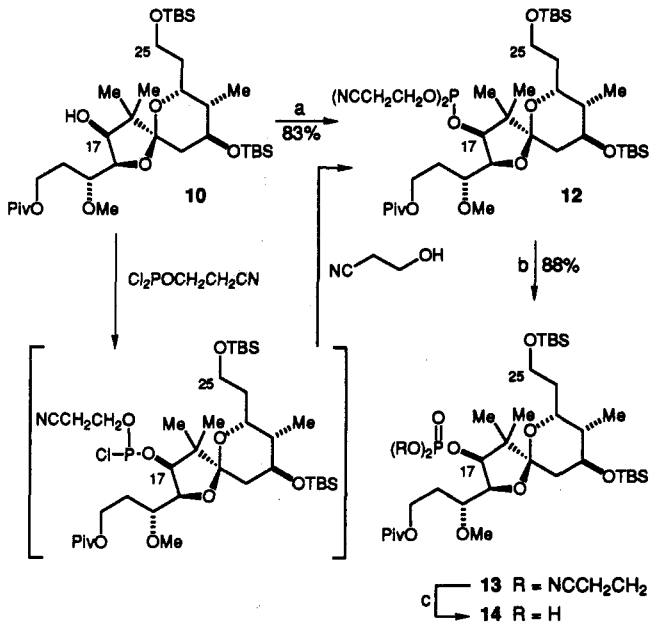
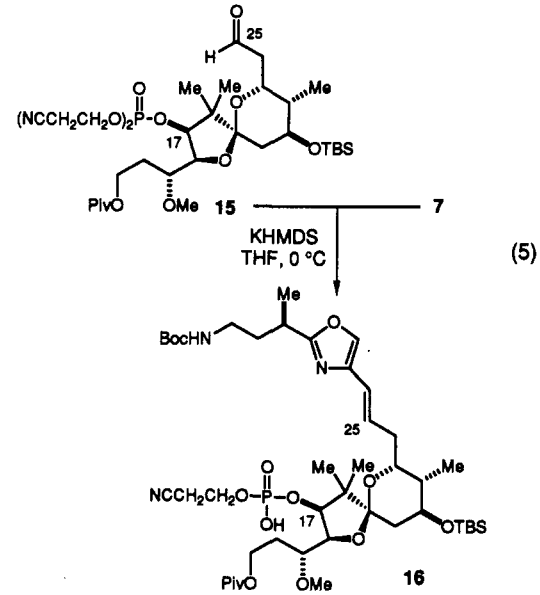
Scheme III[a]



[a] Key: (a) Bis(2-cyanoethyl) chlorophosphite, pyridine, 3-hydroxypropionitrile, 25 °C; (b) 30% aqueous H_2O_2, CH_2Cl_2, 25 °C; (c) DBU, TMSCl, CH_2Cl_2, 25 °C.

component consumed a disproportionate amount of alcohol **10**, forming a mixed chlorophosphite diester (Scheme III). Upon aqueous workup, this intermediate hydrolyzed and tautomerized to an unutilizable H-phosphonate byproduct. This problem was conveniently circumvented by the addition of 3-hydroxypropionitrile to intercept the mixed chlorophosphite diester prior to aqueous workup providing phosphite **12** in 83% yield. Oxidation of **12** with 30% H_2O_2 afforded phosphate triester **13** in 88% yield. *Upon treatment of 13 with DBU (CH_2Cl_2, 25 °C) only one of the cyanoethyl groups is removed*;[12] however, in the presence of chlorotrimethylsilane, complete deprotection is achieved under mild conditions to produce phosphate **14** in excellent yield as an insoluble white solid that could not be characterized by NMR spectroscopy. FABMS analysis of this compound displayed peaks at m/z 763 and 785, corresponding to M + Na and M - H + 2Na, respectively, for the desired phosphorus diacid.[13]

Finally, we have begun to address the possibility of carrying a mixed alkoxy bis(2-cyanoethyl) phosphate derivative through the Wittig reaction. Treatment of a cooled (0 °C) THF solution of phosphonium salt **7** and aldehyde **15**[14] with 2 equiv of KHMDS afforded olefin **16** in good yield with >10:1 E/Z selectivity (eq 5). The extra equivalent of base was intentionally used in this transformation to facilitate partial deprotection of the phosphate moiety.



The incidental loss of one of the 2-cyanoethyl protecting groups is not undesirable as deprotection of the phosphate would be the next step in our projected route to calyculin A. This route involves the synthesis of a modified version of **6** in which the protected phosphate has been installed prior to the key Wittig reaction. These efforts and the completion of the total synthesis of calyculin A are in progress and will be reported in due course.

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health. An NSF predoctoral fellowship to J.R.G. (1986-1989) is gratefully acknowledged. We thank Dr. Andrew Tyler of the Harvard Mass Spectrometry Facility for providing mass spectra and acknowledge the NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 and NSF (CHE88-14019) for providing NMR facilities.

Supplementary Material Available: Full experimental details and analytical and spectral data for all compounds (except **14**, **15**, and **16**) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) Partial deprotection under these conditions was not unexpected. See ref. 11 and Tener, G. M. *J. Am. Chem. Soc.* **1961**, *83*, 159-168.

(13) Further confirmation of the identity of **14** was provided by its partial conversion to the corresponding dimethyl phosphate with diazomethane. Gage, J. R. Ph.D. Thesis, Harvard University, 1991.

(14) Obtained from **13** in 84% yield by deprotection with HF·pyridine followed by Dess-Martin periodinane oxidation.

A Novel and Practical Synthesis of the 6α-Hydroxymethyl Metabolite of Simvastatin

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Summary: The synthesis of the 6α-hydroxymethyl metabolite of simvastatin described here is predicted on the conversion of iodoepoxides **7** to the cyclic ether **8** via a novel radical catalytic cycle in which the rearrangement

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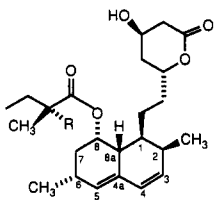
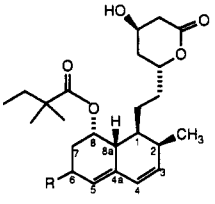
of the epoxycarbinyl radical to the allyloxy radical and the atom-transfer radical reaction are the key elements to the success of this process.

Simvastatin (**1b**)[1] is a semisynthetic derivative of lovastatin (**1a**), a novel fungal metabolite initially isolated from cultures of *Aspergillus terreus*[2] and *Monascus ruber*.[3a,b] Like lovastatin, simvastatin is a lactone prodrug[4] that upon conversion to the corresponding ring-opened dihydroxy acid form becomes a potent, specific, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase,[5] an early and rate-limiting enzyme in cholesterogenesis. More importantly, simvastatin and lovastatin are highly effective hypocholesterolemic agents in humans[6a-d] and are the first members of the HMG-CoA reductase inhibitor class to be approved for clinical use in the management of hypercholesterolemia.[7] The observation that the 6α-methyl group of simvastatin is metabolized by both microorganisms[8] and mammals[9] to a common group of intrinsically-active oxygenated metabolites **2a–d** presented the need to quickly develop viable synthetic routes to **2a–d** in order to supply them for biological evaluation. Of special interest was the development of an efficient synthesis of the least available metabolite **2a**, the subject to which this paper is addressed.



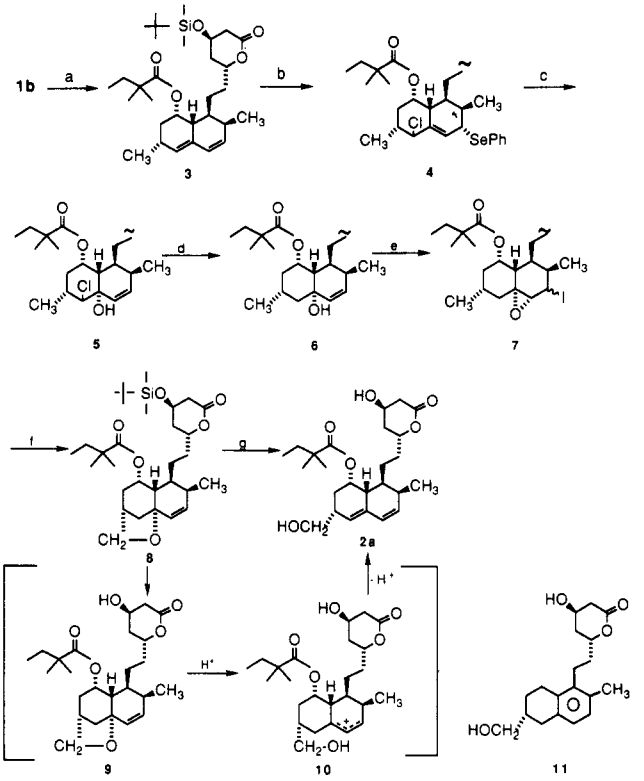
1 a, R=H (Lovastatin)
b, R=CH_3 (Simvastatin)



2 a, R=α-CH_2OH
b, R=α-CO_2H
c, R=β-CH_2OH
d, R=β-CO_2H

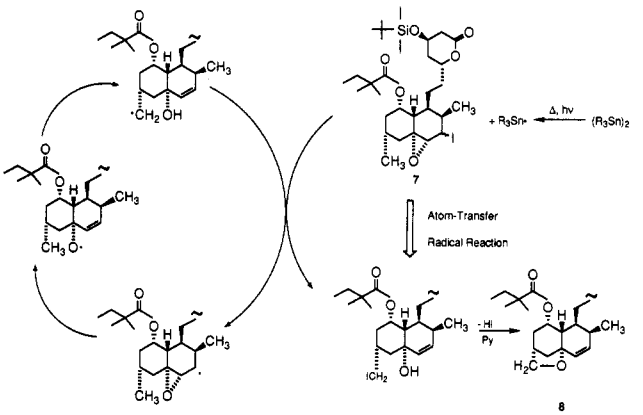
Our strategy for elaborating the metabolite **2a** from **1b** consists of several critical stages. The first stage involves the regio- and stereoselective introduction of a hydroxyl group at the axial **4a** position as shown in **6** (Scheme I). Of critical importance in the second stage is the use of the properly positioned axial **4a** hydroxyl group in **6** as a handle for oxygenating the 6α-methyl group via a radical reaction route to form **8**. Finally, the acidic cleavage of the allylic ether bond followed by regioselective deprotonation should lead to our target compound **2a**. Pursuit of this strategy began with the elaboration of alcohol **6**, which was prepared in four steps from **1b** as shown in

Scheme I[a]



[a] Key: (a) *t*-$BuMe_2SiCl$, imidazole, DMF; (b) PhSeCl, CH_2Cl_2, −78 °C; (c) 30% H_2O_2, THF, 0 °C → rt; (d) *n*-Bu_3SnH, AIBN, benzene, Δ; (e) I_2, HgO, CCl_4, rt, PY; (f) $(n\text{-}Bu_3Sn)_2$ (0.1 equiv), benzene, PY (1 equiv), Δ, *hν*; (g) 48% HF, CH_3CN (1:19), 60 °C.

Scheme II



Scheme I. Protection of the lactone hydroxyl group in **1b** as the *tert*-butyldimethylsilyl ether[1,10] followed by sequential treatment with phenylselenyl chloride in methylene chloride at −78 °C and exposure to 30% hydrogen peroxide in THF afforded **5** in 70% overall yield.[11] Mechanistically, the 1,4-addition of phenylselenyl chloride across the diene moiety in **3** must have proceeded in the indicated regio- and stereoselective manner to afford adduct **4** which, after oxidation to the corresponding selenoxide, underwent a [2,3]-sigmatropic rearrangement and subsequent hydrolysis to give **5**. Dechlorination of **5** with tri-*n*-butyltin hydride and the radical initiator AIBN in refluxing benzene afforded axial 4a-alcohol **6** in excellent

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(11) Satisfactory elemental analyses and/or spectral data consistent with the assigned structures were obtained for all new compounds.

yield (92%). To our surprise **6** failed to undergo the hypoiodite reaction[12] with HgO and I_2 to give the expected cyclic ether **8**; instead, a mixture (9:1; 3α:3β) of iodoexpoxides **7** was produced under these conditions. Subsequently, it was found that photolysis of a solution of **7**, hexabutylditin (0.1 equiv), and pyridine (1 equiv) in benzene with a sun lamp provided **8** in high yield (80% from **6**). The dynamics of this highly efficient transformation are shown in Scheme II. It should be noted that the rearrangement of the epoxycarbinyl radical to the allyloxy radical[13] and the atom-transfer radical reaction[14] are the key elements in this catalytic process cycle. Completion of this synthetic route was accomplished by simply treating **8** with 48% hydrofluoric acid in acetonitrile at 60 °C, a process which gave target metabolite **2a** in 58% yield along with a trace of the byproduct **11**.[15] The conversion of **8** to **2a** was shown to proceed in a stepwise manner via the sequence **8** → **9** → **2a** with the second step presumably proceeding via the intermediacy of a cationic species such as **10** which, upon regioselective deprotonation of the 5-position, affords **2a**.

In summary, a seven-step synthetic route has been developed for elaboratoring 6α-hydroxymethyl metabolite **2a** from simvastatin in 30% overall yield and used to prepare g-scale quantities of **2a**.

Acknowledgment. The authors wish to thank Dr. Paul S. Anderson for his encouragement during the course of this investigation.

Supplementary Material Available: Experimental procedures for the preparation of **5**, **6**, **7**, **8**, and **2a** and spectral and analytical data of the products (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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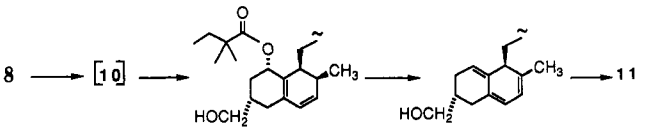
(14) For a comprehensive review of the atom-transfer radical reaction, see: Curran, D. P. *Synthesis* **1988**, 489–513.

(15) Byproduct **11** is probably formed from **10** as indicated below:



Use of a Dilithiomethane Equivalent in a Novel One-Flask [2 + 1 + 2] Cyclopentannulation Reaction: A Highly Efficient Total Synthesis of (±)-Hirsutene

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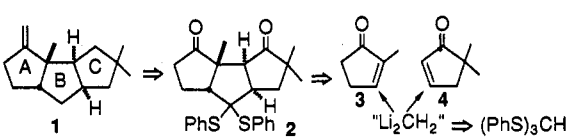
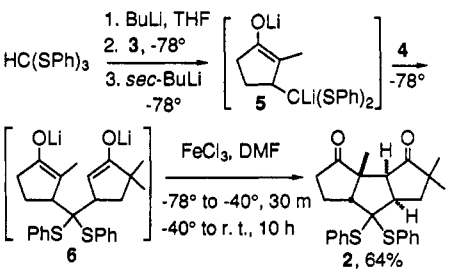
Summary: A brief synthesis of (±)-hirsutene demonstrates the novel use of tris(phenylthio)methane as a dilithiomethane equivalent capable of consecutive conjugate additions to different enones to form a dienolate which can be oxidized to a cyclopentane.

It has been shown that a variety of carbanion–carbenoids can be used in carbon–carbon bond forming processes in which the carbenoid function behaves as an electrophile.[2] Herein we report one of the most efficient total syntheses of the triquinane (±)-hirsutene[3] (**1**), by a process which utilizes the nucleophilic nature of the carbenoid function of a carbanion–carbenoid at low temperature. The synthesis features completely stereoselective construction of the triquinane nucleus by one-flask formation of three of the five carbon–carbon bonds of the B ring, using commercially available tris(phenylthio)methane as a dilithiomethane equivalent (Scheme I).

Scheme I



Scheme II



The synthesis begins with conjugate addition of tris(phenylthio)methyllithium[4] to commercially available 2-methyl-2-cyclopentenone (**3**) at −78 °C, followed by sul-

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(2) (a) Ramig, K.; Bhupathy, M.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 4404 and references cited therein. (b) Cohen, T.; Yu, L.-C., *Ibid.* **1985**, *50*, 3266.

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