methyl-3-phenyl-2-pentene as the nearly exclusive (92%) product.[16] Addition of spiro silane **3** yields the pentafluorophenyl siliconate **4**[17] (Figure 2). While these reactions may involve the iodinanide directly, we have not ruled out the likelihood that "free" pentafluorophenyl lithium is responsible for the observed products.[18]

Supplementary Material Available: Tables of fractional coordinates and isotropic thermal parameters, anisotropic thermal parameters, interatomic and intermolecular distances, and intramolecular angles (4 pages). Ordering information is given on any current masthead page.

(16) Replacement of vinylic fluorine in perfluoro olefins by organolithium reagents is a known reaction. See: Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood Ltd.: Sussex, England, 1976; Chapter 5.

(17) Stevenson, W. H., III; Wilson, S.; Martin, J. C.; Farnham, W. B. *J. Am. Chem. Soc.* **1985**, *107*, 6340.

(18) Although we have not isolated perfluoro-*n*-alkyl congeners of iodinanide **2**, our results suggest a reinterpretation of the finding by P. Johncock (Johncock, P. *J. Organomet. Chem.* **1969**, *19*, 257) that perfluoro-*n*-heptyllithium is stabilized by excess perfluoro-*n*-heptyl iodide. Formation of perfluoroalkyl iodinanide complexes at low temperature would handily account for the results of the earlier work. We thank Professor H. J. Reich for bringing this reference to our attention.

Total Synthesis of (+)-Latrunculin B

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In 1980 Kashman reported the isolation and structure elucidation of two novel toxins, termed latrunculin A and B (**1** and **2**, Scheme I), derived from the Red Sea Sponge, *Latrunculia magnifica* (Keller).[3] Colonies of this sponge, found in the Gulf of Eilat, grow completely exposed to the hostile sea environment.[3] The sponge, however, is not damaged or eaten by fish or other predators. Indeed, when disturbed the sponge emits a reddish fluid which causes nearby fish to flee the vicinity.[3] The structure of latrunculin A (**1**) including absolute stereochemistry was secured through a combination of X-ray analysis[3b,d] and chemical degradation,[3e] while the structure of latrunculin B (**2**) derived from spectroscopic comparison with that of latrunculin A (**1**).

Our interest in the latrunculins stemmed not only from their novel architecture but also from the report that the latrunculins induce a reversible reorganization of the cytoskeletal proteins.[4] We set as our goal the development of an advanced subtarget that would be amenable to the total synthesis of both latrunculin A and B, as well as possible structural analogues of biological interest.[5] We record here the first total synthesis of (+)-latrunculin B (**2**).

(1) Recipient of an ACS Division of Organic Chemistry Graduate Fellowship sponsored by Merck, Sharp & Dohme Research Laboratories (1984-1985).

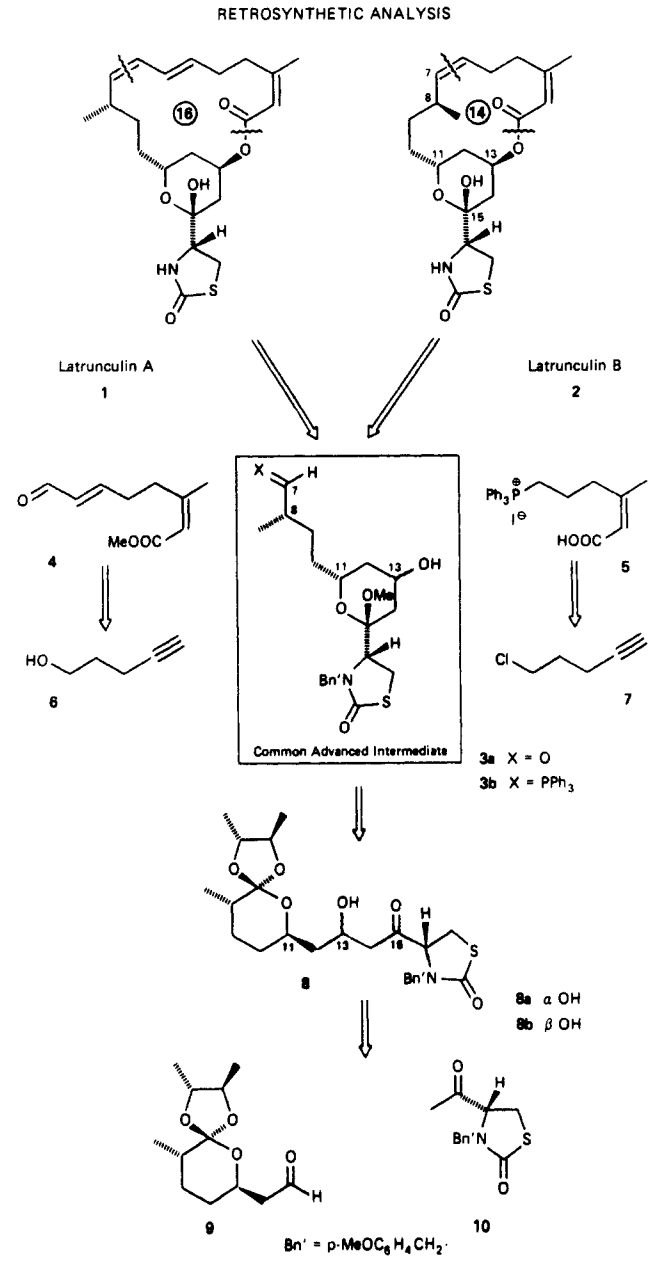
(2) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983, NIH Career Development Awardee, 1980-1985, and J. S. Guggenheim Foundation Fellow, 1985-1986.

(3) (a) Neeman, I.; Fishelson, L.; Kashman, Y. *Mar. Biol.* **1975**, *30*, 293. (b) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629. (c) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science (Washington, D.C.)* **1983**, 493. (d) Groweiss, A.; Shmueli, U.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3512. (e) Kashman, Y.; Groweiss, A.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedtron* **1985**, *41*, 1905.

(4) A recent study by Spector et al. on the effects of the latrunculins on cultured mouse neuroblastoma and fibroblast cells demonstrated that submicromolar amounts of the latrunculins induce changes in the cell morphology (cytoskeletal proteins) which proved reversible upon removal of the toxins.[3c]

(5) Preliminary accounts of this work were presented at the 1984 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, 1984, ORGN 10E36, and the 189th National Meeting of the American Chemical Society, Miami, FL, 1985, ORGN 1.

Scheme I



From the retrosynthetic perspective, cleavage of the macrolide linkage and scission of the cis olefin led to an advanced southern hemisphere (aldehyde **3a** for latrunculin B or ylide **3b** for latrunculin A). The requisite northern hemispheres (**4** or **5**) were envisioned to derive from an appropriately functionalized acetylene; union via a Wittig reaction[6] would then be followed by macrocyclization.[7] Further simplification of advanced intermediate **3a** by ring opening and reorganization led to β-hydroxy ketone **8**, the aldol product of **9** and **10**.

We recognized that our strategy possessed considerable flexibility via-ã-vis the stereochemical outcome of the aldol process. If, for example, the C(13)-*R* configuration were to prevail, direct macrolactonization would be required.[7] Alternatively, if the *S* configuration at C(13) were to predominate, macrolactonization would require inversion.[8] Well aware of the general lack of diastereofacial selectivity observed for methyl ketone enolates,[9a]

(6) For reviews on the Wittig olefination process, see: Trippett, S. *Q. Rev. Chem. Soc.* **1963**, *17*, 406. Maercker, A. *Org. React.* **1965**, *14*, 270.

(7) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(8) Mitsunobu, O. *Synthesis* **1981**, *1*. Kurihara, T., Nakajima, Y., Mitsunobu, O., *Tetrahedron Lett.* **1976**, 2455.

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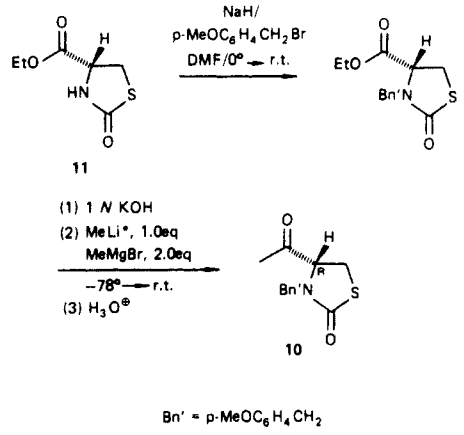
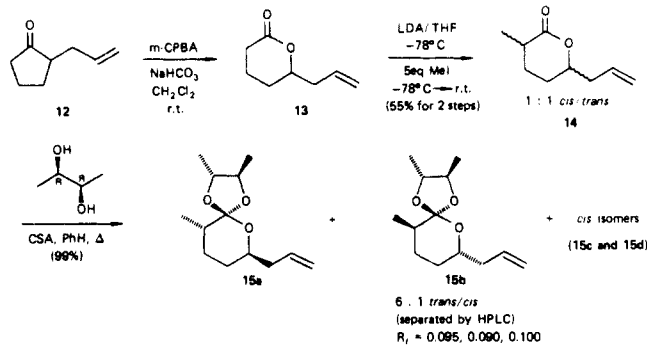
we also had available the possibility of an oxidation–reduction maneuver to set the C(13) center.

With this background, we initiated the synthesis with ethyl 2-oxo-4-thiazolidinecarboxylate (**11**).[10] The amide nitrogen was protected with 4-methoxybenzyl bromide,[11,12] the ester hydrolyzed, and the acid converted to methyl ketone **10**[12] via the method of Rapoport.[13] The overall yield from **11** was 30%.

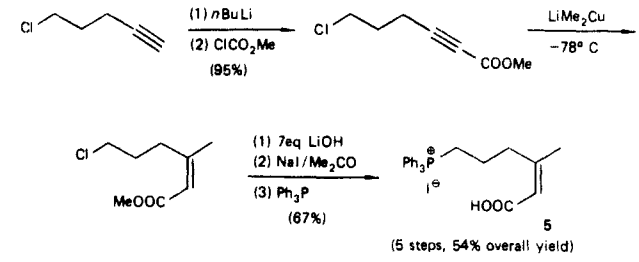


Aldehyde **9** was prepared in four steps beginning with the Baeyer–Villager oxidation of 2-allylcyclopentanone (**12**).[14] Alkylation provided **14**[12a] as a 1:1 mixture of lactones, which in turn was protected as the ortho ester,[12a] employing (+)-(*R*,*R*)-2,3-butanediol.[15] The latter operation served not only to equilibrate the mixture to a 6:1 trans/cis mixture (**15a**,**b**/**15c**,**d**)



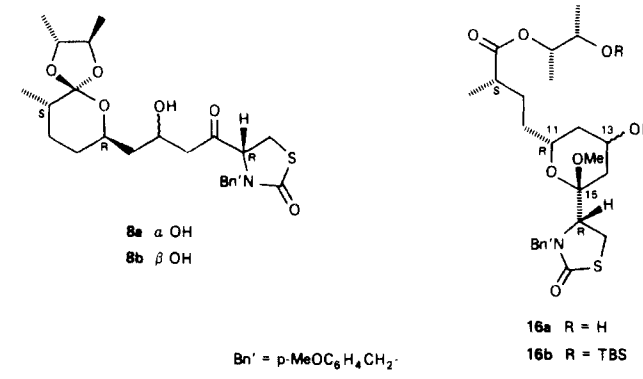
but also resulted in diastereomers readily separable via preparative HPLC (Waters PrepPak-500 with recycle; 10–20-g scale). Homochiral ortho ester **15a** was thus available in 42% yield.[16]

Scheme II



Ozonolysis then provided aldehyde **9**[12a] in near quantitative yield.

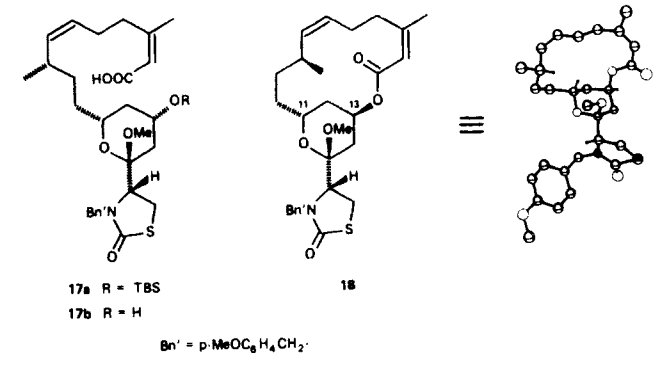
With **9** and **10** in hand we turned to the aldol reaction. Treatment of **10** with $LiN(SiMe_3)_2$ (1.1 equiv/THF/−78 °C) followed by rapid addition to **9** produced a 4:1 mixture of epimeric aldols (**8a**,**b**), which without separation was subjected to TsOH (catalytic) in methanol to provide **16a**, an epimeric mixture at C(13). The overall yield for the two steps was 25%.[9b] This skeletal reorganization is envisioned to involve hydrolysis of ortho ester **8** to give a hydroxy ester intermediate, which in methanol forms the mixed methyl ketal. Diol **16a** was then protected (TBSCl/Et_3N/DMAP/DMF) to give *tert*-butyldimethyl silyl ether **16b**,[12] a diastereomeric mixture readily separable by flash chromatography. Completion of the southern hemisphere (i.e., **3a**, α-OH)[12]



was achieved by DIBAL reduction (53% yield from **16a**). Stereochemical assignments at C(11), C(13), and C(15) derived from a combination of high-field NMR experiments, the anomeric effect[17] [i.e., C(15)], and a number of model studies.[18]

The requisite northern hemisphere (**5**)[12] was prepared in a stereocontrolled manner[19] in five steps (54% overall) from commercial 5-chloro-1-pentyne (Scheme II).

With ample quantities of both the northern and southern hemispheres available, execution of the Wittig coupling [2.9 equiv of dianion of **5** (generated with 5.8 equiv of $KN(SiMe_3)_2$/THF, 0 °C and careful exclusion of oxygen)] proceeded to afford cis olefin **17a** in 81% as the only detectable product. The TBS group



(9) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Florida, 1984; Vol. 3, p 111 and references cited therein. (b) **Note Added in Proof**: The aldol reaction is best carried out by treatment of **10** with $Li(SiMe_3)_2$ (1.1 equiv, THF/−78 °C) followed by the addition of 1.1 equiv of $ZnCl_2$/THF. The resulting zinc enolate[9c] was rapidly added to **9** (containing $ZnCl_2$/THF/−78 °C) which produced a 3:1 mixture of epimeric aldols (**8a**,**b**) in 58% yield. Diol **16a** was obtained upon treatment of the mixture with TsOH/MeOH (46% yield for the two steps). (c) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(10) Kubodera, N.; Nagano, H. Takagi, M.; Matsunaga, I. *Heterocycles* **1982**, *18*, 259.

(11) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

(12) (a) The structure assignment to each new compound was in accord with its infrared and 250-MHz NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or chromatography (LC or TLC) gave satisfactory C and H combustion analysis within 0.4%.

(13) Knudsen, C.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260.

(14) Bernstein, P. R. *Tetrahedron Lett.* **1979**, *1015*.

(15) White, J. D.; Avery, M. A.; Choudry, S. C.; Dhingra, O. P.; Kang, M.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517.

(16) (a) The absolute configuration of **15a** was determined by conversion to the primary alcohol and single-crystal X-ray analysis of the derived *p*-bromophenyl urethane. (b) Unpublished results of P. Carroll, Spectroscopic Service Center, University of Pennsylvania.

(17) Kishi, Y. *Lect. Heterocycl. Chem.* **1980**, *5*, 595. Lemieux, R. U. *Pure Appl. Chem.* **1971**, *27*, 527.

(18) Unpublished results of R. Zibuck, University of Pennsylvania.

(19) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

was then removed [pyridine-$(HF)_x$, THF, 98%][20] in anticipation of macrolactonization.

Given **17b** possessing the *S* configuration at C(13), macrolactonization with inversion of configuration was required. Toward this end, Mitsunobu lactonization (4 equiv of DEAD/Ph_3P in benzene)[8] proceeded smoothly to yield **18**[12] in 68% yield. The structure of **18** was confirmed by single-crystal X-ray analysis.[16b]

Having successfully arrived at **18**, all that remained to complete a synthesis of latrunculin B was removal of the 4-methoxybenzyl group[21] and hydrolysis of the mixed methyl ketal. The former was achieved with 2.0 equiv of $Ce(NH_4)_2(NO_3)_6$ at a concentration of 0.25 M[22] [CH_3CN/H_2O (3:1); 68%], while the latter proceeded with mild acid [HOAc/THF/H_2O (3:1:1), 60 °C]; the yield for the two steps was 42%. That indeed (+)-latrunculin B (**2**) was in hand derived from careful comparison of synthetic material with the 250-MHz ^1H NMR spectrum of natural (+)-latrunculin B kindly provided by Professor Hirama,[23] the ^{13}C NMR and $[\alpha]_D$ data available in the literature,[3d,e] and TLC R_f values in four different solvent systems.

In summation, the first total synthesis of (+)-latrunculin B has been achieved via a highly convergent and stereocontrolled route (longest linear sequence, 14 steps). The synthesis serves both to confirm the structure and to establish the absolute stereochemistry of latrunculin B. Studies directed toward the total synthesis of latrunculin A (**1**) and related macrolides of potential biological interest are currently under way in our laboratory.

Acknowledgment. Support for this investigation was provided by the National Institutes of Health (Grant GM-33833) and Merck Sharp and Dohme. Technical assistance of Michael Becker is also gratefully acknowledged.

(20) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

(21) Several nitrogen protecting groups (e.g., Bn, MOM, MEM, SEM, TBS, and 3,4-dimethoxybenzyl) were explored. The 4-methoxybenzyl group was chosen for its stability throughout the reaction sequence and its removal without destruction of the substrate.

(22) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001. Williams, R. M., Armstrong, R. W., Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733.

(23) We thank Professor Hirama (Tohoku University) for the sample of natural latrunculin B, which in turn was received from Professor Kashman (Tel Aviv University). In addition, we thank Professor Kashman for the high-field ^1H NMR spectrum of latrunculin B.

Novel Cobalt(II)-Catalyzed Oxidative Cleavage of a Carbon-Carbon Double Bond

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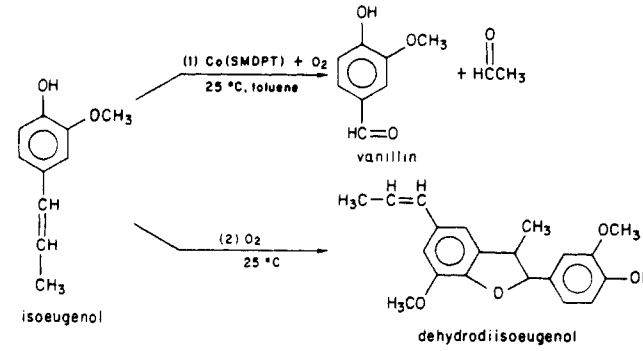
We have recently reported two distinct reaction types for the cobalt-catalyzed, specific oxidation of organic substrates.[1,2] In one, coordination of O_2 to the metal ion was shown to enhance the basicity[3] and radical[4] reactivity of the bound O_2. These features were shown to be important in the cobalt(II)-catalyzed oxidation of substituted phenols where it was demonstrated that metal-bound O_2 was a reactive intermediate. In the second reaction type, the metal complex is involved in the catalytic conversion of O_2 to H_2O_2 or M-O-O-H with accompanying solvent oxidation. Subsequent reactivity involves the reactivity of peroxides. In this paper we report a third type of O_2 activation which results in a novel cleavage of a carbon-carbon double bond by molecular oxygen.

Scheme I. Proposed Reactions in the Oxidation of Isoeugenol by CoSMDPT[a]



[a] The formation of vanillin and acetaldehyde and the side product dehydrodiisoeugenol, the coupled dimer.

Table I. First Order CoSMDPT Dependence of the Oxidation of Isoeugenol

reaction[a]	molarity, M	initial rate[b]	conversion[c]	TO[e]
5.0 mg of CoSMDPT	2.44×10^{-4}	2.25	27.9 (125)	562
11 mg of CoSMDPT	5.36×10^{-4}	3.91	58.3 (345)	535
			60.8 (440)	558
20 mg of CoSMDPT[d]	9.75×10^{-4}	8.10	58.3 (150)	294
			67.2 (365)	339
100 mg of CoSMDPT[d]	48.73×10^{-4}	12.4	68.3 (195)	69
			74.7 (530)	75

[a] Reaction is run at 60 °C, in toluene, at P_0 = 75 psi, and 2.46×10^{-2} mol of isoeugenol. 50-mL total volume of solution is used, which is 0.49 M in isoeugenol. [b] Initial rate is expressed as moles of O_2 absorbed per mole of substrate per minute. Reported values have been multiplied by 1×10^3. [c] Conversion is the moles of O_2 absorbed divided by the moles of isoeugenol present, expressed as a percent. The duration of the reaction, in minutes, is in parenthesis. [d] An average of two runs. [e] Number of turnovers based on moles of O_2 consumed per mole of catalyst.

We discovered the formation of vanillin from the cobalt(II) catalytic oxidation of lignin, a para-substituted polyphenolic polymer comprising 25-30% of the dry weight of trees[5] whose biological function is to provide structural support in vegetation. We were surprised that the oxidation of lignin proceeded rapidly at 60 °C and 75 psi of O_2 pressure because previous reports indicated that oxidation of para-substituted phenols by cobalt dioxygen complexes was sluggish.[6] Due to the complexity of lignin, we decided to probe this reactivity by changing substrates to the model compound isoeugenol,[7] 2-methoxy-4-propenylphenol (see Scheme I). Rapid, catalytic oxidation of isoeugenol occurred in toluene solvent at 60 °C and 75 psi of O_2 to form vanillin (path 1). Several stoichiometric reactions resulting in the conversion of isoeugenol to vanillin are cited in the literature,[5] but our reaction has the benefit of being catalytic while maintaining a high level of selectivity.

In a typical run, isoeugenol is oxidized by O_2 with [bis(salicylidene-γ-iminopropyl)methylamine]cobalt(II) (CoSMDPT) as the catalyst to form about 50% vanillin, 30% unreacted isoeugenol, and 20% dehydrodiisoeugenol, a dimerization product[8] (path 1). The reaction occurs at room temperature in about 24 h and proceeds much more rapidly at 60 °C (see Table I). In this study,

(1) Zombeck, A.; Drago, R. S.; Corden, B. B.; Gaul, J. H. *J. Am. Chem. Soc.* **1981**, *103*, 7580-7585.

(2) Zombeck, A.; Hamilton, D. E.; Drago, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 6782-6784.

(3) Drago, R. S.; Cannady, J. P.; Leslie, K. A. *J. Am. Chem. Soc.* **1980**, *102*, 6014-6019.

(4) Hamilton, D. E.; Drago, R. S.; Telser, J. *J. Am. Chem. Soc.* **1984**, *106*, 5353-5355.

(5) Lignins: Occurrence, Formation, Structure and Reactions; Sarkanen, K. V., Ludwig, C. H., Eds.; Wiley: New York, **1971**.

(6) Zomeck, A. Ph.D. Dissertation, University of Illinois, Urbana, IL, 1980.

(7) For the experimentation, only *trans*-isoeugenol was used, which was obtained by catalytic isomerization of eugenol using $RhCl_3$ under nitrogen at room temperature.[8] When a cis-trans mixture of isomers was used, less vanillin was produced and the catalyst was deactivated more rapidly.

(8) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

0002-7863/86/1508-2453$01.50/0