of the present methodology for the preparation of C_{20} gibberellins from the more readily available C_{19} analogues.

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Registry No. (±)-2 methyl ester, 86064-48-4; (±)-3, 86047-03-2; (±)-4 (isomer 1), 86047-04-3; (±)-4 (isomer 2), 86117-00-2; 5, 86047-05-4; (±)-6 (isomer 1), 86047-06-5; (±)-6 (isomer 2), 86047-07-6; (±)-7, 75801-07-9; (±)-8, 84693-19-6; (±)-9, 86047-08-7; (±)-10, 86047-09-8; (±)-11, 86047-10-1; (±)-12, 86047-11-2; (±)-12·2-TMS, 86047-12-3; (±)-13, 86047-13-4; allyl bromide, 106-95-6.

† Dedicated to the memory of the late Franz Sondheimer.

(23) C_{19} gibberellins have been prepared in 22,[4d] 24,[4c] and 29[4c] steps from commercially available naphthalene derivatives, while the present synthesis extends over 27 steps.

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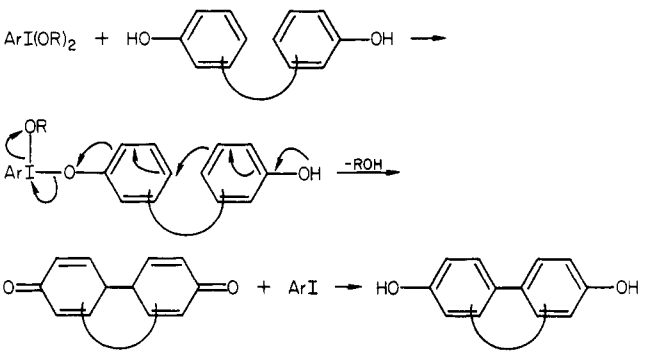
Phenolic Oxidative Coupling with Hypervalent Iodine. A Synthesis of 6a-Epipretazettine

Summary: 6a-Epipretazettine was synthesized in seven steps from piperonal and synephrine. Intramolecular, monophenolic, oxidative coupling of a functionalized benzylic acetal, employing [bis(trifluoroacetoxy)iodo]-benzene as oxidant, gave a spirodienone in 13% yield. Subsequent deprotection of the secondary amine was followed by spontaneous closure to a tetracyclic pyrrolidine possessing an all-cis ring fusion. This substance was reduced with diisobutylaluminum hydride, and the resulting alcohol was transformed, via methanolysis of the corresponding mesylate, to *O*-methyl-6a-epipretazettine. Acidic hydrolysis of the latter yielded 6a-epipretazettine, identical with material previously obtained by Danishefsky.

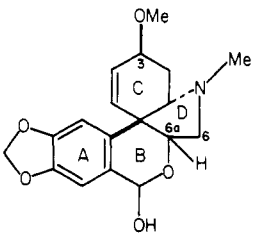
Sir: Intramolecular, oxidative coupling of phenols is a ubiquitous process in secondary metabolism.[1] Its central role in the biosynthesis of alkaloids of the Amaryllidaceae family[2] has prompted numerous attempts to simulate the natural pathway in vitro.[3] Conventional methodology for effecting oxidative, phenolic coupling has been based upon metallic reagents, many of which appear to function as homolytic (one-electron) oxidants. In a departure from this protocol, we have investigated hypervalent iodine(III) species[4] as potential reagents for phenolic coupling[5] via a heterolytic mechanism, as expressed in Scheme I.

The efficacy of this approach was recently demonstrated with a total synthesis of (−)-codeine.[6] We now report a synthesis of 6a-epipretazettine (**2**), in which the focal step

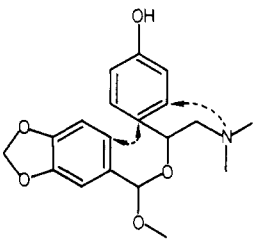
Scheme I



also entails an iodine(III)-mediated linkage of two aryl rings.



1, $\beta 6_aH$
2, $\alpha 6_aH$



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Pretazettine (**7**) and its 6a epimer (**8**) were first described by Wildman,[7] who also prepared **1** from the related alkaloid haemanthidine.[8] Recently, Danishefsky, in a thwarted endeavor to achieve a de novo synthesis of **1**, acquired **2** by an elegant variation of a strategy previously employed for the structurally simpler mesembrine group.[9] By contrast, our plan envisaged construction of the spirocyclic portion of the tazettine skeleton via a biomimetic, oxidative coupling of a fully functionalized dibenzylic ether **3**, with closure of the pyrrolidine D ring[10] at a late stage.

To this end, piperonal (**4**) and *dl*-synephrine (**5**) (Scheme II) were condensed (MeOH, 25 °C, 10 h) to give the crystalline oxazolidine **6** in quantitative yield.[11] Treatment of **6** with 2,2,2-trichloroethyl chloroformate in MeOH–$CHCl_3$ (1:1, 25 °C, 12 h) afforded urethane **8** in 53% yield via the oxazolidinium salt **7**. After considerable experimentation, it was found that the labile acetal **8** could be converted to the oxidative coupling product **9** with [bis-(trifluoroacetoxy)iodo]benzene[12] (2 equiv, CH_2Cl_2, −10 °C, 0.5 h) in the presence of propylene oxide (10 equiv) in 13% yield.[13]

A parallel sequence employing methyl chloroformate led from **6** (via **10**) to the urethane **11** and then to the dienone **12** in analogous fashion. However, hydrolytic attempts to remove the urethane substituent in this case were unrewarding, while nucleophiles (e.g., trimethylsilyl iodide) effected an exceptionally clean conversion of **12** to the biphenyl derivative **13**, presumably via a retroaldol fragmentation originating from the derived hemiacetal.

In contrast, exposure of **9** (Scheme III) to zinc (THF with 10% 1 M NH_4OAc, 25 °C, 40 h)[14] resulted in smooth

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(9) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591.
(10) This designation adheres to the system used originally by Wildman (ref 8).
(11) Satisfactory spectroscopic and analytical data were obtained for all new compounds.
(12) Spyroudis, S.; Varvoglis, A. *Synthesis* **1975**, 445.
(13) The major product from this reaction is piperonal, which is formed even under rigorously anhydrous conditions.

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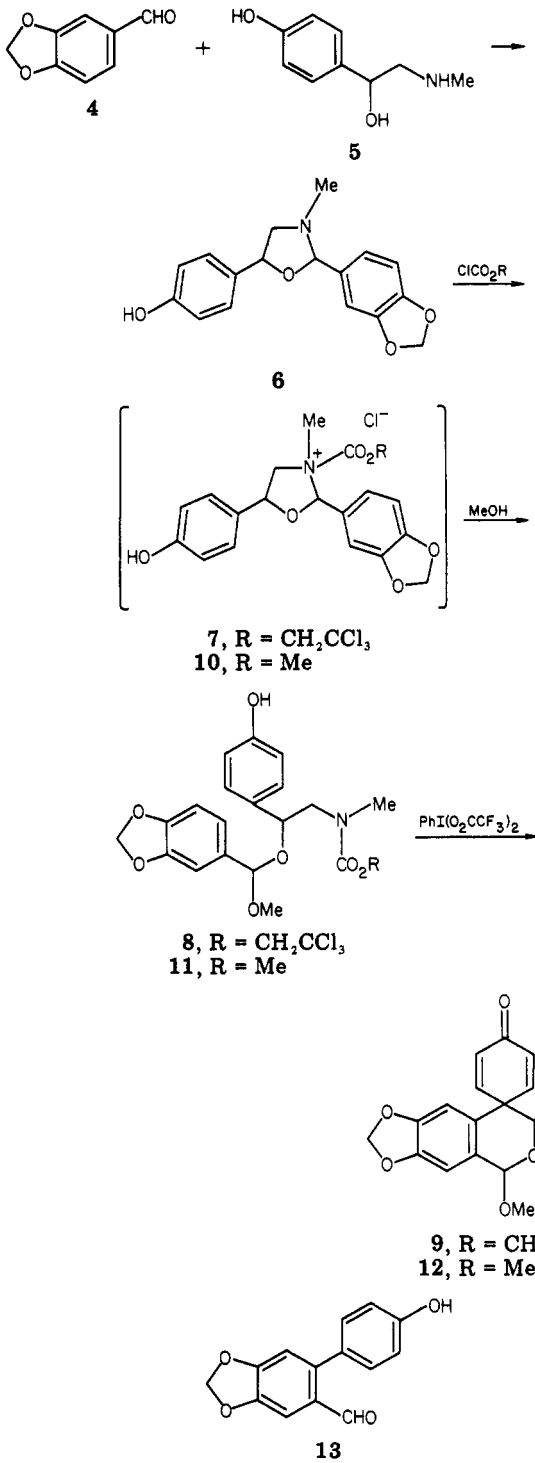
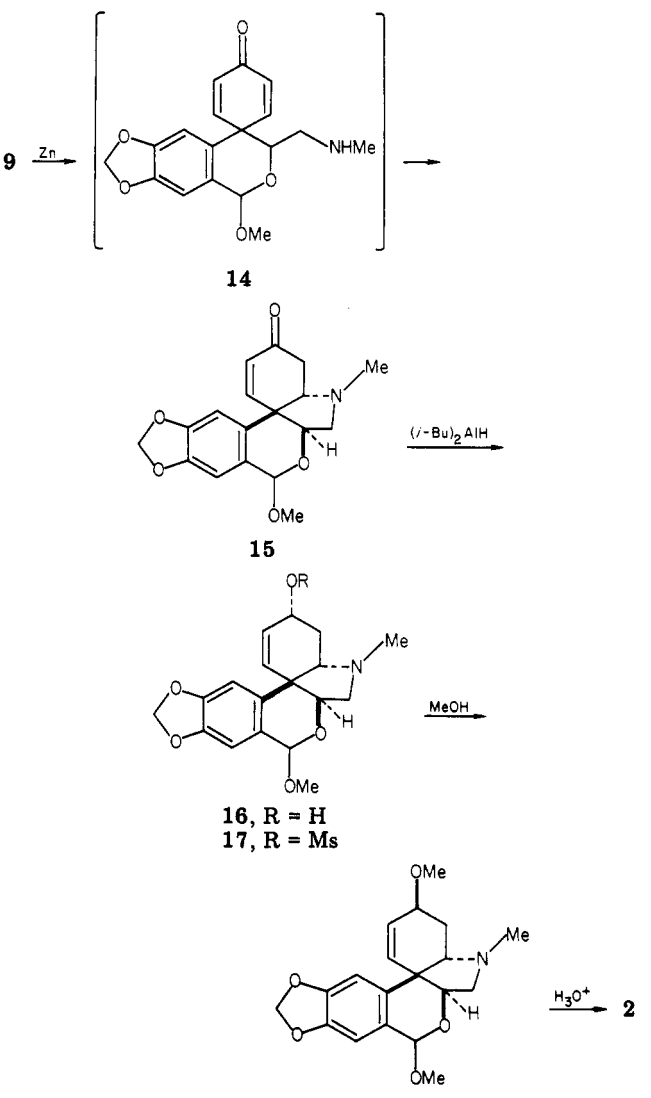
Scheme II



liberation of the secondary amino function of **14**, which underwent a spontaneous, intramolecular addition to give tetracycle **15** in 65% yield. Assignment of cis B/D stereochemistry to **15** was assisted by proton-decoupled NMR spectroscopy at 360 MHz, which showed $J_{6a-6\alpha} \simeq 0$ Hz and $J_{6a-6\beta} = 4.5$ Hz. These values differ from the corresponding proton couplings in pretazettine (**1**, $J_{6a-6\alpha} = 11.0$ Hz, $J_{6a-6\beta} = 7.7$ Hz)[15] and agree with a conformation for **15** in which H_{6a} and $H_{6\alpha}$ are virtually orthogonal. The absence in this reaction of any trace of a trans B/D stereoisomer of **15** implies a powerful impetus in the closure of **14** toward the unnatural but more stable all-cis ring fusion.

Scheme III



A stereoselective reduction of ketone **15** with diisobutylaluminum hydride (CH_2Cl_2, −30 °C) gave alcohol **16** (67%), accompanied by a minor amount of the saturated alcohol from conjugate reduction. Methanolysis of **16**, with inversion of configuration at C-3, was effected via mesylate **17** ($(CH_3SO_2)O$, Et_3N, THF, −10 °C, 0.5 h), following methodology[16] applied in a related system.[9] Finally, acidic hydrolysis (0.1 N HCl) of **18** afforded quantitatively 6a-epipretazettine (**2**), spectroscopically identical with material obtained by Danishefsky.[17]

In conclusion, we find it significant that oxidative coupling of a highly functionalized, acid-sensitive, *monophenolic* substrate can be accomplished with a hypervalent iodine complex even though the yield is low. Further studies designed to improve the efficiency of these oxidative couplings, as well as a realignment of this approach toward pretazettine (**1**), are in progress.

Acknowledgment. High-field NMR measurements were made on a Nicolet 360-MHz spectrometer at the University of Oregon through the courtesy of Professor

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(17) We are indebted to Professor Samuel Danishefsky for copies of infrared and ^1H NMR spectra of 6a-epipretazettine and *O*-methyl-6a-epipretazettine and also for a copy of his manuscript prior to publication.

Charles E. Klopfenstein. Financial support for this research was provided by PHS Grant DA-02722 and by the Nicholas L. Tartar Fund through a Fellowship to W.K. M.C.

Registry No. (±)-2, 86064-46-2; 4, 120-57-0; (±)-5, 582-84-3; 6, 86046-45-9; 8, 86046-46-0; 9, 86046-47-1; 11, 86046-48-2; 12, 86046-49-3; 13, 86046-50-6; 14, 86046-51-7; (±)-15, 86064-47-3; (±)-16, 86101-22-6; (±)-17, 86101-23-7; (±)-18, 86116-85-0; [bis-(trifluoroacetoxy)iodo]benzene, 2712-78-9; 2,2,2-trichloroethyl chloroformate, 17341-93-4.

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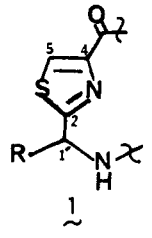
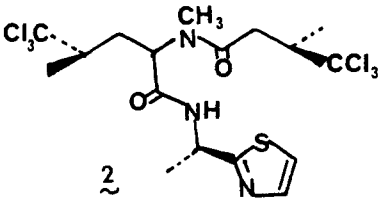
Absolute Configuration of Thiazole Amino Acids in Peptides

Summary: A general method is presented for determining the absolute configuration of 2-(1-aminoalkyl)thiazole-4-carboxylic acids, based on the reaction of thiazoles with $^1O_2$. This newly developed method is used to assign the absolute configuration of thiazole amino acids in the cytotoxic peptides isolated from the marine tunicate *Lissoclinum patella*.

Sir: Previously, we reported the structures and pharmacological profiles of a series of cytotoxic peptides from the tunicate *Lissoclinum patella*,[1,2] all of which contain 2-(1-aminoalkyl)thiazole-4-carboxylic acid moieties (1). These



1



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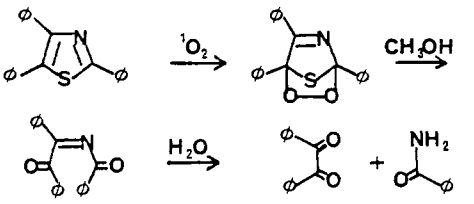
unusual sulfur-containing amino acids are believed to arise biosynthetically from the dehydrative cyclization of a cysteinyl peptide such that C-2 of the thiazole originates from the carboxyl of an amino acid on the N-terminal side of cysteine.[3] Inspite of the probability that thiazoles are derived from chiral precursors, uncertainty existed in the literature, for several years, regarding the chirality of the C-2 substituent. For example, the first thiazole amino acids isolated from the acid hydrolysis of thiostrepton[4] and bottromycin[5] were racemic. We have corroborated this result with the lissoclinum peptides, finding that the thiazoles isolated from 6 N HCl hydrolysis are racemic. Subsequent to degradation studies, the structure of thiostrepton was determined by X-ray studies, and the thiazoles were shown to have the *S* absolute configuration,[6] corresponding to a L-amino acid as the C-2 substitutent. In another X-ray investigation, Tursch's group assigned the *R* configuration to the thiazole in isodysidenin (2), a highly modified peptide from a marine sponge,[7] indicating the presence of a D-alanine in the precursor peptide chain. It is quite clear and not surprising that acid hydrolysis of a peptide results in racemization at C-1′ of a thiazole amino acid of the general formula 1. To our knowledge, the only previous method for determining absolute configuration of these amino acids in peptides was X-ray analysis. We now report a general and mild method for determining the

Scheme I. Reaction of Triphenylthiazole with $^1O_2$[a]



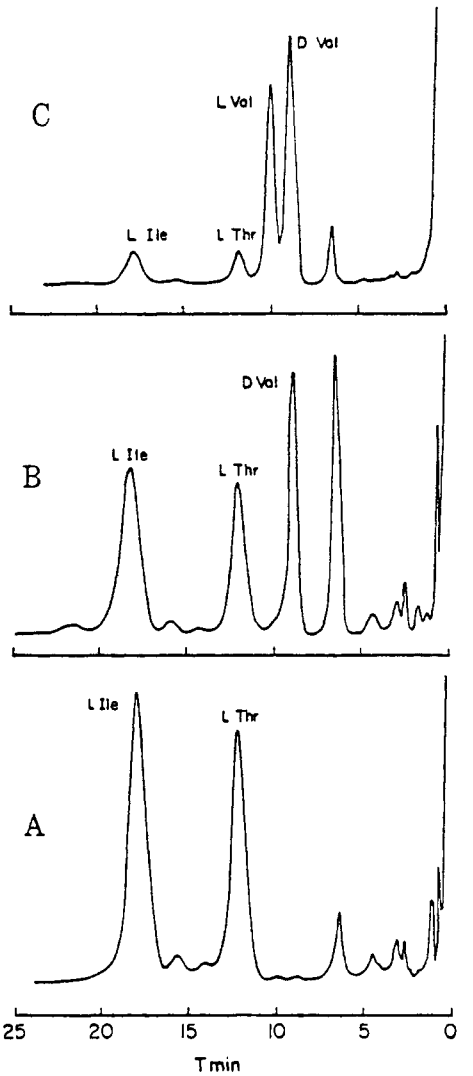


Figure 1. GC analysis of patellamide A (5) hydrolysis products as ME-TFA derivatives (column, SP-300 12 ft × 1/8 in.; program, 110–140 °C at 2°/min, 30 min at T_1. (A) 6 N HCl hydrolysis of 5 without $^1O_2$ pretreatment. L-Serine elutes at 30 min. Valine thiazole does not elute off this column. (B) 6 N HCl hydrolysis of 5 treated with $^1O_2$. (C) Coinjection of the previous sample with D,L-valine.

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