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A STEREORATIONAL TOTAL SYNTHESIS OF (−)-PTILOCAULIN

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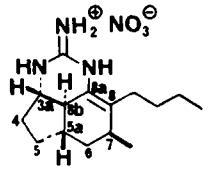
Abstract—A stereorational total synthesis of the structurally (−)-enantiomer of the unique guanidine containing natural product ptilocaulin is described. This efficient synthesis (14 steps, 7.4% overall yield) utilizes an intramolecular 1,3-dipolar cycloaddition as a key step and establishes that the natural product is the most stable of a number of possible isomers. This work also establishes the absolute stereochemistry of ptilocaulin to be that shown in formula **3**.

The isolation of ptilocaulin and isoptilocaulin from the orange Caribbean sponge *Ptilocaulis aff. P. spiculifer* (Lamarck, 1814) was reported by Rinehart and co-workers in 1981.[3,4] These two novel guanidine containing natural products, isolated as nitrate salts, display anti-microbial activity against gram-positive and gram-negative bacteria, yeasts and filamentous fungi, and significant cytotoxicity towards L1210 leukemia cells. Other notable members of the relatively small class of guanidine containing natural products include saxitoxin (**4**)[5] and tetrodotoxin (**5**),[6] both of which are also highly bioactive. The very interesting chemistry of this group of compounds has been recently reviewed by Chevolot.[7]



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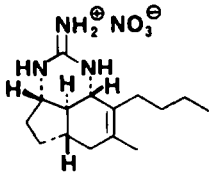

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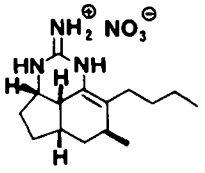

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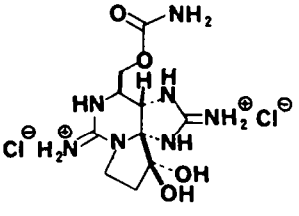

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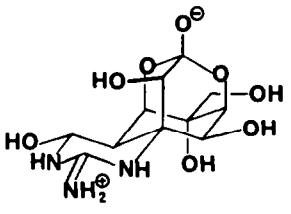

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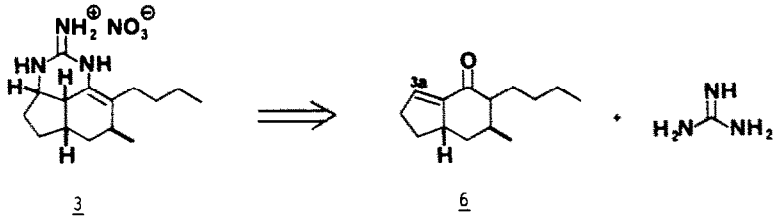
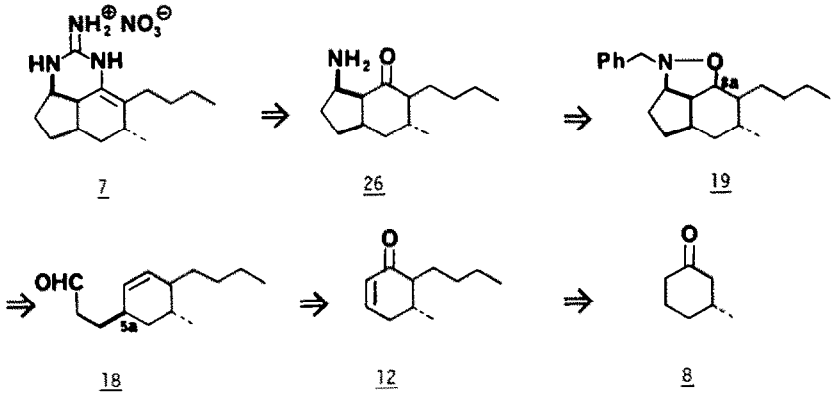
Ptilocaulin and isoptilocaulin contain a unique tricyclic ring system in which a guanidine is fused to a substituted perhydroindene nucleus. Structures **1** (ptilocaulin) and **2** (isoptilocaulin) were assigned on the basis of detailed spectroscopic analyses, with 10 Hz coupling constants between H.8b and H.5a in both compounds suggesting *trans* ring fusions. The assignment for ptilocaulin, however, was amended to that shown in **3** after an X-ray analysis revealed that the ring fusion was in fact *cis*. Rinehart and co-workers suggested that ptilocaulin may be derived from addition of guanidine to a polyketonide chain and may actually be produced by a symbiont rather than the sponge itself.[3]

The unique structure and impressive biological activity of ptilocaulin prompted us to undertake a total synthesis. We initially considered a synthetic approach based on Rinehart and co-workers' biosynthetic proposal (Scheme 1). After examination of molecular models, however, we assumed (incorrectly!)[8] that a synthesis involving condensation of **6** with guanidine would be unsatisfactory. This analysis revealed that Michael addition should occur preferentially to the more exposed convex face of **6** resulting in the incorrect stereochemistry at C.3a. Thus, a synthesis of **3** from **6** as indicated in Scheme 1 would require thermodynamically controlled conditions, and we feared that a number of side reactions could interfere.[9]

We sought instead to develop an approach which would fix each of the stereocenters of **3** in a rational manner. Our retrosynthesis thus took the form shown in Scheme 2, in which an intramolecular 1,3-dipolar cycloaddition[10] of the nitrone derived from aldehyde **18** constitutes the key step. Completion of the synthesis from isoxazolidine **19** would involve adjustment of oxidation state at C.8a followed by introduction of a guanidine residue. We were confident that the key C.5a stereocenter in **18** could be introduced via conjugate



Scheme 1.



Scheme 2.

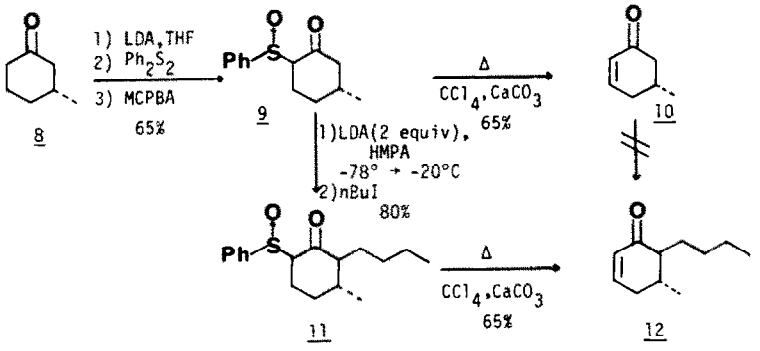
addition of an appropriate propionaldehyde equivalent to enone **12**, which in turn would be prepared from the readily available homochiral 3-methylcyclohexanone **8**.[11,12] Since the absolute configuration of ptilocaulin had not been established, this synthesis would resolve this final stereochemical issue.

We describe herein the details of our successful synthesis of (−)-**7** from **8** (14 steps, 7.4% overall yield) which establishes the absolute stereochemistry of ptilocaulin to be that shown for **3**.[8,13]

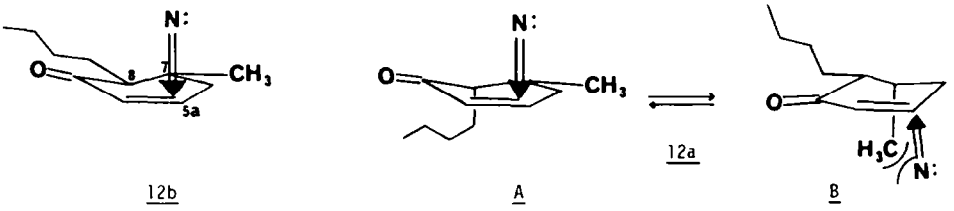
Synthesis of isoxazolidine **19**

Our immediate target was cyclohexenone **12** (Scheme 3) which we hoped to prepare from enone **10**. Thus, *R*-(+)-3-methylcyclohexanone[14] (**8**) was treated with LDA in THF at −78° followed by diphenyldisulfide to give the corresponding α-ketosulfide, which was oxidized with MCPBA to give a mixture of diastereomeric sulfoxides **9** (65% from **8**). Heating a CCl_4 solution of **9** in the presence of $CaCO_3$ then afforded the known cyclohexenone **10** (65%).[15] All attempts to alkylate the kinetic enolate of **10** with 1-iodobutane, unfortunately, resulted in the formation of mixtures of unidentified products.[16] It was possible, however, to prepare **12** by alkylation of the dianion of **9**.[17] Thus, treatment of **9** with LDA (2.2 equiv of 1 M solution in THF, 6 equiv HMPA, −35°, 3 hr) followed by quenching with 1-iodobutane (1.2 equiv, −35°, 2 hr) afforded a mixture of diastereomeric butylated sulfoxides **11**. Under these carefully controlled conditions **11** was obtained reproducibly in yields of 75–82% in up to 10 g quantities. Heating a CCl_4 solution of **11** with 0.95 equiv of $CaCO_3$ afforded the desired cyclohexenone **12a,b** in 65% yield.[18] Compound **12a,b** was a *ca* 6:1 mixture of inseparable diastereomers, with the major isomer (**12b**) assigned the β-configuration at C.8.[19,20]

With **12a,b** in hand we turned to establishment of the crucial C.5a center. Ample precedent exists for the axial 1,4-addition[21] of cuprates to cyclohexenone **10** and we felt that 1,4-additions to **12a,b** (especially **12b**) would proceed in an analogous manner. Although **12a** can in principle react via either of two reasonable conformations, axial 1,4-addition to conformation **B** (leading



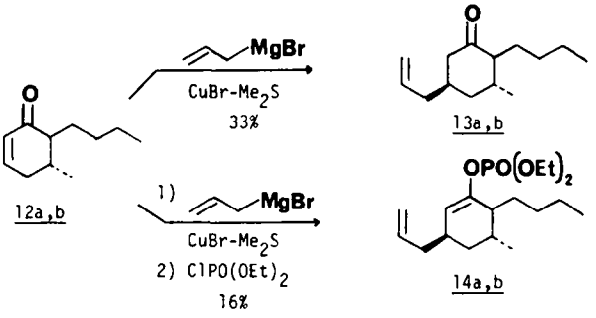
Scheme 3.



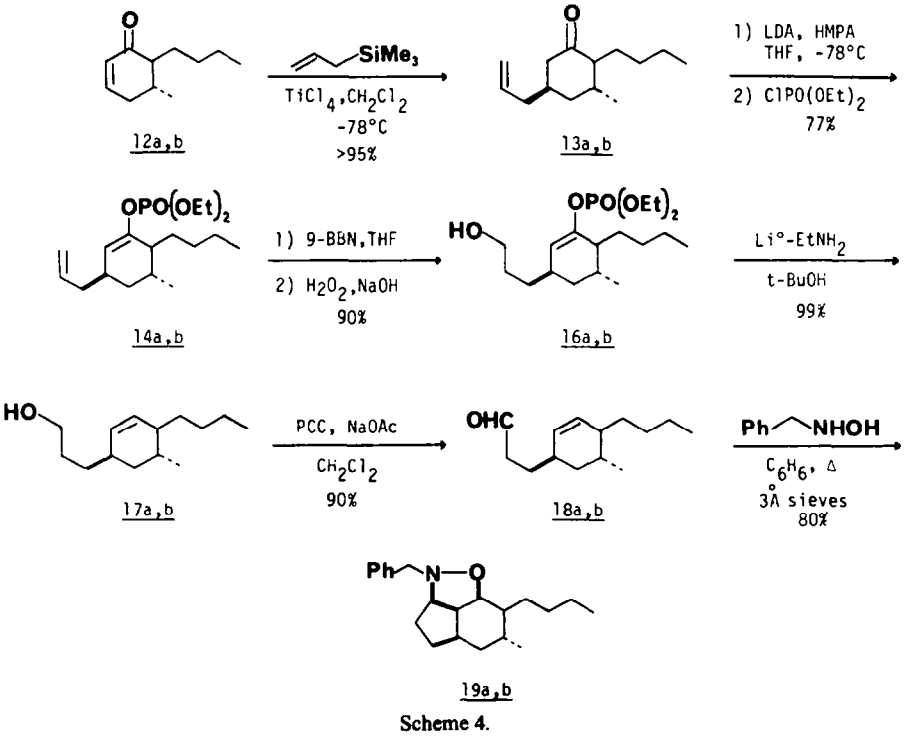
to the unnatural configuration at C.5a) should be disfavored owing to a 1,3-interaction with the axial C.7 methyl group. As a consequence, we expected 1,4-addition to **12a** to proceed selectively via conformation A.

Preliminary experiments on the conversion of **12a,b** to aldehyde **18** were not encouraging. For example, treatment of **12a,b** with allylmagnesium bromide in the presence of CuBr–Me_2S[22] afforded **13a,b** in only 33% yield, along with considerable 1,2-addition products. Attempts to adapt this procedure to the preparation of enolphosphate **14a,b** by quenching the 1,4-addition reaction with chlorodiethylphosphate afforded **14a,b** in only 16% yield. Conjugate addition of 2-(1,3-dioxolan-2-yl)ethyl magnesium bromide[23] to **12a,b** also proved unsatisfactory.

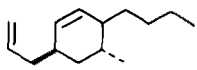
These disappointing results prompted us to examine the Sakurai reaction[24] for synthesis of **13a,b** (Scheme 4). We were delighted, therefore, to discover that treatment of **12a,b** with $TiCl_4$ in CH_2Cl_2 at −78° followed by allyltrimethylsilane afforded a 6 : 1 mixture of allylcyclohexanones **13b** : **13a** in >95% yield with complete control of stereochemistry at C.5a.[25–27] These isomers could be separated chromatographically, and each has been brought independently through the synthesis to (−)-**7**. On a routine basis, however, such mixtures were used without separation.



The conversion of **13a,b** to isoxazolidine **19a,b** is summarized in Scheme 4. Deprotonation of **13a,b** with LDA in THF–HMPA followed by quenching with chlorodiethylphosphate afforded **14a,b** in 77% yield.[28] Attempts to reduce **14a,b** to diene **15a,b** by treatment

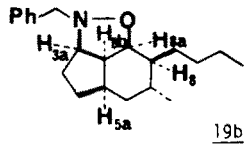


Scheme 4.



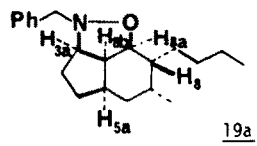
15a,b

with Li in $EtNH_2$ afforded inseparable mixtures of **15a,b** and material which had suffered competing reactions of the terminal vinyl group. Alternatively, **14a,b** could be converted to alcohol **16a,b** in 90% yield by a hydroboration sequence using 9-BBN, with no interference from the enolphosphate functionality. Reduction of **16a,b** with Li in $EtNH_2$ containing ^tBuOH proceeded smoothly to give alcohol **17a,b** (99%), which was oxidized to aldehyde **18a,b** by treatment with PCC in the presence of NaOAc (90%). Aldehyde **18a,b**, without purification, was immediately dissolved in dry benzene (0.05 M solution) and treated with 1.0 equiv of benzylhydroxylamine.[29] The mixture was heated to reflux (80°) for 6 hr while allowing the benzene vapors to condense in a column containing 3 Å molecular sieves. After removal of solvent and chromatography of the crude product the desired isoxazolidine **19a,b** was obtained in 80% yield.[30] When



19b

$J_{8a,8} = 2.7$ Hz
$J_{8a,8b} = 6.0$ Hz
$J_{8b,5a} = 7.9$ Hz
$J_{8b,3a} = 6.0$ Hz



19a

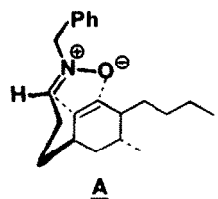
$J_{8a,8} = 1.9$ Hz
$J_{8a,8b} = 5.5$ Hz
$J_{8b,5a} = 9.0$ Hz
$J_{8b,3a} = 5.5$ Hz

pure **18a** or **18b** (from isomerically pure **13a** or **13b**, respectively) was used in this reaction a single isomer **19a** or **19b** was obtained. Isoxazolidines **19a,b** were readily separable by column chromatography and separation of the C.8-butyl isomers was often postponed until this stage of the synthesis.

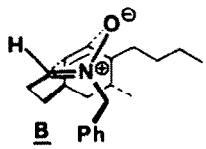
The structures assigned to **19a** and **19b** are fully consistent with the coupling constant data summarized above.[31] It is noteworthy that the *cis*-$H_{8b,5a}$ coupling constants in **19a** (9.0 Hz) and **19b** (7.9 Hz) are similar in magnitude to the large 10 Hz coupling observed in the natural product. Examination of molecular models of **19a,b** reveals that H.8b and H.5a, as in ptilocaulin, possess a dihedral angle close to 0° due to the rigid tricyclic ring system. The stereochemical outcome of this reaction is consistent with either a *Z*-nitrone (the thermodynamically preferred[32a,b] and usually invoked[32c] geometric isomer) undergoing cyclization via exo transition state **A** or an *E*-nitrone proceeding via endo transition state **B**. The alternative *Z*-endo (**C**) and *E*-exo (**D**) transition states, leading to the unobserved C.3a epimers of **19a,b**, suffer serious tortional strain and non-bonded interactions.[33]

Synthesis of (−)-ptilocaulin

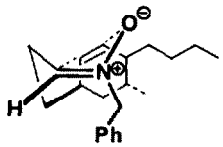
At this juncture the complete carbon skeleton of the natural product was in place, and we were ready to turn to the seemingly straightforward task of converting **19a,b** to ptilocaulin. We began by investigating the cleavage of the isoxazolidine nitrogen–oxygen bond (Scheme 5).[34] Treatment of **19a,b** with a large excess of freshly prepared Al–Hg[35,36] in aqueous THF afforded the desired benzylamino alcohol **20a,b** in 91% yield after extended reaction (2–3 days). The use of Na–Hg[36] in EtOH was even slower, affording only a trace of product (as judged by TLC) after two days, while treatment with $LiAlH_4$ in refluxing THF (22 hr) provided **20a,b** in 70% yield. However, heating **19a,b** in 10 M aqueous AcOH containing a large excess of Zn dust[35] cleanly afforded the desired product **20a,b** in 95% yield. We found that the best yields were obtained



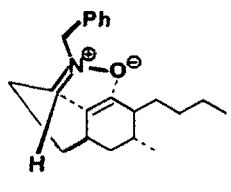
A



B



C



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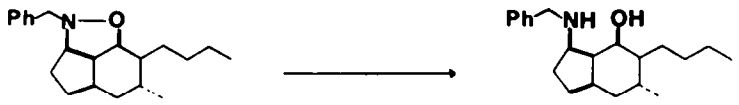


19a,b 20a,b

Reagent	Reaction Time	Yield
Al-Hg, THF-H_2O	2-3 days	91%
Na-Hg, EtOH	very slow	-
$LiAlH_4$, THF, Δ	22h	70%
Zn, 10 M AcOH, 55°C	3.5h	95%

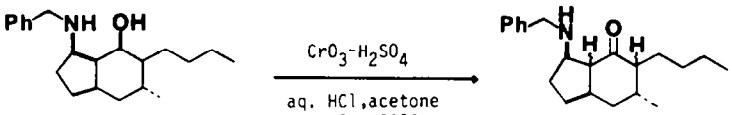
Scheme 5.

when the Zn dust was added to a pre-heated solution of **19a,b** in 10 M aqueous AcOH; addition of Zn dust at room temperature followed by warming to 55° gave lower yields of impure product. The reaction was conveniently monitored by TLC and additional Zn was added periodically until the starting material had been consumed. Because of the rapid reaction and reproducible high yields we adopted this procedure for routine preparation of **20a,b**.

We next attempted the oxidation of **20a,b** to ketone **21a,b**. Jones' reagent is generally quite useful for the oxidation of amino alcohols to amino ketones since the nitrogen atom can be protonated, and thereby protected, by performing the oxidation in the presence of dilute aqueous HCl.[37] Thus, **20a,b** was dissolved in acetone and treated sequentially with 10% HCl and a large (> 100 fold) excess of Jones' reagent. Reaction was very slow, requiring approximately 24 hr to go to completion, and was accompanied by production of a substantial amount of 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol). More significantly, aminoketone **21a,b** was found to consist of several epimers (typically 15–30% epimerized), the ratio of which varied from reaction to reaction. These results were obtained whether pure **20a**, pure **20b** or mixtures of **20a,b** were used. We recognized that this epimerization had grave consequences for our planned stereoselective synthesis, and briefly investigated the use of other oxidants to effect this conversion. While less epimerization was seen (*ca* 10%) using PCC, the yields were lower (50%).

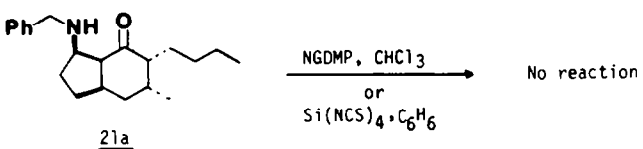
Assuming that the epimerization problem could be resolved in the future, we briefly investigated further functionalization of **21a**. Nitroguanyl-1,3-dimethylpyrazole (NGDMP, **22**) is a useful reagent for guanidination of amines, affording non-polar N-nitro guanidino derivatives.[38] Treatment of partially isomerized **21a** with **22** in $CHCl_3$, however, resulted in complete recovery of starting material. The reagent $Si(NCS)_4$[39] is very reactive, resulting in the formation of a thioamide upon reaction with an amine. However, aminoketone **21a** gave no identifiable products upon treatment with this reagent in benzene. As an alternative we attempted to introduce the guanidine before oxidation of **20a,b**. We hoped that oxidation would be accompanied by immediate cyclization of the guanidine onto the newly formed ketone, thus avoiding epimerization. However, treatment of **20b** with NGDMP (**22**) in methanol or tetrahydrofuran provided only recovered starting material and decomposed reagent.

NGDMP (22) GDMP (23)

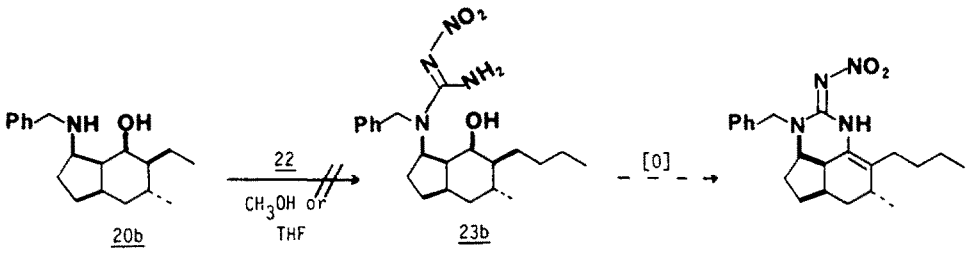


20a,b 70-95% 21a,b

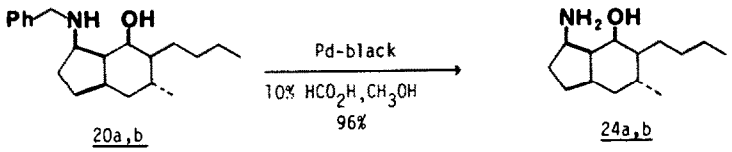
Reasoning that compounds **20a,b** and **21a,b** containing secondary amines were too hindered to allow functionalization, we decided to remove the benzyl group from **20a,b**. This transformation was most easily accomplished by transfer hydrogenation[40] using



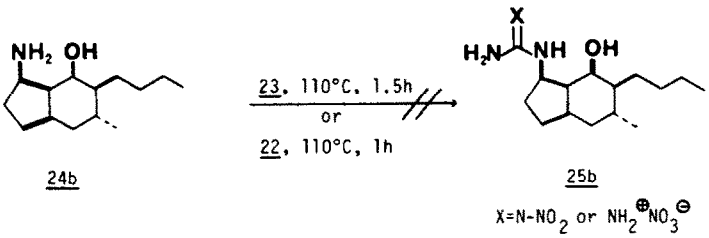
21a No reaction



10% formic acid in methanol and freshly prepared Pd black[41] as catalyst (3 hr, 23°), giving **24a,b** in 96% yield after workup. However, this material also proved resistant to further functionalization with either NGDMP (**22**) or 1-guanyl-3,5-dimethylpyrazole contaminated with diacetone alcohol. Attempts to oxidize **24b** by use of Swern's oxalyl chloride–DMSO procedure[43] afforded no identifiable products, and use of triphenylbismuth carbonate in CH_2Cl_2 (23°) led to no reaction.[44a] When **24b** was treated with 1.5 equiv of

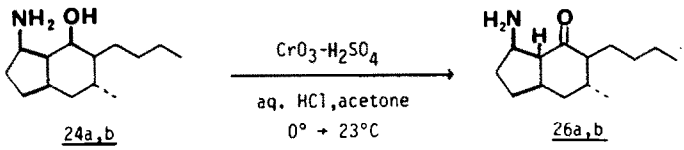


nitrate (GDMP, **23**).[42] The latter reagent has been reported to react with primary and secondary amines, typically by melting the reagent with the amine in the absence of solvent. When amino alcohol **24b** was melted with 1 equiv of GDMP no reaction was this reagent in refluxing $CHCl_3$ for 24 hr, oxidation products were still not observed. Under these more vigorous conditions, however, a less polar material was produced which appeared to be the product of phenyl transfer from Ph_3BiCO_3 to the amino functionality of



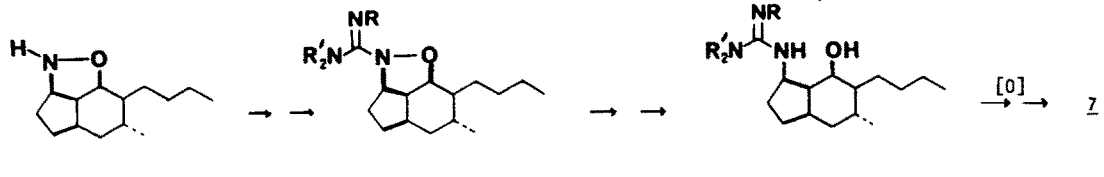
observed. Interestingly, when the melt procedure was applied to NGDMP (**22**) and **24b** a new product (not **25b**, X = N—NO_2) was obtained. The structure of this material, however, was not determined.

24b. Although the identity of this compound was not rigorously determined, such transfers have been previously observed with triphenylbismuth diacetate[44b] and triphenylbismuth carbonate.[44c]

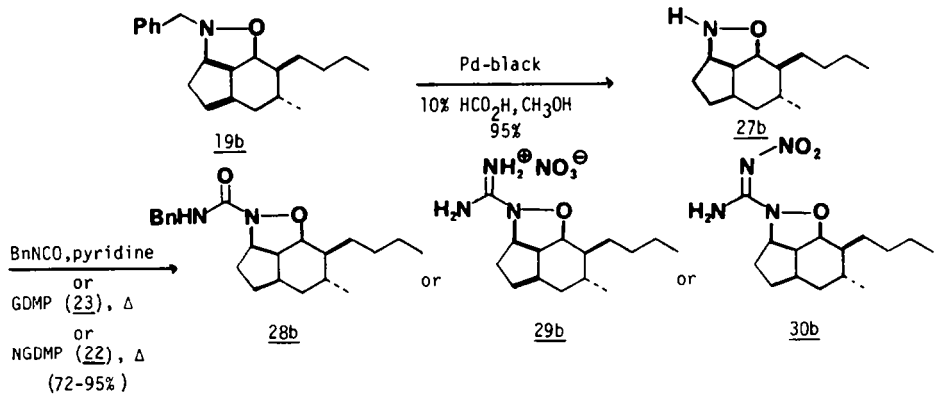


Since amino alcohol **24a,b** was easily obtained in pure form as a single isomer we investigated methods for its oxidation to ketone **26a,b**. Treatment of an acetone solution of **24a,b** containing aqueous HCl with a large excess of Jones' reagent afforded **26a,b** which was again substantially epimerized (30%) and

Plagued by the inability to cleanly oxidize either **20a,b** or **24a,b** and the failure to introduce a guanidine moiety to any of these intermediates, we attempted yet another approach. The essence of this strategy is shown in Scheme 6. We reasoned that if the guanidino group could be introduced at the stage of **27a,b**, subsequent



Scheme 6.

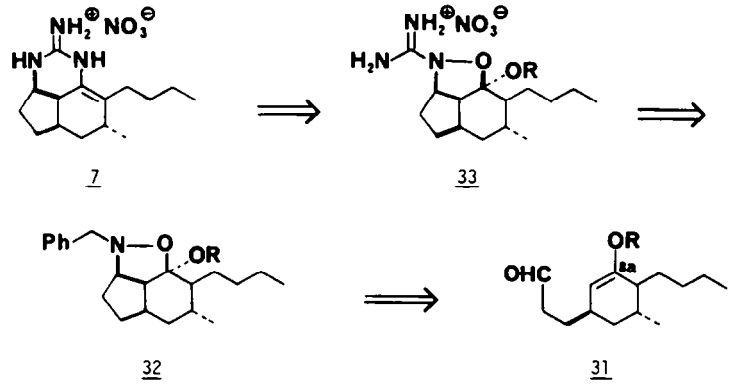


reductive cleavage of the nitrogen–oxygen bond followed by oxidation should be accompanied by cyclization to give ptilocaulin (7).

We found that the benzyl group in **19b** could be cleanly removed by applying the same transfer hydrogenation procedure described earlier (95% yield). Functionalization of **27b** either by treatment with benzylisocyanate, GDMP (melt) or NGDMP (melt) smoothly afforded **28b**, **29b** and **30b**, respectively (72–95% yields). These encouraging results were soon tempered by the reluctance of **28b** and **29b** to undergo nitrogen–oxygen bond cleavage under conditions used successfully in the conversion of **19a,b** to **20a,b** (Zn/HOAc, Δ; Al–Hg; Na–Hg; starting material was recovered in each case).[45] More vigorous conditions such as Zn dust in refluxing aqueous HCl caused extensive decomposition of **29b**.

aldehyde **31** (Scheme 7). In such an approach the need for reductive removal of the C.8a oxygen atom (cf. **16** → **17**) would be eliminated, as would subsequent reoxidation of this position. Since we had already determined that the guanidino group could be cleanly introduced at the stage of isoxazolidine **27b** (cf. **27b** → **29b**) we felt that this approach merited investigation.

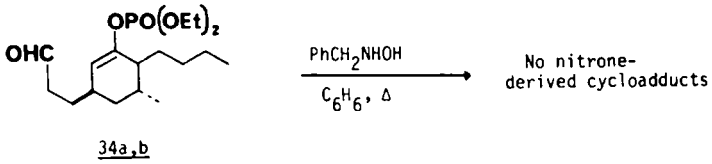
Toward this end, enolphosphate **16a,b** was cleanly oxidized with PCC to give aldehyde **34a,b** in 82% yield.



Scheme 7.

However, several attempts to effect an intramolecular cycloaddition by treatment of **34a,b** with benzylhydroxylamine in benzene met with failure. Only very complex mixtures of products resulted, from which no desired cycloadduct was isolated.

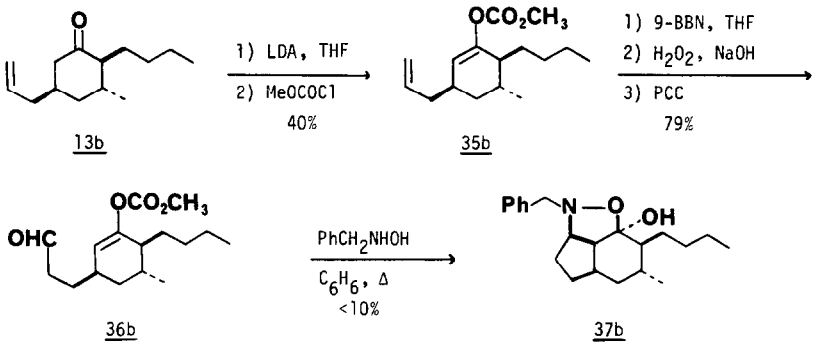
Studies involving enol carbonate **36b** were only slightly more successful (Scheme 8). When **36b** was treated with benzylhydroxylamine a complex mixture



of products was again obtained, from which only trace amounts (< 10%) of cycloadduct **37b** were isolated. This material was identified by comparison of its ^{1}H-NMR spectrum with that of isoxazolidine **19b**.

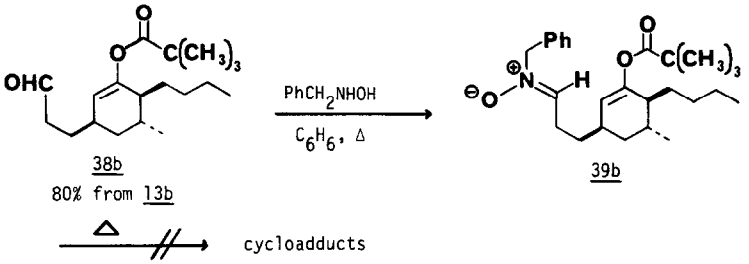
At this stage it appeared that the conversion of **19a,b** to ptilocaulin would be considerably more challenging than originally anticipated. In a reanalysis of our strategy we decided to modify the route so that C.8a would be maintained in the correct oxidation state throughout the synthesis, thus eliminating the need to oxidize amino alcohol intermediates. The key step of this new approach would be an intramolecular 1,3-dipolar cyclization of the nitrone derived from

Literature precedent suggested that intramolecular nitrone cycloadditions with enol ether derivatives should be a feasible process.[46] We speculated that intermediates **34a,b** and **36b** might undergo competitive nucleophilic attack by benzylhydroxylamine at the



Scheme 8.

labile enolphosphate or carbonate centers. In an effort to ameliorate this problem enol pivaloate **38b** was investigated. This intermediate was efficiently prepared in 80% overall yield from **13b** by simple modification of the chemistry outlined in Schemes 4 and 8. When **38b** was treated with benzylhydroxylamine in refluxing benzene a clean reaction ensued, generating nitrone **39b** (structure assigned by ^{1}H-NMR analysis). Unfortunately, heating **39b** in benzene at 80° (6 hr) left this material unchanged, while heating at 110° in toluene (6.5–17 hr) caused extensive decomposition, leading to a mixture of unidentified products. This approach was therefore regrettably discontinued and we returned to the sequences discussed previously.[47]

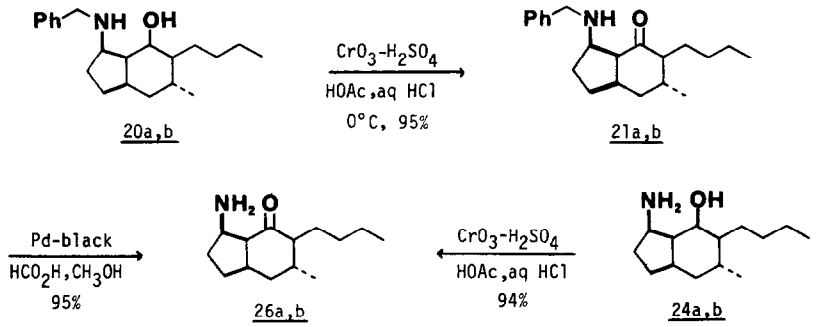


Hoping that ptilocaulin could be obtained from a pure sample of amino ketone **26a,b** (cf. Scheme 2) we sought a method for avoiding the epimerization problems associated with the oxidation of **20a,b** and **24a,b**. A key advancement was made when we observed that oxidation of **20a,b** with CrO_3–H_2SO_4 proceeded much more rapidly in glacial acetic acid than in aqueous acetone.[48] Indeed, by conducting this oxidation in glacial acetic acid containing 2 M aqueous HCl, complete conversion of **20a,b** to **21a,b** was achieved (95% yield) after only 2.5 hr at 0° (Scheme 9). Under these conditions the epimerization problem was largely avoided, although in some runs as much as 5–10% of epimers were detected. Significantly, the formation of acetone derived by-products was now eliminated, thereby simplifying the isolation of **21a,b**. Although this intermediate could be purified by careful chromatography, we routinely used crude **21a,b** immediately in the next step. In initial experiments, however, **21a,b** was chromatographed and epimers **40a** (from experiments with **20a**) and **40b** (from pure **20b**) were separated. The spectroscopic data for these compounds were consistent with the *trans*-fused structures below.

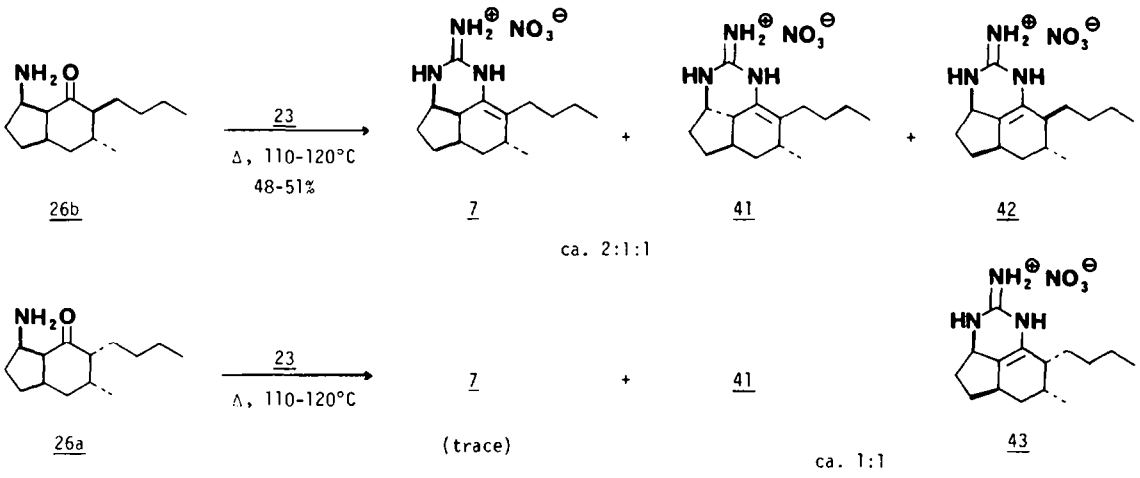
40a, R=Bn
44a, R=H

40b, R=Bn
44b, R=H

Benzylamino ketones **21a,b** were smoothly deprotected by transfer hydrogenation (Scheme 9), affording amino ketone **26a,b** in 95% yield.



Scheme 9.



Unfortunately, additional epimerization (15–30%) occurred even under these relatively mild reaction conditions. A clue to the source of this problem was found when we determined that the formate salt of **26b**, obtained by simple filtration of the hydrogenation mixture to remove the catalyst and concentration *in vacuo*, consisted primarily of a single epimer. After neutralization (by washing a $CHCl_3$ solution of **26b** with saturated aqueous $NaHCO_3$), however, ^{1}H-NMR analysis revealed the presence of epimeric material (30%). Thus, epimerization apparently occurs spontaneously at the stage of **26a,b** after reaction workup. Although epimerization of **26a,b** was apparently unavoidable, isolation of the formate salt of **26a,b** and subsequent neutralization immediately before use in the final step of the synthesis was adopted as standard procedure.

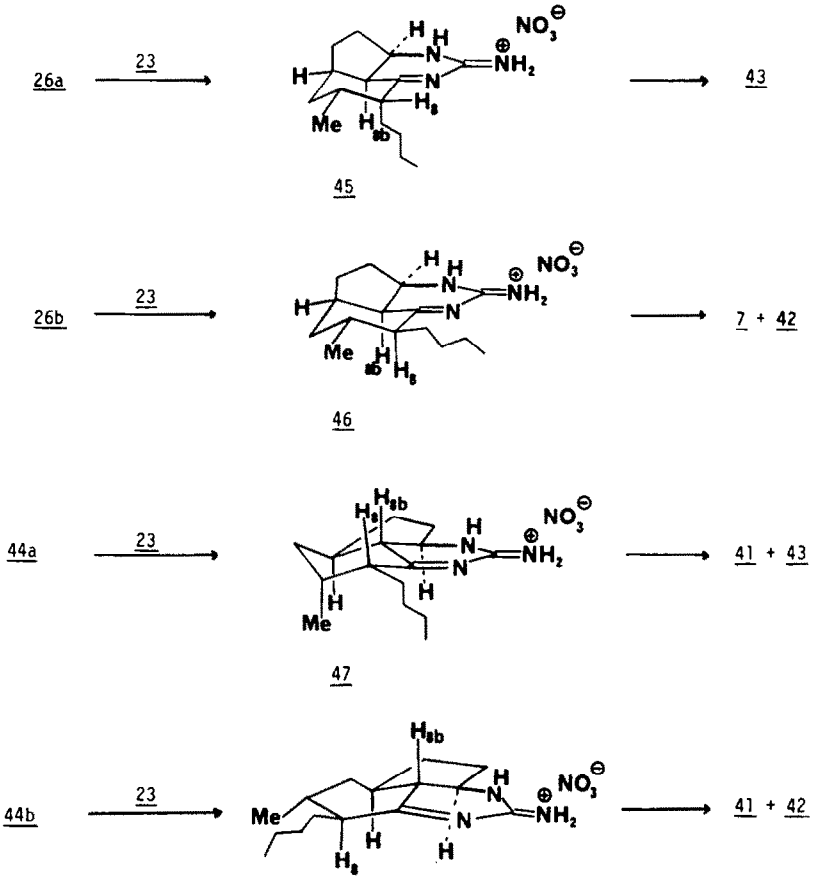
Amino ketone **26a,b** could also be prepared by Jones' oxidation of **24a,b** in glacial acetic acid (94% yield). While the reaction proceeded more rapidly than in aqueous acetone, substantial epimerization was again observed (30%). Because isolation of **26a,b** from the transfer hydrogenation deprotection of **21a,b** was much more convenient than from the Jones' oxidation of **24a,b**, the former procedure was the preferred method for preparation of this intermediate (see Scheme 9).

With amino ketone **26a,b** in hand (albeit epimeric!) we were optimistic about obtaining at least some ptilocaulin (**7**) from the reaction of **26a,b** with GDMP (**23**). When **26b** was subjected to the melt conditions used previously (1 equiv **23**, 120°, 15 min), a mixture of three guanidine containing compounds was obtained in an approximate 2:1:1 ratio (48–51% yield). The major product possessed ^{1}H-NMR characteristics consistent with ptilocaulin **7**, while the other two compounds were tentatively assigned structures **41** and **42**. Compound **41** is derived presumably from *trans*-fused **44b** while **42** represents an olefinic regioisomer of the natural product. Unfortunately, these compounds were inseparable by chromatography. When the same guanidination procedure was applied to **26a** we were dismayed to find that virtually no ptilocaulin was obtained. Instead, two major guanidine containing compounds were produced (*ca* 1:1), one of which corresponded to **41** and the other which was assigned structure **43**.[49] Interestingly, **26a** underwent guanidation with GDMP (**23**) in benzene (80°, 18 hr, *ca* 40% yield) to give a mixture of **43** and **41** in a *ca* 3:1 ratio. Again, only a trace of **7** was detected.

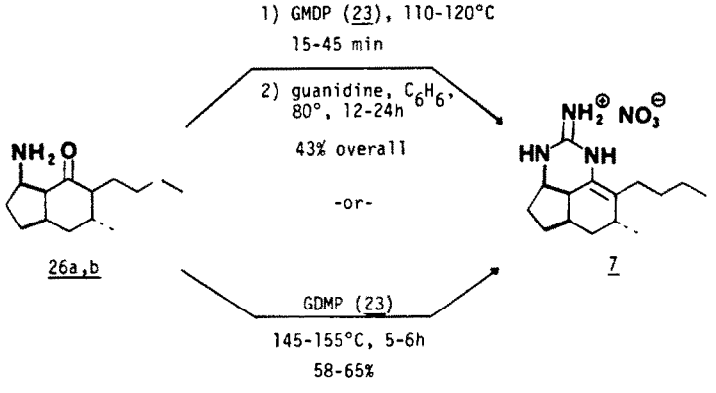
These results can be rationalized by inspection of the presumed intermediates **45–48** (Scheme 10) in the guanidination reaction. Thus, in **46** (from **26b**) the axial C.8 hydrogen is perpendicular to the adjacent C=N π-system and therefore is suitably oriented for tautomerization to ptilocaulin **7**. In **45** (from **26a**), however, the C.8 hydrogen is equatorial and thus not favorably oriented for isomerization to **7**. In both **45** and **46** the axial C.8b hydrogen possesses favorable geometry for isomerization, to **43** and **42**, respectively. Presumably, the *trans*-fused intermediates derived from **44a** and **44b** would exist in the conformations shown for **47** and **48**. In both cases the C.8 hydrogen is axial, thereby allowing the formation of **41** from both intermediates. In addition, elimination of H.8b can occur in either intermediate leading to **43** and **42**, respectively.

While these studies were in progress, Snider reported that the reaction of enone **6** and guanidine afforded ptilocaulin as the sole product (35% yield).[8a] This strongly implied that ptilocaulin should be the most stable isomer, and we were immediately able to test this hypothesis. Indeed, the mixture of **7**, **41**, and **42** obtained from **26b** was dissolved in benzene and treated with a catalytic amount of guanidine. After 24 hr at reflux the reaction was neutralized with 1% HNO_3 and worked up by extraction with $CHCl_3$ and saturated aqueous $NaNO_3$. Examination of the ^{1}H-NMR spectrum of the material so obtained revealed that it consisted of virtually homogeneous ptilocaulin. The recovery of **7** after chromatography was 89%, indicating that equilibration and not selective destruction of the minor isomers had occurred. In a similar manner, the mixture of **41** and **43** (with trace **7**) from **26a** also yielded only **7** after guanidine equilibration. It was now obvious that the epimerization(s) encountered in the preceding steps were no longer a concern. Moreover, we also quickly discovered that **7** could be obtained directly from **26a,b** in 58–65% yield by simply conducting the melt reaction with 1.1 equiv of **23** at higher temperatures (145–155°) for 5–6 hr (equilibrating conditions).

The synthetic ptilocaulin so obtained (m.p. 183–184°; lit.[3] 183–185°) possessed an optical rotation ($[\alpha]_D^{23} - 73.9°$ ($c = 0.31$, 99.9% CH_3OH)) equal, but



Scheme 10.



opposite in sign, to that of the natural material.[50] Natural (+)-ptilocaulin thus possesses the absolute stereochemistry depicted in **3**.

In final analysis it is evident that ptilocaulin is the thermodynamically most stable of the possible double bond and ring fusion isomers. Moreover, it is somewhat ironic (and disappointing) that the element of thermodynamic control which we rejected in initial synthetic planning (Scheme 1) proved to be the saviour of this synthesis. Nonetheless, the strategy to control the stereochemistry of C.3a in the intramolecular nitrone cycloaddition did pay positive dividends, since the efficiency of the final step of this synthesis (**26** → **7**, 58–65%) is substantially better than in approaches defined by **6** → **7** (35–40%).

EXPERIMENTAL

^{1}H-NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in δ units relative to internal $CHCl_3$ (δ 7.24). ^{13}C-NMR spectra

were measured at 68 MHz on the Bruker 270, or at 22.5 MHz on a Jeol FX90Q instrument; carbon resonances are reported in δ_c units calibrated against the 77.0 ppm line of $CDCl_3$. IR spectra were measured on a Perkin–Elmer Model 283B IR Spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. M.ps were recorded on a Fisher–Johns hot stage m.p. apparatus and are uncorrected. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Elemental analyses were performed by Robertson Laboratories, Florham Park, New Jersey.

The standard ptilocaulin numbering system is used for all proton assignments. All intermediates in the "a" series possess α-Bu groups, whereas in the "b" series the Bu group is on the β-face of the intermediates as drawn in text. All compounds containing the guanidine group were isolated and characterized as nitrate salts.

All reactions were conducted in oven (170°) and/or flame dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether and THF were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2 and t-BuOH was distilled from Na metal. Diisopropylamine was distilled from KOH and stored over activated 4 Å molecular sieves. Hexamethylphosphoric triamide was dried by storage over activated 4 Å molecular sieves. Formic acid and acetic acid were distilled before use. All other reagents were used as obtained.

Analytical TLC was performed by using 2.5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). PTLC was performed by using 20 cm × 20 cm plates coated with 0.25 and 0.5 mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with either EtOAc or ether. Flash chromatography was performed as described by Still *et al.*,[52] using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh). Compounds were visualized with short-wave UV light, or by staining with either I_2 vapor or charring with ethanolic H_2SO_4. All chromatography solvents were distilled prior to use.

Butylated sulfoxides **11**

A soln of LDA was prepared by addition of 39.8 ml of n-BuLi (2.54 M in hexane, 101 mmol, 2.2 equiv) to a soln of dry diisopropylamine (10.7 g, 106 mmol, 2.3 equiv) in 100 ml of THF at −78°. This soln was stirred for 1.5 hr and then added dropwise via cannula over 1 hr to a soln of carefully dried **10**[15] (10.9 g, 46.2 mmol, 1.0 equiv) in THF (75 ml) containing 52 g (290 mmol, 6.4 equiv) of dry HMPA at −40°. After *ca* 1.0 equiv of LDA had been added the sulfoxide soln changed from yellow to orange and finally dark red after the addition was complete. This red soln was stirred at −35 to −40° for 2 hr and treated with freshly distilled 1-iodobutane (10.1 g, 55.0 mmol, 1.2 equiv; distilled from $MgSO_4$) in one portion. The red color was almost immediately dispersed, resulting in a pale yellow soln. After being stirred for an additional 2 hr at −35 to −40° the mixture was treated with 150 ml of 10% HCl aq and allowed to warm to room temp. Workup consisted of transferring the soln to a separatory funnel containing Et_2O and 10% HCl (400 ml each), washing with additional portions of 10% HCl (2 × 400 ml), extraction of the combined aqueous layers with Et_2O (5 × 350 ml), washing the combined organic extracts with sat $NaHCO_3$ aq (800 ml) and sat NaCl aq (800 ml). After drying over $MgSO_4$, filtration and removal of the solvent *in vacuo* the oily residue was purified by flash chromatography (silica gel, 95 mm column, 1:1 EtOAc–hexane) to afford 10.2 g (76%) of **11** as a mixture of diastereomers (TLC: series of partially resolved spots, R_f 0.28–0.64, 1:1 EtOAc–hexane). ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 7.8–7.3 (m, 5H), 3.8–3.3 (3 m's, 1H), 2.7–1.2 (series of m, 12H), 1.2–0.75 (series of d's and t's, 6H); ^{13}C-NMR ($CDCl_3$, 22.5 MHz) δ 206.8, 186.9, 177.5, 142.1, 131.3, 129, 125.9, 124.5, 74.3, 73.8, 60.1, 58, 39, 37.2, 33.3, 29, 28.2, 27.5, 25.2, 23.1, 22.8, 22.5, 20.8, 19.9, 14, 13.7; IR (neat) 3050, 2945, 2920, 2860, 1705, 1580, 1460, 1445, 1378, 1084, 1042, 995, 915, 745, 730, 684, 640 cm^{-1}; mass spectrum *m/e* 292 (parent ion).

Butylcyclohexenone **12a,b**

A soln of **11** (3.62 g, 12.4 mmol) in CCl_4 (100 ml) was treated with $CaCO_3$ (1.19 g, 11.9 mmol, 0.96 equiv) under N_2. The mixture was warmed to 65° while being stirred rapidly and maintained at this temp for 24 hr. After being cooled to room temp the mixture was filtered through a pad of Celite and the solvent was removed *in vacuo*. Chromatography of the residue (silica gel, 60 mm column, 4:1 hexane–ether) afforded 1.37 g (66%) of **12** as a *ca* 6:1 mixture of β- and α-C.8 isomers: TLC, R_f 0.41 (4:1 hexane–ether); $[\alpha]_D^{22} - 69.8°$ (*c* = 0.92, $CHCl_3$); ^{1}H-NMR data for **12a** ($CDCl_3$, 270 MHz) δ 6.81 (m, 1H, H.8), 5.95 (m, 1H, H.8b), 2.6–2.3 (m, 2H), 2.25–2.0 (m, 2H), 1.8–1.5 (m, 2H), 1.4–1.15 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H, —CH_3), 0.89 (t, J = 7.1 Hz, 3H, —CH_3); ^{1}H-NMR data for **12b** ($CDCl_3$, 270 MHz) δ 6.81 (m, 1H, H.8), 5.95 (m, 1H, H.8b), 2.6–2.3 (m, 2H), 2.25–2.0 (m, 2H), 1.8–1.5 (m, 2H), 1.4–1.15 (m, 4H), 1.06 (d, J = 6.5 Hz, 3H, —CH_3), 0.89 (t, J = 7.1 Hz, 3H, —CH_3); ^{13}C-NMR data for **12b** ($CDCl_3$, 22.5 MHz) δ 201.8, 147.4, 128.9, 53.5, 32.5, 32.3, 28.5, 27.4, 22.9, 19.6, 13.9. IR (neat) 3032, 2955, 2930, 2870, 2830, 1673, 1460, 1425, 1390, 1246, 1203, 1103, 915, 893, 835, 805, 775, 731, 700 cm^{-1}; mass spectrum *m/e* 166 (parent ion). (Found: C, 79.40; H, 10.94. Calc for $C_{11}H_{18}O$: C, 79.46; H, 10.91%.)

Allylcyclohexenone **13a,b**

A soln of **12a,b** (1.96 g, 11.8 mmol) in CH_2Cl_2 (43 ml) was cooled to −78°. $TiCl_4$ (2.69 g, 14.2 mmol, 1.2 equiv) was added dropwise during 5 min under a stream of Ar, resulting in the formation of an orange–red soln containing a small amount of orange ppt. This mixture was stirred for 5 min at −78° and then allyltrimethylsilane (2.02 g, 17.7 mmol, 1.5 equiv) in CH_2Cl_2 (33 ml) was added dropwise over a 2 hr period. The resultant deep red soln was stirred for 1.5 hr at −78° and then treated with H_2O (20 ml), added dropwise. The mixture was stirred at −78° until the red color had faded to give a colorless soln. After being warmed to room temp the mixture was partitioned between Et_2O and sat NaCl aq (125 ml each). The aqueous layer was further extracted with ether (5 × 75 ml) and the combined organic extracts were washed with sat NaCl aq (300 ml). The extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2.51 g of crude **13a,b**. ^{1}H-NMR analysis of this material revealed that it was an approximate 6:1 mixture of **13b**:**13a** of >95% purity. Flash chromatography of a 1.00 g portion of this material (silica gel, 60 mm column, 10:1 hexane–ether) afforded **13b** (0.751 g, 15:1 mixture of **13b**:**13a**), **13a** (0.152 g, ~8:1 **13a**:**13b**) and a single mixed fraction containing **13a,b** (0.099 g, ~4:1 **13b**:**13a**). The total recovery was thus 1.00 g (100%). Chromatography of the remaining material (and the mixed fraction) afforded a total of 2.35 g (96%) of **13a,b**.

Data for **13a**: TLC, R_f 0.63 (4:1 hexane–ether); $[\alpha]_D^{22} - 24.9°$ (*c* = 2.08, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 5.77 (m, 1H, H.4), 5.03 (d, J = 12.3 Hz, 1H, *Z*-H.3a), 5.03 (d, J = 15 Hz, 1H, *E*-H.3a), 2.46–2.36 (m, 3H), 2.14–1.93 (m, 4H), 1.80–1.59 (m, 3H), 1.38–1.15 (m, 5H), 0.89 (t, J = 6.8 Hz, 3H, —CH_3), 0.77 (d, J = 7.0 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 212.5, 135.7, 116.5, 57.1, 54.0, 48.1, 41.1, 38.9, 34.7, 34.2, 29.5, 25.9, 22.8, 14.0; IR (neat) 3070, 2950, 2920, 2865, 2858, 1708, 1640, 1450, 1380, 1230, 1224, 1202, 1158, 1092, 990, 910 cm^{-1}; mass spectrum *m/e* 208 (parent ion). (Found: C, 80.84; H, 11.37. Calc for $C_{14}H_{24}O$: C, 80.71; H, 11.61%.)

Data for **13b**: TLC, R_f 0.58 (4:1 hexane–ether); $[\alpha]_D^{22} + 41.8°$ (*c* = 1.43, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 5.72 (m, 1H, H.4), 5.03 (d, J = 11.7 Hz, 1H, *Z*-H.3a), 5.02 (d, J = 15.6 Hz, 1H, *E*-H.3a), 2.33–2.04 (m, 7H), 1.77–1.45 (m, 4H), 1.35–1.18 (m, 4H), 0.99 (d, J = 6.7 Hz, 3H, —CH_3), 0.88 (t, J = 6.7 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 213.7, 135.7, 116.4, 56.9, 44.7, 39.8, 34.4, 34.1, 29.5, 22.5, 20.1, 13.7; IR (neat) 3078, 2948, 2923, 2861, 1705, 1640, 1458, 1443, 1423, 1380, 1346, 1234, 990, 910 cm^{-1}; mass spectrum *m/e* 208 (parent ion). (Found: C, 80.55; H, 11.70. Calc for $C_{14}H_{24}O$: C, 80.71; H, 11.61%.)

Equilibration of **13a** *and* **13b**

Isomerically pure **13a** (23 mg, 0.11 mmol) was dissolved in CH_3OH (2.0 ml) and treated with 76 mg (0.55 mmol, 5 equiv) of powdered anhyd K_2CO_3. After being stirred for 2 hr the MeOH was removed *in vacuo*. The residue was dissolved in Et_2O (30 ml) and washed with H_2O (3 × 30 ml). The extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 21 mg of a 1.9:1 mixture of **13a**:**13b** (^{1}H-NMR analysis). An identical 1.9:1 mixture of **13a**:**13b** was obtained when pure **13b** was subjected to these conditions.

Enolphosphate **14a,b**

A soln of LDA was prepared by the addition of 1.19 ml of 2.61 M n-BuLi in hexane (3.11 mmol, 1.6 equiv) to diisopropylamine (418 mg, 4.14 mmol, 2.1 equiv) in THF (6.2 ml) at −78°. To this soln at −78° was added carefully dried ketone **13b** (404 mg, 1.94 mmol) in 3.1 ml of cold (−78°) THF. After being stirred for 1.5 hr the soln was warmed to 0°, treated with HMPA (696 mg, 3.88 mmol, 2.0 equiv) and stirred for an additional 30 min. Freshly distilled chlorodiethylphosphate (938 mg, 5.44 mmol, 2.8 equiv; distilled from K_2CO_3) was then added dropwise, and the resulting mixture was warmed to room temp and stirred for 3 hr. Workup involved addition of sat $NaHCO_3$ aq (50 ml) and repeated extraction with Et_2O (5 × 50 ml). The combined extracts were washed successively with H_2O (50 ml), sat NaCl aq (50 ml) and dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo*, chromatography of the residue (silica gel, 40 mm column, 2:1 hexane–EtOAc) afforded 506 mg (77%) of **14b**.

Data for **14a**: R_f 0.36 (2:1 hexane–EtOAc); $[\alpha]_D^{20}$ + 41.7° (*c* = 0.96, $CHCl_3$; sample contained *ca* 10% **14b**); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 5.78 (m, 1H, H.4), 5.40 (br s, 1H, H.8b), 5.02 (br d, J = 15.6 Hz, 1H, *E*-H.3a), 5.01 (br d, J = 10.4 Hz, 1H, *Z*-H.3a), 4.15 (quint, J = 6.9 Hz, 4H), 2.29 (br s, 2H), 2.07 (m, 3H), 1.7–1.5 (m, 2H), 1.4–1.2 (m, 6H), 1.34 (two overlapping t, J = 7.2 Hz, 6H), 0.90–0.88 (overlapping d and t, 6H, two —CH_3's); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 150.3, 136.8, 116.1, 113.3 (d), 64.0 (d), 41.4, 40.4, 33.6, 31.8, 29.9, 28.8, 27.2, 23.0, 16.1 (d), 15.1, 14.0; IR (neat) 3065, 2950, 2922, 2865, 1665, 1638, 1452, 1442, 1378, 1272, 1040, 1030, 980, 910, 810 cm^{-1}; mass spectrum *m/e* 344 (parent ion). (Found: C, 62.26; H, 9.71. Calc for $C_{18}H_{33}PO_4$: C, 62.77; H, 9.66%.)

Data for **14b**: $[\alpha]_D^{20}$ − 18.0° (*c* = 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 5.83–5.70 (m, 1H, H.4), 5.43 (br s, 1H, H.8b), 5.03 (br d, J = 16.1 Hz, 1H, *E*-H.3a), 5.02 (br d, J = 11.2 Hz, 1H, *Z*-H.3a), 4.15 (quint, J = 7.1 Hz, 4H), 2.30 (br s, 1H), 2.08 (br t, J = 6.9 Hz, 2H), 2.0–1.8 (m, 2H), 1.75–1.55 (m, 1H), 1.5–1.2 (m, 7H), 1.35 (two overlapping t, J = 7.0 Hz, 6H), 0.98 (d, J = 6.9 Hz, 3H, —CH_3), 0.90 (t, J = 6.3 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 150.2, 136.6, 116.2, 113.2 (d), 64.0 (d), 44.2, 40.2, 31.6, 31.0, 29.5, 29.4, 22.8, 19.3, 16.0, 14.0; IR (neat) 3075, 2955, 2930, 2870, 1672, 1642, 1458, 1445, 1378, 1275, 1132, 1094, 1040, 970, 910, 870, 815, 750 cm^{-1}; mass spectrum *m/e* 344 (parent ion). (Found: C, 62.84; H, 9.57. Calc for $C_{18}H_{33}PO_4$: C, 62.77; H, 9.66%.)

Hydroxyenolphosphate **16a,b**

Enolphosphate **14b** (506 mg, 1.47 mmol) was dissolved in 4 ml of THF under Ar. This soln was cooled to 0°, treated with 5.20 ml of a freshly prepared soln of 9-BBN (0.5 M in THF, 3.02 mmol, 2.05 equiv) and stirred for 3 hr. The mixture was allowed to warm to room temp (0.5 hr) and then was recooled to 0° and treated with MeOH (2 ml). When gas evolution had subsided 1.0 ml each of 3 M NaOH aq and 30% H_2O_2 aq were simultaneously added dropwise. The soln (which contained a white ppt) was warmed to room temp and stirred for 2 hr. Workup consisted of dilution with ether (50 ml) and extraction with sat NaCl aq (50 ml). The aqueous layer was further extracted with ether (4 × 50 ml) and the combined organic extracts were washed with sat $Na_2S_2O_3$ aq, sat $NaHCO_3$ aq, sat NaCl aq and dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo* the residue was purified by flash chromatography (silica gel, 40 mm column, 20:1 CH_2Cl_2–MeOH) to give 480 mg of **16b** (90%). The yield of **16a** from **14a** using this procedure was 94%.

Data for **16a**: TLC, R_f 0.46 (20:1 $CHCl_3$–MeOH); $[\alpha]_D^{19}$ + 20.8° (*c* = 1.00, $CHCl_3$; sample contained *ca* 10% **16b**); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 5.42 (br s, 1H, H.8b), 4.14 (quint, J = 7.3 Hz, 4H), 3.62 (t, J = 6.5 Hz, 2H, —CH_2—OH), 2.26 (br s, 2H), 2.2–2.0 (m, 1H), 1.82 (br s, 3H), 1.7–1.5 (m, 4H), 1.5–1.2 (m, 9H), 1.35 (two overlapping t, J = 7.1 Hz, 6H), 0.90–0.88 (overlapping d and t, 6H, two —CH_3's); IR (neat) 3440, 2925, 2860, 1668, 1445, 1378, 1263, 1148, 1035, 975, 815, 728 cm^{-1}; mass spectrum *m/e* 362 (parent ion). (Found: C, 59.47; H, 9.89. Calc for $C_{18}H_{35}PO_5$: C, 59.65; H, 9.73%.)

Data for **16b**: $[\alpha]_D^{19}$ − 16.7° (*c* = 0.46, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 5.43 (br s, 1H, H.8b), 4.14 (quint, J = 7.2 Hz, 4H), 3.64 (t, J = 6.4 Hz, 2H, —CH_2OH), 2.24 (br s, 1H), 2.0–1.5 (m, 9H), 1.5–1.2 (m, 12H), 1.36 (two overlapping t, J = 7.1 Hz, 6H), 0.97 (d, J = 6.9 Hz, 3H, —CH_3), 0.89 (t, J = 6.2 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 150.1, 113.8 (d), 63.9 (d), 62.9, 44.4 (d), 32.1, 31.7, 31.4, 31.1, 30.1, 29.8, 29.4, 22.8, 19.4, 16.0 (d), 13.9; IR (neat) 3430, 2950, 2930, 2865, 1675, 1455, 1380, 1268, 1130, 1040, 970, 815 cm^{-1}; mass spectrum *m/e* 362 (parent ion). (Found: C, 59.75; H, 9.62. Calc for $C_{18}H_{35}PO_5$: C, 59.65; H, 9.73%.)

Alcohol **17a,b**

A soln of Li in $EtNH_2$ was prepared by adding Li wire (85 mg, 12.3 mmol, 10 equiv) to anhyd $EtNH_2$ (25 ml) at 0°. When the Li wire had been consumed, the resulting deep blue soln was treated with 0.23 ml of dry t-BuOH (182 mg, 2.46 mmol, 2.0 equiv). To this stirred soln was rapidly added **16a,b** (446 mg, 1.23 mmol) as a soln in 4 ml of THF containing 0.43 ml of t-BuOH (342 mg, 4.61 mmol, 3.75 equiv). After being stirred for 1.5 hr at 0° the soln was treated with excess solid NH_4Cl (*ca* 5 g, in several portions). The $EtNH_2$ was evaporated by gentle warming and the residue was treated with H_2O (25 ml). The aqueous layer was extracted with ether (4 × 50 ml) and the combined organic extracts were washed with sat $Na_2S_2O_3$ aq, sat NaCl aq and dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo* the residue was purified by column chromatography (silica gel, 40 mm, 1:1 EtOAc–hexane) affording 256 mg of **17a,b** (99%).

Data for **17a**: (data obtained on mixture containing ~15% of **17b**): TLC, R_f 0.58 (1:1 EtOAc–hexane); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 5.48 (A of AB, J_{AB} = 10.2 Hz, 1H), 5.41 (B of AB, J_{AB} = 10.2 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H, —CH_2OH), 2.15–1.8 (m, 3H), 1.7–1.5 (m, 4H), 1.45–1.1 (m, 9H), 0.87 (br t, 3H), 0.78 (d, J = 6.9 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 130.5, 130.2, 63.2, 39.0, 36.1, 32.3, 31.9, 30.1, 29.5, 29.2, 22.9, 14.1, 13.5; IR (neat) 3330, 3010, 2960, 2920, 2850, 1450, 1375, 1050 cm^{-1}; mass spectrum *m/e* 210 (parent ion).

Data for **17b**: $[\alpha]_D^{19}$ − 11.0° (*c* = 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 5.63 (br s, 2H, H.8b and H.8a), 3.64 (t, J = 6.6 Hz, 2H, —CH_2OH), 2.05 (m, 1H), 1.7–1.1 (m, 15H), 0.94 (d, J = 6.4 Hz, 3H, —CH_3), 0.89 (br t, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 130.7, 130.3, 63.2, 42.3, 34.3, 34.0, 32.7, 32.1, 30.6, 29.5, 29.1, 23.0, 20.1, 14.0; IR (neat) 3340, 3010, 2920, 2860, 1648, 1455, 1375, 1052, 720 cm^{-1}; mass spectrum *m/e* 210 (parent ion). (Found: C, 79.69; H, 12.47. Calc for $C_{14}H_{26}O$: C, 79.93; H, 12.46%.)

Aldehyde **18a,b**

To 5 ml of dry CH_2Cl_2 containing *ca* 30 mg of NaOAc was added 395 mg of pyridinium chlorochromate (1.83 mmol, 1.5 equiv). This suspension was treated with a soln of **17a,b** (**17b**:**17a** = 1.5:1) in 2 ml of CH_2Cl_2 and vigorously stirred. TLC analysis after 1.5 hr revealed the complete consumption of starting material. Addition of ether (40 ml) to the rapidly stirred mixture resulted in the formation of a black granular ppt. This soln was filtered through Florisil and the ppt was thoroughly washed with ether (*ca* 150 ml total). After removal of the solvent *in vacuo* 229 mg (90%) of crude **18a,b** (>95% pure by ^{1}H-NMR analysis) was obtained. A portion of **18b** (from an oxidation of isomerically pure **17b**) was purified by preparative thin layer chromatography (silica gel, 2:1

hexane–EtOAc) for characterization. In preparative runs, however, crude **18a,b** was used immediately in the subsequent step.

Data for **18b**: TLC, R_f 0.71 (1:1 EtOAc–hexane); $[\alpha]_D^{19}$ −11.5° (*c* = 0.34, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 9.79 (t, J = 1.8 Hz, 1H, H.3a), 5.7–5.5 (m, 2H), 2.48 (d of t, $J_{3a,4}$ = 1.8 Hz, $J_{4,5}$ = 7.7 Hz, 2H, H.4), 2.07 (m, 1H), 1.8–1.5 (m, 4H), 1.5–1.2 (m, 8H), 0.96–0.80 (overlapping d and t, two CH_3's, 6H); IR (neat) 3010, 2950, 2920, 2860, 2720, 1727, 1650, 1458, 1410, 1375, 1200, 742, 730 cm^{-1}; mass spectrum *m/e* 208 (parent ion).

Benzylisoxazolidine **19a,b**

Freshly prepared aldehyde **18a,b** (**18b**:**18a** = ~1.9:1) (229 mg, 1.10 mmol) was dissolved in dry benzene (20 ml) and the soln was degassed by flushing with Ar. The soln was treated with benzylhydroxylamine[29,30] (137 mg, 1.11 mmol, 1.01 equiv) and gently heated to reflux. Removal of water was accomplished by allowing the benzene to condense in a column containing 3 Å molecular sieves. After 8 hr TLC analysis revealed that reaction was complete, so the solvent was removed *in vacuo*. Purification of the residue by flash chromatography (silica gel, 40 mm column, 9:1 hexane–ether) afforded isomerically pure **19b** (185 mg), and 105 mg of a 7:1 mixture of **19a**:**19b**. The combined yield of **19a,b** was thus 290 mg (84%).

Data for **19a**: TLC, R_f 0.50 (4:1 hexane–ether); $[\alpha]_D^{19}$ +5.2° (*c* = 0.81, $CHCl_3$; sample contained *ca* 10% of **19b**); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.45–7.2 (m, 5H, aromatic), 4.35 (d of d, $J_{8a,8}$ = 1.9 Hz, $J_{8a,8b}$ = 5.5 Hz, 1H, H.8a), 4.19 (A of AB, J_{AB} = 12.6 Hz, 1H, benzylic H), 3.90 (B of AB, J_{AB} = 12.6 Hz, 1H), 3.60 (t, $J_{3a,4cis}$ = $J_{3a,8b}$ = 5.5 Hz, 1H, H.3a), 2.77 (t of d, $J_{8b,5a}$ = 9.1 Hz, $J_{8b,8a}$ = $J_{8b,3a}$ = 5.5 Hz, 1H, H.8b), 2.12 (m, 1H, H.7), 2.0–1.8 (m, 2H), 1.8–1.55 (m, 2H), 1.55–1.0 (m, 10H), 0.94 (t, J = 6.5 Hz, 3H, $—CH_3$), 0.87 (d, J = 7.0 Hz, 3H, $—CH_3$); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 137.7, 129.2, 128.3, 127.1, 78.3, 72.1, 61.8, 45.1, 39.4, 37.0, 34.5, 31.5, 31.2, 30.0, 25.5, 23.1 (2), 18.6, 14.1; IR (neat) 3085, 3060, 3030, 2910, 1950, 1840, 1810, 1605, 1495, 1452, 1375, 1325, 1300, 1265, 1218, 1180, 1142, 1070, 1030, 1012, 990, 940, 901, 825, 750, 730, 694, 630 cm^{-1}; mass spectrum *m/e* 313 (parent ion). (Found: C, 80.43; H, 9.81. Calc for $C_{21}H_{31}NO$: C, 80.46; H, 9.97%.)

Data for **19b**: TLC, R_f 0.57 (4:1 hexane–ether); $[\alpha]_D^{19}$ −50.6° (*c* = 0.52, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.45–7.2 (m, 5H, aromatic), 4.39 (d of d, $J_{8a,8}$ = 2.7 Hz, $J_{8a,8b}$ = 6.0 Hz, 1H, H.8a), 4.12 (A of AB, J_{AB} = 12.6 Hz, 1H, benzylic H), 3.85 (B of AB, J_{AB} = 12.6 Hz, 1H), 3.61 (d of d, $J_{3a,4cis}$ = 6.1 Hz, $J_{3a,8b}$ = 6.0 Hz, 1H, H.8a), 2.77 (t of d, $J_{8b,5a}$ = 7.9 Hz, $J_{8b,8a}$ = $J_{8b,3a}$ = 6.0 Hz, 1H, H.8b), 2.0–1.8 (m, 2H), 1.8–1.2 (m, 13H), 0.89 (overlapping d and t, 6H, two CH_3's); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 137.7, 129.2, 128.6, 127.1, 75.1, 71.8, 61.4, 48.6, 43.8, 37.4, 36.8, 35.1, 30.5, 29.3, 28.9, 24.9, 23.1, 20.3, 14.1; IR (neat) 3082, 3060, 3025, 2950, 2870, 1605, 1495, 1452, 1378, 1335, 1172, 1155, 1028, 925, 725, 692, 630; mass spectrum *m/e* 313 (parent ion). (Found: C, 80.60; H, 9.70. Calc for $C_{21}H_{31}NO$: C, 80.46; H, 9.97%.)

Benzylamino alcohol **20a,b**

Benzylisoxazolidine **19b** (105 mg, 0.335 mmol) was dissolved in 8 ml of 10 M AcOH aq. The soln was heated to 55° and then excess Zn dust (220 mg, 3.36 mmol, ~10 equiv) was added with vigorous stirring. An additional portion of Zn (~100 mg) was added after 40 min. After 3 hr TLC analysis revealed the complete consumption of **19b**. Thus, the reaction mixture was cooled, diluted with 25 ml of H_2O and basified (pH 14) by addition of 6 M KOH. The soln was extracted with $CHCl_3$ (4 × 50 ml) and the extracts filtered through adsorbent cotton. Removal of solvent *in vacuo* afforded 100 mg (95%) of analytically pure **20b**, which was used in subsequent steps as obtained. The yield of **20a** was 95% following this procedure.

Data for **20a**: TLC, R_f 0.45 (20:1 $CHCl_3$–CH_3OH); $[\alpha]_D^{22}$ +4.0° (*c* = 3.43, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.39–7.26 (m, 5H, aromatic), 4.02 (t, J = 3.8 Hz, 1H, H.8a), 3.84 (A of AB, J_{AB} = 13 Hz, 1H, benzylic H), 3.77 (B of AB, J_{AB} = 13 Hz, 1H), 3.48 (m, 1H, H.3a), 2.75 (broad s, 2H, —OH, —NH), 2.26 (m, 1H), 2.2–1.85 (m, 4H), 1.65–1.03 (m, 11H), 0.89 (d, J = 6.9 Hz, 3H, $—CH_3$), 0.88 (t, J = 6.2 Hz, 3H, $—CH_3$); ^{13}C-NMR ($CDCl_3$, 68 MHz), δ 140.0, 128.4, 128.1, 127.1, 69.8, 61.5, 53.6, 45.1, 40.5, 37.7, 31.0, 30.7, 29.5, 24.2, 23.3, 23.1, 18.5, 14.1; IR (neat) 3400, 3300, 3038, 2960, 2940, 2878, 1500, 1458, 1030, 745, 698 cm^{-1}. (Found: C, 79.81; H, 10.84. Calc for $C_{21}H_{33}NO$: C, 79.95; H, 10.54%.)

Data for **20b**: TLC, R_f 0.36 (20:1 $CHCl_3$–CH_3OH); m.p. 48–50°; $[\alpha]_D^{20}$ −26.0° (*c* = 0.4, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz), δ 7.36–7.26 (m, 5H, aromatic), 4.06 (m, 1H, H.8a), 3.82 (s, 2H, benzylic H), 3.46 (m, 1H, H.3a), 2.50–1.10 (m, 18H), 0.91 (t, J = 7.3 Hz, 3H, $—CH_3$), 0.89 (d, J = 7.3 Hz, 3H, $—CH_3$); IR (neat) 3410, 3310, 3060, 3025, 2955, 2930, 2865, 1605, 1495, 1454, 1375, 1112, 1065, 1028, 960, 908, 732, 694 cm^{-1}; mass spectrum *m/e* 315 (parent ion). (Found: C, 79.76; H, 10.72. Calc for $C_{21}H_{33}NO$: C, 79.95; H, 10.54%.)

Benzylamino ketone **21a,b**

Benzylamino alcohol **20a** (76 mg, 0.241 mmol) was dissolved in 5 ml of glacial AcOH and treated with 75 drops (*ca* 2.5 ml) of 2 M HCl aq at 23°. After being stirred for 15 min the solution was cooled to 0–5° and slowly treated with 120 drops (*ca* 4 ml) of Jones' reagent. A cloudy orange–brown soln resulted, which after 2.5 hr became clear orange with a small amount of dark ppt. The cold soln was transferred slowly via pipette to a separatory funnel containing sat $NaHCO_3$ aq and $CHCl_3$. The aqueous phase was extracted thoroughly with $CHCl_3$ (6 × 30 ml) and the combined organic extracts were filtered through adsorbent cotton. After removal of the solvent *in vacuo* 77 mg (quantitative yield) of **21a** was obtained as a pale yellow oil. Analysis of the product by ^{1}H-NMR indicated that the oxidation product (containing ~5–20% of **40a**) was 95% pure. The yield of **21b** using this procedure was 87–95%. Because **21a,b** was prone to epimerize this intermediate was typically used immediately in the next step. However, ketones **21a** or **21b** (from **20b**) could be purified by careful chromatography on silica gel (0.5 mm silica gel preparative plate, 20:1 CH_2Cl_2–CH_3OH) with mass recoveries of roughly 75%. Small quantities of *trans*-fused isomers **40a** and **40b** were separated in such purifications.

Data for **21a**: TLC, R_f 0.41 (20:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −69° (*c* = 0.3, $CHCl_3$; sample contained *ca* 20% of **40a**); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.34–7.20 (m, 5H, aromatic), 3.76 (A of AB, J = 13 Hz, 1H, benzylic H), 3.68 (B of AB, J = 13 Hz, 1H), 3.30 (q, J = 7.1 Hz, 1H, H.3a), 2.82 (t, J = 7.1 Hz, 1H, H.8b), 2.52–2.35 (series of m, 3H), 2.30–2.20 (m, 1H), 2.05–1.90 (m, 1H), 1.86–1.45 (series of m, 6H), 1.42–1.15 (m, 5H), 0.92–0.87 (overlapping d and t, 6H, two $—CH_3$'s); IR (neat) 3335, 3060, 3030, 2960, 2930, 2870, 1695, 1620, 1608, 1494, 1455, 1380, 732, 698 cm^{-1}.

Data for **21b**: TLC, R_f 0.33 (20:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ −19.5° (*c* = 0.56, $CHCl_3$; sample contained ~10% **40b**); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.38–7.19 (m, 5H, aromatic), 3.83 (A of AB, J = 12.8 Hz, 1H, benzylic H), 3.70 (B of AB, J = 12.8 Hz, 1H), 3.08 (t of d, J = 8.7, 5.1 Hz, 1H, H.3a), 2.73 (d of d, J = 5.1, 8.0 Hz, 1H, H.8b), 2.6–2.4 (m, 1H, H.5a), 2.10–1.9 (m, 2H), 1.9–1.5 (m, 9H), 1.4–1.2 (m, 4H), 1.02 (d, J = 5.9 Hz, 3H, $—CH_3$), 0.90 (t, J = 6.8 Hz, 3H, $—CH_3$); IR (neat) 3335, 3085, 3065, 3030, 2955, 2930, 2870, 1700, 1608, 1495, 1465, 1455, 1382, 1185, 1153, 1030, 734, 698 cm^{-1}; mass spectrum *m/e* 313 (parent ion); high resolution mass spectrum, obsd. 313.241 (±0.001), $C_{21}H_{31}NO$ requires 313.2406.

Data for trans-*ring fusion isomer* **40a**: TLC, R_f 0.5 (20:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.34–7.22 (m, 5H, aromatic), 3.80 (A of AB, J = 13.1 Hz, 1H, benzylic H), 3.68 (B of AB, J = 13.1 Hz, 1H), 3.39 (t of d, J = 9.1, 5.8 Hz, 1H, H.3a), 2.44 (m, 2H), 2.22 (d of d, J = 9.1, 12.5 Hz, 1H, H.8b), 2.1–1.9 (m, 2H), 1.84–1.60 (m, 4H), 1.6–1.45 (m, 2H), 1.4–1.1 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H, $—CH_3$), 0.76 (d, J = 7.0 Hz, 3H, $—CH_3$).

Data for trans-*ring fusion isomer* **40b**: TLC, R_f 0.5 (20:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.35–7.15 (m,

5H, aromatic), 3.83 (A of AB, J = 13 Hz, 1H, benzylic H), 3.69 (B of AB, J = 13 Hz, 1H), 3.38 (t of d, J = 9, 6 Hz, 1H, H.3a), 2.39 (d of d, J = 9, 12.5 Hz, 1H, H.8b), 2.25–1.4 (series of m, 12H), 1.35–1.15 (m, 4H), 0.97 (d, J = 7 Hz, 3H, —CH_3), 0.88 (t, J = 7 Hz, 3H, —CH_3).

Amino alcohol **24a,b**

Benzylamino alcohol **20b** (33.4 mg, 0.106 mmol) was dissolved in 3 ml of anhyd MeOH and treated with 0.30 ml of anhyd formic acid. Freshly prepared Pd black[41] (40 mg) was added to the rapidly stirring soln. After 19 hr the reaction mixture was filtered through Celite, washed with MeOH (30 ml) and concentrated. Redissolution in $CHCl_3$, treatment with anhyd K_2CO_3, filtration through adsorbent cotton and removal of solvent *in vacuo* afforded **24b** (22.9 mg, 96%) as white leafs (m.p. 84–86°).

Data for **24a**: R_f 0.11 (3:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 3.98 (t, 1H), 3.73 (m, 1H), 2.5–1.8 (series of m, 7H), 1.6–1.1 (series of m, 12H), 1.0–0.8 (overlapping d and t, 6H).

Data for **24b**: R_f 0.11 (3:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 4.04 (t, J = 1.9 Hz, 1H), 3.71 (m, 1H) 2.1–1.0 (series of m, 18H), 0.95–0.80 (overlapping d and t, 6H); mass spectrum *m/e* 225 (parent ion); high resolution mass spectrum, obsd. 225.209 (±0.001), $C_{14}H_{27}NO$ requires 225.209.

Amino ketone **26a,b**

Method A. Benzylamino ketone **21a,b** (18 mg, 0.058 mmol) was dissolved in 2 ml of anhyd MeOH and treated with 0.20 ml of anhyd HCO_2H. Freshly prepared Pd black[41] (40 mg) was added to the rapidly stirring soln. After 1.5–2.0 hr the mixture was filtered through Celite, washed with MeOH (20 ml) and concentrated *in vacuo*. Immediately before use in the subsequent guanidination reaction the residue was dissolved in CH_2Cl_2, washed with sat $NaHCO_3$ aq and concentrated *in vacuo* to give 13 mg of epimeric **26a,b** (quantitative yield).

Method B. Amino alcohol **24a** (7 mg, 0.031 mmol) was dissolved in 1 ml glacial acetic acid and treated with 10 drops of 2 M HCl aq. After being cooled to 0° the mixture was treated with 20 drops of Jones' reagent. After 2.5 hr the mixture was diluted with sat $NaHCO_3$ aq and extracted with $CHCl_3$ (4 × 6 ml). Filtration through adsorbent cotton and removal of solvent *in vacuo* afforded epimeric **26a** (6.5 mg, 94%): TLC of mixture: R_f 0.22 (3:1 $CHCl_3$–MeOH).

Data for **26a** (sample contained *ca* 30% of C.8b and C.8 isomers): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 3.54 (m, 1H, H.3a), 2.75–1.10 (series of m, 18H), 1.00–0.80 (overlapping d and t, 6H, two —CH_3's); IR (neat) 2960, 2935, 2865, 1708, 1585, 1460, 1380 cm^{-1}.

Data for **26b** (sample contained *ca* 30% of C.8b and C.8 isomers): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 3.35 (m, 1H), 2.75–2.4 (series of m, 3H), 2.35–1.10 (series of m, 15H), 1.05 (d, J = 7.0 Hz, 3H, —CH_3), 0.92 (t, J = 7.0 Hz, 3H, —CH_3); IR (neat) 2960, 2935, 2865, 1705, 1575, 1460, 1380 cm^{-1}; mass spectrum *m/e* 223 (parent ion).

Isoxazolidine **27b**

Benzylisoxazolidine **19b** (10 mg, 0.03 mmol) was dissolved in 1.0 ml of anhyd MeOH and treated with 0.1 ml of anhyd HCO_2H. Freshly prepared Pd black[41] (30 mg) was added to the rapidly stirring soln. After 2 hr TLC analysis revealed that reaction was complete. The mixture was filtered through Celite, washed with MeOH (10 ml) and concentrated *in vacuo*. Redissolution in $CHCl_3$, stirring with anhyd K_2CO_3, filtration through adsorbent cotton and removal of solvent *in vacuo* afforded 7 mg of **27b**. *Purification by chromatography* (silica gel, 250 preparative plate, 3:1 Et_2O–hexane) afforded 6.7 mg (95%) of **27b**: TLC, R_f 0.60 (20:1 $CHCl_3$–MeOH); m.p. 109–110°; ^{1}H-NMR ($CDCl_3$, 250 MHz), δ 3.94 (t, J = 6.6 Hz, 1H, H.8a), 3.66 (d of d, J = 2.7, 3.0 Hz, 1H, H.3a), 2.65 (q, J = 6.9 Hz, 1H, H.8b), 2.0–1.8 (m, 2H), 1.8–1.1 (series of m, 14H), 1.0–0.8 (overlapping d and t, 6H, —CH_3's); IR (CH_2Cl_2) 2948, 2865, 1458, 1378, 1345, 1178, 1082, 1025, 998, 920, 870, 852, 832; mass spectrum *m/e* (rel. intensity) 223 (M^+, 3), 206 (100).

(−)-*Ptilocaulin* (7)

Method A. Amino ketone **26b** (7.8 mg, 0.035 mmol) was transferred to a 1 ml pear tipped reaction tube and mixed with 7.0 mg (0.035 mmol, 1 equiv) of GDMP (**23**).[42] After degassing and flushing with Ar the mixture was heated to 120° for 15–45 min. The mixture was cooled to 23° and the brown residue purified by chromatography (silica gel, 10 mm column, 83:17 $CHCl_3$–MeOH) to afford 5.6 mg (51%) of a mixture of three compounds tentatively assigned structures **7**, **41** and **42** (~2:1:1). When **26b** (24 mg, 0.108 mmol) was heated with **23** (22.7 mg, 0.113 mmol, 1.05 equiv) for 1.25 hr at 125° a similar 2:1:1 mixture was obtained (16.2 mg, 48%) after chromatographic purification. Performing the reaction at 100° (30 min) afforded a *ca* 1:1:1 mixture of **7**, **41** and **42**. When **26a** was heated with **23** at 120° (15 min) a *ca* 1:1 mixture of products, tentatively assigned structures **41** and **43**, was obtained along with a trace of **7**.

Data for mixture of **7**, **41** *and* **42**: TLC of mixture: R_f 0.65 (3:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 9.29, 9.23, 9.15 (3s, *ca* 2:1:1, 1H, NH), 8.20, 8.15, 7.92 (series of s and m, 1H, NH), 7.6–7.3 (series of bs, 2H, NH_2), 4.25 (m, 0.25H, H.3a of **41**), 3.92 (m, 0.25H, H.3a of **42**), 3.78 (m, 0.50H, H.3a of **7**), 2.7–1.15 (series of m, 15H), 1.15–0.70 (series of d and t, 6H).

Data for mixture of **41**, **43** *and* **7**: TLC of mixture: R_f 0.65 (3:1 $CHCl_3$–MeOH); ^{1}H-NMR ($CDCl_3$, 250 MHz, data reported for crude sample), 9.15, 8.86, 8.75, 8.32, 8.25, 8.18 (series of s), 8.75–7.2 (series of s and m), 4.25 (m, *ca* 0.45H, H.3a of **41**), 3.85 (m, *ca* 0.45H, H.3a of **43**), 3.78 (m, 0.1H, C.3a of **7**), 2.7–1.2 (series of m), 1.15–0.70 (series of d and t).

A sample containing **7**, **41** and **42** (4.5 mg, 2:1:1) was dissolved in 1.5 ml of dry benzene and treated with a crystal of guanidine.[53] The mixture was heated at 80° for 24 hr, cooled to 23°, treated with 2 drops of 1% HNO_3 aq and extracted with $CHCl_3$ and 10 ml sat $NaNO_3$ aq. Removal of solvent *in vacuo* and chromatography of the residue (silica gel, 10 mm column, 85:15 $CHCl_3$–MeOH) afforded 4.0 mg (89%) of (−)-ptilocaulin (**7**) containing only a trace (< 5%) of **41**. The ^{1}H-NMR data of **7** was identical to that summarized below. Application of this procedure to a mixture of **43** and **41** (*ca* 3:1) likewise afforded homogeneous **7** (74% after chromatography).

Method B. Amino ketone **26b** (27 mg, 0.121 mmol) was transferred to a 1 ml pear tipped reaction tube and mixed with GDMP (26 mg, 0.129 mmol, 1.1 equiv). After thorough degassing and flushing with Ar, the mixture was gradually warmed to 150° over 1 hr and maintained at this temperature for 4 hr. After being cooled to 23° the dark reaction mixture was purified by chromatography (silica gel, 30 mm, $CHCl_3$ (75 ml) then 2–17% gradient of MeOH–$CHCl_3$) to afford 21.5 mg of **7** (58%, > 90% isomeric purity). Application of the high temperature melt procedure (155°, 6 hr) to **26a** (24 mg, 0.107 mmol) afforded **7** (22.5 mg, 66%, > 80% isomeric purity (8:1:1, **7**:**41**:**43**)). After washing a $CHCl_3$ soln of **7** with sat $NaNO_3$ aq (10 ml, containing 3 drops of 1% HNO_3) removal of solvent and repeated washing of the residue with anhyd ether, pure crystalline **7** was obtained (> 99% isomeric purity): m.p. 183–184° (lit.[3] 183–185°); TLC, R_f 0.27 (5:1 $CHCl_3$–MeOH), 0.33 (4:1 $CHCl_3$–MeOH), 0.41 (5:1 CH_2Cl_2–MeOH); $[\alpha]_D^{22}$ −73.9° (*c* = 0.31, 99.9% MeOH); lit.[50] $[\alpha]_D^{23}$ +74.4° (99.5% MeOH); ^{1}H-NMR ($CDCl_3$, 270 MHz), δ 8.86 [9.20][51] (s, 1H, —NH), 8.33 [8.62][51] (br d, 1H, —NH), 7.45 [7.55][51] (s, 2H, —NH_2), 3.75 (m, 1H, H.3a), 2.50–2.35 (m, 4H), 2.1–1.90 (m, 2H), 1.75–1.6 (m, 2H), 1.55–1.20 (two m's, 7H), 1.02 (d, J = 6.7 Hz, 3H, CH_3), 0.87 (t, J = 7.3 Hz, 3H, —CH_3); ^{13}C-NMR ($CDCl_3$, 68 MHz), δ 151.7, 127.1, 121.0, 53.2, 36.5, 34.0, 33.1, 32.2, 29.6, 27.8, 26.8, 24.6, 22.4, 19.5, 13.9; IR ($CHCl_3$) 3260, 3018, 2960, 2930, 2870, 1680, 1608, 1540, 1465, 1458, 1402, 1378, 1344, 1265, 1200, 710, 660 cm^{-1}; UV (EtOH) 225 (ε = 8500); mass spectrum (EI), *m/e* (rel. intensity %) 247 (M^+, 31), 232 (77), 204 (100), 190 (63), 176 (19); high resolution mass

spectrum obsd. 247.206 (±0.001), $C_{15}H_{25}N_3$ requires 247.2050.

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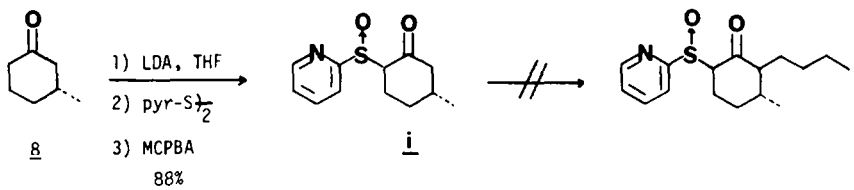

[19] The C.8 α-butyl isomer is designated as the "a" series and the C.8 β-butyl isomer as "b" throughout this paper. Yields for all transformations were comparable whether pure a, pure b or a,b mixtures were used.

[20] This assignment is based in part on the observation that the C.7 methyl group in the major isomer (**12b**) appears at δ 1.06 while that of the minor isomer (**12a**) appears at δ 0.95 ppm. This suggests that the methyl group in **12a** is in an axial position.

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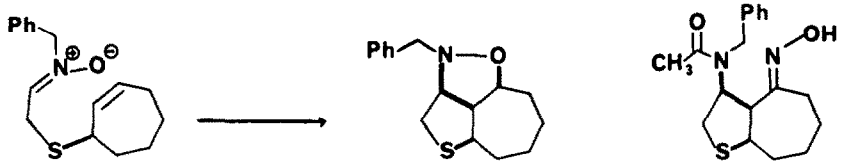

i ii iii

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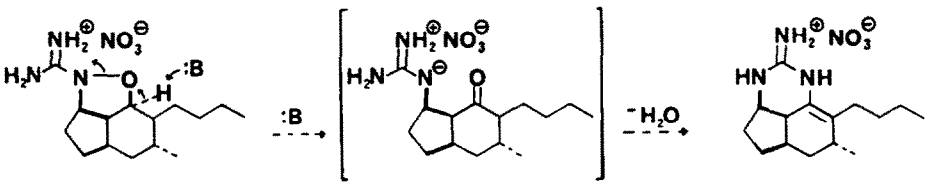

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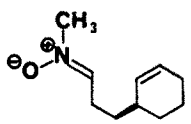

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[50] Natural ptilocaulin nitrate has $[\alpha]_D^{23} + 74.4°$ (99.5% CH_3OH) (Prof. K. L. Rinehart). We thank Prof. Rinehart for providing the optical rotation data, as well as a sample of natural ptilocaulin nitrate (**3**). We are also grateful to Prof. B. B. Snider for providing spectral data and a sample of racemic **3**.

[51] The chemical shifts of the guanidinium protons of ptilocaulin depend on the previous handling of the sample. The values in brackets are those obtained for both synthetic and natural ptilocaulin after dissolution in CH_3OH. Chemical shifts identical to those reported by Rinehart are restored after a $CHCl_3$ solution of ptilocaulin is washed with saturated aqueous $NaNO_3$ solution.

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