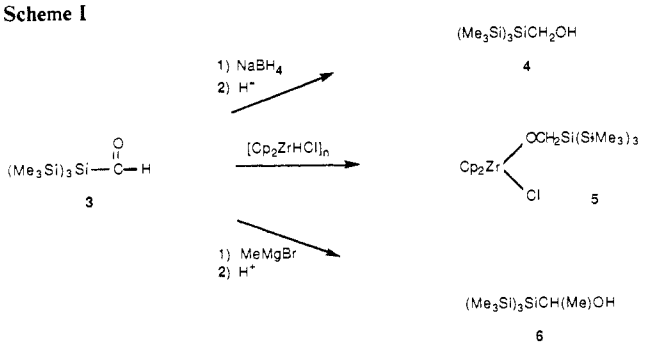
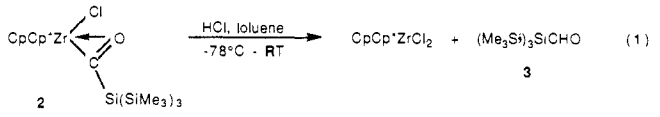
Scheme I



carbon monoxide (100 psi) in pentane. The carbonyl stretching frequency (1440 cm^{-1}) and the ^{13}C NMR shift of the carbonyl carbon for **2** are similar to corresponding values for $Cp_2Zr(\eta^2$-$COSiMe_3)Cl$.[4d] A possible explanation for the greater reactivity of **1** over $Cp_2Zr[Si(SiMe_3)_3]Cl$ toward carbon monoxide is that increased steric interactions about the metal center promote CO insertion in **1**. A similar effect has been observed for Cp_2Zr-$[CH(SiMe_3)_2]Me$, insertion of CO occurring exclusively into the more sterically hindered Zr–C bond.[9]

The formylsilane **3** was prepared by addition of anhydrous HCl gas (1 equiv) to a cold (−78 °C) toluene solution of **2** (0.60 g, 1 mmol), followed by warming to room temperature (eq 1).



(1)

Removal of volatiles under vacuum and extraction of the residue with pentane allowed separation of **3** from $CpCp^*ZrCl_2$, which was isolated in 90% yield. Pentane was removed from the resulting filtrate to afford reasonably pure **3** (≥95% by ^1H NMR) as a colorless oil in 55% yield. Compound **3** may be further purified by distillation under vacuum (70 °C, 10^{-2} mmHg, ca. 80% yield), but this is not necessary for most purposes. Low yields (20–30%) of **3** are also obtained, among other uncharacterized products, by reaction of ethyl formate and $(THF)_3LiSi(SiMe_3)_3$ in pentane at −78 °C (by ^1H NMR).

The ^1H NMR spectrum of **3** consists of singlets at δ 0.20 and 12.36 (benzene-d_6). Labeled [^{13}C]-**3**, prepared from $CpCp^*Zr$-$[\eta^2$-$^{13}COSi(SiMe_3)_3]Cl$ ([^{13}C]-**2**), gave a doublet at δ 12.36. The $^1J_{CH}$ coupling constant of 147 Hz for **3** is rather low for an aldehyde but is consistent with the expected substituent effect of the electropositive silyl group.[10] The carbonyl carbon of [^{13}C]-**3** was observed at δ 243.01 in the ^{13}C NMR spectrum, in the region expected for a $-COSi(SiMe_3)_3$ group.[1g] For comparison, $Me_3Si^{13}CHO$ exhibited a peak at δ 11.77 ($^1J_{CH}$ = 141 Hz) in its ^1H NMR spectrum and a ^{13}C NMR chemical shift at 248.9 ppm.[4d] In addition, ^{29}Si NMR resonances for **3** were observed at −74.68 ($(Me_3Si)_3SiCHO$) and −11.41 ($(Me_3Si)_3SiCHO$) ppm (benzene-d_6). The ν(CO) infrared stretching frequency for compound **3** (1633 cm^{-1}) is slightly higher than values found for acylsilanes $(Me_3Si)_3SiCOR$ (1613–1620 cm^{-1}),[1g] and the ν(CH) stretching frequency (2585 cm^{-1}) is unusually low for an aldehyde. The corresponding infrared stretches for $(Me_3Si)_3SiCDO$, prepared from **2** and DCl, were observed at 1625 and 1950 cm^{-1}, respectively. Mass spectral analysis of **3** using electron ionization techniques gave m/z fragments corresponding to M − Me^+ (261 m/z) and M − $SiMe_3^+$ (203 m/z) but no parent ion as was observed for some analogous acylsilanes.[1g]

Compound **3** decomposes instantly and exothermically upon exposure to air. This may account for the lack of success of some other, more standard attempts to prepare formylsilanes. Formylsilane **3** is thermally stable for weeks under nitrogen. At 100 °C in benzene-d_6, decomposition of **3** is first-order with a half-life of 53.3 h (k = 3.61 ± 0.06 × 10^{-6} s^{-1}). A number of uncharacterized decomposition products were observed, including small amounts of $(Me_3Si)_3SiH$ (ca. 10–15%).

Some preliminary reactivity studies of **3** are shown in Scheme I. **3** is readily reduced by $NaBH_4$ to give the alcohol **4**[11] in 90% isolated yield. Reaction with $[Cp_2ZrHCl]_n$ forms zirconium alkoxide **5**[12] quantitatively (by ^1H NMR in benzene-d_6). Compound **5** was independently prepared in 92% isolated yield from $Cp_2ZrMeCl$[13] and **4**. Finally, alkylation of **3** with MeMgBr affords the alcohol **6**,[14] isolated in 89% yield by vacuum sublimation (100 °C, 10^{-2} mmHg).

Acknowledgement is made to the Air Force Office of Scientific Research, Air Force Systems Command, USAF, for support of this work under Grant no. AFOSR-85-0228.

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(11) Brook, A. G.; Chrusciel, J. J. *Organometallics* **1984**, *3*, 1317.

(12) For **5**: mp 145–147 °C; ^1H NMR (benzene-d_6, 22 °C, 300 MHz) δ 0.32 (s, 27 H, $SiMe_3$), 4.49 (s, 2 H, OCH_2Si), 6.00 (s, 10 H, C_5H_5); $^{13}C\{^1H\}$ NMR (benzene-d_6, 22 °C, 75.5 MHz) δ 1.39 ($SiMe_3$), 67.59 ($ZrOCH_2Si$), 113.38 (Cp); $^{29}Si\{^1H\}$ NMR (benzene-d_6, 22 °C, 59.6 MHz) δ −80.42 ($Si(SiMe_3)_3$), −12.97 ($Si(SiMe_3)_3$). Anal. ($C_{20}H_{39}ClOSi_4Zr$) C, H.

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(14) For **6**: IR (Nujol) ν(OH) = 3460 br; ^1H NMR (benzene-d_6, 22 °C, 300 MHz) δ 0.27 (s, 27 H, $SiMe_3$), 0.60 (br s, 1 H, OH), 1.31 (d, J = 7.2 Hz, 3 H, CH_3), 3.82 (q, J = 7.2 Hz, 1 H, SiCHO). Anal. ($C_{11}H_{32}OSi_4$) C, H.

Palladium-Mediated Biomimetic Synthesis of Narwedine

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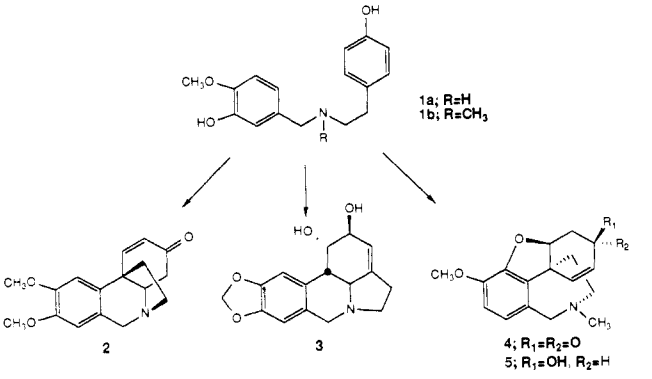
Oxidative phenolic coupling comprises the key step in the biosynthesis of a wide variety of natural products.[2] The three main structural types of the Amaryllidaceae alkaloids, represented by oxomaritidine (**2**), lycorine (**3**), and narwedine (**4**), are all formed in vivo by intramolecular phenolic coupling of norbelladine derivatives **1a** and **1b**.[3]



The first successful laboratory emulation of these processes was reported in 1962 by Barton and Kirby, who obtained narwedine

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(2) (a) For a recent review see: Dhingra, O. P. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Part D, p 207. Academic Press, New York, 1982. (b) McDonald, P. D.; Hamilton, G. A. *Ibid.* Part B, p 97, 1973.

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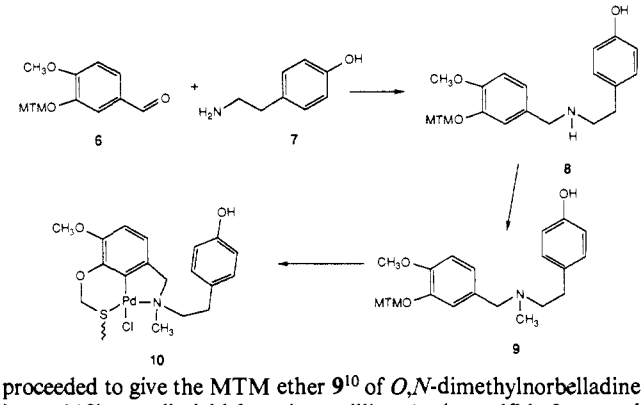
(**4**) in 1.4% yield from potassium ferricyanide oxidation of **1b**.[4] Since that time, the development of new oxidizing agents has led to efficient laboratory syntheses of alkaloids having the oxomaritidine skeleton.[5] However, lack of regiocontrol in the cyclization has remained a problem, and more recent syntheses of galanthamine (**5**) (which requires coupling with the ortho–para regiochemistry) have utilized blocking groups to prevent the undesired, but more facile, para–para coupling mode.[4,6]

Our approach to this problem involved the regiospecific activation of 3,4-dioxygenated benzylic amines at either C-2 or C-6, followed by the intramolecular replacement of activating functionality by a carbon moiety. Almost 10 years ago we reported the realization of the first of these goals in the form of ligand-directed aromatic orthopalladation.[7] We now report the biomimetic synthesis of narwedine with use of this strategy.

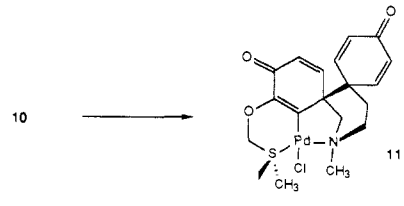
The synthesis of an appropriate norbelladine derivative was straightforward. The methylthiomethyl (MTM) ether of isovanillin[8] (**6**) was reductively aminated[9] with phenethylamine **7** (CH_3OH, 25 °C, 2 h; 0 °C, 0.5 h; $NaBH_4$, 0 °C, 1 h) to give **8** quantitatively. Methylation of **8** (CH_2O, MeOH, $NaBH_3CN$)[9]



proceeded to give the MTM ether **9**[10] of *O,N*-dimethylnorbelladine in ca. 90% overall yield from isovanillin. Amino sulfide **9** reacted rapidly with lithium tetrachloropalladate (LTP) in methanol in the presence of diisopropylethylamine at −78 °C[7] to give palladocycle **10**[10] as an ca. 1:1 mixture of diastereomers in 95% yield.

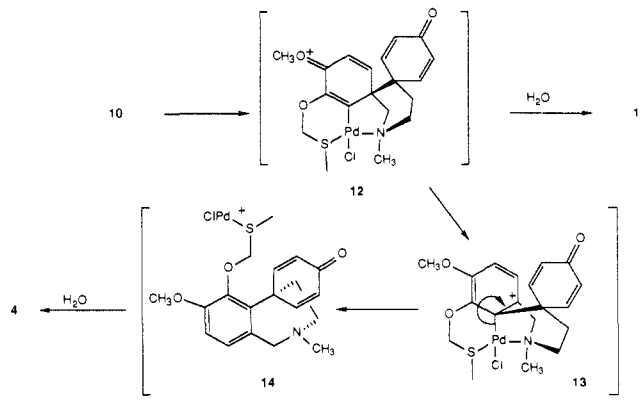
We had planned to induce palladocycle **10** to undergo an intramolecular palladation by exploiting the nucleophilic character of the corresponding phenolate. However, we soon found that both the sodium (NaH) and potassium (KH) salts of **10** were unreactive even at temperatures exceeding 150 °C.

We then turned our attention to the oxidation of **10** with the hope of producing a more electrophilic Pd(IV) species. A variety of oxidizing agents (CAN, $CuBr_2$, $FeCl_3$, $VOCl_3$) were found either to be unreactive with **10** or to produce an intractable mixture



of products. However, treatment of **10** with 2 mol equiv of thallic trifluoroacetate[5c] (2:1 CH_2Cl_2/TFA) at −10 °C for 90 min gave, upon quenching with water, a crystalline substance in 98% yield. On the basis of extensive spectral data we have assigned this substance the structure **11**,[10] and, although **11** is a single diastereomer, we have not been able to obtain unambiguous evidence to support our assignment of the relative stereochemistry at nitrogen and sulfur.

Scheme I

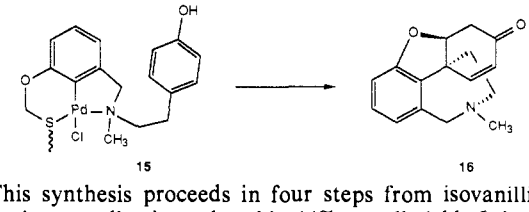


We soon found that, if, instead of quenching the above reaction after 90 min at −10 °C, we allowed the mixture to warm to 25 °C for several hours, narwedine (**4**)[11] was obtained. The best conditions we have found for the formation of narwedine are (a) treatment of a 2:1 CH_2Cl_2/TFA solution of **10** with 2 mol equiv of $Tl(OCOCF_3)_3$ at −10 °C for 1.5 h, followed by (b) addition of 2 mol equiv of triphenylphosphine and warming the solution to 25 °C for 14 h. From this reaction mixture narwedine could be isolated by flash chromatography in 51% yield.[12]

Our rationale for these observations is shown in Scheme I. At low temperature we envision the formation of cationic intermediate **12**. The addition of water at this stage then leads to the bis dienone **11**. Alternatively, at higher temperature **12** slowly rearranges to **13**, which, through loss of Pd(II), would be converted to **14**. Palladium-mediated hydrolysis of the MTM ether, either before or during workup, gives the phenolic dienone which subsequently undergoes Michael addition to provide **4**.

We have partially completed studies of this cyclization in which other ligands have been substituted for chloride in **10**. Although this study is still incomplete, we have observed that the rate of cyclization depends heavily on the ligand present on palladium. The details of these studies and others involving the use of various additives and solvent combinations will be reported at a later time.

It is interesting to note that the desmethoxy derivative **15** also undergoes cyclization under the conditions described above to give desmethoxynarwedine **16** in 31% yield. We believe that palladium may play an active role in stabilizing various intermediates along the reaction pathway. Other studies are currently underway which we hope will more clearly define the role of palladium in these events.



This synthesis proceeds in four steps from isovanillin, and racemic narwedine is produced in 44% overall yield. It is the first

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(11) Identified by comparison of NMR and IR data with published spectra, see ref 6.
(12) It should be noted that norbelladine derivatives not containing palladium do not cyclize to narwedine. Oxidation of **1b** with TTFA led to an intractable mixture of products which contained no narwedine. Oxidation of derivatives of **1** in which the nitrogen was protected as an amide or carbamate gave para–para coupling products but no trace of the ortho–para coupled materials.[5c]

biomimetic synthesis of an *Amaryllidaceae* alkaloid which features use of an "activating" group instead of a blocking group to direct the regiochemistry of the cyclization step. It is our hope that further investigation of the ideas set forth here will ultimately lead to an even more efficient solution to this problem.

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Comparison of Stereochemistry of Fatty Acid and Cladosporin Biosynthesis in *Cladosporium cladosporioides* Using ^2H Decoupled ^1H, ^{13}C NMR Shift Correlation

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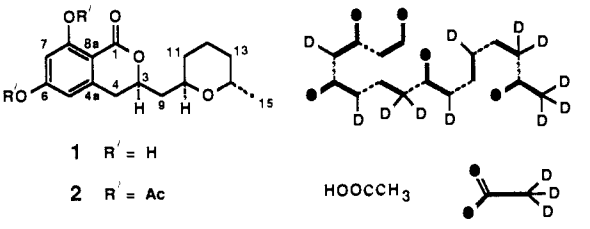
Extensive experiments employing stable isotope labeling support the idea that partially reduced polyketides are assembled by a process similar to fatty acid biosynthesis.[1] At many sites along carbon chains the correct oxidation state and stereochemistry are believed to appear as a result of the assembly process.[1,2-4] In a few cases intact six- or eight-carbon fatty acids have been employed as chain starter or terminator units.[5] Very recently Hutchinson, Cane, and co-workers demonstrated that functionally and stereochemically correct "diketides" derived from two propionate units can be incorporated intact by *Streptomyces* species into macrolides like tylactone and erythromycin A,[3,4] but this has not yet been achieved with fungi (which generally utilize acetate rather than propionate). A possible approach to examining the relationship of polyketide and fatty acid biosyntheses in fungi involves comparison of the cryptic stereochemistry of acetate-derived hydrogens in both types of metabolites in a single organism.[6] This may be especially useful since the stereochemistry of the last reductive enzyme of fatty acid biosynthesis (enoyl thiol ester reductase) varies with its source.[6a,7] The present report and the following paper[8] employ a new combination of methods, namely incorporation of a $^{13}C,^2H$ doubly labeled precursor and stereochemical analysis by ^2H decoupled $^1H,^{13}C$ heteronuclear shift correlation NMR spectroscopy,[9] to examine this problem.



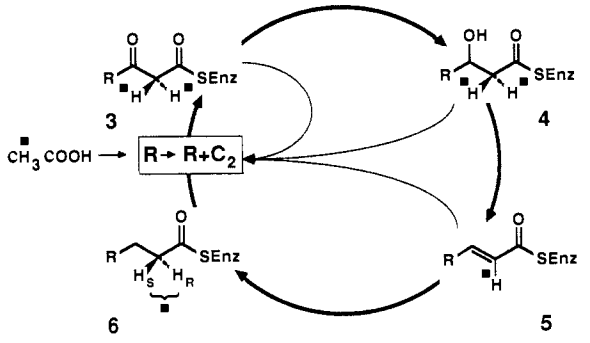
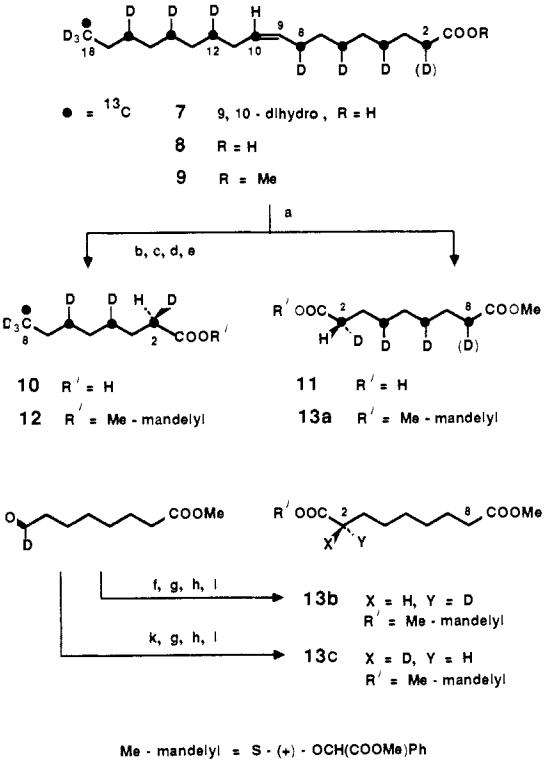


Figure 1. Acetate-derived bonds intact in cladosporin (**1**) and proposed assembly cycle on fatty acid and polyketide synthases.

Scheme I[a]



[a] a. $KMnO_4$, $NaIO_4$; b. CH_2N_2; c. PhMgCl; d. TsOH; e. $NaIO_4$, $RuCl_3$; f. (−)-pinene, 9-BBN; g. TsCl, pyr; h. $Na_2Fe(CO)_4$; l. I_2, methyl *S*-(+)-mandelate; k. (+)-pinene, 9-BBN.

Herein we show that the stereochemistries of cladosporin (**1**) biosynthesis and fatty acid formation by *Cladosporium cladosporioides* NRRL 5507 are *opposite* at several locations.

Cladosporin (**1**) is an antibiotic and plant growth regulator produced by various fungal sources.[10,11] Researchers at Merck

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