Scheme II

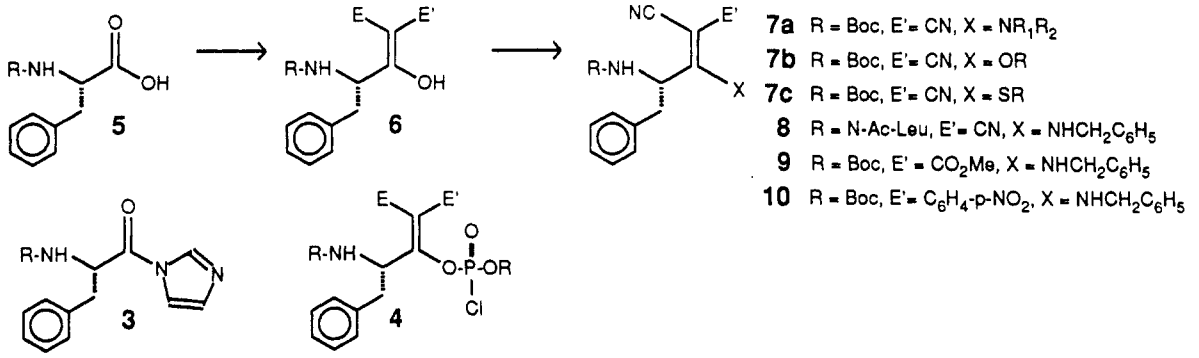
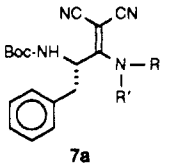
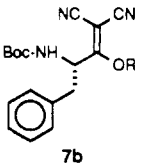


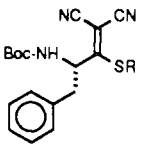
Table II. Preparation of Enamines 7a, Enol Ethers 7b, and Thioenol Ethers 7c



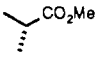
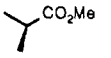
7a



7b



7c

entry	R'	R	yield, %	R	yield, %	R	yield, %
1	H	H	73			H	34
2	H	Ph	80	Ph	45	Ph	70
3	H	Bn	62	Me	41	Et	82
4	H	*i*-Pr	57	*i*-Pr	15	*i*-Pr	49
5		$-(CH_2)_4-$	35	*t*-Bu	0	*t*-Bu	15
6	H		79				45

6) is obtained with methyl mercaptopropionate[14] as the nucleophile. This methodology has been applied on *N*-Ac-leucylphenylalanine dicyano enol **6f**, a chymotrypsin substrate analogue, and to other Boc-phenylalanine functionalized enols. For instance, **6f**, **6b**, and **6c** afforded the corresponding enamines **8**, **9**, and **10** in 25%, 35%, and 40% yields, respectively, under similar reaction conditions with benzylamine as the nucleophile. The ^1H NMR spectrum of dipeptide enamine **7a** (Table II, entry 6) did not show the presence of the other diastereomer formed by racemization, indicating that optical integrity is preserved during the reaction.

This is the first time that difunctionalized enamines, enol ethers, and thioenol ethers have been reported as modifications for the peptide amide function, both at endo and C-terminal positions. As a result, effective electron-withdrawing functionalization has now been performed on α-chymotrypsin dipeptide substrates. Furthermore, the enol hydroxyl function has been elaborated through the use of phenyl phosphorodichloridate as an activating reagent. Importantly, the chiral integrity of peptides is maintained in these reactions. This methodology allows easy introduction of functionalities at the three positions of the vinyl isosteric peptide bond with several electron-withdrawing groups and different leaving groups. We are currently applying these transformations to peptidic enzyme substrates that may serve as useful probes for studying analogue–enzyme interactions. Full experimental details and the results of enzymatic studies using these analogues will be reported elsewhere.

(14) Preparation of methyl (*R*)-2-mercaptopropionate: Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664-3671.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada and the Fonds FCAR (Québec). N.L.B. is the recipient of a Fonds FCAR graduate fellowship and B. Z. is the recipient of a J.-L. Lévesque (I.A.F.) postdoctoral fellowship.

Supplementary Material Available: Experimental procedure and characterization data (^1H NMR spectra) for all products; ^{13}C NMR, IR, optical rotations, elemental analysis, and mass spectra for several products (15 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Isovelleral, a Mutagenic Sesquiterpene Dialdehyde from *Lactarius vellereus*

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Summary: The mutagenic sesquiterpene dialdehyde (±)-isovelleral, a component in the chemical defense mechanism of many basidiomycetes, has been prepared by the total synthesis outlined in the scheme.

Basidiomycetes of several genera, including *Lactarius* and *Russula*, have a complicated chemical defense mechanism in which fatty acid esters of the unstable sesquiterpene hemiacetal velutinal (1) appear to function as the

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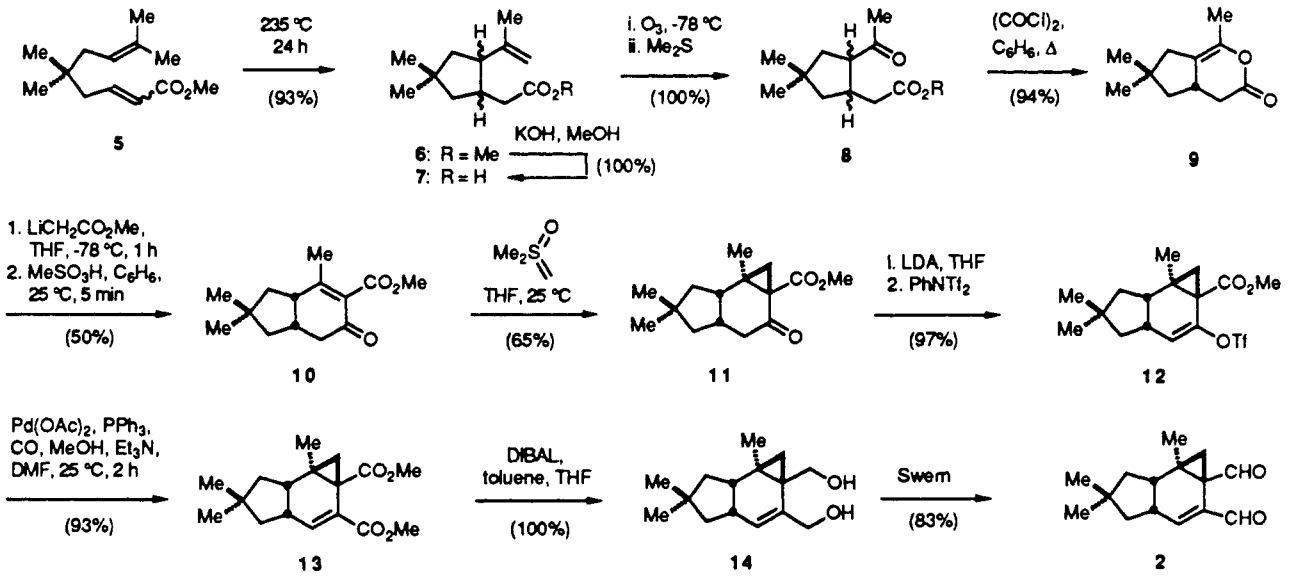
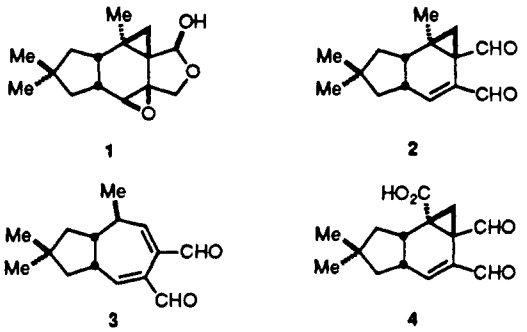
Scheme I



ammunition.[1] For example, injury of a sample of *Lactarius vellereus* causes rapid enzymatic conversion of these esters to **1**, which is further transformed into the strongly antifungal and antibacterial sesquiterpene dialdehydes isovelleral (**2**)[2] and velleral (**3**).[3] Compounds **2** and **3** impart a robust pungent taste to the fungi and **2** is a potent opossum antifeedant.[4] Isovelleral shows significant mutagenic activity in the Ames *Salmonella*/microsome assay and may be a contributing mutagen in other species of *Russulaceae*, such as *L. rufus*, *L. necator*, *R. aeruginea*, *R. consobrina*, and *R. foetens*.[5] In this communication, we report a total synthesis of (±)-isovelleral.[6,7]



The synthesis is summarized in Scheme I. Pyrolytic cyclization of dienic ester **5** (a 20:1 mixture of *E* and *Z* isomers)[8] provides **6** (a 70:30 mixture of cis and trans isomers). Saponification gives **7**, which is ozonized to obtain keto acid **8**. Enol lactone **9**, obtained by reaction of **8** with oxalyl chloride, is treated sequentially with the lithium enolate of methyl acetate and methanesulfonic acid in benzene to obtain the unsaturated β-keto ester **10**. This substance reacts with the Corey–Chaykovsky reagent[9] to give **11**, a single diastereomer. The smooth cyclopropanation of **10** is uncommon, as the dimethyloxosulfonium methylide usually deprotonates ketones with enolizable α-protons.[10] The lithium enolate of **11** is triflated[11] to obtain enol triflate **12**. Methoxycarbonylation of **12**[12] furnishes diester **13**. Reduction of **13** gives diol **14**, which is oxidized by the Swern protocol[13] to obtain (±)-isovelleral (**2**), identical by 500-MHz ^{1}H NMR spectrometry with an authentic specimen provided by Professor B. Wickberg of the University of Lund.

The synthesis of **2** requires 14 steps from 3-methylbut-2-enal and provides the sesquiterpene in 15% overall yield. It is highly stereoselective and can be readily adapted through the use of ^{13}CO or ^{14}CO in the Stille reaction to provide labeled material for use in biosynthetic investigation. Since isovelleral has been converted into velutinal,[14] the current synthesis can be used to provide access to that important mushroom defense substance.[15]

Supplementary Material Available: Analytical data (^{1}H and ^{13}C NMR spectra, CH analysis) for compounds **2** and **6**–**14** and 500-MHz ^{1}H NMR spectra of synthetic and natural isovelleral (6 pages). Ordering information is given on any current masthead page.

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(11) (a) Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438. (b) Stang, P. J.; Treptow, W. *Ibid.* **1980**, 283. (c) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(12) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
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(15) This work was supported by a research grant from the National Science Foundation (CHE-8418427). We thank Professor Wickberg for a sample of authentic isovellaral.