A total synthesis of myrrhine, (±)-hippodamine, and (±)-convergine

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A seven-step, stereoselective, total synthesis of the ladybug defensive substance myrrhine (**5**) from 2,4,6-collidine is presented. Successive alkylation and acylation of 2,4,6-collidine followed by ketalization provides 2-(3-[2-(1,3-dioxolanyl)]propyl)-6-(2-methyl-2-[1,3-dioxolanyl]methyl)-4-methylpyridine (**14**). Sodium–alcohol reduction gives the corresponding all-*cis* piperidine **17**. Hydrolysis of **17** followed by acid-catalyzed cyclization provides ketone **26**. Reduction of the carbonyl group in **26** gives myrrhine (**5**). Cyclization using pyrrolidine – acetic acid gives a mixture of ketones (**26** and **31**). Reduction of **31** gives (±)-hippodamine (**4**). Oxidation of (±)-hippodamine with peracid gives (±)-convergine (**3**).

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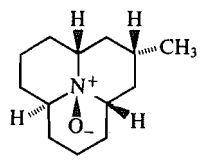
On présente une synthèse totale stéréosélective en sept étapes à partir de la collidine-2,4,6 pour la myrrhine (**5**), la substance défensive du moustique femelle. Une alkylation et une acylation de la collidine-2,4,6 suivies par une acétalisation fournit la ([(dioxolanyl-1,3)-2]-3 propyl)-2 (méthyl-2[dioxolanyl-1,3]-2 méthyl)-6 méthyl-4 pyridine (**14**). La réduction par le sodium dans l'éthanol conduit à la pipéridine toute *cis* correspondante (**17**). L'hydrolyse de **17**, suivie par une cyclisation acido catalysée, fournit la cétone **26**. La réduction du groupement carbonyle dans **26** donne la myrrhine (**5**). La cyclisation sous l'influence de la pyrrolidine et de l'acide acétique donne un mélange de cétones (**26** et **31**). La réduction de **31** donne la (±)-hippodamine (**4**). L'oxydation de la (±)-hippodamine par un peracide fournit la (±)-convergine (**3**).

[Traduit par le journal]

Coccinellidae (ladybugs or ladybirds) are colorful insects of importance in the natural control of aphids, mealy bugs, and scale insects (1). When molested these insects release droplets of orange liquid at their joints, known as *reflex bleeding*, and this has been shown to provide efficient protection against certain predators (2, 3). In recent years, Tursch and co-workers have isolated and determined the structures of the defensive substances present in several species of Coccinellidae[1] and have shown that most of these are stereoisomers of 2-methylperhydro-9b-azaphenalene and the corresponding *N*-oxides. These include coccinelline **1**, and the corresponding free base precoccinelline **2** (5, 6), convergine **3**, and its free base hippodamine **4** (7), and myrrhine **5** (4). We wish at this time to report the total synthesis of myrrhine **5**, and racemic convergine **3**, and hippodamine **4**.

Some years ago we reported (8) the synthesis of (±)-dihydrodeoxyepiallocernuine, **6**, a degradation product of the *Lycopodium* alkaloid cernuine (enantiomer of **7**). The striking similarity between the BCD ring system of **6** and myrrhine prompted us to investigate a similar approach to the synthesis of the ladybug defen-



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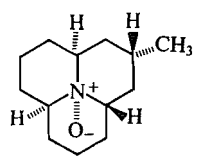
2 (free base of **1**)



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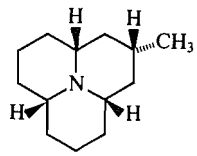
4 (free base of **3**)



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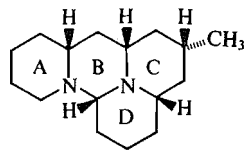

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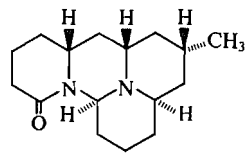

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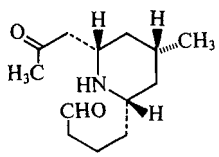
[1]For summarizing articles see refs. 3 and 4.

sive substances. In particular, our initial objective was the all-*cis* keto aldehyde **8**, designed to serve as a precursor of the immonium ion **9**, which we hoped could be induced to cyclize to the perhydro-9b-azaphenaline system of precoccinelline, **2**, and/or myrrhine, **5**.

Alkylation of the monolithium derivative, **10**, of 2,4,6-collidine, generated by treatment of the latter with either *n*-butyllithium or phenyllithium in ether, with β-bromopropionaldehyde dimethyl acetal (9) gave the acetal **11** in 41% yield. Alternatively, **11** could be prepared in 40% overall yield by alkylation of collidyllithium, **10**, with β-chloropropionaldehyde diethyl acetal followed by acid-catalyzed acetal exchange.



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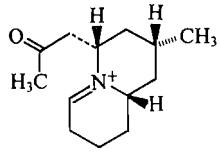

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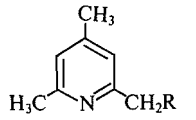
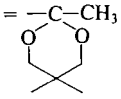
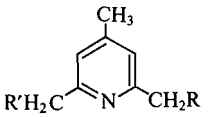
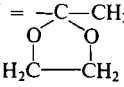


10 R = Li
11 R = $-CH_2CH_2CH(OCH_3)_2$
15 R = $-COCH_3$
16 R = 

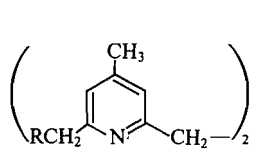


12 R = $-CH_2CH_2CH(OCH_3)_2$
R′ = $-COCH_3$
14 R = $-CH_2CH_2CH$
R′ = 

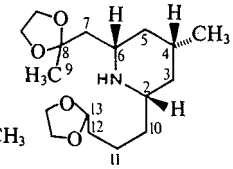
The introduction of an acetyl group into the 6-methyl group of **11** proved somewhat troublesome. The acylation of the methyl group of α-picoline has been studied in some detail by Wibaut and co-workers (10), who found acetonitrile to be the most convenient acetylating agent. Treatment of **11** with phenyllithium in ether, followed by very slow addition of one equivalent of acetonitrile in ether provides, after workup, the ketone **12** in 35–45% yield along with considerable amounts of unreacted starting material. Use of excess acetonitrile led to diminished yields, presumably due to the competition between addition and proton abstraction. Use of acetyl chloride as the acylating agent gave mainly **13**, the product of double addition. Treatment of the lithio derivative of **11** with *N*,*N*-dimethylacetamide in ether at −30 °C (11) provided ketone **12** in only 15% yield.

Separation of keto acetal **12** from starting material **11** either by distillation or chromatography proved difficult. Since the next step in the projected synthesis involved protection of the carbonyl function in **12**, it was found more efficient to treat a toluene solution of the crude product obtained from the acylation reaction with an excess of ethylene glycol and an acid catalyst. During this treatment the dimethyl acetal was exchanged for the ethylene acetal (in both **11** and **12**) and the keto group in **12** was transformed to the ethylene acetal to give **14**. The mixture of acetals could be separated by careful chromatography over alumina. In this way **11** may be transformed into **14** in 40–45% yield using acetonitrile as the acylating agent. In addition approximately 40% of **11** is recovered (as the ethylene acetal).

8-Acetoxyquinoline has been used successfully as an acylating agent for Grignard reagents (12). Treatment of an ether solution of the lithio derivative of **11** with 8-acetoxyquinoline at 0 °C followed by transformation of the crude products into the ethylene acetals and chromatography provided **14** in 37% yield, along with starting material **11** (as the ethylene acetal, 14%), and **13** (as the ethylene acetal, 9%). Although this method provides **14** almost as efficiently as the acetonitrile method, the latter is preferred since the reagent is much less expensive. Proof that acetylation has occurred at the 6-methyl group rather than the 4-methyl of **11** is provided by the proton magnetic resonance (pmr) spectra of **12** and **14** which clearly show the presence of a pyridine γ-methyl group (δ 2.38 in each) (8, 13).



13 R = $CH_2CH_2CH(OCH_3)_2$



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The alternative route to **14** involving first addition of the keto side chain then addition of the aldehyde side chain was investigated briefly. Treatment of collidyllithium, **10**, with acetonitrile gave the ketone **15** in 34% yield. Treatment of the ethylene acetal of **15** with phenyllithium in ether followed by allyl bromide led to a product mixture which did not contain an ethylene acetal signal in the nmr. Since ethylene acetals are known to be unstable towards strong bases (14), **15** was transformed to the neopentyl acetal **16**. Treatment of **16** with one equivalent of phenyllithium followed by deuterium oxide gave a monodeuterated **16** in which the signal for the methylene group adjacent to both the protecting group and the pyridine ring (δ 3.18) integrated for only one proton, indicating the formation of the lithio derivative at this position rather than at the desired 6-methyl position. This approach was not pursued further.

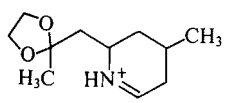
Reduction of the diacetal **14** with sodium in isoamyl alcohol provided a mixture of stereoisomers of which the major component was the desired all-*cis* piperidine **17**. Separation of **17** (in about 60% yield) from the remaining stereoisomers was achieved by chromatography over silica gel. Compound **17** has a higher R_f value than the remaining isomers and is eluted first on chromatography. The more polar isomers (tlc indicated at least two) were not separated from one another by this method. Structure **17** was assigned to the major component of the reduction on the following basis. The mass spectrum showed a weak molecular ion at *m/e* 313, a base peak at *m/e* 198 corresponding to ion **18**, and a peak at *m/e* 212 corresponding to **19**. The pmr spectrum is consistent with the assigned constitution (see Experimental). Dissolving metal reduction of **14** is expected to give the thermodynamically more stable all-*cis* isomer **17** as the major product (8). Confirmation of this assignment is obtained by consideration of the ^{13}C nuclear magnetic resonance (cmr) spectrum (Table 1) of **17**. By application of chemical shift theory and standard decoupling techniques (15, 16) it is possible to assign all the carbon shifts for compound **17**. The proton decoupled cmr spectrum displays 16 signals, one signal corresponding to two carbons, and the off-resonance decoupled spectrum reveals the substitution (methyl, methylene, etc.) of these carbons as shown in Table 1. The shifts of the

TABLE 1. ^{13}C chemical shifts for **17**[a]

Chemical shift (δ TMS)	Substitution	Assignment[b]
20.6	$>CH_2$	C-11
22.3	$-CH_3$	C-4 methyl
24.3	$-CH_3$	C-9
31.5	$>CH$	C-4
34.0	$>CH_2$	C-10
36.9	$>CH_2$	C-12
41.1	$>CH_2$	C-5[c]
42.3	$>CH_2$	C-3[c]
45.3	$>CH_2$	C-7
53.2	$>CH$	C-6
56.4	$>CH$	C-2
64.4	$>CH_2$	ethylene acetals
64.7	$>CH_2$	ethylene acetals
64.8[d]	$>CH_2$	ethylene acetals
104.6	$>CH$	C-13
110.2	$-\overset{\vert}{\underset{\vert}{C}}-$	C-8

[a]Spectrum determined in $CDCl_3$.
[b]See **17** for numbering system.
[c]C-5 and C-3 may be reversed.
[d]Two carbons.

side-chain carbons were assigned by direct analogy with the reported values for **20** (17). The models chosen for calculating the shifts of the carbons of the piperidine ring and the 4-methyl group were piperidine, 2-methylpiperidine, 2-propylpiperidine (16), 4-methylpiperidine (15), and the isomeric 1,3,5-trimethylcyclohexanes (15*a*). For example, the methine carbon of 4-methylpiperidine resonates at δ 31.3. In **17** the C-4 methine signal appears at δ 31.5. If either the C-2 or C-6 side chain were axial, a γ-gauche effect would shift the C-4 resonance upfield by 5–6 ppm (15). The methyl group in 4-methylpiperidine (equatorial) resonates at δ 22.5, in **17** the C-4 methyl signal is at δ 22.3. In the 1,3,5-trimethylcyclohexanes, an axial methyl resonates about 4 ppm to higher field than equatorial methyl and a similar shift would be expected in the 2,4,6-substituted piperidines if the methyl were axially orientated. Similar considerations lead to the remaining assignments in Table 1. The cmr data, combined with proof of the *cis*-relationship of the side chains at C-2 and C-6 discussed below, provide firm evidence that the major product of the reduction is the desired all *cis* isomer **17**.



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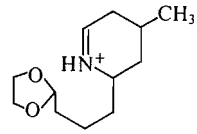

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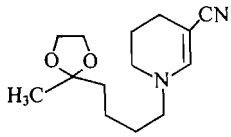

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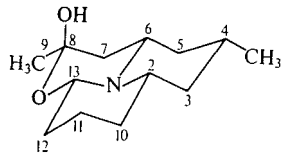

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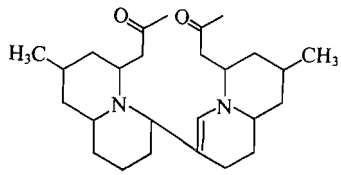

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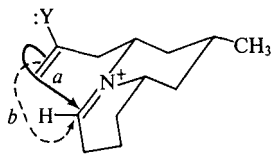
Removal of the protecting groups from **17** was accomplished by hydrolysis with 5% aqueous hydrochloric acid. The crystalline product has the molecular composition $C_{13}H_{23}NO_2$ expected for the keto aldehyde **8**, but does not show carbonyl absorption in the infrared (ir). The ir spectrum does however show hydroxyl absorption, as well as intense Bohlmann bands (18) in the region 2600–2870 cm^{-1}. The pmr spectrum shows a methyl doublet at δ 0.90, a methyl singlet at δ 1.43, and a one proton multiplet at δ 4.02. The product is thus the hemiketal **21** of the carbinolamine form of keto aldehyde **8**. The appearance of intense Bohlmann bands in the infrared spectrum of **21** indicates that at least two of the hydrogens on carbons α to nitrogen *and* the nitrogen lone pair are antiperiplanar (18). *Assuming that all the six-membered rings are in the chair conformation, the only configuration which meets this condition is the all cis (referring to H's at ring junctions) configuration shown for* ***21***. This provides additional evidence that the side chains at C-2 and C-6 in **17** are *cis*-related. The methyl group at C-4 in **21** resonates at δ 22.0 in the cmr spectrum, indicating its equatorial nature (see above). The methyl at C-8 appears at δ 30.2 and is also assigned the equatorial configuration, using 5-*tert*-butyl-2,2-dimethyl-1,3-dioxane (equatorial methyl δ 27.98, axial methyl δ 20.28 (19)) as a model compound.

When the hemiketal **17**, which crystallizes in hydrated form, is heated to 60–70 °C *in vacuo*, it is transformed into a compound showing strong carbonyl absorption (1715 cm^{-1}) and olefinic absorption (1655 cm^{-1}) in the ir. The mass spectrum of this material shows an apparent molecular ion at *m/e* 414 and an intense fragment peak at *m/e* 357. It is known that *N*-substituted 2-piperideines dimerize readily (20) and structure **22** is suggested for this substance, the peak at *m/e* 357 in the mass spectrum resulting from loss of an acetonyl side chain.

Our attention now turned to methods for generating the immonium salt **9** and its enol **23** (Y = OH) or enamine **23** (Y = NR_2) forms which should be capable of cyclization as illustrated in **23**. 'Top-side' addition of the enol or enamine to the immonium double bond (arrow *a*) would lead to the ketone **24** possessing the stereochemistry of precoccinelline (**2** = **25**), while 'bottom-side' attack (arrow *b*) would lead to the ketone **26**, possessing the myrrhine (**5** = **27**) configuration. *A priori*, the preferred direction of cyclization could not be predicted with con-



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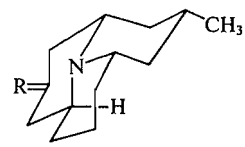
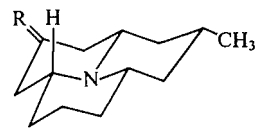
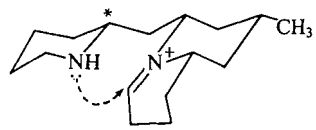


24 R = O
25 R = H,H



26 R = O
27 R = H,H



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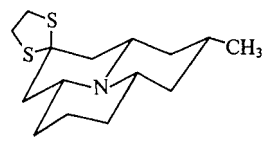
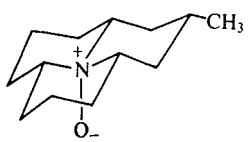


29

fidence. In the case of the immonium ion **28**, an intermediate in the synthesis of dihydrodeoxyepiallocernuine (8), addition of the amine to the immonium double bond occurs exclusively from the 'bottom-side'. However, in the case of the compound epimeric with **28** at the carbon bearing the asterisk, both modes of cyclization are observed (8).

Attempts to cyclize the hemiketal **21** by heating with aqueous acid or base were unsuccessful. However, when a toluene solution of **21** was heated in the presence of two equivalents of *p*-toluenesulfonic acid the ketone **26** was obtained in high yield. The ir spectrum of the ketone shows carbonyl absorption at 1728 cm^{-1} and strong Bohlmann bands, this latter feature serving to distinguish **26** from the other possible isomer, **24**. Ketone **26** proved to be rather unstable, rapidly discoloring when exposed to air, and in most cases the crude product resulting from the cyclization was converted directly into the thioketal **29**. After chromatography, the crystalline thioketal **29** was obtained in 60% overall yield from hemiketal **21**. The thioketal also shows very pronounced Bohlmann bands in the ir confirming the stereochemical assignment.

The thioketal **29** was desulfurized using W-2 Raney nickel in refluxing ethanol. Distillation of the crude product, which showed only one spot on tlc, gave myrrhine[2] (**5** = **27**) in 64% yield. Oxidation of the synthetic myrrhine with *m*-chloroperbenzoic acid provided crystalline myrrhine *N*-oxide, **30**, identical in all respects[3] with that prepared from myrrhine. In connection with the cmr assignments discussed above, it is worthwhile noting that the signal for the methyl carbon in **30** appears at δ 21.4, approximately the same shift as in **17** and **21**.



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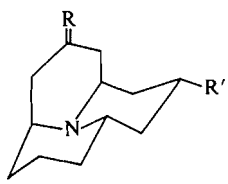


31 R = H,H, R′ = CH_3
32 R = O, R′ = CH_3
33 R = O, R′ = H

[2]The ir spectrum of synthetic myrrhine was identical with that of natural myrrhine. We wish to thank Prof. B. Tursch for the ir spectrum of myrrhine.

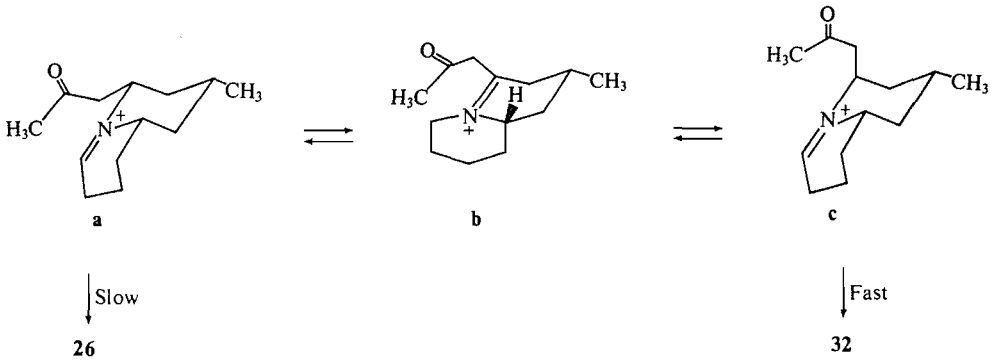
[3]We wish to thank Prof. B. Tursch for making this comparison.

The acid-catalyzed cyclization of **21**, presumably through the intermediate enol immonium ion **23** (Y = OH), appears to proceed completely via 'bottom-side' attack (arrow *b* in **23**), although this may be the result of a thermodynamic rather than a kinetic process. In an effort to obtain the coccinelline geometry, other methods of cyclization were investigated. When the hemiketal **21** was heated with pyrrolidine and acetic acid in tetrahydrofuran, the resulting product (ir 1725 cm^{-1}) consisted of two components (by tlc), one having the same R_f as ketone **26**, the other being more polar. The mixture was treated with ethanedithiol–BF_3, and the resulting mixture of thioketals (two spots on tlc) desulfurized in the usual manner. The crude product from the desulfurization also showed two spots on tlc, one having an R_f value identical with that of myrrhine, the other similar to that of precoccinelline (**2** = **25**). The two components were separated by preparative tlc and the component of higher R_f was identified as myrrhine (**5** = **27**). The other component, isomeric with myrrhine (mass spectrum) and lacking Bohlmann bands in the ir, was expected to be precoccinelline. However, the ir spectrum was clearly different from that of precoccinelline. This isomeric base was transformed to the *N*-oxide. Comparison of the spectra of this *N*-oxide and its hydrochloride with those of coccinelline, **1**, and coccinelline hydrochloride again revealed differences. *However, comparison of the spectra of our synthetic base and its N-oxide with those of hippodamine, **4**, and convergine, **3**, respectively, showed that they were identical.*[4] The overall yields of myrrhine and racemic hippodamine from hemiketal **21** were 33% and 23%, respectively.

The formation of hippodamine (**4** = **31**) requires epimerization of the side chain at C-6 prior to cyclization. In the presence of both acid and base this may involve a reversible shift of the immonium double bond as illustrated in Scheme 1. Although ion **c** is expected to be a minor component in the equilibrium mixture, the axial side chain is ideally situated for ring closure (to **32**) and the rate of cyclization of **c** may well exceed that of **a**.

We have been unable to define reaction condi-

[4]We wish to thank Prof. B. Tursch for providing comparison samples and spectra of coccinelline, precoccinelline, hippodamine, and convergine.



SCHEME 1

ions which lead to cyclization of **21** to give ketone **24**, and thus coccinelline. However, it is noted that ketone **33**, *potentially* available by this route starting from 2,6-lutidine instead of 2,4,6-collidine, is a possible precursor of precoccinelline, **2**. Replacement of the carbonyl group in **33** with an equatorial methyl group gives **2**. This route is being investigated.

Experimental

Solutions were dried over anhydrous magnesium sulfate unless otherwise specified. Skellysolve B refers to Skelly Oil Company light petroleum, bp 62–70 °C. Melting points were determined on a Fisher-Johns or Leitz–Wetzlar hot-stage melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating ir spectrophotometer, a Unicam SP 1000 grating ir spectrophotometer, or a Perkin-Elmer Model 421 dual grating ir spectrophotometer.

Proton magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard. Spectra were determined in $CDCl_3$ unless otherwise noted. Only significant signals are quoted.

^{13}C nuclear magnetic resonance spectra were obtained on natural abundance samples in $CDCl_3$ at 22.63 MHz (Bruker HFX-90 interfaced to a Nicolet 1085 computer) in the pulse Fourier mode. Shifts are quoted relative to internal tetramethylsilane (δ_{TMS}).

Mass spectra including high resolution measurements (hrms) were recorded on a A.E.I. model MS-9 mass spectrometer and are reported as *m/e* (relative intensity). Unless diagnostically significant only peaks over *m/e* 50 and at least 20% as intense as the base peak are recorded.

3-Bromo-1,1-dimethoxypropane, ***9***

A stirred solution of anhydrous methanol (23.1 g) and freshly distilled acrolein (40.3 g) was cooled to −15 °C and hydrogen bromide bubbled in until 123.4 g had absorbed. The resulting mixture was poured into a cold separatory funnel and the layers allowed to separate. The bottom layer was drawn off, dried over $CaCl_2$, and then distilled rapidly (60–80 °C/16 Torr) to prevent polymerization. The resultant mixture of 1,3-dibromo-1-methoxypropane and 3-bromo-1,1-dimethoxypropane (80 g) was added slowly to anhydrous methanol (300 ml) cooled in an ice bath. The resulting solution was kept at room temperature for 20 h. The methanol was then removed under reduced pressure on a rotary evaporator to leave a clear brown oil (59.2 g) which by nmr (δ 2.23 (2,H q, J = 6.5 Hz), 3.37 (3H, s), 3.43 (2H, t, J = 6.5 Hz), 4.55 (1H, t, J = 6.5 Hz)) appears to be essentially pure 3-bromo-1,1-dimethoxypropane. Distillation of the product gives a clear distillate which by pmr appears to be a mixture of the desired compound and 1,1,3-trimethoxypropane. Undistilled material was used directly in the next step.

2-(4,4-Dimethoxybutyl)-4,6-dimethylpyridine, ***11***

Using 3-Bromo-1,1-dimethoxypropane

2,4,6-Collidine (26.0 g, 0.215 mol, freshly distilled Eastman–Kodak or BDH reagent grade; Matheson, Coleman and Bell technical grade proved unsatisfactory since it contains considerable amounts of 2,3,6-trimethylpyridine which are not readily removed by distillation) in ether (200 ml) was added dropwise over 30 min to a solution of phenyllithium (18 g, 0.215 mol, prepared from bromobenzene and lithium metal) in ether (200 ml) under nitrogen. The resultant blood-red solution was stirred at room temperature for 1 h, then a solution of 3-bromo-1,1-dimethoxypropane (39.2 g, 0.214 mol) in ether (70 ml) was added dropwise over 1 h. The solution was stirred overnight and then water (80 ml) added dropwise. The layers were separated, the aqueous layer washed with ether (2 × 50 ml), and the combined ether solutions washed with water and saturated brine. Removal of the ether left a reddish brown oil (43.4 g) which was distilled under reduced pressure. After a forerun consisting mainly of 2,4,6-collidine and the bromoacetal (10.2 g, bp 25–73 °C/5 Torr), compound **11** (19.3 g, 41%), bp 107–112 °C/1 Torr, n_D^{22} 1.4904, was obtained as a colorless liquid. *Anal.* calcd. for $C_{13}H_{21}NO_2$: C 69.96, H 9.42, N 6.28; found: C 70.16, H 9.54, N 6.26.

Infrared spectrum: ν_{max} (neat) 1610, 1570, 1120, and 1065 cm^{-1}. Proton magnetic resonance spectrum: δ 2.28 (3H, s, C-2 methyl), 2.51 (3H, s, C-4 methyl), 3.35 (6H, s,

methoxyls), 4.43 (1H, t, J = 5 Hz, acetal H), and 6.87 (2H, s, aromatic protons). Mass spectrum: 223 (1, M^+), 192(92), 191(28), 176(35), 148(49), 121(100), 75(84). *Mol. Wt.* calcd. for $C_{13}H_{21}NO_2$ (molecular ion): 223.1572; found: 223.1566.

Using 3-Chloro-1,1-diethoxypropane Followed by Ketal Exchange

To a solution of phenyllithium (6.72 g, 0.08 mol) in ether (250 ml) under nitrogen was added dropwise a solution of 2,4,6-collidine (9.7 g, 0.08 mol) in ether (30 ml). The mixture was stirred for 2 h at room temperature and then to the blood-red solution was added dropwise a solution of 3-chloro-1,1-diethoxypropane (Aldrich Chemicals, 13.3 g, 0.08 mol) in ether (30 ml). The mixture was stirred overnight and worked up as above. Distillation afforded 2-(4,4-diethoxybutyl)-4,6-dimethylpyridine (9.1 g, 45%), bp 120–124 °C/1.2 Torr, n_D^{23} 1.4844. Infrared spectrum: ν_{max} (neat) 1610, 1570, 1125, and 1060 cm^{-1}. *Anal.* calcd. for $C_{15}H_{25}NO_2$: C 71.71, H 9.96, N 5.58; found: C 71.59, H 9.99, N 5.56. *Mol. Wt.* calcd. for $C_{15}H_{25}NO_2$: 251; found (ms): 251.

The diethyl acetal (10.3 g) was dissolved in dry methanol (250 ml) and *d*-10-camphorsulfonic acid (10.2 g) added. The solution was distilled slowly during which time methanol was added dropwise to maintain the volume. After 100 ml of methanol was collected, the solution was cooled and sodium carbonate (10 g) added. The mixture was stirred vigorously, filtered, and evaporated. The residue was partitioned between ether and water. The ether solution was dried and distilled to give 2-(4,4-dimethoxybutyl)-4,6-dimethylpyridine (**11**, 8.3 g), identical with that described above.

2-(3-[2-(1,3-Dioxolanyl)]propyl-6-(2-methyl-2-[1,3-dioxolanyl]methyl)-4-methylpyridine, ***14***

Acetonitrile Method

A solution of 2-(4,4-dimethoxybutyl)-4,6-dimethylpyridine (**11**, 12.0 g, 0.054 mol) in anhydrous ether (20 ml) was added dropwise, under nitrogen, to a stirred solution of phenyllithium (4.54 g, 0.054 mol) in ether (40 ml) at room temperature. After 30 min, freshly distilled acetonitrile (2.1 g, 0.051 mol) in ether (100 ml) was added dropwise over a period of 4 h. The solution was stirred for an additional hour, then 2.4 *N* HCl in dry methanol (100 ml) was added dropwise. The solution turned yellow (from blood-red) and a precipitate separated. This mixture was stirred overnight, then triethylamine (25 g, 0.25 mol) was added dropwise, and the solution poured into saturated sodium bicarbonate (100 ml). The layers were separated, the aqueous layer washed with ether (2 × 50 ml), and the combined ether layers washed with saturated sodium bicarbonate, then saturated brine. Removal of the ether gave a dark brown oil (13.7 g, ν_{max} (neat) 1720 cm^{-1}, crude **12**) which was dissolved in toluene (20 ml) and added to a solution of ethylene glycol (15.0 g, 0.24 mol) and *p*-toluenesulfonic acid monohydrate (13.1 g, 0.07 mol) in toluene (350 ml). The mixture was heated under reflux (Dean–Stark water separator) for 18 h, then cooled and triethylamine (7.1 g, 0.07 mol) added. The solution was washed with 5% sodium bicarbonate, water, and brine. Removal of the toluene under reduced pressure gave a dark oil which was chromatographed over alumina (300 g, Alcoa F-20, activity I-II), Elution with toluene (6 l) provided the ethylene acetal of **11** (4.8 g), elution with toluene–ether (1 l of 4:1) gave a mixture of **11** (ethylene acetal) and **14**, and elution with toluene–ether (4 l of 1:1) gave the title compound **14** (5.7 g, 41%), bp 146–149 °C/0.08 Torr, n_D^{23} 1.5132. *Anal.* calcd. for $C_{17}H_{25}NO_4$: C 66.45, H 8.14, N 4.56; found: C 66.58, H 8.27, N 4.53. *Mol. Wt.* calcd. for $C_{17}H_{25}NO_4$: 307.1784; found (hrms): 307.1769.

Infrared spectrum: ν_{max} 1610, 1570, 1130, and 1045 cm^{-1}. Proton magnetic resonance spectrum: δ 1.36 (3H, s), 1.82 (4H, m), 2.28 (3H, s), 2.77 (2H, m), 3.05 (2H, s), 3.90 (8H, m), 4.87 (1H, t, J = 4.5 Hz), 6.85 (1H, s), and 6.95 (1H, s). Mass spectrum: 307(1, M^+), 221(55), 207(16), 187(100).

8-Acetoxyquinoline Method

A solution of compound **11** (2.23 g, 8.9 mmol) in anhydrous ether (20 ml) was added dropwise to a solution of phenyllithium (0.87 g, 10.4 mmol) in ether (8 ml) at room temperature. The solution was stirred for 2 h, then cooled to 0 °C, and a solution of 8-acetoxyquinoline (1.87 g, 10 mmol) in ether (20 ml) was rapidly added. The temperature rose to 15 °C and the solution was stirred at this temperature for 15 min, then water (20 ml) added. The yellow precipitate which separated was removed by filtration, the filtrate diluted with chloroform (150 ml), washed with saturated sodium bicarbonate, and evaporated to leave a brown oil (2.95 g). This oil was then ketalized as described under 'acetonitrile method'. The resulting product (2.57 g) was chromatographed over alumina (100 g). Elution with benzene (500 ml) gave starting material (0.30 g, as ethylene acetal). Elution with benzene–ether (500 ml of 4:1) gave the title compound **14** (1.15 g, 37%), identical with that described above. Elution with ether (300 ml) gave the ethylene acetal of the double addition product **13** (0.39 g, 9%), ν_{max} 3300 (br), 1612, and 1570 cm^{-1}. The structure of this product is apparent from the molecular weight (M^+ = 484) and the pmr spectrum: δ 1.14 (3H, s, HO—C(—CH_3)—), 1.6–2.0 (8H, m), 2.27 (6H, s, pyridine γ-methyls), 2.74 (4H, t, J = 6.5 Hz), 2.88 (4H, s), 3.75–3.95 (8H, m), 4.87 (2H, t, J = 4.5 Hz), 6.82 (2H, s), and 6.86 (2H, s).

2-(3-[2-(1,3-Dioxolanyl)]propyl)-cis-4-methyl-cis-6-(2-methyl-2[1,3-dioxolanyl]methyl)-piperidine, ***17***

Sodium (5.2 g) was added to a refluxing solution of compound **14** (2.63 g) in freshly distilled isoamyl alcohol (70 ml) in a nitrogen atmosphere. Heating was continued until all the sodium had reacted (*ca.* 1.5 h), then water (70 ml) was added and the layers separated. The aqueous layer was extracted with chloroform (3 × 50 ml) and the combined organic layers washed with water and brine. Removal of the solvents under reduced pressure left a viscous oil (3.1 g) which was chromatographed over silica gel (60 g) using chloroform–methanol–dimethylamine (100:10:1) as the eluant at a flow rate of 3 ml/h. Three ml fractions were collected. Fractions 51 to 68 gave the title compound **17** (1.65 g, 62%) as a colorless oil. Fractions 71 to 100 gave material (0.66 g) isomeric (by ms) with **17**.

An analytical sample of **17** was prepared by molecular distillation (120–130 °C/0.05 Torr), n_D^{20} 1.4784. *Anal.* calcd. for $C_{17}H_{31}NO_4$: C 65.18, H 9.90, N 4.47; found:

C 65.39, H 10.08, N 4.64. *Mol. Wt.* calcd. for $C_{17}H_{31}NO_4$: 313.2253; found (hrms): 313.2246.

Infrared spectrum: ν_{max} 3320, 1120, and 1030 cm^{-1}. Proton magnetic resonance spectrum: δ 0.90 (3H, d, J = 5.5 Hz), 1.35 (3H, s), 3.95 (8H, m), and 4.87 (1H, t, J = 4 Hz). ^{13}C magnetic resonance spectrum: see Table 1. Mass spectrum: 313(1, M^+), 212(12), 198(100), 87(20).

Hemiketal 21

A solution of compound **17** (1.25 g) in 5% aqueous hydrochloric acid (25 ml) was stirred at room temperature for 18 h. The solution was made basic by the addition of 5% aqueous sodium bicarbonate and extracted with methylene chloride. Evaporation left a solid residue (1.10 g) which was recrystallized from ether–hexane to give **21** (0.76 g), mp 58–60 °C (dec.). Hemiacetal **21** crystallizes in hydrated form and it has not been possible to obtain consistent combustion analyses. The infrared spectrum of crystalline **21** dissolved in chloroform shows, besides hydroxyl absorption at 3595, bands due to water (21) at 3680 and 1605 cm^{-1}. After azeotropic removal of the water and redissolving in chloroform, the bands at 3680 and 1605 cm^{-1} are no longer present. Attempts to remove water by heating *in vacuo* lead to 'dimerization' to **22**. *Mol. Wt.* calcd. for $C_{13}H_{23}NO_2$: 225.1729; found (hrms): 225.1724.

Infrared spectrum: ν_{max} (KBr) 3500, 3200 (broad), 2820, 2780, 2740, 2630, and 2610 cm^{-1} (Bohlmann bands). Proton magnetic resonance spectrum: δ 0.88 (3H, d, J = 6 Hz), 1.42 (3H, s), and 4.00 (1H, m). ^{13}C magnetic resonance spectrum: δ 94.6(C-8), 84.8(C-13), 59.3(C-6), 55.3(C-2), 41.9(CH_2), 41.6(CH_2), 41.2(CH_2), 32.7(CH_2), 31.8(CH_2), 30.2(C-4), 30.2(C-9), 22.3(CH_2), and 22.0(CH_3 at C-4). Mass spectrum: 225(8, M^+), 224(17), 210(11), 207(20), 150(100).

Thioketal 29

The hemiketal **21** (296 mg) was dissolved in toluene (50 ml) and *p*-toluenesulfonic acid monohydrate (499 mg) added. The vigorously stirred mixture was heated under reflux (Dean–Stark water separator) in a nitrogen atmosphere for 3 h, then cooled and triethylamine (1 ml) added. The solution was poured into saturated sodium bicarbonate and the layers separated. The aqueous layer was washed twice with methylene chloride and the organic layers combined and concentrated under reduced pressure to give crude ketone **26** as a pale yellow oil (294 mg). Infrared spectrum: ν_{max} (neat) 2795, 2755, 2715, 2610 (Bohlmann bands), and 1725 (C=O) cm^{-1}. Proton magnetic resonance spectrum: δ 0.92 (3H, d, J = 5.5 Hz). Mass spectrum: 207(62, M^+), 206(48), 192(27), 165(21), 164(100), 150(43). The crude ketone **26** (294 mg) was dissolved in ethanedithiol (2 ml) and boron trifluoride–etherate (0.4 ml) added. After 18 h at room temperature the solution was diluted with methylene chloride (50 ml) and washed with 4 *N* aqueous sodium hydroxide (4 × 20 ml), water and brine. Removal of solvent left a pale yellow oil (356 mg) which was chromatographed over silica gel. The eluant was chloroform–methanol–aqueous ammonia (95:5:0.5); 3 ml fractions were collected. Fractions 12 and 13 provided thioketal **29** (218 mg), mp 51–52 °C (from ether–Skellysolve B). *Anal.* calcd. for $C_{15}H_{25}NS_2$: C 63.55, H 8.89, N 4.94; found: C 63.33, H 8.78, N 4.87. *Mol. Wt.* calcd. for $C_{15}H_{25}NS_2$: 283.1429 (^{32}S); found (hrms): 283.1410.

Infrared spectrum: ν_{max} 2800, 2755, 2735, 2680, 2610 (Bohlmann bands), and 1125 cm^{-1}. Proton magnetic resonance spectrum: δ 0.88 (3H, d, J = 5.5 Hz) and 3.27 (4H, bs). Mass spectrum: 283(41, M^+), 282(26), 222(30), 190(51), 151(100).

Myrrhine (5 = 27)

To a solution of thioketal **29** (0.38 g) in ethanol (20 ml) was added a slurry of W-2 Raney nickel (*ca.* 4 g) in ethanol (25 ml). The mixture was heated under reflux with vigorous stirring for 2 h, then filtered and concentrated HCl (1 ml) added. The solvent was removed under reduced pressure. The residue was dissolved in methylene chloride and anhydrous potassium carbonate added with stirring. Filtration and evaporation of solvent gave a pale-yellow oil (0.21 g) which was distilled at 90 °C (bath temperature) (0.1 Torr) to give myrrhine (**5** = **27**, 166 mg) as a colorless oil. The infrared spectrum was identical with that of authentic myrrhine. Infrared spectrum: ν_{max} (film) 2790, 2760, 2725, 2610 (Bohlmann bands), 1445, 1385, 1325, 1255, 1220, 1130, 1120, 1042, 1020, and 730 cm^{-1}. Proton magnetic resonance spectrum: δ 0.88 (3H, d, J = 5.5 Hz). Mass spectrum: identical with the published (4) spectrum.

Myrrhine N-oxide, 30

Myrrhine (11 mg) in chloroform (2 ml) was treated with *m*-chloroperbenzoic acid (15 mg) in chloroform (1 ml). After 4 h the reaction mixture was poured onto a column of alumina (1 g) and eluted with chloroform (25 ml). Evaporation left a colorless solid (11 mg) which was crystallized from methylene chloride – ether. The colorless needles slowly decomposed when heated above 150 °C. The synthetic material was identical (ir, nmr, ms) with authentic myrrhine *N*-oxide.

^{13}C magnetic resonance spectrum: δ 73.6(CH), 73.3(2 × CH), 35.8(2 × CH_2), 35.6(2 × CH_2), 30.1(CH), 27.4(2 × CH_2), 23.4(2 × CH_2), and 21.4(CH_3).

(±)-Hippodamine (4 = 31)

Pyrrolidine (0.042 ml) and acetic acid (0.058 ml) were added to a solution of hemiketal **21** (113 mg) in dry tetrahydrofuran (10 ml) and the resulting solution was heated under reflux in a nitrogen atmosphere for 24 h. After addition of saturated aqueous sodium bicarbonate (10 ml) most of the tetrahydrofuran was removed under reduced pressure. The aqueous solution was extracted with methylene chloride to give a pale yellow oil (103 mg) which showed carbonyl absorption at 1725 cm^{-1} and two spots on tlc (silica gel). A portion (84 mg) of the oil was dissolved in ethanedithiol (2 ml), boron trifluoride–etherate (0.2 ml) added, and the solution left overnight. Work-up as above gave a pale yellow oil (115 mg) which showed two spots on tlc differing in R_f values from the ketones above. The crude thioketals were desulfurized in the same manner as for **29**. The product (65 mg) showed two spots, R_f values 0.8 and 0.2, on tlc (alumina, developed with ethyl acetate). The components were separated by preparative tlc (alumina, ethyl acetate). The component of higher R_f value (27 mg) was identical with myrrhine. The component of lower R_f value (19 mg) was purified by molecular distillation (90 °C/0.1 Torr). The ir, pmr, and ms were identical with those of authentic hippodamine (**4** = **31**).

(±)-*Convergine*, *3*

(±)-Hippodamine (10 mg) was transformed to the *N*-oxide in the same manner as described for myrrhine. The hygroscopic solid obtained showed spectral properties (ir, ms, pmr) identical with those of authentic convergine. The synthetic material was transformed into the hydrochloride which was recrystallized from methylene chloride – ether, mp 225–230 °C (dec.). The infrared spectrum was identical with that of authentic convergine hydrochloride.

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