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(3) The preparation of 3a-methylpyrrolo[2,3-*b*]indole derivatives (I) has been well documented in connection with physostigmine. We have recently developed a simple synthesis of 3a-hydroperoxy- or 3a-hydroxypyrroloindole derivatives (ii) by the dye-sensitized photooxygenation of tryptamines[4] and tryptophans.[5]
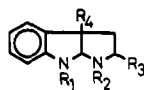
i) R$_4$ = CH$_3$

ii) R$_4$ = OH or OOH

iii) R$_1$ = H R$_2$, R$_3$ = CO$_2$Me R$_4$ = OH

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(8) The excess acid should be quenched by way of pouring the mixture into a mixture of 10% sodium carbonate and methylene chlroide in an ice bath.

(9) The NMR spectrum showed the presence of two rotamers due to hindered rotation around the carbamate N–C bond. A similar spectrum was obtained in pyridine-*d$_5$* at 25 °C, becoming a simple spectrum at 80 °C.

(10) The stereochemistry of the stable isomer **2a** is not established unequivocally, but comparison of its spectral data and its rate of N$_a$-acetylation with those of the *cis*- and *trans*-3a-hydroxypyrroloindole derivatives (iii),[5] whose structures (see note 3) have been established by X-ray analysis, indicates trans with respect to the 3a hydrogen and the ester group configuration for the stable isomer **2a**.

(11) The conversion of isomers may proceed via iv and v. The N$_a$-protonated form (v) was found to be a major species from the uv spectrum of 2 in 85% phosphoric acid. Deuterium exchange was observed not only at the 3a and 8a hydrogens, but also at benzene ring hydrogens of **2a**. Cf. S. Kang, T. H. Witherup, and S. Gross, *J. Org. Chem.*, **42**, 3769 (1977).

$$1 \underset{H^+}{\overset{H^+}{\rightleftharpoons}} 4 \rightleftharpoons \quad iv \quad \rightleftharpoons \quad v$$
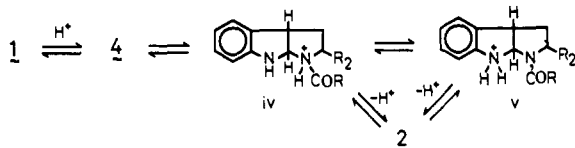
(12) *N$_b$*-Acetyltryptamine in 85% phosphoric acid, on the other hand, gave a dimeric product related to the skatole dimer as the main product. Tryptamine itself behaves similarly. These results indicate that the tautomerization to **2** competes with the dimerization. Furthermore, the nucleophilicity of the carbamate group seems to be greater than that of acetamido group in acidic media.

(13) The protection of the 2 position of indoles by sodium bisulfite adducts has been reported: J. Thesing, G. Semler, and M. Mohr, *Chem. Ber.*, **95**, 2205 (1962).

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Total Synthesis of Confertin via Metal-Promoted Cyclization–Lactonization

Sir:

Confertin (**1**) is one of the simplest of the sesquiterpene α-methylene-γ-lactones, a class of compounds which have attracted attention as synthesis targets because of general cytotoxicity.[1] This member of the pseudoguaianolide family of sesquiterpenes has been the object of a successful total synthesis[2] and the closely related structure, damsin, has been prepared by three research groups.[3] In common with all previous syntheses of natural α-methylene-γ-lactones, the strategy
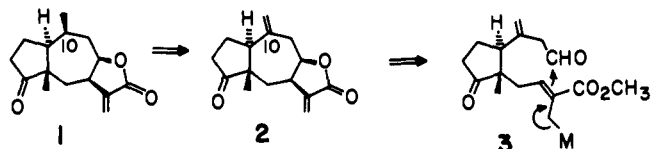
Scheme I
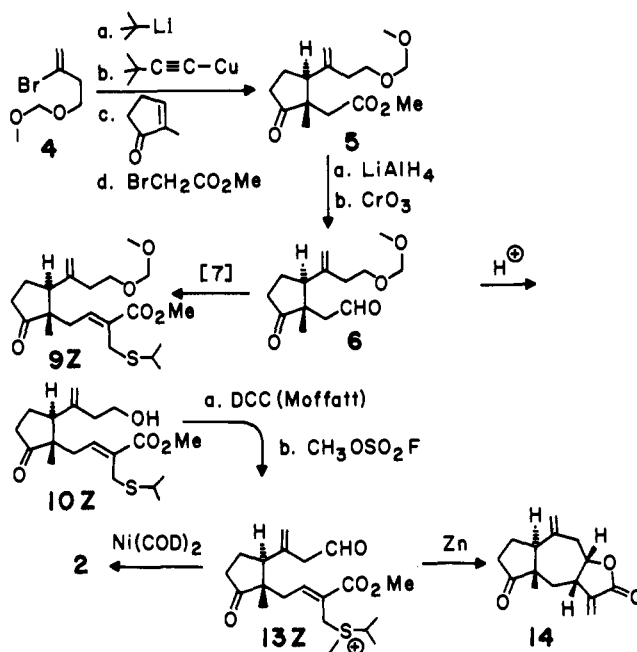
in these efforts involved addition of an α-methylene group to a carefully constructed γ-butyrolactone derivative.[4] We wish to report a new approach to sesquiterpene α-methylene-γ-lactones which we demonstrate with the total synthesis of confertin. Our strategy involves intramolecular coupling of an allylic metal species (e.g., **3**) with an aldehyde unit (cyclization) followed by spontaneous lactonization, making use of the natural functionality of the α-methylene carbonyl unit to facilitate formation of the allyl metal intermediate. The method is based on simple intermolecular examples of α-methylene-γ-lactone formation using allylzinc[5] and allylnickel[6] intermediates, and on our own model studies for intramolecular applications.[7]

Confertin (**1**) has five centers of chirality which have been assigned as shown based on spectral and chemical correlation with other natural sesquiterpene lactones.[8] Our strategy relies on selective hydrogenation of a C-10 *exo*-methylene group (in **2**) to introduce the proper stereochemistry at C-10, and selectivity for the β-cis lactone ring fusion from cyclization of **3** to **2**. The model studies[7] indicated a strong tendency for formation of cis ring fusion, but there was no obvious rational for predicting β-cis (natural) or α-cis lactone ring fusion. We entered into the synthesis of confertin partly to establish the stereochemical preferences for the cyclization–lactonization and to probe for control over stereoselectivity through the reaction variables implicit in general intermediate **3**. Scheme I presents the successful route, showing all isolated intermediates.[9] Vinyl bromide **4** was obtained from 4-hydroxy-1-butyne using the method of Boeckman.[10] Following the general strategy of organocuprate conjugate addition–enolate trapping,[11] vinyl bromide **4** was combined with 2-methyl-2-cyclopentenone and methyl bromoacetate to produce **5**. Halogen–metal exchange of **4** with *tert*-butyllithium followed by addition of (3,3-dimethyl-1-butynyl)copper(I)[12] gave an organocuprate to which was added 2-methylcyclopentenone at -45 °C. The resulting enolate in tetrahydrofuran–ether (1:4) was added to a 5-fold excess of methyl bromoacetate in ether–hexamethylphosphoric triamide (1:1, v:v) at -20 °C.[13] The product (**5**) was obtained in 85% yield, contaminated with <5% of the epimer (at C-5, pseudoguainolide numbering). The stereochemistry of **5** is as expected,[14] supported by ^{1}H NMR[15] and confirmed by the structure of the final product **1**.

The side-chain ester in **5** was converted to an aldehyde by

reduction with lithium aluminum hydride (the ketone is reduced also), followed by oxidation with chromium trioxide-pyridine in dichloromethane.[16] The yield of **6** for the two operations was 85%.

A mixture of the 2-phosphonoacrylate **7** and sodium iso-propylmercaptide produced the phosphonate anion **8** in situ.[17]
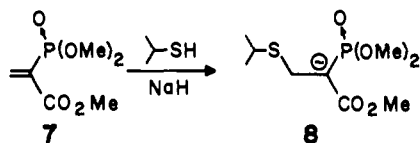
Then addition of the aldehyde **6** resulted in selective reaction at the aldehyde carbonyl group (5 h, 25 °C) to give the 2-thi-omethyl acrylate derivative **9** in 70–85% yield, as a mixture of *Z* and *E* isomers. As in the earlier studies of this reaction,[17] the configuration of the double bond depends upon the reaction conditions. Using the lithium salt of **8** (from *n*-butyllithium-isopropyl mercaptan) in toluene, the product was a mixture of **9E** and **9Z** in a ratio of 8:1. With the sodium salt of **8** (from sodium hydride–isopropyl mercaptan) in tetrahydrofuran the ratio is 1:4.

The β,γ-unsaturated aldehyde unit required in **3** was obtained by hydrolysis of the acetal protecting group (*p*-toluenesulfonic acid, methyl alcohol, reflux for 20 h) to give **10** and delicate oxidation using the method of Moffatt.[18] It was essential to avoid oxidation of sulfur and isomerization of the β,γ double bond (**11**) into conjugation (as in **12**). The double-bond isomerization could not be avoided entirely and inevitably occurred during attempts at purification of the oxidation product. Therefore, the oxidation was carried out under mild conditions (dicyclohexylcarbodiimide, trifluoroacetic acid, 25 °C), the crude product was simply triturated at 25 °C with hexane to remove the urea by-product, and a pentane solution was cooled to −78 °C to precipitate an oil which was a mixture of aldehydes, with a ratio of **11:12** of ~9:1. This material was used in the next step.
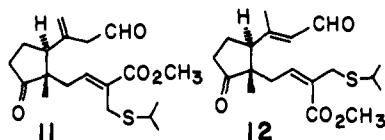
In our model studies, the ring closure was initiated by insertion of Zn(0) or Ni(0) into an allylic bromide unit.[7] The sensitivity of the β,γ-unsaturated aldehyde unit precluded conversion of the allylic thioether to the allylic bromide. An effective alternative was found through treatment with methyl fluorosulfonate to give an intermediate presumed to be the sulfonium ion **13**; this derivative showed reactivity toward Zn(0) and Ni(0) reagents similar to that of an allylic bromide. The products from oxidation and from methylation (**13Z** and **13E**) were not purified or fully characterized. The crude sample of **13** was studied in reaction with low valent metals. Optimum yields in cyclization–lactonization were obtained with zinc/copper couple[19] and bis(1,5-cyclooctadiene)nickel.[20]

Reaction with excess zinc/copper couple in tetrahydrofuran of 40 °C for 20 h produced isomer **14** in 30% yield overall from alcohol **10**. The product was isolated by medium-pressure liquid chromatography, mp 133–134 °C, and was shown by x-ray diffraction on a single crystal to bear the cis-fused lactone in the unnatural α configuration (i.e., **14**).[21]

Treatment of **13** (1:4 *E:Z*) with excess bis(1,5-cyclooctadiene)nickel(0) in tetrahydofuran at −20 to 25 °C produced a mixture of two α-methylene-γ-lactones in 43% yield overall from alcohol **10**, in the approximate ratio of 2:1. The major isomer was isolated as before, mp 123–124 °C. Since the cyclization-lactonization method tends to produce cis-fused

lactones,[7] the structure was assumed to be **2**. Selective hydrogenation of **2** to give **1** has not yet succeeded; the two olefin units have similar reactivity. Protection of the α-methylene-γ-lactone unit by conjugate addition of *n*-propyl mercaptan[22] allowed hydrogenation (10% Pd/C, CH₃OH, 48 h) of the C-10 methylene unit with the anticipated stereoselectivity to give only the natural configuration at C-10. Elimination of *n*-propylmercaptan was accomplished by the well-established sequence[22] of methylation at sulfur (methyl fluorosulfonate, CHCl₃, 3 h, 25 °C), followed by base treatment (saturated aqueous sodium bicarbonate solution, two phase, 24 h, 25 °C). A single α-methylene-γ-lactone, mp 116–117 °C, was obtained in low yield overall from **2**. The 270-MHz ¹H NMR spectrum of this material was identical with a spectrum of natural (±)-confertin (mp 145–146 °C)[8] obtained under closely similar conditions.[23] Final confirmation of the structure of the racemic product of synthesis was obtained by x-ray diffraction analysis.[24]

Preliminary experiments indicate that the stereoselectivity in the ring-closure step depends on the olefin geometry (in **13**) as well as on the metal reagent. The isomer **13E** reacts with bis(1,5-cyclooctadiene)nickel(0) to give a mixture relatively richer in isomer **2**. Further studies of the stereochemical features of this key step are underway.[25]

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(14) For an example of predominant trans stereochemistry in a closely parallel alkylation, see ref 11c.
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(21) Crystals of **14** are monoclinic, space group *P*2₁/n with *a* = 6.561 (4), *b* = 21.299 (13), *c* = 9.253 (4) Å; β = 100.44 (4)°; *Z* = 4. The structure was solved by direct method, and refined to *R* = 0.056 for the 1516 reflections with *I* ≥ 3σ(*I*). Full crystallographic details will be disclosed in a forthcoming full paper.

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(24) Crystals of confertin are monoclinic, space group $P2_1/c$ with a = 12.746 (2), b = 7.495 (1), c = 14.064 (2) Å; β = 101.83 (1)°; Z = 4. The structure was solved by direct method, and refined to R = 0.056 for the 1516 reflections with $I \geq 3\sigma(I)$. Full crystallographic details will be disclosed in a forthcoming full paper.

(25) We wish to acknowledge support from the National Institutes of Health for a postdoctoral fellowship to J. C. Tomesch (1975–1976) and for a research grant (CA-18333). In addition, we thank Dr. James Springer (Merck Research, Rahway, N.J.) for assistance in collecting x-ray diffraction data on (±)-confertin. Professor Jon Clardy provided important suggestions in the chemical aspects of this project as well as in helping to arrange for the x-ray studies at crucial times. Finally, a sample of natural confertin was provided by Professor Eloy Rodriguez, through the agency of Professor Paul Grieco (Pittsburgh) to whom we are grateful.

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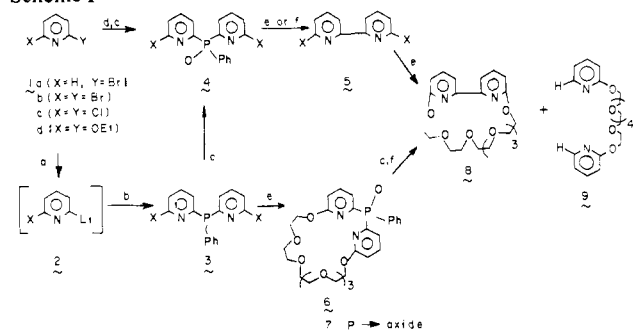Ithaca, New York 14853*
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A New Contractive Coupling Procedure. Convenient Phosphorus Expulsion Reaction

Sir:

The utility of contraction reactions is probably best demonstrated by procedures that have been devised for the ring compression of carbophanes and heterophanes.[1] Historically, several fundamental routes, based on sulfur chemistry, have have been widely used: (1) thermolysis of sulfoxides,[2] (2) photolysis of sulfides[3] or disulfides,[4] (3) Stevens rearrangement,[5] and (4) Ramberg–Bäcklund rearrangement.[6] Ring contraction of cyclic ethers has been reported;[7] however, this route has never received proper recognition. In these known heteroatom contraction procedures, an inherent common limitation is that the bridge(s) must possess an $ArCH_2X$-CH_2Ar' moiety, which contracts to $ArCH_2CH_2Ar'$. We herein report a novel complimentary procedure, based upon phosphorus expulsion, that will now permit the facile construction of a (hetero)aryl-(hetero)aryl bond.

With the current interest in the synthesis and chemistry of phosphorus containing macrocycles, we envisioned the nucleophilic displacement of halide from phosphine **3b** with a glycolate dianion[8] to afford **6** (Scheme I). Reaction of lithiodiphenylphosphide with aryl[9] or heteroaryl[10] halides has been shown to afford the triarylphosphines in variable but respectable yields. Thus, when either (a) dilithiophenylphosphide[11] was reacted with halopyridines **1** or (b) dichlorophenylphosphine was treated with substituted 2-lithiopyridines **2**, the desired substituted phosphines **3** were isolated in a 50–60% yield. Procedure b is most commonly used, when the organo-

metallic reagents can be easily prepared, whereas procedure a is advantageous when the heterocyclic halide can not be conveniently transformed into the corresponding organometallic (e.g., **1c**) or is prone to coupling reaction under metalation conditions. The free phosphine **3b** was smoothly converted (47%) into **6** (oil; NMR (CDCl₃) δ 3.64 (m, β-ξ-CH₂, 20 H), 4.28 (t, α-CH₂, J = 5 Hz, 4 H), 6.66 (dd, 5-pyr H, J = 8, 1 Hz, 2 H), 6.97 (ddd, 3-pyr H, J = 7, 4, 1 Hz, 2 H), 7.20–7.85 (m, 4-pyr H, Ph H, 7 H)) upon treatment with sodium hexaethyleneglycolate, generated from the glycol and sodium hydride, at 135 °C in xylene under nitrogen for 12 h.

Owing to the facile aerobic oxidation of these heteroarylphosphines, the free phosphines (**3** and **6**) were oxidized with dilute hydrogen peroxide to corresponding P→oxides **4** and **7**. Attempted conversions of either P→oxides **4b** or **4c** into **7** by the above procedure afforded (30–55%) **5b** (mp 222–223 °C)[12] or **5c** (mp 202–203 °C),[13] respectively, along with unreacted starting material, and traces of **8**. Repetition of this procedure with **4b** at 140 °C with (a) glycol and *no* sodium hydride, (b) sodium hydride and *no* glycol, and (c) neither sodium hydride nor glycol gave predominately unreacted starting material. These P→oxides are generally stable to prolonged exposure to 140 °C in an inert atmosphere. Refinement of reaction conditions (sodium ethoxide (2 equiv), toluene, 100 °C) gives rise to a smooth transformation of **4a–c** to **5a–c**, each in 50–60% yield. With prolonged reaction times, **5b** reacts with sodium ethoxide to give (90%) **5d** (mp 78–79 °C; NMR (CDCl₃) δ 1.43 (t, -CH₃, J = 7 Hz, 6 H), 4.51 (q, -CH₂-, J = 7 Hz, 4 H), 6.71 (dd, 5-pyr H, J = 7, 2 Hz, 2 H), 7.54 (dd, 4-pyr H, J = 7, 7 Hz, 2 H), 7.97 (dd, 3-pyr H, J = 7, 2 Hz, 2 H)), which can be isolated as the potential side product under more drastic conditions.

Treatment of P→oxide **7** with sodium hexaethyleneglycolate at 90–100 °C in toluene afforded (32%) the ring-contracted bipyridyl macrocycle **8**[14] (mp 41–43 °C; NMR (CDCl₃) δ 3.17 (m, ξ-CH₂O, 4 H), 3.28 (m, ϵ-CH₂O, 4 H), 3.45 (m, δ-CH₂O, 4 H), 3.68 (m, γ-CH₂O, 4 H), 3.94 (t, β-CH₂O, J = 5 Hz, 4 H), 4.73 (t, α-CH₂O, J = 5 Hz, 4 H), 6.77 (dd, 5,5'-pyr H, J = 8, 1 Hz, 2 H), 7.67 (dd, 4,4'-pyr H, J = 8, 8 Hz, 2 H), 7.90 (dd, 3,3'-pyr H, J = 8, 1 Hz, 2 H)) along with traces of openchained dipyridyl ether **9**. In an attempt to ascertain further insight into the mechanism, a mixture of **4a** and **4b** was subjected to the modified conditions; only **5a** and **5b** were isolated and no evidence for the mixed bipyridyl was detected. This lack of mixed bipyridyl is indicative of an intramolecular reaction pathway which leads to the coupled product.

Rationale for this intramolecular contraction procedure is shown in Scheme II. Initial nucleophilic attack on phosphorus generates the bipyramidal phosphorane **10**, in which one pyridyl group is in the apical position. Migration of (hetero)aryl groups from phosphorane intermediates depends on (a) the nature of substituents attached to phosphorus and (b) the stabilization of the migrating group by an electrophilic center adjacent to phosphorus.[15-17] Thus a "benzylic acid-type" rearrangement affords a new 1,2-dihydropyridine anion **11**, which subsequently rearomatizes via loss of a phosphorus moiety.

This facile contractive conversion of phosphine oxides to biheteroaryls reported here offers an easy complimentary reaction to the known sulfur expulsion reactions. In light of the wide range of industrial and medicinal compounds as well as

Scheme I[a]

Scheme II

[a] a, buLi, ether, −60 °C; b, PhPCl₂; c, H₂O₂; d, PhPLi₂; e, HO-(CH₂CH₂O)₅CH₂CH₂OH, NaH (2.5 equiv), C₆H₄Me₂, 140 °C; f, EtONa, C₆H₅Me, 100 °C.