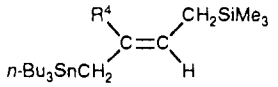
Table I. 1,4-Silylstannation of 1,3-Dienes[a]

entry	silylstannane 1				diene 2			product 3	
		R^1	R^2	R^3		R^4	R^5		yield,[b] %
1	a	*n*-Bu	Me	Me	a	H	H	a	84, 93[c] (98)
2[d]	a	*n*-Bu	Me	Me	a	H	H	a	52 (62)
3[e]	a	*n*-Bu	Me	Me	a	H	H	a	*trace*
4	a	*n*-Bu	Me	Me	b	Me	H	b	84
5[f]	a	*n*-Bu	Me	Me	c	C_6H_5	H	c	85
6	b	*n*-Bu	Me	*t*-Bu	a	H	H		0
7	c	Me	Me	C_6H_5	a	H	H	d	35
8	c	Me	Me	C_6H_5	b	Me	H	e	30
9	d	Me	Me	*t*-Bu	a	H	H	f	26
10	a	*n*-Bu	Me	Me	d	Me	Me	g[g]	70

[a] **1** (0.5 mmol), **2** (1.5 mmol), $Pt(CO)_2(PPh_3)_2$ (0.025 mmol), toluene (2.0 mL), at 100 °C for 6-8 h. [b] Isolated yield. Numbers in parentheses show GLC yields determined by the internal standard method. [c] Isolated yield from larger scale reaction (**1a**; 1.0 mmol). [d] At 80 °C. [e] Catalyst; $Pd(PPh_3)_4$ (0.025 mmol). [f] **2c** (0.5 mmol). [g] The stereochemistry is not determined.

Isoprene (**2b**) and 2-phenyl-1,3-butadiene (**2c**) also react with **1a** to afford the corresponding single 1,4-silylstannation products in high isolated yield (Table I, entries 4 and 5). The most important feature of the reaction is its high regio- and stereoselectivities. The regiochemistry of the products was determined by C-H COSY spectra. For the isoprene adduct (**3b**), the methylene carbon resonance (δ 22.25: with ^{117,119}Sn-satellites; $^1J_{Sn-C}$ = 261, 271 Hz) of the Sn—CH_2—C= linkage has a cross peak coupled with the proton resonance (δ 1.77) which appears as a *singlet*. The same type of C-H correlation was obtained for 2-phenyl-1,3-butadiene adduct (**3c**). These observations definitely indicate



3b: $R^4 = CH_3$
3c: $R^4 = C_6H_5$

that the regiochemistry of the products is what is shown by the structures of **3b** and **3c**. As for the stereochemistry, the (*E*)-1,4 configurations are unambiguously confirmed by NOE difference spectra with irradiation at the olefin protons. Thus, the 1,4-silylstannation of **2a**, **2b**, and **2c** is found to be highly regio- and stereoselective, affording the corresponding single (*E*)-1,4 isomer exclusively.[13]

Other organosilylstannanes with more bulky substituents are less reactive. (*tert*-Butyldimethylsilyl)tributylstannane (**1b**) did not give the 1,4-silylstannation product (entry 6). However, (dimethylphenylsilyl)trimethylstannane (**1c**) and (*tert*-butyldimethylsilyl)trimethylstannane (**1d**) afforded the corresponding single 1,4-silylstannation products (**3d-f**) regio- and stereoselectively (entries 7-9), although the yields decreased considerably as compared with **1a**. With 2,3-dimethyl-1,3-butadiene (**2d**), the reaction proceeded regioselectively (1,4-addition) in high yield (entry 10). The reaction of 1,3-pentadiene (**2e**) with **1a** was sluggish, giving (*E*)-1,4 adduct in a low yield (25%) and with low regioselectivity. Further studies on the scope and limitation of the 1,4-silylstannation and on reactivity and synthetic utility of the 1,4-silylstannation products are currently under investigation.

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Supplementary Material Available: ^{1}H, ^{13}C NMR, and MS spectral and elemental analysis data for **3c**, NOE difference spectral data for **3b**, **3c**, and **3e**, and ^{1}H and ^{13}C NMR and some MS spectral data for **3d-g** (4 pages). Ordering information is given on any current masthead page.

(12) Other selected transition-metal catalyst precursors (5 mol %) such as $RhCl(PPh_3)_3$, $IrCl(CO)(PPh_3)_2$, $Ru(COD)(COT)$, and $Mn_2(CO)_{10}$ did not give any 1,4-silylstannation products at all.

(13) The reaction of **1**[4] or disilanes[14] with alkynes affords only (*Z*)-alkenes stereoselectively. 1,4-Disilylation of 1,3-dienes with disilanes[15] also gave (*Z*)-1,4-disilyl products. In the present 1,4-silylstannation reaction, there might be some possibility that (*Z*)-1,4 adducts are kinetic products and the (*E*)-1,4 products are formed via (*Z*)-(*E*) isomerization. However, any (*Z*)-1,4 adducts were not detected in the reaction mixtures even at lower conversions of **1**, indicating that such (*Z*)-(*E*) isomerization during the course of the reaction is unlikely.

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Synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-Uvaricin: A Bis(tetrahydrofuranyl) Annonaceous Acetogenin Analogue

Thomas R. Hoye,* Paul R. Hanson,[1] Albert C. Kovelesky, Timothy D. Ocain, and Zhiping Zhuang

Department of Chemistry, University of Minnesota Minneapolis, Minnesota 55455

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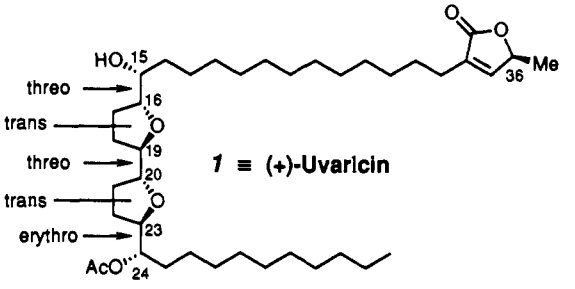
Uvaricin (**1**) was the first reported member of the family of Annonaceous acetogenins.[2] Over thirty relatives are now known; their structural and considerable biological features have been recently reviewed.[3] Our interest in this area was provoked by the opportunity to develop polyepoxide cascade reactions[4a,b] for the purpose of determining important stereochemical issues[4c,d] related to the relative configurations of the central tetrahydrofuran rings present in these natural products. It continues with synthesis issues. Described here is the first preparation of a member of this series—albeit a diastereomeric, non-natural one (vide infra).



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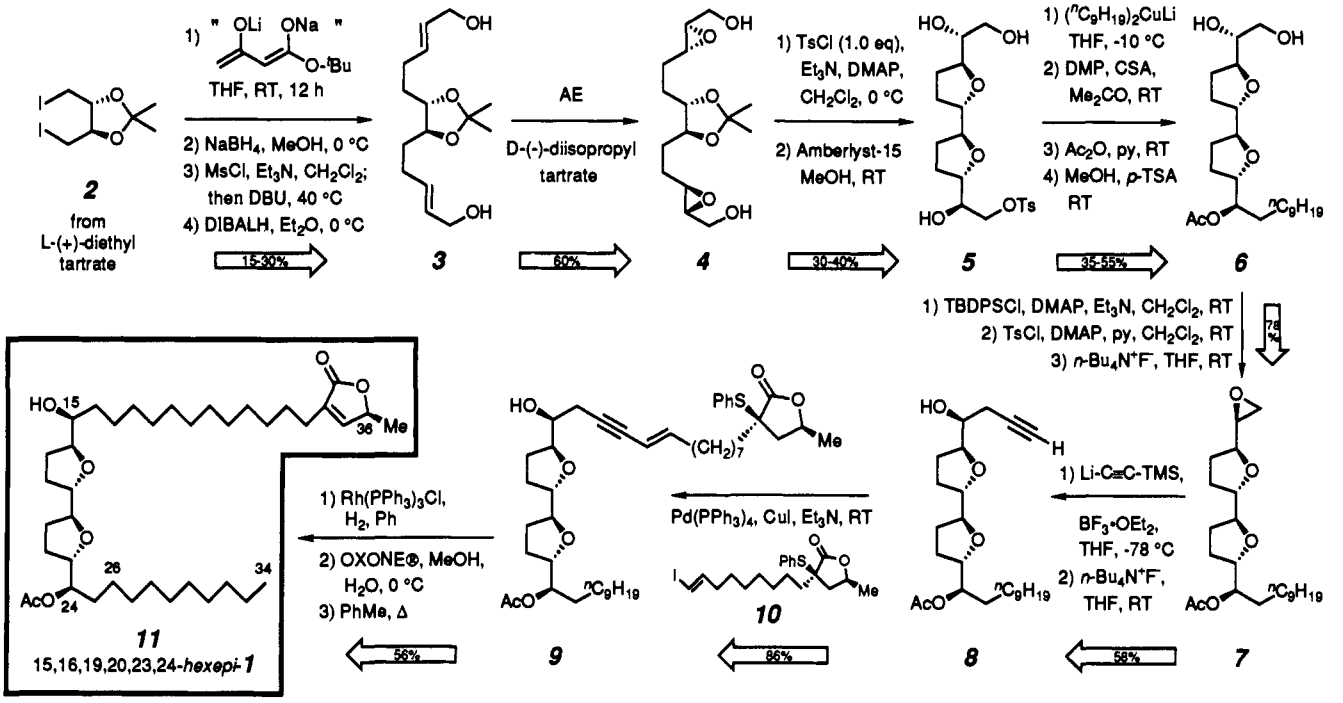
Scheme I



In 1982 and 1985 the constitution[2a] and absolute stereochemistry at C(36)[2b] of (+)-uvaricin were reported. In 1987 our assignment of the threo/trans/threo/trans/erythro relative stereochemical relationships across C(15)–C(24)[4c,d] left open only the question of absolute stereochemistry of the embedded six stereogenic centers. Armed with the considerable versatility of the "inside-out" epoxide cascade reaction of substrates available from the "two-tartrate approach" (cf. **4**), we arbitrarily chose to buy the C(19)/C(20) stereocenters as L-(+)-diethyl tartrate. The derived diiodide **2**[5] (Scheme I) was converted to the *E,E*-bisallyl alcohol **3** through Weiler dianion alkylation[6] using *tert*-butyl acetoacetate[7] followed by ketone reduction, dehydration via the bis-mesylate, and enoate ester reduction (15–30% overall). The choice of D-(−)-diisopropyl tartrate as catalyst for the Sharpless asymmetric epoxidation of **3** (~60%) was dictated by the requirement of that relative configuration in **4** which leads to the pair of trans-substituted tetrahydrofurans in **5** (and uvaricin).

As with any synthesis of an unsymmetrical target relying on the two-directional chain synthesis strategy,[8] it was necessary to eventually desymmetrize[8a,9] the system. Although the possibility for more elegant solutions exists, we opted for the practical approach of treating the C_2-symmetric diol **4** with 1.0 equiv of *p*-toluenesulfonyl chloride. This limited the theoretical amount of the monotosylate (**4-OTs**) which could be formed,[10] but it sufficed since the ditosylate byproduct is entirely useful to us for ongoing analogue synthesis. Acid catalyzed acetonide removal within **4-OTs** simultaneously opened the epoxides to produce the erythro/trans/threo/trans/erythro-configured monotosylate **5** (30–40% from **4**). Coupling of the tosylate with excess lithium dinonylcuprate, acetonide formation of the vicinal diol, acetylation, and acetonide removal installed both the necessary C(26)–C(34) tail and the C(24)-acetate enroute to **6** (35–55% from **5**).

In preparation for attachment of the lactone-containing head group, it was necessary to identify both an opportunity for inversion of configuration at C(15) (to convert the C(15)/C(16) array from erythro to threo) and a carbon–carbon bond forming reaction compatible with the C(24)-acetate. Both needs were met by preparation of the terminal epoxide **7** (78% from **6**) which was then smoothly opened through the Yamaguchi protocol[11] with lithium trimethylsilylacetylide/BF_3•OEt_2 (67%). The terminal acetylene **8** was then produced by TBAF removal of the TMS group (86%).

The remainder of the carbon skeleton was added through the efficient Pd°-catalyzed coupling of **8** with the non-racemic vinyl iodide **10** which bore the correct *S* configuration at C(36).[12] Notice the compatibility of ester, hydroxyl, sulfide, and lactone functionalities with this carbon–carbon bond forming event which produced **9** in 86% yield. Enyne reduction with Wilkinson's catalyst in the presence of the sulfide, OXONE oxidation to the sulfoxide,[14] and heating in toluene produced compound **11** as a waxy solid (mp ~23–33 °C) whose TLC (SiO_2) as well as ^1H and ^{13}C NMR and IR spectra were indistinguishable from those obtained from a sample of natural uvaricin.[15] However, the specific rotation of **11** ($[\alpha]^{RT}_D$ = +9.5° (*c* = 1.07, MeOH)) differed in magnitude from that reported for the natural material ($[\alpha]^{25}_D$ = +11.3° (MeOH)).[2a] Mosher ester formation of the secondary alcohol in both **11** and uvaricin followed by ^1H and ^{19}F

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(10) Under the assumption that both the α- and ω-primary alcohols react at identical rates, in theory the use of 1.0 equiv of *p*-TsCl maximizes the yield of the monotosylate (to 50%) and 1.33 equiv leads to the formation of equivalent amounts of mono- and ditosylates (~45% each).

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(15) We are indebted to Professors J. R. Cole and J. J. Hoffmann for providing natural uvaricin.

NMR analysis confirmed that the MTPA methodology[16a] is applicable in this series.[16b] Since the R-MTPA derivative of **1** and the S derivative of **11** have identical NMR spectra[17] (which are distinct from those of S-MTPA-**1** and R-MTPA-**11**), it can be concluded that the natural material is diastereomeric with our synthetic sample of **11** which has unambiguous stereochemistry. Therefore, the precise stereostructure of uvaricin can now be formulated as that shown in **1**, and **11** can be named (+)-15,16,19,20,23,24-*hexepi*-uvaricin [or (+)-(36-*epi*)-*ent*-uvaricin since the *relative* stereochemistry of **1** and **11** differs only at C(36)].

The work described here sets the stage for syntheses and biological evaluation of (i) more complex and more potent naturally occurring members of the bis(tetrahydrofuranyl) acetogenin family,[3] (ii) other non-natural stereoisomeric uvaricin analogues, and (iii) structurally simpler analogues as part of a quest to identify the minimum pharmacophore.

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Supplementary Material Available: Experimental procedures and characterization data for all new compounds (20 pages). Ordering information is given on any current masthead page.

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(17) The C(35), C(36), and C(37) protons have identical chemical shifts in the **1**/**11**, S-MTPA-**1**/R-MTPA-**11**, and R-MTPA-**1**/S-MTPA-**11** diastereomeric pairs, suggesting that those sites are sufficiently far removed from the C(15) Mosher ester attachment site to be unaffected.

Spectral Characterization of 4-Carboxy-5,6-dihydroxy-2,4-cyclohexadienone, a Likely Component of Intermediate II in *p*-Hydroxy Benzoate Hydroxylase

Gábor Merényi*,† and Johan Lind‡

Department of Physical Chemistry and Department of Nuclear Chemistry The Royal Institute of Technology 10044 Stockholm, Sweden

Robert F. Anderson

Gray Laboratory of the Cancer Research Campaign, Post Office Box 100 Mount Vernon Hospital Northwood, Middlesex HA6 2JR, United Kingdom

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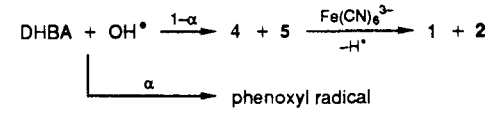
During aromatic hydroxylation by *p*-hydroxy benzoate hydroxylase or phenol hydroxylase three distinct intermediates have been observed.[1] Intermediates I and III have been identified as the corresponding 4a-hydroperoxy- and 4a-hydroxyflavins, respectively.[2] Among the several proposals for intermediate II we find a ring-opened flavin species[2,3] and a radical pair[4,5] consisting of flavin and substrate moieties. While rationalizing certain aspects[2,4-6] of intermediate II, these suggestions fail to explain the entirety of experimental observations.[7-10] An early model[11] assumed Chart I to account for aromatic hydroxylation. Although the large deuterium effect observed in phenol hydroxylase[12] for the conversion of intermediate II into III strongly supports this model, it has been abandoned on the assumption that the cyclohexadienone species in Chart I is probably transparent[13] around 400 nm and thus fails to account for the color of intermediate II. The present work will provide evidence on the contrary by producing the 2,4-cyclohexadienone of the substrate 2,4-dihydroxy benzoate (DHBA). In a modified version of the pulse-radiolytic method described in ref 4 the cyclohexadienones were produced through the reaction of the $OH^{\bullet}$ radical according to



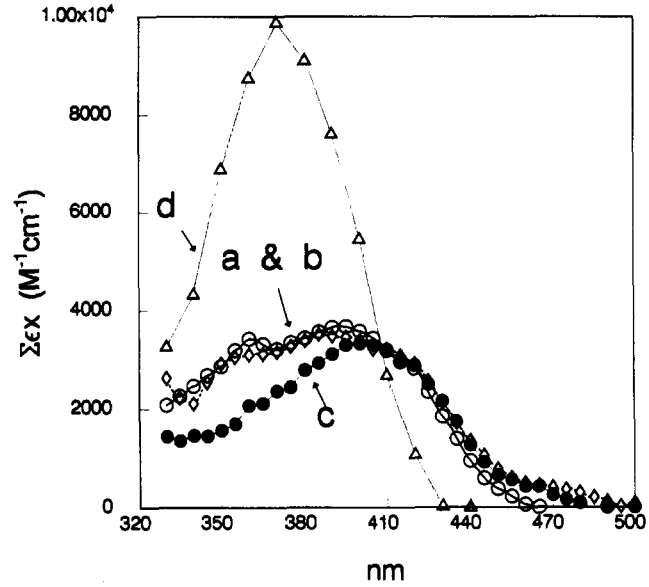


Figure 1. Composite spectra representing the cyclohexadienones **1**, **2** (a-c), and **3** (d). The spectra were obtained upon pulse irradiating N_2O saturated aqueous solutions containing 1.5×10^{-3} M 2,4-dihydroxy benzoate or 2,4,6-trihydroxy benzoate (d) and 10^{-3} M $Fe(CN)_6^{3-}$ and were corrected according to the text: (a) pH 5.75, (b) pH 8.35, (c) pH 3.75, and (d) the spectrum of **3** at pH 7.

Figure 1 presents $\sum x_i\epsilon_i$, where x_i and ϵ_i denote the fraction and extinction coefficient of the ith cyclohexadienone isomer, i.e., $\sum x_i = 1$. Figure 1 was constructed as follows: α, which varies with the substrate and somewhat with pH was determined in each case by measuring the absorbance between 470 and 500 nm where all other species are transparent. The phenoxyl radicals were unreactive toward $Fe(CN)_6^{3-}$ on the experimental time scale, while **4** and **5** were rapidly oxidized by $Fe(CN)_6^{3-}$ ($k = 3 \times 10^9$ M^{-1} s^{-1}). The spectra were recorded ca. 5 μs after the end of the pulse, by which time the concentration of cyclohexadienones amounts to $(1 - \alpha)c_0$, where c_0 is the initial concentration of $OH^{\bullet}$ radicals. This is paralleled by the conversion of the same amount of $Fe(CN)_6^{3-}$ into $Fe(CN)_6^{4-}$. Denoting by ϵ_{Ph}, $\epsilon_{Fe(III)}$, and $\epsilon_{Fe(II)}$,

† Department of Physical Chemistry.
‡ Department of Nuclear Chemistry.

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