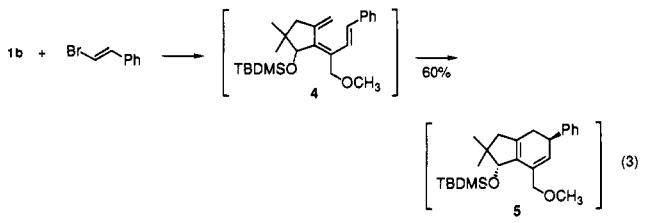
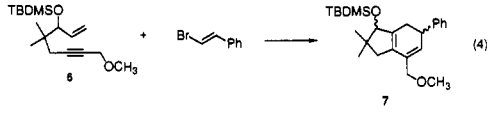
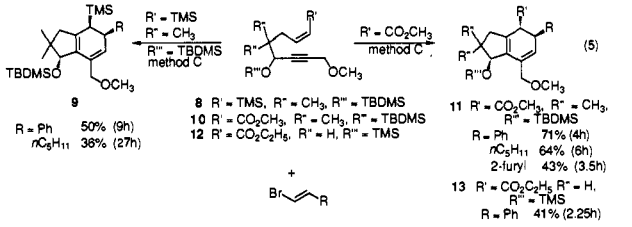


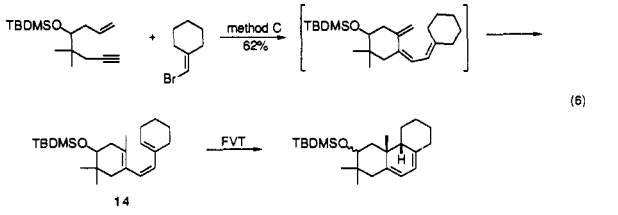
rotoselectivity[8] of the triene derives from the interaction of the siloxy and methoxymethyl substituents since the isomeric enyne **6** produces the expected diastereomeric mixture (eq 4). The tentative stereochemical assignment of **5** derives from mechanistic considerations.



Equation 5 illustrates the ability to introduce both electron-donating and electron-withdrawing substituents on the terminal olefinic carbon of the enyne and to vary the substituent on the vinyl bromide. All reactions were performed using 5 mol % $Pd(OAc)_2$, 15 mol % TPP, and 1 equiv of triethylamine in refluxing toluene (method C) without optimizing conditions in any example. In spite of increasing the reactivity of the olefin toward carbametalation by incorporating an ester, kinetic carbapalladation of the acetylene still dominates. Chromatographic and spectroscopic analyses indicate that each product is a single diastereomer. The 4,5-stereochemistry of **9**[7] (R = Ph and n-C_5H_{11}) as *Z* derives from J = 5.5 Hz for H_4-H_5; the stereochemistry of **11**[7] (R = Ph, n-C_5H_{11}, and C_4H_3O) as *E* derives from J = 12.3 ± 0.3 Hz for H_4-H_5. While the latter result is in accord with that anticipated from a mechanism invoking *cis*-carbapalladation, *cis*-β-hydrogen insertion, and disrotatory cyclization of the presumed hexatriene, the former is not. Clearly, the mechanistic details of this process must yet be established.



Cyclization of enyne **12** with β-bromostyrene explores the effects of ring substitution (eq 5). The more modest yield of bicycle **13**[7] compared to **9** (R = Ph) in eq 5 may derive from the higher sensitivity of the product toward decomposition during workup. The alkylative cyclization depicted in eq 6 illustrates the successful extension to six-membered rings. In this case, the hexatriene **14** may be isolated (71% yield) or flash vacuum thermolyzed to the tricycle.



The reaction has good chemoselectivity, as illustrated by the compatibility with free alcohols, esters, vinyl- and allylsilanes, dienes, and furans. The sequence of alkylative cyclization–electrocyclic reaction constitutes an equivalent of a [2 + 2 + 2] bicyclization minus HBr.

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Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs. We are indebted for partial support for J.D. from Université René Descartes (Paris V) and NATO and for W.P. from NATO administered by DAAD. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Registry No. 1a, 122917-11-7; **1b**, 138572-83-5; **2a**, 138572-81-3; **2b**, 138572-99-3; **3**, 138572-82-4; **5**, 138572-84-6; **6**, 138572-85-7; *cis*-**7**, 138572-86-8; **8**, 138572-87-9; **9** (R = Ph), 138572-88-0; **9** (R = n-C_5H_{11}), 138572-93-7; **10**, 138572-89-1; **11** (R = Ph), 138572-90-4; **11** (R = n-C_5H_{11}), 138572-94-8; **11** (R = 2-furyl), 138572-95-9; **12**, 138605-35-3; **13**, 138572-91-5; **14**, 138572-92-6; (*E*)-BrCH=CHPh, 588-72-7; PhI, 591-50-4; *trans*-**7**, 138573-00-9; (*E*)-BrCH=CH-n-C_5H_{11}, 53434-74-5; (*E*)-BrCH=CH-2-furyl, 138572-96-0; H_2C=$CHCH_2CH(OTBDMS)$-$C(CH_3)_2CH_2C$≡CH, 138572-97-1; (bromomethylene)cyclohexane, 1121-49-9; 2,2-dimethyl-3-((dimethyl-*tert*-butylsilyl)oxy)-1,2,3,4,4a,4b,5,6,7,8-decahydrophenanthrene, 138572-98-2.

Supplementary Material Available: Characterization data for **2a,b**, **5**, **9**, **11**, **13**, and **14** (3 pages). Ordering information is given on any current masthead page.

New Strategy for the Total Synthesis of 1α-Hydroxyvitamin D Derivatives

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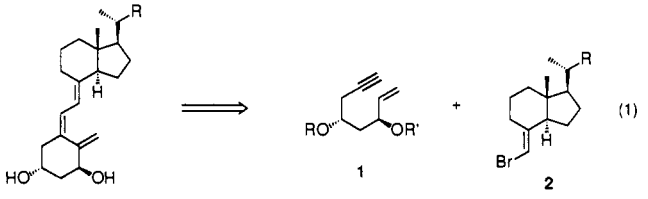
The increasing number of potential clinical applications of 1α-hydroxyvitamin D analogues enhances interest in simplifying their syntheses.[1] Two strategies are currently employed: one based on a biomimetic path from a normal steroid precursor[2] and one based on a convergent approach of attaching a preformed ring-A system to a CD fragment (Grundmann ketone or an analogue thereof).[3,4] We wish to record a new convergent strategy in which ring A is created from an acyclic unit as a result of the method of attachment of this unit to a Grundmann's ketone derivative utilizing a Pd-catalyzed alkylative enyne cyclization[5] as outlined in eq 1.



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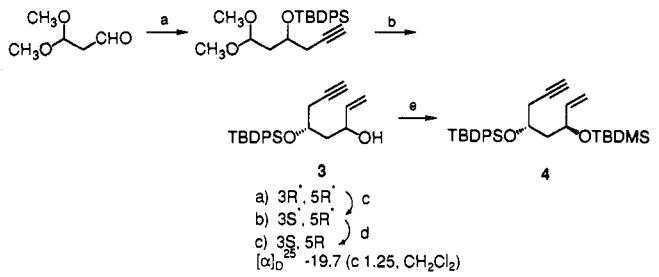
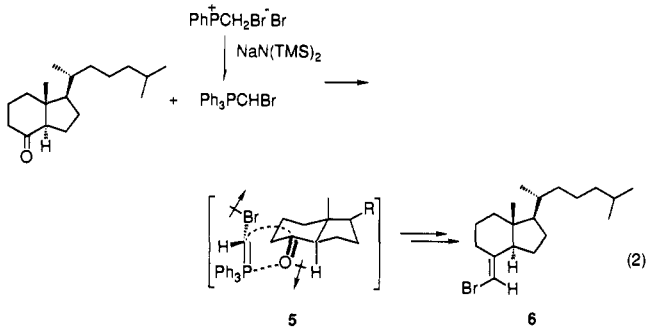
Scheme I. Asymmetric Synthesis of Enyne Unit[a]



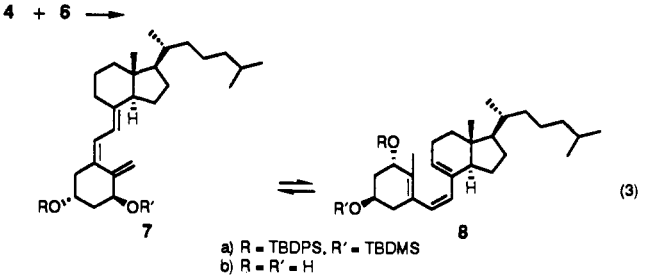
[a](a) $HC{\equiv}CH_2Br$, Mg, THF, 0 °C → room temperature, then TBDPS-Cl, $C_3H_4N_2$, DMF, 55 °C, 78%. (b) CF_3CO_2H, H_2O, THF, room temperature, then $CH_2{=}CHMgBr$, THF, −78 °C, 61%. (c) $PhCO_2H$, Ph_3P, DEADCAT, THF, room temperature then DIBAL-H, CH_2Cl_2, −78 °C, 73%. (d) t-C_4H_9OOH, D-(+)-dicyclohexyl tartrate, $Ti(OC_3H_9\text{-}i)_4$, CH_2Cl_2–isooctane, −20 °C, 92% yield (46% calculated considering 50% as the maximum theoretical yield), 98% ee. (e) TBDMS-Cl, $C_3H_4N_2$, DMF, 55 °C, 90%.

Scheme I outlines an asymmetric synthesis of the enyne unit **4** (=**1**, R = TBDPS, R′ = TBDMS) from the monoacetal[6] of malonaldehyde in a straightforward manner. The relative stereochemistry of **3a** and **3b** is established by NMR analysis of the acetonide derived from **3a**.[7] Kinetic resolution[8] of the racemic allylic alcohol **3b** gives virtually quantitative recovery of the desired scalemic alcohol **3c** of 98% ee. The determination of the ee and verification of the absolute configuration derive from the NMR analysis of the corresponding *O*-methylmandelate ester.[9]

Obtention of the other half requires a geometrically controlled bromoolefination. Extrapolating from the *Z* selectivity in the bromoolefination of aldehydes with the requisite phosphorus ylide,[10] it may be predicted that the undesired *Z* olefin would dominate. In the event, a 30:1 *E*:*Z* selectivity for bromoolefin **6**[11] as established by the ratio of the signals for the vinyl protons (*E* δ 5.62; *Z* δ 5.92) is observed in the olefination of Grundmann's ketone (eq 2). We suggest that this surprisingly high *E* selectivity derives from a dipole–dipole effect depicted in **5** since steric effects should not play an important role.



The alkylation cyclization according to eq 3 is performed as follows. To a stirred solution of 10 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 30 mol % triphenylphosphine in 1:1 toluene–triethylamine is added a solution of 1 equiv of enyne **4** and 1.5 equiv of vinyl bromide **6** in toluene. After heating (oil bath at 120 °C) for 1.5 h, workup



gives a 10:1 mixture of the silylated vitamin **7** and the silylated previtamin **8**. Thermal equilibration of triene **8** (toluene, 80 °C) to the triene **7** and combining the latter with the originally isolated triene **7** gives an overall yield of the silylated vitamin **7a** of 76%. In addition, desilylation (TBAF, THF, room temperature, 79%) gives calcidiol, mp 133–4 °C, $[\alpha]^{25}_D$ +26.5° (*c* 0.89 ether), identical in physical and spectroscopic properties to that reported.[12]

This simple convergent strategy can readily be adopted for the synthesis of many of the hydroxylated vitamin D analogues which differ in the side chain of the Grundmann's ketone. Being able to use a simple acyclic unit like **1** as the precursor for the A ring should also facilitate variation of substituents on the A ring. The successful creation of this short synthetic strategy illustrates the power of our newly developed alkylative cyclization. In addition, this study opens the question of the importance of dipole effects on the Wittig olefination.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institute, for their generous support of our program. We are indebted for partial support for J.D. from Université René Descartes (Paris V) and NATO. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources. We are especially indebted to Dr. M. R. Uskokovic and Hoffmann-LaRoche for a generous sample of the alcohol precursor of Grundmann's ketone.

Supplementary Material Available: Characterization data for **3a–c**, **4**, **6**, and **7b** (3 pages). Ordering information is given on any current masthead page.

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