mmol) and ca. 0.5 g of potassium fluoride dihydrate in 5 mL of DMF was stirred at 25 °C for 13 h and then diluted with 35 mL of ether and 35 mL of water. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with water and saturated NaCl solution, dried over Na_2SO_4, filtered, and concetrated to yield 0.160 g of **21a** as a pale yellow oil used in the next step without purification.

A solution of 0.160 g of **21a** and 0.020 g of Lindlar catalyst ($Pd/CaCO_3/PbO$) in 10 mL of ethyl acetate was stirred under 1 atm of H_2 at room temperature for 1 h. Filtration and concentration of the reaction mixture gave 0.201 g of a pale yellow oil. Preparative radial thin-layer chromatography on silica gel (elution with ethyl acetate–hexane) furnished 0.143 g (93%) of 4-methyl-1-phenyl-5-hexen-3-ol (**29**) as a colorless oil: IR (film) 3400, 3095, 3075, 3040, 2980, 2940, 2885, 1645, 1610, 1500, 1460, 1420, 1385, 1255, 1160, 1040, 1000, 915, 750, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (d, 3 H, J = 6.8 Hz), 1.50 (br s, 1 H), 1.60–1.89 (m, 2 H), 2.26–2.34 (m, 1 H), 2.58–2.70 (m, 1 H), 2.80–2.92 (m, 1 H), 3.48–3.55 (m, 1 H), 5.04–5.13 (m, 2 H), 5.77 (ddd, 1 H, J = 7.5, 9.9, 17.6 Hz), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.2, 140.7, 128.4, 125.8, 115.5, 74.1, 43.7, 35.8, 32.4, 14.3; MS, m/e 134 ($M^+ - C_4H_7$); HRMS, m/e calcd for $C_9H_{11}O$ ($M^+ - C_4H_7$) 135.0810, found 135.0802.

2-Methyl-5-phenyl-1,3-pentanediol (30). A mixture of ozone and oxygen (ca. 0.9 mmol) was bubbled through a solution of the alkene **29** (0.046 g, 0.24 mmol) in 8 mL of THF at −78 °C for 1 min, and the resulting blue solution was then purged with oxygen for 10 min. Dimethyl sulfide (1.5 mL) was then added, and the reaction mixture was allowed to warm to room temperature over 0.5 h and then concentrated at reduced pressure. The residual liquid was dissolved in 8 mL of THF, cooled to 0 °C, and then treated with lithium aluminum hydride (0.100 g, 2.6 mmol). After being warmed to 25 °C over 0.5 h, the reaction mixture was recooled to 0 °C, carefully treated with water and 10% HCl solution, and then diluted with ether. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with water and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.046 g of a yellow oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) provided 0.037 g (79%) of 2-methyl-5-phenyl-1,3-pentanediol (**30**) as a colorless oil: IR (film) 3325, 3070, 3020, 2950, 2930, 2860, 1600, 1490, 1450, 1410, 1380, 1330, 1240, 1160, 1100, 1060, 1040, 990, 980, 930, 900, 805, 705, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (d, 3 H, J = 7.2 Hz), 1.66–1.89 (m, 3 H), 2.68 (s, 2 H), 2.58–2.70 (m, 1 H), 2.78–2.90 (m, 1 H), 3.69 (d, 2 H, J = 5.5 Hz), 3.82–3.88 (m, 1 H), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.1, 128.4, 125.8, 73.9, 67.0, 39.4, 35.8, 32.6, 10.3; MS, m/e 176 ($M^+ - H_2O$); HRMS, m/e calcd for $C_{12}H_{16}O$ ($M^+ - H_2O$) 176.1201, found 176.1207.

2,2,5-Trimethyl-4-(2-phenylethyl)-1,3-dioxane (31). A solution of the diol **30** (0.031 g, 0.16 mmol) and *p*-toluenesulfonic acid (0.002 g, 0.01 mmol) in 2.5 mL of 2,2-dimethoxypropane was stirred for 3 h at room temperature and then diluted with equal amounts of ether and 10% aqueous sodium hydroxide. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.037 g of a pale yellow oil. Preparative thin-layer chromatography (elution with ethyl acetate–hexane) yielded 0.028 g (76%) of the acetonide **31** as a colorless oil: IR (film) 3080, 3060, 3020, 2990, 2940, 2860, 1600, 1495, 1450, 1380, 1270, 1190, 1110, 1000, 930, 840, 740, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (d, 3 H, J = 6.9 Hz), 1.42 (s, 6 H), 1.51–1.69 (m, 2 H), 1.78–1.93 (m, 1 H), 2.52–2.64 (m, 1 H), 2.68–2.79 (m, 1 H), 3.57 (dd, 1 H, J = 1.0, 11.5 Hz), 3.87–3.93 (m, 1 H), 4.06 (dd, 1 H, J = 2.5, 11.5 Hz), 7.18–7.31 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 142.1, 128.5, 128.3, 125.8, 98.7, 70.4, 67.0, 34.6, 32.0, 31.6, 29.8, 19.2, 10.7; MS, m/e 234 (M^+); HRMS, m/e calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620, found 234.1620.

1-Cyclohexyl-2-methyl-3-butyn-1-ol (22). Reaction of cyclohexanecarboxaldehyde (0.204 g, 1.80 mmol) with titanium tetrachloride (0.376 g, 1.98 mmol) and 3-methyl-1-(trimethylsilyl)allene (0.314 g, 2.49 mmol) in 7.2 mL of methylene chloride at −78 °C for 15 min according to general procedure B gave 0.475 g of a yellow oil. Further reaction of this material with anhydrous potassium fluoride (0.302 g, 5.19 mmol) in 6.9 mL of Me_2SO at 25 °C for 12 h provided 0.321 g of a yellow oil. Gas chromatographic analysis (12.5 m × 0.2 mm crosslinked dimethyl silicone fused silica gel capillary column, 115 °C) indicated that this material consisted of a 4.1:1 mixture of syn and anti diastereomers. A portion of this material (0.216 g) was purified by column chromatography on silica gel (elution with tetrahydrofuran–hexane) to yield 0.163 g (81%) of a mixture of *syn*- and *anti*-1-cyclohexyl-2-methyl-3-butyn-1-ol (**22**) as a colorless oil which crystallized upon storage: mp 65–67 °C; IR (film) 3430, 3310, 2980, 2930, 2860, 2115, 1450, 1375, 1260, 1115, 1090, 1050, 1035, 975, 890, 630 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (d, 3 H, J = 6.8 Hz, syn isomer), 1.26 (d, 3 H, J = 7.1 Hz, anti isomer), 0.95–1.99 (m, 12 H), 2.11 (d, 1 H, J = 2.4 Hz), 2.59–2.76 (m, 1 H), 3.05–3.12 (m, 1 H, anti isomer), 3.33–3.39 (m, 1 H, syn isomer); ^{13}C (67.9 MHz, $CDCl_3$) syn isomer δ 87.0, 78.4, 69.9, 39.8, 29.6, 29.4, 27.5, 26.4, 26.2, 25.9, 15.0; in addition, peaks for the anti diastereomer were observed at 78.6, 70.9, 41.6, 28.3, 18.1; MS, m/e 123 ($M^+ - 43$). Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.53; H, 10.99.

1-Cyclohexyl-2-methyl-4-(trimethylsilyl)-3-butyn-1-ol (32). To a solution of a 4.1:1 mixture of syn and anti homopropargylic alcohols **22a** and **22b** (0.186 g, 1.12 mmol) in 6 mL of THF at −78 °C was added *n*-butyllithium solution (2.42 M in hexane, 2.93 mL, 2.24 mmol) in one portion. After 30 min, the reaction mixture was treated with chlorotrimethylsilane (0.243 g, 2.24 mmol) in one portion, maintained at −78 °C for 0.5 h, and then allowed to warm to room temperature. Aqueous HCl (10%) solution (50 mL) was added, and the resulting solution was stirred for 2 h and then diluted with ether. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.255 g of a yellow oil. Partial separation of the diastereomeric alcohols was achieved by using preparative radial thin-layer chromatography on silica gel (elution with ethyl acetate–hexane) providing 0.038 g of the anti diastereomer, 0.152 g of the syn diasteromer, and 0.028 g of a 7.5:1 (syn:anti) mixture of isomers (83% combined overall yield from cyclohexanecarboxaldehyde). Anti diastereomer: IR (film) 3460, 2940, 2860, 2170, 1455, 1390, 1375, 1350, 1250, 1190, 1105, 1055, 1000, 975, 935, 900, 860, 845, 760, 700, 640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 0.86–1.94 (m, 12 H), 1.21 (d, 3 H, J = 7.0 Hz), 2.74 (dq, 1 H, J = 4.6, 7.0 Hz), 3.07 (ddd, 1 H, J = 4.6, 7.0, 7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 107.9, 87.6, 78.5, 42.0, 31.3, 29.9, 28.0, 26.5, 26.4, 26.1, 18.1, 0.2. Syn diastereomer: IR (film) 3440, 2940, 2860, 2170, 1455, 1410, 1380, 1300, 1250, 1110, 1070, 990, 935, 900, 885, 845, 760, 700, 645 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)

δ 0.15 (s, 9 H), 0.97-2.00 (m, 12 H), 1.16 (d, 3 H, J = 6.8 Hz), 2.61-2.72 (m, 1 H), 3.33 (br s, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 109.6, 86.2, 78.0, 40.1, 30.8, 29.6, 27.7, 26.4, 26.3, 26.0, 15.0, 0.1.

2-(3-Butynyl)-1-cyclohexanol (23). Reaction of cyclohexanone (0.097 g, 0.99 mmol) with titanium tetrachloride (0.206 g, 1.08 mmol) and 3-methyl-1-(trimethylsilyl)allene (0.172 g, 1.36 mmol) in 4 mL of methylene chloride at -78 °C for 1 h, -78 °C to 25 °C over 0.5 h, and at 25 °C for 1 h according to general procedure B gave 0.217 g of an orange oil. Subsequent reaction of this material with anhydrous potassium fluoride (0.145 g, 2.50 mmol) in 4 mL of Me_2SO at 25 °C for 14 h afforded 0.145 g of an orange oil. Column chromatography on silica gel (elution with tetrahydrofuran-hexane) furnished 0.116 g (77%) of 2-(3-butynyl)-1-cyclohexanol (**23**) as a colorless oil: IR (film) 3450, 3300, 2980, 2930, 2850, 2100, 1450, 1380, 1240, 1150, 1040, 1000, 960, 925, 900, 840, 760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (d, 3 H, J = 7.0 Hz), 1.14-1.73 (m, 11 H), 2.14 (d, 1 H, J = 2.4 Hz), 2.51 (dq, 1 H, J = 7.0, 2.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 86.2, 72.0, 70.9, 37.5, 35.1, 33.7, 25.7, 21.9, 21.8, 14.6; MS, m/e 109 (M^+ - 43). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.60. Found: C, 78.61; H, 10.42.

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Registry No. **2**, 74542-82-8; **3**, 71320-96-2; **6**, 14657-22-8; **7**, 74542-81-7; **8**, 590-19-2; **9**, 14583-74-5; **10**, 81435-37-2; **11**, 74542-86-2; **12**, 74542-85-1; **13**, 74542-87-3; **14**, 74552-19-5; **15**, 74552-18-4; **16**, 36185-09-8; **17**, 36185-12-3; **18**, 19135-08-1; **19**, 74542-84-0; **20**, 74552-17-3; **21a**, 103934-05-0; **21b**, 103934-12-9; **22a**, 103934-06-1; **22b**, 104051-34-5; **23**, 103934-07-2; **24**, 103934-08-3; **25**, 77494-37-2; **26**, 103934-09-4; **27**, 103934-10-7; **28a**, 103934-11-8; **28b**, 103934-13-0; **29**, 104011-57-6; **30**, 92945-17-0; **31**, 75643-02-6; **32a**, 81435-59-8; **32b**, 81435-48-5; cyclohexanecarboxaldehyde, 2043-61-0; 3-phenylpropionaldehyde, 104-53-0; 3-methyl-2-butanone, 563-80-4; cyclohexanone, 108-94-1; 1-phenyl-2-propanone, 103-79-7; acetone, 67-64-1.

New Methods of Formation of Meta-Substituted Aromatic Compounds

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The addition of organolithium reagents to the oxa tricyclic ketone 1 occurs stereospecifically to produce the corresponding tertiary carbinols **2a-d**. When the alcohols **2a-d** are treated with $TiCl_4$, ring fragmentation and dehydration occur to produce good yields of 5,6-dihydrobenzaldehydes **3a-d**. Oxidation of aldehydes **3a-d** then leads to the corresponding meta-substituted benzaldehydes **4a-d**. Alternatively, use of the Lewis acid Me_2BBr did not stop at the dihydrobenzaldehyde stage. Tautomerization of the diene aldehydes **3a-d** produced meta-substituted benzyl alcohols **7a-d** or benzyl bromides **8a-d** under prolonged reaction times. The addition of silica gel to the reactions accelerated the formation of the benzyl bromides.

The formation of strained bridged polycyclic ring systems may provide synthetically useful reactive synthons that may be induced to undergo selective ring-fragmentation reactions. The advantages of such processes can allow for flexibility in the placement of functional substituents as well as the control of stereochemical elements in accordance with the geometric contraints of small rings. The chemical literature contains numerous examples of this approach,[1] and of particular interest to us were tricyclic ring systems containing a highly strained cyclopropane unit.

We recently described[2] the synthesis and reactivity of the oxa tricyclic ketone **1**, conveniently prepared from commercially available sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (Scheme I). The cyclopropyl ring could be fragmented under mild-acid conditions to produce oxabicyclo[2.2.2]octanones. Among the reaction described with **1** was the stereospecific addition of organolithium agents to the ketone (from the less hindered face), to produce the corresponding tertiary alcohols **2**.

We undertook the reactivity study of these oxa tricyclic alcohols **2** employing acid catalysis to effect ring fragmentations. This paper describes the novel discovery that these alcohols undergo sequential cleavage of the cyclopropyl ring followed by regiospecific opening of the ether

Scheme I. Synthesis of Oxa Tricyclic Ketone

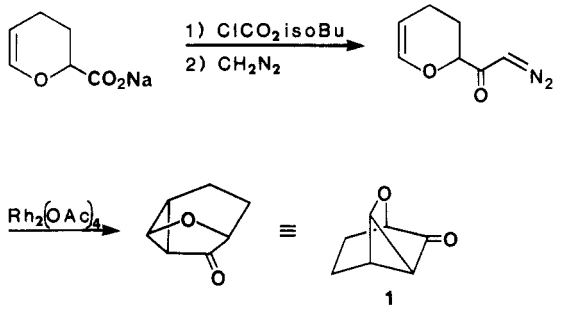
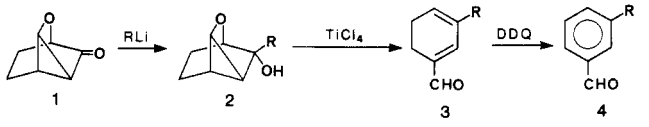


Table I



	R	% yield 2	3	4
a	Me	76	69[a,b]	30
b	*t*-Bu	73	100[b]	90[c]
c	Ph	79	100[d]	88
d	2-thienyl	80	62[a,d]	63[e]

[a] Diene aldehyde unstable. [b] 5 equiv of $TiCl_4$/1.1 equiv of Et_3N. [c] Reaction time 2 days. [d] 0.2 equiv of $TiCl_4$, no Et_3N. [e] Yield from oxatricyclanol **2d** without isolation of **3d**.

cycle to form cyclohexadiene aldehydes and meta-substituted benzaldehydes, benzyl alcohols, or benzyl bromides,

(1) An early example of this approach appears in Woodward's reserpine synthesis. The synthesis and stereochemistry of the E ring are controlled through strained policyclic ring formation and fragmentation: Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.
(2) Adams, J.; Belley M. *Tetrahedron Lett.* **1986**, *27*, 2075.

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