oxide-promoted dehydrofluorination of p-NO_2-III to yield p-NO_2-IV. Dehydrofluorination reactions usually have a greater activation energy than the corresponding alkene reaction. The partial loss of p-NO_2-III would therefore be significant only for the 25 °C point. The PKIE associated with this elimination is near unity,[1,3] and the same deviation is observed for reaction in MeOD. Both p-CN-I and m-NO_2-I result in curved plots. There is a similar curvature associated with reactions run in MeOD, and this results in linear plots for ln (k^H/k^D) vs. $1/T$, when k^H/k^D is calculated with eq 2.

Scheme I is similar to ones proposed for methoxide-catalyzed proton exchange with methanol when reaction is accompanied by internal return, $k_2 > k_{-1}$.[13] The solvent, MeOD, would exchange with MeOH in a diffusion-controlled step from II-F, and the kinetic expression for this exchange reaction is

$$k_{exch}{}^H = k_{-2}{}^H k_{-1}{}^H/(k_2{}^H + k_{-1}{}^H) \quad (4)$$

We have published the effect that internal return has on the Arrhenius behavior of PKIE.[8] These calculations predict A^H/A^D values greater than unity, equal to unity, and less than unity as well as the possibility of negative values for $\Delta E_a{}^{D-H}$. Since the PKIE reported in this study are the reverse process of exchange reactions, the experimental results found in Table I are consistent with a reaction occurring via Scheme I. We have not obtained enough experimental data to perform meaningful model calculations for these systems, and we are continuing work along these lines.

(13) Streitwieser, A., Jr.; Holtz, D.; Ziegler, G. R.; Stoffer, J. O.; Brokaw, M. L.; Guibe, F. *J. Am. Chem. Soc.* **1976**, *98*, 5229-5234.

Experimental Section

Materials. Synthesis of the substituted β,β-difluorostyrenes has been reported previously.[2] Methanolic sodium methoxide solutions were made from a reaction of sodium with methanol. Small chunks of freshly cut sodium were washed with MeO^{i}H prior to placing them into MeO^{i}H which was used for the reaction. Methanol-*O-d* was purchased from Aldrich and used without further purification.

Product Studies. A 25-mL Erlenmeyer flask was charged with 15 mL of methanolic sodium methoxide (ca. 0.3 N), fitted with a well-rolled cork, and placed into a constant-temperature bath. When temperature had been reached (10-15 min), 25 μL of compound and 25 μL of standard were added. Studies with p-NO_2-I and m-NO_2-I were carried out for approximately 10 half-lives, at which point 3 5-mL aliquots were transferred to a 125-mL separatory funnel (Teflon stopcock) containing ca. 100 mL of dilute HCl and 1.6 mL of CCl_4. The separatory funnel was shaken vigorously for about a minute, and after layer separation, the CCl_4 was drawn off into an autosampler vial. Each sample was analyzed at least five times with a Varian VISTA CDS 401 equipped with an autosampler, TCD detectors, and a $2 \times {}^1/_8$ in., 10% OV 101 on 100/120 Supelcon AW DMCS column. The p-CN-I studies at -70, -50, and -25 °C were carried out by sealing the flask with a septum and taking aliquots at 1, 2, and 10 half-lives, while runs at 0, 25, and 50 °C used two separate runs at each temperature. One run was sampled at 1 and 2 half-lives, while the other was allowed to react for 10 half-lives.

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Registry No. I (X = m-CF_3), 90605-29-1; I (X = m-NO_2), 84750-94-7; I (X = p-CN), 38936-00-4; I (X = p-NO_2), 1742-99-0; MeOH, 67-56-1; D_2, 7782-39-0.

Chirospecific Syntheses of (+)- and (-)-Anatoxin *a*

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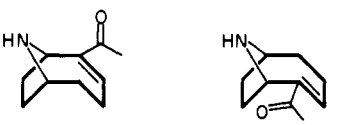
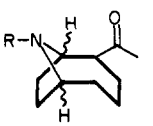
Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received January 13, 1984. Revised Manuscript Received March 6, 1984*

Abstract: (+)- and (-)-anatoxin *a* of high optical purity have been synthesized directly from D- and L-glutamic acid, respectively. Initial carbon-carbon bond formation proceeding from the pyroglutamate via sulfide contraction and transfer of the amino acid chirality by catalytic hydrogenation are central to the synthesis. Cyclization to the bicyclic system was effected by nucleophilic attack on the iminium ion, generated by decarbonylation of the α-amino acid. The dihydroanatoxin thus formed, whose α and β diastereomers were both characterized, was ultimately converted to the enone by dehydrogenation with palladium acetate.

The study of neurotoxins has contributed significantly to the understanding of neuronal processes.[2] Among these toxins, anatoxin *a*, a potent nerve-depolarizing agent, has been the subject of considerable study despite the difficulties of obtaining this natural product.[3] Also, comparison of the activity of the natural (+)-anatoxin (**1**) with racemic anatoxin has left some ambiguity



1 (+) anatoxin-a **2** (-)



3

as to the action of (-)-anatoxin (**2**), which would be difficult to clarify without a source of (-)-anatoxin.[3a,d] Consequently we have developed improved and chirospecific alternatives to our earlier synthetic efforts[4] that now make available both enantiomers of

(1) Fellow of the Deutsche Forschungsgemeinschaft. Present address: Max Planck Institut für Ernahrungsphysiologie, Dortmund.

(2) (a) Rochat, H., Ed. *Toxicon* **1982**, *20*, 1-157. (b) Witkop, B.; Gossinger, E. "The Alkaloids"; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 218.

(3) (a) Spivak, C. E.; Waters, J.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1983**, *23*, 337. (b) Carmichael, W. W.; Biggs, D. F.; Peterson, M. A. *Toxicon* 1979, *17*, 229. (c) Isolation of anatoxin *a*: Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367. (d) (+)- and (-)-perhydrohistrionicotoxin have been shown to have similar but weaker activities: Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.

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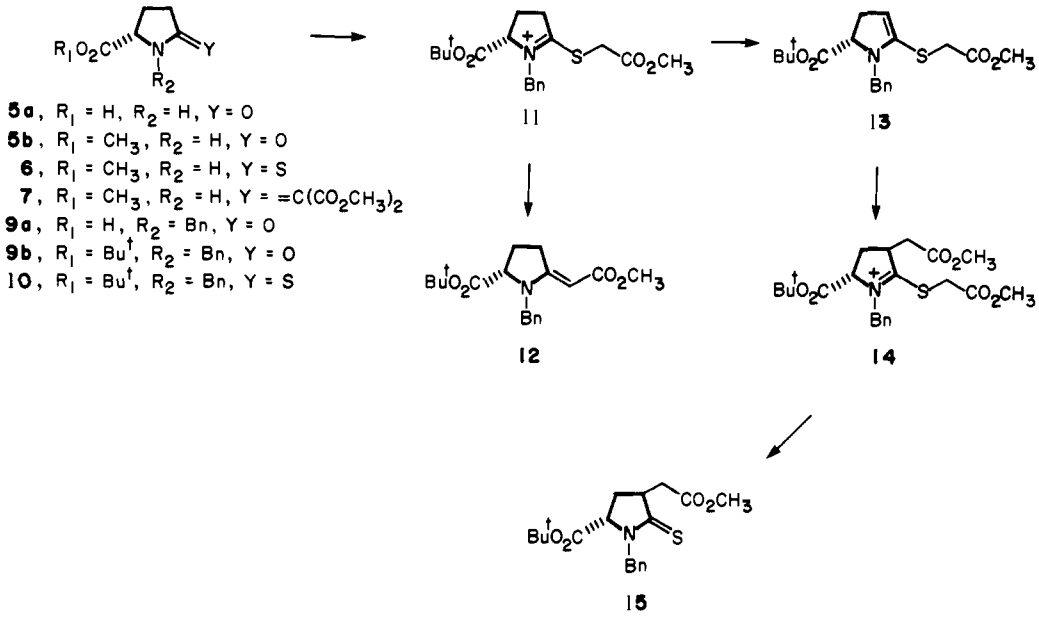
Scheme I. Sulfide Contraction with Thiolactams Derived from Pyroglutamates



dihydroanatoxin (**3**) and anatoxin.

A common solution to the problem of synthesizing optically active molecules is the use of educts derived from the chiral pool, and an important subset of this pool is the naturally occurring α-amino acids.[5] Our earlier work has shown that a racemic 5-substituted proline can be used to synthesize (±)-anatoxin by iminium ion cyclization.[4a] If an optically active proline derivative were used, the chirality of the product would depend only on the stereochemistry at C-5 of the proline. We now report the successful implementation of this process in which glutamic acid is used to prepare the desired 5-substituted proline derivative. The chiral center of glutamic acid is used to induce the desired C-5 stereochemistry, and this process is highly efficient, occurring across a five-membered ring.

Results and Discussion

We planned to introduce the C-5 carbon–carbon bond by a sulfide-contraction reaction.[6] The required thioamides were first synthesized from L-glutamic acid (**4**) (Scheme I). Methyl pyroglutamate (**5b**) was synthesized from pyroglutamic acid (**5a**) as described.[7,8] Thiolactam **6** then could be prepared under homogeneous[9a] or heterogeneous[9b] conditions, the latter giving cleaner products and equally good yields. To drive the reaction to completion, incremental additions of P_4S_{10} were required.

When a nitrogen substituent was desired, it was introduced prior to lactam formation. By modification of the reported procedure[10] and precipitation of the amino acid at its isoelectric point, excellent yields of *N*-benzylglutamic acid (**8**) were realized. Cyclization and esterification[11] proceeded readily to afford optically pure products in better yields than N-alkylation of pyroglutamate esters[7] and without the danger of racemization.

Table I. Sulfur Contraction with 1-Benzyl-5-thioxoproline *tert*-Butyl Ester (**10**)

reaction conditions[a]	products, % yield 10	15	9b	12
TEA	15	10	15	30
TEA, 5 min, $(C_6H_5)_3P$	15[b]		nd[c]	60
$C_6H_5P(CH_2CH_2CH_2\overline{NCHCH_2CH_2OCH_2CH_2})_2$	5	nd	18	70
$(C_6H_5)_3P$, 5 min, TEA	2	2	5	85

[a] All experiments were conducted with 1.5 mmol of **10** under the conditions used to prepare **12** as described in the experimental section, except as noted. [b] Sum of **10** and **15**. [c] Not determined.

The reactions of several different alkylating reagents with thiolactams **6** and **10** were examined. In all cases alkylation of the secondary thiolactam **6** proceeded more readily than alkylation of tertiary thiolactam **10**. On the other hand, the sulfide-contraction reactions of **10** proceeded much more readily than those of **6**.[6] In the case of **6**, the only reaction that took place under conditions sufficiently mild to avoid racemization was the sulfide contraction with dimethyl bromomalonate.[12] In this case, sulfur extrusion to **7** could be achieved with either aqueous bicarbonate or triethylamine. Unfortunately, the vinylogous carbamate in **7** proved resistant to catalytic reduction[6d] so this path was abandoned and we turned our attention to the tertiary thiolactam **10**.

Our study of the sulfide contraction of thiolactam **10** with methyl bromoacetate to yield olefin **12** revealed some mechanistic subtleties. Table I shows the product distributions for four different reaction conditions. It is interesting that the sulfide contraction reaction with thioiminium ion **11** proceeds in the presence of base alone, although in low yield. Isolation of the α-alkylated thiolactam **15** suggests the intermediacy of ketene *S,N*-acetal **13** formed by proton abstraction at C-4 of thioiminium ion **11** rather than the desired proton abstraction from the methylene of the side chain. The isolation of lactam **10a** also suggests the presence of **13**, which is hydrolyzed during isolation. A further demonstration that C-4 proton abstraction is a competing process under these conditions is the thio-Claisen rearrangement of the *S*-allylthio-

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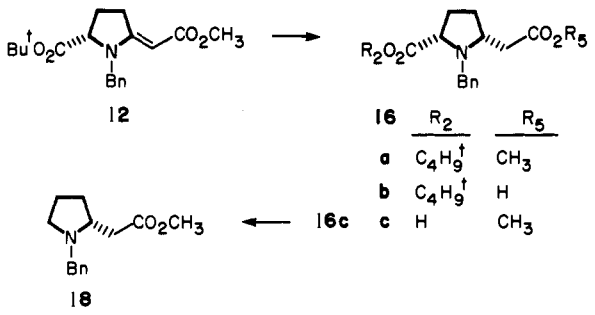
Scheme II. Catalytic Hydrogenation of Vinylogous Carbamate **12**



iminium ion.[9b,13] The important conclusion is that the phosphine plays a role other than simple sulfur scavanging. Perhaps the phosphine coordinates with the thioiminium ion and enhances side-chain proton abstraction at the expense of ketene *S,N*-acetal formation. Thus the morpholinophosphine is less effective than the $(C_6H_5)_3P$/TEA system since it mandates simultaneous amine and phosphine addition, and proton abstraction at C-4 becomes competitive with phosphine coordination.

Catalytic hydrogenation is often a highly stereoselective process[14] and this proved to be the case in the reduction of vinylogous carbamate **12** (Scheme II). Reduction with Pd/C gave both olefin reduction and debenzylation. Debenzylation also occurred with platinum catalysts in protic solvents but could be avoided by using ethyl acetate. In general, Pt/C was a superior catalyst to platinum oxide. Reduction with cyanoborohydride was less selective and gave a 3/1 mixture of cis **16a** and trans **17**[6b] while the catalytic reduction process gave a cis/trans ratio of 98/2.[15]

Confirmation of the stereochemical outcome of the reduction process was obtained by conversion of diester **16a** to α-amino acid **17c**, iminium salt formation, and cyanoborohydride reduction to give 1-benzylhomoproline methyl ester (**18**). Comparison of this product with the corresponding homologated product from L-proline[16] showed their rotations to be approximately equal and opposite. Thus the stereochemistry of the side chain was fixed and L-glutamic acid would ultimately lead into the unnatural (−)-anatoxin series.

Finally, it was necessary to ascertain the optical purity of diester **16a**. The optical purity of the educt was assessed at the *N*-benzylpyroglutamic acid stage. Coupling with α-phenylethylamine gave amides **9c** and **9d**, which were separated by HPLC. When optically pure amine was used less than 0.5% of the minor diastereomer was observed. Similarly the thioamide ester **10** was hydrolyzed to give *N*-benzylpyroglutamic acid. In this case the crude thioamide prepared in refluxing THF had an ee of 96%. However, the recrystallized product had an ee >99%. Preparation of the thioamide at room temperature gave directly crude **10** with an ee >99%.[17]

Maintenance of chiral integrity through the next three steps, namely, formation of thioiminium ion **11**, sulfur extrusion to vinylogous carbamate **12**, and hydrogenation to 5-substituted proline **16a**, was then examined. Selective hydrolysis of the methyl *tert*-butyl diester **16a** gave β-amino acid **16b** from which the diastereomeric amides **16d** and **16e** were formed via their imidazolides. Separation of the amides by HPLC showed that the pyrrolidine still possessed an ee >99%. This was true for the products derived from sulfide contraction with $(C_6H_5)_3P$/TEA, the morpholinophosphine,[6a] or the (dimethylamino)phosphine.[18]

We proceeded to elaborate the side chain by a Wittig reaction which offered the additional potential that the β,γ olefin **21** thus produced might be convertible into the α,β olefin **24** required for direct cyclization to anatoxin (Scheme III). Diisobutylaluminum hydride reduction[19] of diester **16a** gave a 3/2 mixture of aldehydes derived from methyl ester and *tert*-butyl ester reduction along with a number of byproducts, but β-amino acid **16b** could be reduced to β-amino alcohol **19** with borane/THF.[20] A more direct approach was lithium borohydride reduction of the diester **16a**, which gave the amino alcohol in 95% yield,[20,21] and oxidation with Me_2SO/oxalyl chloride gave the desired amino aldehyde **20**.[22] Chromatography allowed purification of **20** but this was accompanied by partial equilibration of the cis to the trans isomer.[6b] Even storage of crude aldehyde at 20 °C for 4 h gave a 94/6 mixture of the cis and trans aldehydes. However, immediate use in reaction with phosphonium salt **23**[23] gave a 97/3 mixture of *cis*-**21a** and *trans*-**21b**, while the chromatographed aldehyde gave a 2/1 mixture of **21a**/**21b**. Although equilibration through a retro-Michael/Michael process is well-known, that it occurred under the mild conditions used here was surprising.

The β,γ-unsaturated ketal *tert*-butyl ester **21a** was hydrolyzed to give the unsaturated ketone **24** as a mixture of double-bond isomers. Since attempted cyclization of **24** under usual (acidic) conditions gave none of the desired *N*-benzylanatoxin (**25**), unsaturated ketal **21a** was hydrogenated to **22a**, and hydrolysis then gave *N*-benzyl amino acid **26**. In analogy to the previous cyclization of the corresponding racemic *N*-methyl amino acid,[4a] *N*-benzyldihydroanatoxins (**27a** and **28a**) were isolated in 50% yield from ketal ester **22a**. Use of a reductive isolation procedure also gave the *N*-benzylpyrrolidine **29** in 30% yield. *N*-Benzyldihydroanatoxin **27a** was resubjected to the reaction conditions to examine whether this product mixture represents the equilibrium composition. Below 50 °C reaction rates became prohibitively slow, and above 60 °C more monocycle was formed. The diastereomeric ketones **27a** and **28a** could be separated chromatographically, but for synthetic purposes they were used as a mixture.

Our failure to cyclize the unsaturated ketone **24** had eliminated one of the potential advantages of constructing the side chain from C-2 plus C-4 units. Therefore we explored the possibility of introducing the C-6 side chain as a single unit. Our success with branched triflates in the sulfide-contraction reaction[6a] led us to prepare the benzyl hydroxy ester **36a**, which we anticipated attaching to thiolactam **10**, leading directly to the pyrrolidine-saturated ketal (Scheme IV).

Presence of the ketal in **36a** made many of the usual methods for α-hydroxy ester preparation unsuitable. We chose to examine reactions of the Grignard reagent derived from bromo ketal **34**[24] with several two-carbon electrophiles **33**. The most direct approach, reaction with benzyl glyoxalate,[25] invariably gave low yields of the hydroxy ester.[26] Because some success in ketone formation from the reactions of acid chlorides with Grignard reagents at low temperatures has been reported, we tried the reaction with benzyl oxalyl chloride[27] and isolated hydroxy ester **36a** in 15% yield. Presumably the intermediate keto ester is reduced by the excess "activated" magnesium present. Finally, reaction of dibenzyl oxalate with the Grignard reagent from **34** gave keto ester **35**,[28] and catalytic hydrogenation with Pt/C in the presence of triethylamine gave good overall yields of the

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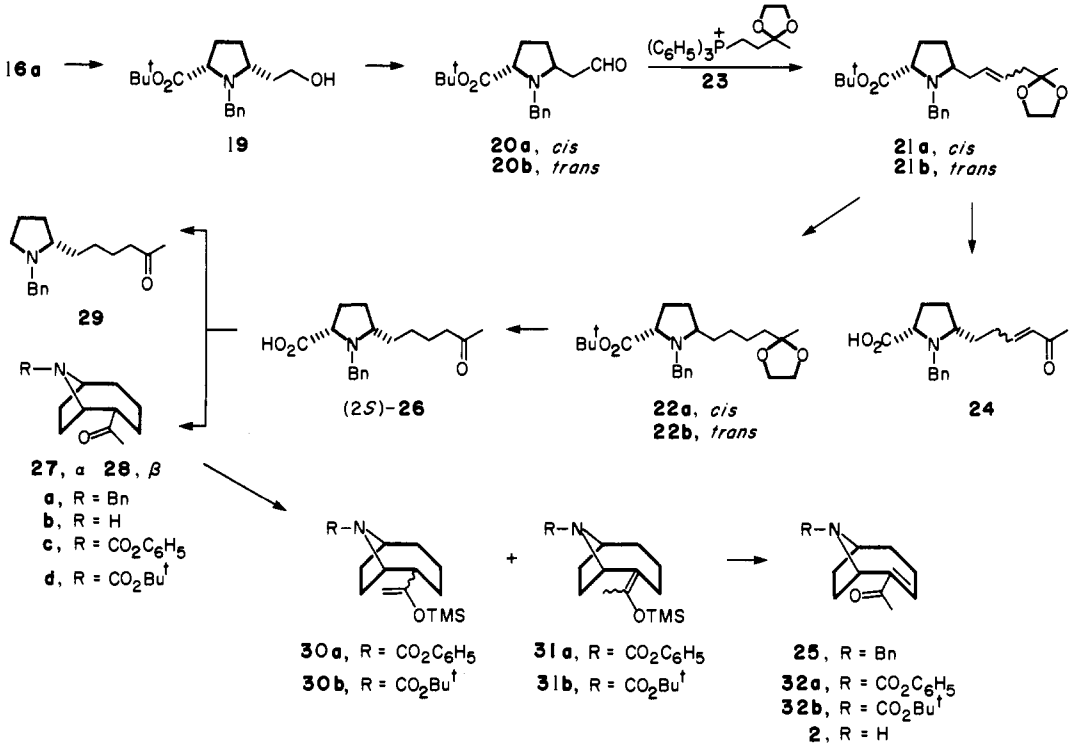
Scheme III. Side-Chain Extension of (2S)-*cis*-1-Benzyl-5-((methoxycarbonyl)methyl)proline **16a** and Conversion to (−)-Anatoxin *a* (2)



hydroxy ester **36a**. This approach should offer general access to functionalized α-hydroxy esters.

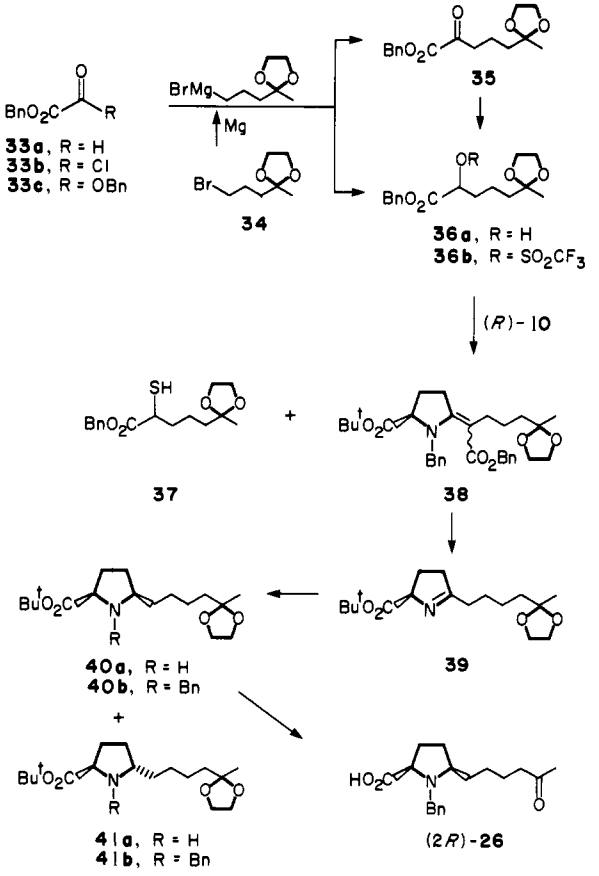
Presence of the ketal also presented difficulties in formation of triflate **36b**. With pyridine/triflic anhydride the major product was the pyridinium salt formed from a subsequent reaction of the desired triflate. The use of 2,6-di-*tert*-butyl-4-methylpyridine[29] as the proton acceptor circumvented this difficulty and gave the desired triflate, which was used without further purification.[30] Formation of the thioiminium ion proceeded uneventfully, and sulfide contraction gave the vinylogous carbamate **38** in 64% yield as a mixture of diastereomers. The α-thiol ester **37** was isolated in 11% yield and presumably is derived from the ketene *S,N*-acetal. Thioiminium ions from branched esters may be more prone to ketene *S,N*-acetal formation because the desired proton abstraction is slowed both sterically and electronically. This series of reactions was begun with *R* thiolactam **10** to allow preparation of the natural (+)-anatoxin.

Transfer hydrogenation smoothly transformed the vinylogous carbamate **38** into pyrroline **39**,[31] which was then reduced over platinum to give the pyrrolidines **40a** and **41a**. Rebenzylation gave the enantiomers of the compounds **22**, prepared earlier by the Wittig route, as a 98/2 mixture of cis and trans isomers. The triflate sequence is two steps shorter than the Wittig sequence and proceeds in better overall yield (39% vs. 29%).

The remaining synthetic problem was conversion of the ketone to an enone. For this conversion we protected the nitrogen as a carbamate both to simplify purification of the penultimate products as well as to allow examination of various ketone to enone transformations.

Hydrogenolysis of N-benzyldihydroanatoxin in acid over Pd/C was readily effected to give dihydroanatoxins **27b** and **28b**. One diastereomer predominates (15/1) regardless of the stereochemistry of the *N*-benzyl starting material. Presumably the acidic debenzylation conditions result in ketone enolization and equilibration. Under alkaline conditions a 2/1 mixture of diastereomers is formed. While the diastereomers are readily distinguished chromatographically and spectroscopically, steric assignments are difficult to make because of the conformational mobility of the seven-membered ring. On the basis of the formation of almost a single compound in acidic solution, we formulate the major product as the β-ketone **28b**, which can hydrogen bond to the ammonium salt.

Scheme IV. C_6 Side-Chain Synthesis and Attachment to (*R*)-Pyroglutamate **10** for Conversion to (+)-Anatoxin *a* (1)



Dihydroanatoxin was then acylated with phenyl chloroformate

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(31) In analogy to unpublished work done by K. Shiosaki.

to give the β-ketone **28c** as the major product. Direct oxidation of this ketone with palladium(II) salts under a variety of conditions[32] gave none of the desired enone. Attempted preparation of the thermodynamic enol acetates under acidic conditions gave decomposition of the starting material. However, formation of the thermodynamic silyl enol ether with trimethylsilyl triflate[33] followed by oxidation with palladium acetate[34] gave enone **32a** in 70% yield. The silyl enol ether was formed in the presence of pinacolone to facilitate driving the equilibrium from ketones **27c/28c** to silyl enol ethers **30a/31a**.

It was now necessary to remove the (phenyloxy)carbonyl protecting group from enone carbamate **32a**. Attempted alkoxide exchange was unsuccessful,[35] and it became clear that we needed a different, acid-labile protecting group. For this purpose we decided to prepare Boc-anatoxin which would also afford a stable penultimate compound for purification. Dihydroanatoxins **27b/28b** reacted readily with di-*tert*-butyl dicarbonate in protic solvents to give the Boc β-ketone **28d** as the major product. Although the α- and β-ketones were readily separated, both behave similarly in subsequent reaction, and they were carried forward as the mixture. Both ^1H and ^{13}C NMR spectra of these compounds are complicated by the presence of rotational isomers. Attempted silyl enol ether formation with trimethylsilyl triflate gave Boc cleavage. Alternatively a mixture of the kinetic and thermodynamic isomers was obtained from reaction of the Boc ketones **27d/28d** with potassium hydride followed by trimethylsilyl chloride. Palladium acetate oxidation then gave the enone **32b** in 41% yield along with 31% of recovered ketone, which could be recycled. This sequence of reactions was applied in both the *R* and *S* series with identical results. Both carbamate rotamers were again apparent by NMR. Direct oxidation of the potassium enolates with $Pd(OAc)_2$ gave the enone in only 11% yield.[36]

The Boc protecting group was readily cleaved with 1 M trifluoroacetic acid in methylene chloride. As expected, the anatoxin-*a* (**1** and **2**) hydrochlorides prepared from the deprotected free bases were chromatographically homogeneous and had spectral data largely in accord with those reported previously.[3c,4c] Both the UV spectral extinction coefficients and the optical rotations were higher than the literature values, suggesting that the material prepared previously was somewhat impure.

The optical purity of our synthetic anatoxins was assessed by preparing the diastereomeric MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] amides **32c**, which were readily differentiated by ^1H NMR and HPLC. Inspection of models indicates that the amide rotamer in which the MTPA residue lies over the enone is greatly favored. As a result large shifts of the C-3 proton and methyl ketone are seen in the NMR spectra of the diastereomers. The MTPA amide **32c** from unnatural (−)-anatoxin-*a* (Wittig route) was a 98/2 mixture of diastereomers by HPLC, while the amide from natural (+)-anatoxin-a (triflate route) was a 94/6 mixture. Corrected for the purity of the MTPA (98% ee),[37] our products had ee's of 98% and 90%, respectively. The rotations of the Boc-anatoxin precursors and anatoxin hydrochlorides are in good agreement with these values. Presumably the loss of optical purity in the triflate route is related to racemization in the sulfur-extrusion process, and this possibility is being investigated.

Summary

Syntheses of the natural (+)-anatoxin-*a* (15 steps from D-glutamic acid, 5% overall yield) and unnatural (−)-anatoxin-*a* (17 steps from L-glutamic acid, 4% overall yield) with high optical purity have been developed. The methods are general in scope and are being adapted to the synthesis of analogues. Study of these compounds and their derivatives should provide further insight into the mechanisms of neuronal conduction.

Experimental Section

General Methods. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone; acetonitrile, *tert*-butyl alcohol, and Me_2SO were distilled from CaH_2 and stored over 0.3-nm molecular sieves. Pyridine and dimethylformamide (DMF) were dried and stored over molecular sieves, and methylene chloride was distilled from P_2O_5 and stored over molecular sieves. Boiling points and melting points (Buchi apparatus, open capillary) are uncorrected. NMR spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million (δ) downfield from Me_4Si (^1H) or relative to $CDCl_3$ at 77.0 ppm (^{13}C).

(2*S*)-5-Thioxoproline Methyl Ester (6). A solution of L-pyroglutamic acid methyl ester[7,8] (4.86 g, 34 mmol) in THF (450 mL) and P_4S_{10} (4.28 g, 9.6 mmol) was refluxed 24 h. The solution was cooled and filtered, $CHCl_3$ (200 mL) was added, the organic phase was washed with saturated $NaHCO_3$ (200 mL), and the aqueous phase was extracted with $CHCl_3$ (200 mL). The combined organic phase was dried, evaporated, and distilled to give **6** as a yellow oil: 3.60 g, 67% yield; bp 130 °C (0.05 torr); TLC (ether/hexane, 3/1) R_f 0.28; GC (180 °C) R_t 2.6 min; ^1H NMR δ 2.3–2.7 (2 H, m), 2.8–3.2 (2 H, m), 3.84 (3 H, s), 4.62 (1 H, t, J = 7 Hz), 9.30 (1 H, s); $[\alpha]_D^{22}$ +12.7° (*c* 2.0, MeOH). Anal. ($C_6H_9NO_2S$) C, H, N.

(2*S*)-5-[1,1-Bis(Methoxycarbonyl)methylidene]proline Methyl Ester (7). A solution of thiolactam **6** (787 mg, 4.95 mmol) and dimethyl bromomalonate[12] (1.16 g, 5.5 mmol) in CH_2Cl_2 (4 mL) was stirred for 2 h; then triethylamine (0.83 mL, 5.95 mmol) was added. After 2 h the solution was diluted with CH_2Cl_2 (30 mL) and washed with 1 M HCl (3 × 15 mL). The aqueous phases were extracted with CH_2Cl_2 (15 mL), and the organic phases were combined, dried, and evaporated. Column chromatography (Et_2O) gave **7** as a clear oil: 610 mg, 2.4 mmol, 48% yield; bp 135–140 °C (.07 torr); TLC (Et_2O) R_f 0.42; GC (190 °C) R_t 7.8 min; ^1H NMR δ 2.0–2.6 (2 H, m), 2.9–3.4 (2 H, m), 3.69 (3 H, s), 3.72 (3 H, s), 3.75 (3 H, s), 4.3–4.6 (1 H, t), 8.6 (1 H, s); ^{13}C NMR δ 25.7, 33.1, 50.7, 51.0, 52.4, 60.6, 88.3, 167.4, 169.6, 171.3, 172.4. Anal. ($C_{11}H_{15}NO_6$) C, H, N.

***N*-Benzylglutamic acids [(*S*)-8 and (*R*)-8]** were prepared by the published procedure:[10a] 97% yield; mp 162–163 °C; (*S*)-**8**, $[\alpha]_D^{22}$ +18.5° (*c* 1, 6 M HCl); (*R*)-**8**, $[\alpha]_D^{23}$ −18.2° (*c* 1.28, 6 M HCl).

1-Benzyl-5-oxoproline [(*S*)-9a and (*R*)-9a]. A solution of *N*-benzylglutamic acid (**8**) (51.0 g, 215 mmol) in water (340 mL) was refluxed for 15 h, the solution was cooled, water (50 mL) was added, the solution was extracted with $CHCl_3$, and the organic phases were washed with saturated NaCl (150 mL), dried, and evaporated to give **9a**: 37.7 g, 172 mmol, 80% yield; mp 92–93 °C (lit.[7] mp 122–123 °C); (*S*)-**9a**, $[\alpha]_D^{22}$ +54.6° (*c* 2.32, MeOH); (*R*)-**9a**, $[\alpha]_D^{22}$ −55.7° (*c* 2.36, MeOH).

***N*-(1-Phenylethyl)-1-benzyl-5-oxoprolinamide [(*S*)-9c and (*R*)-9c]** were prepared from the acid chloride of acid **9a** and (+)-1-phenylethylamine. Isolation in the usual way gave **9c** as a white solid in 100% yield. The diastereomeric ratio was determined by ^1H NMR and HPLC of this material. Recrystallization gave the pure amide (*S*)-**9c**: mp 159–161 °C ($CHCl_3$/hexane); HPLC (MeOH/$CHCl_3$, 1.25/98.75, Li-Chrosorb Si60, 1.0 mL/min) R_t 6.0 min; ^1H NMR δ 1.38 (3 H, d, J = 7.0 Hz), 1.95–2.10 (1 H, m), 2.15–2.65 (3 H, m), 3.80 (1 H, dd, J = 5.3, 8.8 Hz), 3.90 (1 H, d, J = 14.8 Hz), 4.94 (1 H, d, J = 14.7 Hz), 5.00–5.20 (1 H, m), 5.90–6.05 (1 H, d), 7.05–7.40 (10 H, m). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N. (*R*)-**9c**: mp 155–157 °C; HPLC (as above) R_t 4.4 min; ^1H NMR δ 1.48 (3 H, d, J = 6.9 Hz), 1.95–2.10 (1 H, m), 2.15–2.50 (2 H, m), 2.50–2.70 (1 H, m), 3.78 (1 H, dd), 3.79 (1 H, d), 5.06 (1 H, d, J = 15.1 Hz), 5.05–5.20 (1 H, m), 6.00–6.20 (1 H, s), 7.10–7.40 (10 H, m).

1-Benzyl-5-oxoproline *tert*-Butyl Ester [(*S*)-9b and (*R*)-9b]. To a mechanically stirred solution of CH_3CN (95 mL) and DMF (37.5 mL), cooled to −25 °C, was added a solution of oxalyl chloride (15.5 mL) in CH_3CN (15 mL). After 15 min the acid **9a** (35.8 g, 163 mmol) was added to the slurry; then a solution of *tert*-butyl alcohol (30.0 g) in pyridine (40.1 g) was added, and after 15 h at room temperature, the solution was poured into 20% aqueous $KHCO_3$ (350 mL). Extracting with Et_2O (2 × 350 mL), washing the Et_2O with 1 M aqueous HCl (3 × 250 mL) and saturated aqueous NaCl (300 mL) plus saturated aqueous $NaHCO_3$ (50 mL), evaporating the combined, dried Et_2O phase, and distilling the residue gave **9b**: 41.9 g, 152 mmol, 93% yield; mp 62–63 °C; bp 125–135 °C (0.10 torr); TLC (EtOAc/hexane, 20/80) R_f 0.16; GC (215 °C) R_t 2.9 min; ^1H NMR δ 1.44 (9 H, s), 1.95–2.65 (4 H, m), 3.83 (1 H, dd, J = 3.4, 9.0 Hz), 3.96 (1 H, d, J = 14.8 Hz), 5.06 (1 H, d, J = 14.8 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR δ 22.9, 27.9, 29.6, 45.5, 59.6, 82.2, 127.7, 128.5, 128.6, 135.9, 170.8, 175.0; (*S*)-**9b**, $[\alpha]_D^{22}$ +16.2 (*c* 2.6, CH_2Cl_2); (*R*)-**9b**, $[\alpha]_D^{25}$ −16.0 (*c* 2.6, CH_2Cl_2). Anal.

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($C_{16}H_{21}NO_3$) C, H, N.

1-Benzyl-5-thioxoproline *tert*-Butyl Ester [(*S*)-10 and (*R*)-10]. A solution of pyroglutamate **9b** (10.2 g, 37 mmol) in THF (340 mL) was mechanically stirred in a Morton flask while P_4S_{10} (5.04 g, 11.3 mmol) was added. Three additional portions of P_4S_{10} (1.70, 1.62, and 1.60 g, total 11.0 mmol) were added at 1-h intervals. After 8-h total the solution was filtered, the precipitate was washed with Et_2O (400 mL), the combined washings and filtrate were evaporated, the residue was dissolved in Et_2O (200 mL), and the Et_2O was washed with 10% aqueous $KHCO_3$ (2 × 150 mL) and saturated aqueous NaCl (150 mL), the aqueous phases being back extracted with Et_2O (100 mL). The combined organic phase was dried and evaporated, and the residue was recrystallized from isooctane, giving thiolactam **10**: 9.32 g, 87% yield; mp 78–79 °C; TLC (EtOAc/hexane, 20/80) R_f 0.42; GC (215 °C), t_R 4.95 min; ^1H NMR δ 1.44 (9 H, s), 2.00–2.35 (2 H, m), 3.05–3.20 (2 H, m), 4.15 (1 H, dd, J = 3.4, 9.2 Hz), 4.27 (1 H, d, J = 14.6 Hz), 5.81 (1 H, d, J = 14.6 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR δ 24.9, 28.0, 43.5, 50.5, 64.5, 82.8, 128.2, 128.7, 128.9, 134.9, 169.2, 203.7; (*S*)-**10**, $[\alpha]^{25}_D$ +190° (*c* 1.85, CH_2Cl_2); (*R*)-**10**, $[\alpha]^{25}_D$ −200° (*c* 1.74, CH_2Cl_2). Anal. ($C_{16}H_{21}NO_2S$) C, H, N.

(*S*)-1-Benzyl-(*E*)-5-((methoxycarbonyl)methylidene)proline *tert*-Butyl Ester (12). A solution of thiolactam **10** (2.05 g, 7.0 mmol) and methyl bromoacetate (1.31 g, 8.6 mmol) in CH_3CN (5 mL) was stirred for 40 h; then CH_2Cl_2 (40 mL) was added and the solution stirred for 10 min. Triphenylphosphine (2.77 g, 10.6 mmol) and 2 min later triethylamine (2.95 mL, 21.2 mmol, 300 mol %) were added, and the solution was stirred for 20 h. The solution was washed with 1 M aqueous NaH_2PO_4, the aqueous phases were extracted with CH_2Cl_2 (35 mL), the combined organic phase was dried and evaporated, and the residue was chromatographed ($CHCl_3$) to give **12**: 2.1 g, 6.3 mmol, 90% yield; mp 58–59 °C (hexane); TLC (EtOAc/hexane, 1/4) R_f 0.34; GC (215 °C) t_R 9.7 min; IR (neat) 1730, 1670, 1600 cm^{-1}; UV (CH_2Cl_2) λ_{max} 277 nm; ^1H NMR δ 1.41 (9 H, s), 2.00–2.30 (2 H, m), 3.00–3.15 (1 H, m), 3.39 (1 H, dddd, J = 1.1, 3.3, 9.3, 17.9 Hz), 3.59 (3 H, s), 3.95 (1 H, dd, J = 3.0, 8.9 Hz), 4.19 (1 H, d, J = 15.6 Hz), 4.52 (1 H, d, J = 15.6 Hz), 4.75 (1 H, s), 7.10–7.40 (5 H, m); ^{13}C NMR δ 26.2, 27.8, 30.9, 49.4, 49.9, 65.0, 80.2, 81.9, 127.5, 128.6, 135.5, 164.9, 169.4, 170.9; $[\alpha]^{23}_D$ +128° (*c* 0.984, CH_2Cl_2). Anal. ($C_{19}H_{25}NO_4$) C, H, N. From similar reactions the α-alkylated thiolactam **15** was isolated in 2–3% yield as a 3/1 mixture of diastereomers: bp 170 °C (0.10 torr); TLC (EtOAc/hexane, 1/4) R_f 0.36; HPLC (EtOAc/hexane, 5/95, 5-μm Spherisorb silica gel) t_R 6.2 (minor), 6.9 (major) min; ^1H NMR (major isomer) δ 1.44 (9 H, s), 1.7–2.7 (3 H, m), 3.05–3.50 (2 H, m), 3.69 (3 H, s), 4.10 (1 H, dd, J 1.9, 9.6 Hz), 4.29 (1 H, d, J = 14.6 Hz), 5.78 (1 H, d, J = 14.7 Hz), 7.20–7.40 (5 H, m); (minor isomer) 1.45 (s), 3.70 (s), 5.93 (1 H, d, J = 14.7 Hz). Anal. ($C_{19}H_{25}NO_4S$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-((methoxycarbonyl)methyl)proline *tert*-Butyl Ester (16a). A solution of vinylogous carbamate **12** (10.3 g, 31.0 mmol) in EtOAc (80 mL) was degassed (N_2), 5% Pt/C (2.56 g) was added, and the solution was hydrogenated (50 psig, H_2) for 20 h. The catalyst was removed by filtration; fresh catalyst (2.71 g) was added and the solution hydrogenated for 4 h. Filtration and evaporation of the filtrate left a residue, which was distilled to give the diester **16a**: 9.17 g, 89% yield (contaminated with 2% of the trans isomer **17**); bp 110–120 °C (0.10 torr); TLC (EtOAc/hexane, 1/4) R_f 0.46; HPLC (TEA/isooctane, 1/99, 5-μm LiChrosorb Si60 silica gel) *t*R 6.0 min; IR (neat) 1730 cm^{-1}; ^1H NMR δ 1.35 (9 H, s), 1.50–2.05 (4 H, m), 2.33 (1 H, dd, J = 8.9, 15.2 Hz), 2.57 (1 H, dd, J = 4.5, 15.3 Hz), 3.10–3.30 (2 H, m), 3.61 (3 H, s), 3.79 (1 H, d), 3.87 (1 H, d), 7.15–7.40 (5 H, m); ^{13}C NMR δ 27.8, 28.2, 30.7, 40.4, 51.0, 57.8, 61.6, 67.0, 79.9, 126.8, 128.0, 128.9, 139.0, 172.4, 173.4. Anal. ($C_{19}H_{27}NO_4$) C, H, N.

(2*S*)-*trans*-1-Benzyl-5-((methoxycarbonyl)methyl)proline *tert*-Butyl Ester (17). A solution of vinylogous carbamate **12** (202 mg, 0.61 mmol) in methanol (4.5 mL) was titrated to a yellow end point (bromocresol green) with 2 M methanolic HCl. Sodium cyanoborohydride (0.38 g, 0.61 mmol) was added and additional 2 M HCl was periodically added to maintain the yellow color. After 2.5 h, CH_2Cl_2 (25 mL) was added and the solution was washed with 10% aqueous $KHCO_3$ (25 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic phase dried and evaporated to give a 3/1 mixture of the cis and trans diesters (201 mg). Column chromatography (EtOAc/isooctane, 1/6) gave the pure trans isomer **17**: bp 100 °C 0.10 torr); TLC (EtOAc/hexane, 1/4) R_f 0.54; HPLC (TEA/isooctane, 1/99, 5-μm LiChrosorb Si60 silica gel) t_R 4.7 min; ^1H NMR δ 1.44 (9 H, s), 1.60–1.90 (2 H, m), 1.95–2.36 (3 H, m), 2.58 (1 H, dd, J = 4.0, 14.5 Hz), 3.44 (1 H, dd, J = 1.5, 8.0 Hz), 3.55–3.70 (1 H, m), 3.65 (3 H, s), 3.80 (1 H, d, J = 13.8 Hz), 3.87 (1 H, d, J = 13.8 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR δ 27.7, 28.2, 29.6, 39.7, 51.3, 52.7, 58.7, 64.0, 80.4, 126.9, 128.2, 128.6, 139.7, 172.6, 173.6. Anal. ($C_{19}H_{27}NO_4$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-(carboxymethyl)proline *tert*-Butyl Ester (16b). A solution of diester **16a** (1.02 g, 3.06 mmol) in methanol 30 mL) and 1 M aqueous K_2CO_3 was stirred for 21 h, water (35 mL) was added, and the solution was extracted with Et_2O (45 mL). The aqueous phase was adjusted to pH 7 with 1 M aqueous HCl (35 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 phases were combined, dried, and evaporated to give **16b**: 910 mg, 93% yield; mp 98–101 °C (Et_2O/hexane); HPLC (0.1 M aqueous KH_2PO_4/KOH, pH 6.0/MeOH, 40/60, LiChrosorb C-18 RP) t_R 8.4 min; ^1H NMR δ 1.30 (9 H, s), 1.65–2.25 (4 H, m), 2.46 (1 H, dd, J = 2.5, 17.1 Hz), 2.59 (1 H, dd, J = 4.7, 17.1 Hz), 3.15–3.30 (1 H, m), 3.45 (1 H, dd, J = 6.0, 9.1 Hz), 3.68 (1 H, d, J = 12.8 Hz), 4.00 (1 H, d, J = 12.8 Hz), 7.25–7.45 (5 H, m). Anal. ($C_{18}H_{25}NO_4$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-[((1-phenylethyl)carbamyl)methyl]proline *tert*-butyl esters (16d and 16e) were prepared from amino acid **16b** and 1,1′-carbonyldiimidazole followed by the addition of (+)- or (−)-1-phenylethylamine. Isolation in the usual way left an oil containing less than 0.5% of the minor diastereomer by HPLC and ^1H NMR. Column chromatography (EtOAc/hexane, 1/1) gave amide **16** (193 mg, 58% yield). **16d** [from (+)-amine]: TLC (EtOAc/hexane, 60/40) R_f 0.18; HPLC (0.1 M aqueous KH_2PO_4/KOH, pH 6.0/CH_3CN, 30/70, LiChrosorb C-18 RP) t_R 15.6 min; ^1H NMR δ 1.28 (9 H, s), 1.54 (3 H, d, J = 7.0 Hz), 1.80–2.20 (4 H, m) 2.33 (1 H, dd, J = 3.4, 16.4 Hz), 2.55 (1 H, dd, J = 4.0, 16.4 Hz), 3.00–3.15 (1 H, m), 3.28 (1 H, dd, J = 5.1, 9.1 Hz), 3.49 (1 H, d, J = 12.9 Hz), 3.87 (1 H, d, J = 12.9 Hz), 5.25–5.40 (1 H, m), 7.00–7.60 (10 H, m), 9.00–9.15 (1 H, d). Anal. ($C_{26}H_{34}N_2O_3$) C, H, N. **16e** [from (−)-amine]; TLC (EtOAc/hexane, 60/40) R_f 0.18; HPLC (as above); t_R 14.1 min; ^1H NMR δ 1.31 (9 H, s), 1.59 (3 H, d, J = 7.1 Hz), 1.75–2.20 (4 H, m), 2.32 (1 H, dd, J = 3.6, 16.5 Hz), 2.61 (1 H, dd, J = 4.3, 16.5 Hz), 3.00–3.15 (1 H, m), 3.30 (1 H, dd, J = 5.2, 9.5 Hz), 3.62 (1 H, d, J = 13.1 Hz), 3.96 (1 H, d, J = 13.1 Hz), 5.10–5.25 (1 H, m), 7.10–7.50 (10 H, m), 9.05–9.15 (1 H, d).

(2*S*)-*cis*-1-Benzyl-5-((methoxycarbonyl)methyl)proline (16c). A solution of diester **16a** (460 mg, 1.38 mmol) in *n*-PrOH (20 mL), water (20 mL), and glacial acetic acid (4 mL) was refluxed for 4 h. Most of the solvent was evaporated and the residue partitioned between $CHCl_3$ (20 mL) and 1 M aqueous KH_2PO_4/Na_2HPO_4 buffer (20 mL, pH 6). The aqueous phase was extracted with $CHCl_3$ (2 × 20 mL), and the combined organic phase was dried and evaporated to give **16c** as an oil (330 mg, 86% yield), which was used without further purification: ^1H NMR δ 1.6–1.8 (2 H, m), 2.0–2.2 (2 H, m), 2.58 (1 H, dd, J = 7.1, 15.8 Hz), 2.72 (1 H, dd, J = 4.9, 15.8 Hz), 3.40–3.55 (2 H, m), 3.69 (3 H, s), 3.88 (1 H, d, J = 13.0 Hz), 4.10 (1 H, d, J = 13.0 Hz), 7.20–7.40 (5 H, m).

(2*R*)-1-Benzyl-2-((methoxycarbonyl)methyl)pyrrolidine (18). A solution of α-amino acid **16c** (330 mg, 1.19 mol) in $POCl_3$ (2.04 g, 13.3 mmol) was heated at 95 °C for 7 min. Most of the $POCl_3$ was evaporated, and the residue was dissolved in MeOH (7 mL). Saturated aqueous $NaHCO_3$ was added until the solution became green (bromocresol green). Sodium cyanoborohydride (140 mg, 2.2 mmol) was added, and the solution was stirred for 1.5 h, then poured into 1 M aqueous K_2CO_3 (25 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phase was dried, evaporated, and distilled to give **18**: 221 mg, 80% yield; bp 90 °C (0.10 torr); TLC (EtOAc/hexane, 20/80) R_f 0.18; IR 1730 cm^{-1}; ^1H NMR δ 1.55–1.80 (3 H, m), 2.00–2.30 (2 H, m), 2.36 (1 H, dd, J = 8.6, 15.0 Hz), 2.69 (1 H, dd, J = 4, 14.8 Hz), 2.80–3.00 (2 H, m), 3.28 (1 H, d, J = 12.8 Hz), 3.68 (3 H, s), 3.97 (1 H, d, J = 12.8 Hz), 7.20–7.40 (5 H, m); $[\alpha]^{22}_D$ +76.4° (*c* 2.38, $CHCl_3$) (lit.[16] $[\alpha]^{25}_D$ −67.8° (*c* 2, $CHCl_3$) for 2*S*-**18**). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-(2-hydroxyethyl)proline *tert*-Butyl Ester (19). A solution of $LiBH_4$ in Et_2O[20] (30 mL, 34.2 mmol, 124 mol %) was added to a solution of diester **16a** (9.17 g, 27.5 mmol) in Et_2O (80 mL). After 4 h the solution was washed with 1 M aqueous K_2CO_3 (2 × 50 mL) and saturated aqueous NaCl (50 mL). The aqueous phases were extracted with Et_2O (60 mL), and the combined organic phase was dried, filtered, and evaporated to an oil (7.96 g, 95% yield), suitable for use in subsequent reactions. Pure amino alcohol was isolated by column chromatography (EtOAc/isooctane, 80/20): bp 105 °C (0.05 torr); TLC (EtOAc/hexane, 60/40) R_f 0.31; GC (215 °C) t_R 2.65 min; ^1H NMR δ 1.27 (9 H, s), 1.4–1.6 (1 H, m), 1.80–2.00 (3 H, m), 2.00–2.20 (2 H, m), 3.15–3.35 (2 H, m), 3.56 (1 H, d, J = 12.9 Hz), 3.7–3.80 (1 H, m), 4.0–4.1 (1 H, m), 4.07 (1 H, d, J = 12.9 Hz), 5.15–5.30 (1 H, s), 7.20–7.35 (5 H, m). Anal. ($C_{18}H_{27}NO_3$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-(formylmethyl)proline *tert*-Butyl Ester (20). A solution of Me_2SO (3.7 mL, 52 mmol) in CH_2Cl_2 (5 mL) was added at 1.2 mL/min to a solution of oxalyl chloride (2.5 mL, 29 mmol) in CH_2Cl_2 (70 mL) at −60 °C. After 4 min a solution of amino alcohol **19** (7.96 g, 26.1 mmol) in CH_2Cl_2 (30 mL) was added at 3 mL/min. Twenty minutes after completion of the addition, triethylamine (13.5 mL,

97 mmol) was added. The solution was stirred at −55 °C for 10 min then allowed to warm to room temperature over 1 h, CH_2Cl_2 (70 mL) added, and the solution washed with saturated aqueous $NaHCO_3$ (3 × 30 mL). The aqueous phases were extracted with CH_2Cl_2 (70 mL), and the combined organic phase was dried, filtered, and evaporated. The residue was dried to an oil (7.82 g, 99% yield), which was used immediately in the Wittig reaction. Longer storage times or higher temperatures gave increasing amounts of the trans isomer **20b**. After 4 h neat or 22 h in solution ($CDCl_3$) the cis/trans ratio was 94/6 and after chromatography (EtOAc/hexane, 1/3) it was 2/1. *cis*-**20a**: TLC (EtOAc/hexane, 20/80) R_f 0.18; IR 1720 cm^{-1}; ^1H NMR δ 1.36 (9 H, s), 1.60–2.20 (4 H, m), 2.43 (1 H, ddd, J = 2.0, 7.4, 16.8 Hz), 2.61 (1 H, ddd, J = 2.0, 4.1, 16.8 Hz), 3.20–3.35 (2 H, m), 3.82 (2 H, s), 7.20–7.40 (5 H, m), 9.78 (1 H, t, J = 2.0 Hz). *trans*-**20b**: TLC (EtOAc/hexane, 1/4) R_f 0.26; ^1H NMR δ 1.45 (s), 3.48 (d), 3.65–3.80 (m), 9.81 (t, J = 2.5 Hz).

(2*S*)-*cis*-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)-2-butenyl]proline *tert*-Butyl Ester (21a). The phosphonium salt **23**[23] (14.2 g, 31.1 mmol, dried 12 h, 110 °C, 0.10 torr) was dissolved in Me_2SO (30 mL) at 90 °C, THF (20 mL) was added, and the cooled solution was added at 5 mL/min to a solution of LDA (from diisopropylamine, 4.4 mL, 31.4 mmol, and *n*-BuLi in hexane, 18.8 mL, 29.5 mmol) in THF (100 mL) at 0 °C. After 1 h a solution of aldehyde **20** (7.82 g, 25.8 mmol) in THF (30 mL) was added at 5 mL/min and the solution stirred 1 h at 0 °C. A 50% saturated aqueous $NaHCO_3$ solution (100 mL) was added, the solution was extracted with Et_2O (3 × 100 mL), and the Et_2O phases were washed with 50% saturated aqueous $NaHCO_3$, combined, dried, filtered and evaporated. Chromatography (EtOAc/CH_2Cl_2, 5/95) of the residue gave *cis*-**21a** (4.56 g, 44% yield) containing 1.5% *trans*-**21b**. The cis/trans ratio in the crude product was 97/3. **21a**: TLC (EtOAc/hexane, 20/80) R_f 0.45; IR 1738 cm^{-1}; HPLC (EtOAc/hexane, 10/90, LiChrosorb Si60) t_R 6.1 min; ^1H NMR δ 1.29 (3 H, s), 1.34 (9 H, s), 1.55–1.75 (1 H, m), 1.75–2.15 (4 H, m), 2.25–2.45 (3 H, m), 2.70–2.85 (1 H, m), 3.15–3.27 (1 H, m), 3.76 (1 H, d, J = 13.7 Hz), 3.85–3.97 (5 H, m), 5.40–5.70 (2 H, m), 7.20–7.40 (5 H, m). Anal. ($C_{24}H_{35}NO_4$) C, H, N. **21b**: TLC (EtOAc/hexane, 20/80) R_f 0.50; HPLC (EtOAc/hexane, 10/90, LiChrosorb Si60, 1.0 mL/min) t_R 4.8 min; IR 1713 cm^{-1}; ^1H NMR δ 1.31 (3 H, s), 1.44 (9 H, s), 1.50–1.65 (1 H, m), 1.65–1.80 (1 H, m), 1.95–2.20 (3 H, m), 2.30–2.40 (3 H, m), 3.25–3.40 (1 H, m), 3.45 (1 H, dd), 3.75 (1 H, d, J = 13.6 Hz), 3.90–4.05 (5 H, m), 5.45–5.65 (2 H, m), 7.20–7.40 (5 H, m). Anal. ($C_{24}H_{35}NO_4$) C, H, N.

(2*S*)-*cis*-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-Butyl Ester (22a). A solution of Wittig product **21** (4.54 g, 11.3 mmol) in EtOAc (80 mL) was degassed (N_2), 5% Pt/C (1.53 g) was added, and the solution was hydrogenated (50 psig) for 6 h. The solution was filtered, the filtrate was evaporated, and the hydrogenation process was repeated twice with fresh catalyst (1.54 g, 1.34 g) to give **22a**: 4.23 g, 93% yield; TLC (EtOAc/hexane, 20/80) R_f 0.45; IR 1750 cm^{-1}; ^1H NMR δ 1.30 (3 H, s), 1.34 (9 H, s), 1.20–2.00 (12 H, m), 2.60–2.73 (1 H, m), 3.14–3.24 (1 H, dd), 3.72 (1 H, d, J = 13.7 Hz), 3.88 (1 H, d, J = 13.7 Hz), 3.90–3.97 (4 H, m), 7.15–7.35 (5 H, m); ^{13}C NMR δ 23.6, 24.2, 26.3, 27.8, 28.1, 29.9, 34.4, 39.0, 57.1, 64.4, 66.5, 79.7, 109.9, 126.6, 127.8, 129.1, 138.7, 173.8. Anal. ($C_{24}H_{37}NO_4$) C, H, N.

(2*S*)-*trans*-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-butyl ester (22b) was prepared from trans Wittig product **21b** by the same procedure used for the cis compound. **22b**: TLC (EtOAc/hexane, 20/80) R_f 0.50; IR 1740 cm^{-1}; ^1H NMR δ 1.31 (3 H, s), 1.45 (9 H, s), 1.15–2.25 (12 H, m), 3.15–3.30 (1 H, m), 3.44 (1 H, dd, J = 1.6, 7.9 Hz), 3.73 (1 H, d, J = 13.5 Hz), 3.89–4.00 (5 H, m), 7.18–7.41 (5 H, m). Anal. ($C_{24}H_{37}NO_4$) C, H, N.

Benzyl 5-(2-Methyl-1,3-dioxolan-2-yl)-2-oxopentanoate (35). 1,2-Dibromoethane (6.8 mL, 79 mmol) was added to a mechanically stirred solution of Mg (2.00 g, 82 mmol) in THF (165 mL). After 10 min the reaction was heated to reflux for 45 min; then it was cooled to 30 °C, potassium (5.86 g, 150 mmol) was added, and the solution was refluxed for 1 h and then cooled to 0 °C. A solution of bromo ketal **34** (12.7 g, 60.8 mmol) in THF (35 mL) was added at 1.4 mL/min. The solution was stirred at 0 °C for 30 min and then added via syringe (6.7 mL/min) to a solution of dibenzyl oxalate (20.3 g, 75.1 mmol) in CH_2Cl_2 (300 mL) at −40 °C. After addition was complete, the solution was allowed to warm to −10 °C over 1 h, it was transferred by cannula into 0.5 M aqueous KH_2PO_4 (750 mL), CH_2Cl_2 (300 mL) was added, and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (500 mL) and saturated aqueous NaCl (500 mL), back extracting the aqueous solutions with CH_2Cl_2 (300 mL). The organic phases were combined, dried, filtered, and evaporated to a residue (28.0 g), which was directly reduced to the hydroxy ester. The yield of keto ester was 68% by ^1H NMR. Column chromatography (CH_2Cl_2) allowed partial purification of the keto ester **35**: TLC (CH_2Cl_2) R_f 0.17; ^1H NMR δ 1.30 (3 H, s), 1.55–1.95 (4 H, m), 2.87 (2 H, t, J = 7.0 Hz), 3.80–3.95 (4 H, m), 5.27 (2 H, s), 7.25–7.45 (5 H, m).

Benzyl (±)-5-(2-Methyl-1,3-dioxolan-2-yl)-2-hydroxypentanoate (36a). The crude keto ester **35** (28.0 g) was dissolved in EtOAc (200 mL) and the solution degassed (N_2). Triethylamine (2.8 mL) and 5% Pt/C (2.81 g) were added, and the solution was hydrogenated for 16 min at 50 psig. The solution was filtered, the filtrate evaporated, and the residue dissolved in CH_2Cl_2 (90 mL) and washed with saturated aqueous $NaHCO_3$ (90 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL), and the organic phases were combined, dried, filtered, and evaporated. The residue was heated (75 °C, 0.10 torr, 2 h) in a Kugelrohr apparatus to remove the benzyl alcohol and leave pure hydroxy ester **36a**: 9.87 g, 55% yield from bromo ketal **34**; TLC (EtOAc/hexane, 60/40) R_f 0.42; IR 3500, 1725 cm^{-1}; ^1H NMR δ 1.29 (3 H, s), 1.40–1.90 (6 H, m), 2.78 (1 H, d), 3.85–4.00 (4 H, m), 4.20–4.30 (1 H, m), 5.25 (2 H, s), 7.30–7.45 (5 H, m); ^{13}C NMR δ 19.2, 23.5, 34.2, 38.4, 64.3, 66.8, 70.2, 109.6, 128.0, 128.2, 128.3, 135.1, 174.7. Anal. ($C_{16}H_{22}O_5$) C, H.

Benzyl (±)-5-(2-Methyl-1,3-dioxolan-2-yl)-2[((trifluoromethyl)-sulfonyl)oxy]pentanoate (36b). A solution of hydroxy ester **36a** (10.4 g, 35 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (8.70 g, 42.3 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and trifluoromethanesulfonic anhydride (6.4 mL, 38.0 mmol) was added at 0.6 mL/min. The solution was stirred at 0 °C for 30 min and room temperature for 1 h. Most of the solvent was evaporated and the residue was triturated with hexane (200 mL). The hexane was evaporated and the residual oil was dried (22 °C, .10 torr, 2 h) to give triflate **36b** (16.0 g containing 15–20 mol % of the di-*tert*-butylpyridine). The crude product was used immediately in the next reaction. **36b**: TLC (EtOAc/hexane) R_f 0.33; ^1H NMR δ 1.25 (3 H, s), 1.30–1.75 (4 H, m), 1.95–2.10 (2 H, m), 3.80–4.00 (4 H, m), 5.15 (1 H, t, J = 6.1 Hz), 5.25 (2 H, s), 7.30–7.45 (5 H, m).

(*R*)-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)-1-((benzyloxy)-carbonyl)butylidene]proline *tert*-Butyl Ester (38). Crude triflate **36b** (16.0 g) was cooled to 0 °C and dissolved in CH_3CN (25 mL). Thiolactam (*R*)-**10** (8.71 g, 29.9 mmol) was added and the solution stirred at 0 °C (30 min) and room temperature (19 h); then CH_2Cl_2 (225 mL) was added and the solution cooled to 0 °C. Triphenylphosphine (9.41 g, 35.9 mmol) was added followed after 15 min by the addition of a solution of *N*-methylpiperidine (3.89 g, 39.2 mmol) in CH_2Cl_2 (35 mL) at 2 mL/min. The solution was stirred at 0 °C for 4 h and then washed with 1 M aqueous KH_2PO_4 (2 × 150 mL) and saturated aqueous $NaHCO_3$ (1 × 150 mL). The aqueous phases were extracted with CH_2Cl_2 (150 mL), and the combined organic phase was dried, filtered, and evaporated. Column chromatography (CH_2Cl_2 then EtOAc/CH_2Cl_2, 5/95) of the residue gave impure carbamate (2.93 g) followed by pure carbamate **38** (8.81 g, 55% yield). MPLC (EtOAc/hexane, 20/80) of the impure material gave thiol ester **37** (1.00 g, 11% yield) and additional pure carbamate **38** (1.49 g, 9% yield). The carbamate was always isolated as a 5/1 mixture of diastereomers. **38**: TLC (EtOAc/hexane, 20/80) R_f 26; IR (neat) 1740, 1685, 1590, 1565 cm^{-1}; ^1H NMR (major diastereomer) δ 1.21 (3 H, s), 1.42 (9 H, s), 1.40–2.50 (8 H, m), 3.05–3.30 (2 H, m), 3.70–4.00 (5 H, m), 4.34 (1 H, d, J = 16.6 Hz), 4.88 (1 H, d, J = 16.8 Hz), 5.13 (2 H, s), 7.10–7.45 (10 H, m); (minor diastereomer) 1.44 (s), 4.73 (1 H, d, J = 15.2 Hz), 5.04 (1 H, d, J = 12.9 Hz), 5.14 (1 H, d); ^{13}C NMR δ 23.6, 25.8, 26.7, 27.5, 27.9, 33.9, 38.8, 52.6, 64.4, 65.0, 66.2, 81.6, 96.1, 109.8, 126.7, 127.3, 127.4, 127.7, 128.2, 128.7, 137.5, 137.6, 162.1, 170.0, 171.5. Anal. ($C_{32}H_{41}NO_6$) C, H, N.

Benzyl 5-(2-Methyl-1,3-dioxolan-2-yl)-2-mercaptopentanoate (37): bp 130 °C (0.10 torr); TLC (EtOAc/hexane, 20/80) R_f 0.35; IR 1730 cm^{-1}; ^1H NMR δ 1.28 (3 H, s), 1.40–1.90 (5 H, m), 1.90–2.02 (1 H, m), 2.06 (1 H, d, J = 9.2 Hz), 3.37 (1 H, d of t, J = 7.4, 9.2 Hz), 3.85–4.00 (4 H, m), 5.18 (2 H, s), 7.28–7.45 (5 H, m); ^{13}C NMR δ 21.7, 23.6, 35.5, 38.2, 40.8, 64.5, 66.9, 109.5, 128.1, 128.2, 128.4, 135.4, 172.9. Anal. ($C_{16}H_{22}O_4S$) C, H, S.

(*R*)-5-[4-(2-Methyl-1,3-dioxolan-2-yl)butyl]-1,5-dehydroproline *tert*-Butyl Ester (39). A solution of vinylogous carbamate **38** (10.3 g, 19.2 mmol) in MeOH (100 mL) was degassed (N_2) and 5% Pd/C (8.24 g) was added. 1,4-Cyclohexadiene (18.2 mL, 192 mmol) was cautiously added by syringe over 10 min. The solution was stirred at room temperature (5 min) and refluxed (35 min) then cooled, the catalyst allowed to settle, and MeOH (60 mL) removed by decantation. Methanol (60 mL) was added to the catalyst, the suspension heated to reflux (10 min) then cooled, and the methanol decanted. This digestion was repeated and the methanol solutions were filtered and evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phase was dried, filtered, evaporated, and distilled to give **39**: 4.55 g, 76% yield; bp 120 °C (0.10 torr); TLC (EtOAc/hexane) R_f 0.37; IR (neat) 1725, 1640 cm^{-1}; ^1H NMR δ 1.29 (3 H, s), 1.44 (9 H, s), 1.60–2.70 (12 H, m), 3.85–3.95 (4 H, m), 4.50–4.60 (1 H, m); ^{13}C NMR δ 23.2, 23.3, 26.1, 27.4, 33.1, 37.0, 38.3,

64.0, 74.2, 80.1, 109.3, 171.8, 180.8; $[\alpha]^{23}_D$ −65.8° (*c* 0.395, CH_2Cl_2). Anal. ($C_{17}H_{29}NO_4$) C, H, N.

(2*R*)-*cis*-5-[4-(2-Methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-Butyl Ester (40a). A solution of pyrroline **39** (4.51 g, 14.5 mmol) in absolute EtOH (80 mL) and PtO_2 (0.48 g) were shaken with hydrogen for 2 h. The solution was filtered and evaporated, the residue was dissolved in CH_2Cl_2 (90 mL) and washed with 1 M aqueous K_2CO_3 (50 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phase was dried, filtered, evaporated, and distilled to give **40a**: 4.34 g, 96% yield; bp 120 °C (0.10 torr); TLC (EtOAc/hexane, 60/40) R_f 0.16; IR (neat) 1720 cm^{-1}; ^1H NMR δ 1.31 (3 H, s), 1.46 (9 H, s), 1.25–2.20 (12 H, m), 2.90–3.05 (1 H, m), 3.61 (1 H, dd, *J* = 5.3, 9.0 Hz), 3.85–4.00 (4 H, m); ^{13}C NMR δ 23.4, 23.9, 27.3, 27.7, 30.4, 31.5, 35.6, 38.8, 59.9, 60.3, 64.3, 80.5, 109.7, 174.3; $[\alpha]^{23}_D$ +1.7° (*c* 0.47, CH_2Cl_2). Anal. ($C_{17}H_{31}NO_4$) C, H, N.

(2*R*)-*cis*-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-Butyl Ester (40b). Benzyl bromide (2.46 g, 14.4 mmol) in CH_3CN (5 mL) and K_2CO_3 (5.83 g, 42.2 mmol) were added to a solution of pyrrolidine **40a** (4.32 g, 13.8 mmol) in CH_3CN (25 mL). After 12 h water (100 mL) was added, the solution was extracted with Et_2O (1 × 200, 2 × 50 mL), and the Et_2O phases were washed with saturated aqueous NaCl (100 mL), combined, dried, filtered, and evaporated. MPLC (EtOAc/hexane, 20/80) gave **40b** (4.62 g, 83% yield) contaminated with 1.5% of the trans isomer, identical (except for rotation) with **22a**.

1-Benzyl-5-(5-oxohexyl)proline [(2*S*)-*cis*-26 and (2*R*)-*cis*-26]. Ketal ester **22a** (4.59 g, 11.4 mmol) was refluxed in a mixture of *n*-PrOH (50 mL), water (50 mL), and glacial acetic acid (10 mL) for 4 h, followed by cooling, pouring into 1.5 M aqueous K_2HPO_4 (150 mL), and extracting with CH_2Cl_2 (1 × 200, 2 × 100 mL). The combined organic phase was dried, filtered, and evaporated, and the residue was dried at 45 °C (0.10 torr) to give **26** as a viscous oil (3.68 g, 12.1 mmol), which was used without further purification. **26**: TLC ($MeOH/CHCl_3$, 10/90) R_f 0.24; ^1H NMR δ 1.20–1.40 (2 H, m), 1.40–1.85 (6 H, m), 2.00–2.35 (2 H, m), 2.14 (3 H, s), 2.41 (2 H, t, *J* = 7.1 Hz), 3.11–3.25 (1 H, m), 3.84 (1 H, dd, *J* = 4.0, 8.8 Hz), 4.11 (1 H, d, *J* = 13.3 Hz), 4.23 (1 H, d, *J* = 13.3 Hz), 7.35–7.50 (5 H, m).

2-Acetyl-9-benzyl-9-azabicyclo[4.2.1]nonane [(1*S*)-27a,28a, and (1*R*)-27a,28a]. Amino acid **26** (3.68 g, 11.4 mmol) was dissolved in $POCl_3$ (14.5 g, 94.6 mmol) and heated to 95 °C for 14 min. The solution was evaporated (50 °C), and the residue (5.8 g) was cooled to 0 °C. Methanol (150 mL) and 12 M aqueous HCl (10.5 mL) were added, the solution was heated to 57 °C for 21 h then cooled to room temperature, 5% Pt/C (0.6 g) was added, and the mixture was shaken with hydrogen (20 psig) for 20 min. Filtration and evaporation of the methanol was followed by addition of water (80 mL) and washing with Et_2O (100 mL). The Et_2O was extracted with 0.2 M HCl (25 mL), the combined aqueous phase was cooled to 0 °C, and the pH was adjusted to 7 with K_2CO_3. Then 1 M aqueous K_2CO_3 (30 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 phase was dried, filtered, and evaporated to a residue, which on MPLC ($CHCl_3$) gave **27a** and **28a** (1.47 g, 50% yield from **22a**) as a 1/4 mixture of diastereomers. Further elution (TEA/$CHCl_3$, 1/99) gave the pyrrolidine **29** (0.95 g, 32% yield from **26a**). **27a** (minor diastereomer): (1*R*,2α and 1*S*,2α) TLC ($MeOH/CHCl_3$, 10/90) R_f 0.71; ^1H NMR δ 1.20–2.40 (10 H, m), 2.00 (3 H, s), 2.82–2.95 (1 H, m), 3.27–3.40 (1 H, m), 3.66 (1 H, ddd, *J* = 2.0, 4.1, 8.7 Hz), 3.84 (2 H, s), 7.15–7.45 (5 H, m); ^{13}C NMR δ 23.0, 25.3, 29.1, 31.8, 35.4, 57.8, 58.5, 61.3, 63.6, 126.8, 128.1, 210.8. **28a** (major diastereomer): (1*R*,2β and 1*S*,2β) TLC (MeOH, $CHCl_3$, 10/90) R_f 0.48; IR 1705 cm^{-1}; ^1H NMR δ 1.30–1.85 (8 H, m), 1.90–2.20 (1 H, m), 1.98 (3 H, s), 2.22–2.50 (2 H, m), 3.22–3.32 (1 H, m), 3.50–3.60 (1 H, m), 3.67 (1 H, d, *J* = 13.4 Hz), 3.72 (1 H, d, *J* = 13.4 Hz), 7.15–7.40 (5 H, m); ^{13}C NMR δ 22.7, 27.0, 27.1, 27.6, 33.9, 36.5, 61.3, 61.5, 63.4, 64.0, 126.6, 127.9, 128.5, 140.9, 211.4; mass spectrum, exact mass calcd for $C_{17}H_{23}NO$, *m*/*z* 257.1779, found 257.1777.

1-Benzyl-2-(5-oxohexyl)pyrrolidine [(*S*)-29 and (*R*)-29]: bp 120 °C (0.10 torr); TLC ($MeOH/CHCl_3$, 1/9), R_f 0.38; IR 1715 cm^{-1}; ^1H NMR δ 1.20–2.15 (10 H, m), 2.14 (3 H, s) 2.25–2.40 (1 H, m), 2.44 (2 H, t, *J* = 7.4 Hz), 2.85–2.95 (1 H, m), 3.14 (1 H, d, *J* = 12.8 Hz), 4.01 (1 H, d, *J* = 12.8 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR δ 21.6, 23.8, 25.4, 29.5, 30.0, 33.5, 43.2, 53.9, 58.4, 63.8, 126.5, 127.8, 128.6, 139.3, 208.5. Anal. ($C_{17}H_{25}NO$) C, H, N.

2-Acetyl-9-azabicyclo[4.2.1]nonane [(1*S*)-27b,28b and (1*R*)-27b,28b]: A solution of *N*-benzyldihydroanatoxin (1.45 g, 5.67 mmol) in MeOH (50 mL) and 12 M aqueous HCl (4.0 mL) was hydrogenated at 50 psig over 5% Pd/C (150 mg) for 18 h. The solution was filtered, most of the methanol was evaporated, water (20 mL) was added, and the solution was washed with Et_2O (20 mL). The Et_2O was extracted with H_2O (2 × 5 mL), the combined aqueous phase was cooled to 0 °C, and K_2CO_3 was added to pH 7. Then 1 M aqueous K_2CO_3 (6 mL) was added and the solution extracted with $CHCl_3$ (4 × 15 mL). The combined $CHCl_3$ phase was dried, filtered, and evaporated to an oil (1.26 g, 7.54 mmol), which was a 9/1 mixture of diastereomers. **28b** (1*R*,2β and 1*S*,2β; major diastereomer): TLC ($MeOH/CHCl_3$, 10/90) R_f 0.04; (HOAc/$MeOH/CHCl_3$, 4/9/87) R_f 0.27; ^1H NMR δ 1.30–2.00 (9 H, m), 2.10–2.30 (1 H, m), 2.17 (3 H, s), 2.45–2.55 (1 H, m), 3.60–3.70 (1 H, m), 3.76–3.83 (1 H, m); ^1H NMR (minor diastereomer) δ 2.16 (s), 2.75–2.85 (m), 3.98–4.06 (m); ^{13}C NMR δ 22.4, 27.5, 28.1, 29.9, 34.3, 37.3, 57.1, 57.5, 60.2, 211.7; mass spectrum, exact mass calcd for $C_{10}H_{17}NO$, *m*/*z* 167.1311, found 167.1319.

(1*S*)-2-Acetyl-9-(phenoxycarbonyl)-9-azabicyclo[4.2.1]nonane (27c and 28c). A solution of dihydroanatoxin (**27b** and **28b**) (from *N*-benzyldihydroanatoxin, **27a** and **28a**, 1.22 g, 4.74 mmol) in CH_2Cl_2 (11 mL) was cooled to 0 °C; then phenyl chloroformate (0.91 mL, 7.1 mmol) and 1 M aqueous K_2CO_3 (9 mL) were added. After 2.5 h, Et_2O (50 mL) was added, and the phases were separated. The organic phase was washed with 1 M aqueous HCl (20 mL) and 1 M aqueous K_2CO_3, dried, filtered, and evaporated. Column chromatography (EtOAc/hexane, 33/67) of the residue gave a mixture of **27c** and **28c** (617 mg, 45% yield from **27**/**28a**). The diastereomers could be separated chromatographically (EtOAc/hexane, 20/80). **27c**: TLC (EtOAc/hexane, 20/80) R_f 0.30; IR 1710 cm^{-1}; ^1H NMR δ 1.35–1.95 (7 H, m), 1.95–2.40 (3 H, m), 2.18, 2.19 (3 H, two s), 3.10–3.30 (1 H, m), 4.35–4.55 (1 H, m), 4.70–4.90 (1 H, m), 7.10–7.45 (5 H, m); ^{13}C NMR δ 22.5, 24.0, 24.6, 24.7, 25.3, 28.9, 31.5, 32.5, 33.2, 34.4, 54.1, 54.9, 55.0, 56.0, 56.8, 57.1, 121.3, 124.9, 128.9, 150.9, 151.5, 151.9, 208.4, 208.8. **28c**: bp 150 °C (0.10 torr); TLC (EtOAc/hexane, 20/80) R_f 0.18; IR 1710 cm^{-1}; ^1H NMR δ 1.40–2.65 (11 H, m), 2.21, 2.28 (3 H, two s), 4.40–4.60 (1 H, m), 4.70–4.90 (1 H, m), 7.05–7.40 (5 H, m): ^{13}C NMR δ 21.1, 21.3, 25.7, 26.0, 26.7, 27.1, 27.5, 32.4, 33.2, 33.6, 34.3, 55.8, 56.3, 56.5, 59.6, 59.8, 121.1, 124.6, 128.6, 128.7, 150.5, 150.8, 151.2, 152.0, 207.8, 208.4. Anal. ($C_{17}H_{21}NO_3$) C, H, N.

(1*S*)-2-Acetyl-9-(phenoxycarbonyl)-9-azabicyclo[4.2.1]-2-nonene (32a). A solution of *N*-(phenoxycarbonyl)dihydroanatoxin (**27c**/**28c**) (170 mg, 0.59 mmol), pinacolone (0.37 mL, 3 mmol), and triethylamine (0.54 mL, 3.9 mmol) in CCl_4 (5 mL) was cooled to 0 °C; then trimethylsilyl triflate (.68 mL, 3.7 mmol) was added dropwise. After 30 min, additional pinacolone (0.11 mL) and trimethylsilyl triflate (0.13 mL) were added. After 48 h triethylamine (0.30 mL) was added, the phases were separated and the solvent was evaporated. The residue was dissolved in hexane and clarified by centrifugation and the solution was evaporated (40 °C, 0.10 torr) to give crude silyl enol ethers **30a**/**31a**. A solution of these silyl enol ethers and $Pd(OAc)_2$ (128 mg) in CH_3CN (10 mL) was stirred for 42 h, then filtered, and evaporated. Column chromatography (EtOAc/hexane, 50/50) of the residue gave recovered ketone **27c**/**28c** (22 mg, 11%) and the enone **32a**: 107 mg, 69% yield; TLC (EtOAc/hexane, 20/80) R_f 0.12; ^1H NMR δ 1.60–1.90 (4 H, m), 2.10–2.60 (4 H, m), 2.30, 2.33 (3 H, s), 4.50–4.70 (1 H, m), 5.25–5.35, 5.40–5.50 (1 H, m), 6.87 (t, *J* = 6.1 Hz), and 6.94 (t, *J* = 5.8 Hz) total 1 H, 7.00–7.40 (5 H, m); mass spectrum, exact mass calcd for $C_{17}H_{19}NO_3$, *m*/*z* 285.1365, found 285.1361.

2-Acetyl-9-((*tert*-butyloxy)carbonyl)-9-azabicyclo[4.2.1]nonane [(1*S*)-27d,28d and (1*R*)-27d,28d]. A solution of dihydroanatoxin (**27b**/**28b**, 1.25 g, 5.67 mmol) and di-*tert*-butyl dicarbonate (1.7 g, 7.8 mmol) in MeOH (20 mL) was stirred for 8 h, Et_2O (100 mL) was added, and the solution was washed with 0.2 M aqueous H_3PO_4 (75 mL) and saturated aqueous $NaHCO_3$ (75 mL). The aqueous phases were extracted with Et_2O (50 mL) and the organic phases dried, filtered, and evaporated. MPLC (EtOAc/hexane, 20/80) gave pure α-Boc-dihydroanatoxin (**27d**, 73 mg, 5% yield from **27a**/**28a**), a mixture of **27d** and **28d** (50 mg, 3% yield), and after distillation pure β-Boc-dihydroanatoxin (**28d**, 1.06 g, 70% yield from **27a**/**28a**). **27d**: bp 110 °C (0.10 torr); TLC (EtOAc/hexane, 25/75) R_f 0.34; IR 1691, 1368 cm^{-1}; ^1H NMR δ 1.20–2.40 (10 H, m), 1.45, 1.49 (9 H, s), 2.14, 2.16 (3 H, s), 2.90–3.00, 3.10–3.20 (1 H, m), 4.10–4.20, 4.20–4.33 (1 H, m), 4.45–4.55, 4.57–4.67 (1 H, m); ^{13}C NMR δ 22.5, 22.6, 24.3, 24.7, 24.8, 28.4, 28.5, 29.0, 29.2, 32.1, 32.6, 33.8, 34.6, 54.1, 54.6, 54.8, 56.3, 56.6, 56.8, 79.1, 152.9, 153.4, 209.0, 209.5. Anal. ($C_{15}H_{25}NO_3$) C, H, N. **28d**: bp 110 °C (0.10 torr); TLC (EtOAc/hexane, 25/75) R_f 0.26; IR 1691, 1408 cm^{-1}; ^1H NMR δ 1.38–2.60 (11 H, m), 1.40, 1.44 (9 H, s), 2.21, 2.28 (3 H, s), 4.17–4.27, 4.33–4.43 (1 H, m), 4.45–4.53, 4.53–4.63 (1 H, m); ^{13}C NMR δ 21.9, 22.0, 26.3, 26.6, 27.5, 27.7, 28.2, 28.4, 32.8, 33.6, 33.9, 35.4, 55.6, 56.1, 60.9, 61.4, 79.0, 79.9, 153.0, 208.3. Anal. ($C_{15}H_{25}NO_3$) C, H, N.

2-Acetyl-9-((*tert*-butyloxy)carbonyl)-9-azabicyclo[4.2.1]-2-nonene [(1*S*)-32b and (1*R*)-32b]. β-Boc-dihydroanatoxin (**28d**, 380 mg, 1.42 mmol) in THF (5 mL) was added to a suspension of KH (from 241 mg of a 24.6% dispersion in oil, 1.48 mmol) in THF (2 mL). After 1 h the solution was cooled to 0 °C and triethylamine (0.40 mL, 2.87 mmol) and

trimethylsilyl chloride (.22 mL, 1.73 mmol) were added. After 20 min CH_2Cl_2 (30 mL) was added, the solution was washed with 1 M aqueous Na_2HPO_4/KH_2PO_4 (20 mL), the aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phase was dried, filtered, and evaporated to give the crude silyl enol ethers (436 mg, 90% yield). These ethers and $Pd(OAc)_2$ (367 mg) in CH_3CN (16 mL) were stirred for 42 h, during which time a Pd mirror formed. Filtration through silica (EtOAc/hexane, 33/67) followed by MPLC (EtOAc/hexane, 1/4) gave pure **27d** (72 mg, 19% recovery), a 1/4 mixture of **27d** and **28d** (46 mg, 12% recovery), and after distillation Boc-anatoxin (**32b**, 154 mg, 41% yield): bp 110 °C (0.10 torr); TLC (EtOAc/hexane, 25/75) R_f 0.22; IR 1691, 1667, 1400 cm^{-1}; ^1H NMR δ 1.36, 1.43 (9 H, s), 1.60–1.80 (3 H, m), 2.00–2.55 (5 H, m), 2.28 (3 H, s), 4.25–4.45 (1 H, m), 5.15–5.25 (1 H, m), 6.82 (1 H, t, J = 5.9 Hz); (1*S*)-**32b**; $[\alpha]^{24}_D$ +51.9° (*c* 0.795, CH_2Cl_2); (1*R*)-**32b**, $[\alpha]^{24}_D$ −47.2° (*c* 0.839, CH_2Cl_2); ^{13}C NMR δ 23.9, 25.2, 28.2, 28.5, 30.1, 31.2, 32.3, 52.8, 55.5, 79.0, 142.0, 150.1, 152.9, 197.5. Anal. ($C_{15}H_{23}NO_3$) C, H, N.

2-Acetyl-9-azabicyclo[4.2.1]-2-nonene [(1*S*)-2 and (1*R*)-1]. A solution of Boc-anatoxin (**32b**, 39 mg, 0.147 mmol) and trifluoroacetic acid (0.39 mL) in CH_2Cl_2 (5 mL) was stirred for 1 h, the solution was poured into cold saturated aqueous $NaHCO_3$ (10 mL); then $CHCl_3$ (20 mL) and 1 M aqueous K_2CO_3 (20 mL) were added. The phases were separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The organic phases were dried and filtered. This solution could be evaporated to give the free base. Alternatively a 1.2 M ethanolic HCl solution (1.5 mL) was added; the solution was stirred briefly, evaporated, and dried (25 °C, 0.10 torr, 15 h) to give anatoxin-*a* hydrochloride as a glass (29 mg, 97% yield). Anatoxin (free base): TLC ($MeOH/CHCl_3$, 10/90) R_f 0.05 (streaking); ^1H NMR δ 1.50–2.25 (7 H, m), 2.28 (3 H, s), 2.40–2.55 (2 H, m), 3.70–3.83 (1 H, m), 4.65 (1 H, d, J = 8.5 Hz), 6.88 (1 H, ddd, J = 1.2, 4.8, 7.0 Hz). Anatoxin hydrochloride: TLC ($MeOH/CHCl_3$, 10/90) R_f 0.05–0.12; UV (absolute EtOH) λ_{max} 226 nm, ϵ 10 700 (lit.[4c] UV (95% EtOH) λ_{max} 226 nm, ϵ 8500); ^1H NMR δ 1.75–2.00 (3 H, m), 2.20–2.75 (5 H, m), 2.32 (3 H, s), 4.27–4.40 (1 H, m), 5.15–5.25 (1 H, m), 7.12 (1 H, dd, J = 3.7, 7.7 Hz), 9.30–9.50 (1 H, s), 9.85–1 0.05 (1 H, s); ^{13}C NMR δ 23.6, 25.2, 27.5, 27.8, 30.3, 52.1, 58.3, 143.8, 145.4, 196.4; (1*S*)-2, $[\alpha]^{23}_D$ −46.3 (*c* 0.574, absolute EtOH); (1*R*-**1**, $[\alpha]^{24}_D$ +43.2 (*c* 0.676, absolute EtOH) [lit.[4c] $[\alpha]^{24}_D$ +36° (*c* 0.85, EtOH)].

2-Acetyl-9-azabicyclo[4.2.1]nonane [(1*S*)-27b,28b and (1*R*)-27b,28b] Hydrochloride. Boc-dihydroanatoxin (**27d/28d**, 148 mg) was converted to a 3/1 mixture of β- and α-dihydroanatoxin hydrochlorides (106 mg, 94% yield) by use of the procedure described for Boc-anatoxin. The amorphous solid was recrystallized from CH_2Cl_2/EtOAc to give pure β-dihydroanatoxin (**28b**) hydrochloride: mp 170–172 °C; TLC ($MeOH/CHCl_3$, 10/90) R_f 0.10–0.20 (streaking); ^1H NMR δ 1.50–2.40 (10 H, m), 2.17 (3 H, s), 2.62 (1 H, dd), 4.20–4.35 (1 H, m), 4.60–4.75 (1 H, m), 9.00–9.20 (1 H, s), 10.00–10.20 (1 H, s); ^{13}C NMR δ 21.5, 26.7, 27.1, 27.7, 30.9, 31.1, 55.4, 55.8, 58.1, 207.7. α-Dihydroanatoxin (**27b**) hydrochloride: TLC ($MeOH/CHCl_3$, 1/9, R_f 0.23–0.27); ^1H NMR δ 2.20 (s), 3.35–3.50 (m); ^{13}C NMR δ 21.5, 24.3, 24.6, 28.9, 31.2, 31.4, 52.7, 56.5, 57.6, 207.4.

2-Acetyl-9-(methoxy(trifluoromethyl)phenylacetyl)-9-azabicyclo-[4.2.1]-2-nonene [(1*S*)-32c and (1*R*)-32c]. A solution of anatoxin (from Boc-anatoxin, 45 mg, 0.17 mmol) and *N*-methylmorpholine (0.04 mL) was added to a solution of (−)-MTPA chloride[38] (75 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 1.5 h, CH_2Cl_2 (25 mL) was added, the solution was washed with 0.5 M aqueous H_3PO_4 (20 mL), the aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phase was dried, filtered, and evaporated to an oil. The diastereomeric ratio was determined by ^1H NMR and HPLC of this material. Column chromatography (EtOAc/hexane, 1/2) gives the pure amide **32c** (51 mg, 79% yield). Amide **32c** from (+)-anatoxin: TLC (EtOAc/hexane, 1/2) R_f 0.21; HPLC (CH_3CN/H_2O, 45/55, Ultrasphere (ODS 5 RP, 1.5 mL/min) t_R 18.6 min, 6.5% minor diastereomer; ^1H NMR δ 1.20–2.60 (8 H, m), 2.26, 2.35 (3 H, s), 3.60–3.70 (3 H, m), 4.70–4.90 (1 H, m) 4.93–5.04 (1 H, m), 6.70–6.78 (m) and 6.84 (t, J = 5.4 Hz) total 1 H, 7.35–7.60 (5 H, m). Anal. ($C_{20}H_{22}F_3NO_3$) C, H, N. Amide **32c** from (−)-anatoxin: TLC (EtOAc/hexane, 1/2) R_f 0.21; HPLC (as above) t_R 15.1 min, 2% minor diastereomer; ^1H NMR δ 1.50–2.55 (8 H, m), 1.77 (3 H, s), 3.70 (3 H, q, J = 2.4 Hz), 4.70–4.85 (1 H, m), 5.47 (1 H, d), 6.27 (1 H, t, J = 5.5 Hz), 7.20–7.60 (5 H, m). Anal. ($C_{20}H_{22}F_3NO_3$) C, H, N.

Stereocontrolled Total Synthesis of (−)-Picrotoxinin and (+)-Coriamyrtin via a Common Isotwistane Intermediate

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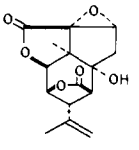
Abstract: Stereocontrolled total synthesis of (−)-picrotoxinin (**1**) and (+)-coriamyrtin (**2**), toxic sesquiterpenoids of plant origin, is described, utilizing isotwistane compounds as common and key intermediates.

Picrotoxin, the poisonous principle isolated first in 1811 from the plant *Menispermum cocculus*,[1] is a molecular compound composed of toxic picrotoxinin (**1**) and nontoxic picrotin. It took about 150 years for the complex structure of **1** to be elucidated.[2] Picrotoxinin (**1**) has been known not only as one of the most toxic compounds of plant origin but also as the substance indispensable to the neuropharmacological studies.[3] Coriamyrtin (**2**), the toxin isolated initially in 1864 from the European *Coriaria* species[4a] and later from the same species native in Japan,[4b] belongs to the picrotoxane group, and the unique structure **2** was established in 1964.[5] The biological properties of **2** are known to be similar to those of **1**.[6] Total synthesis of (−)-**1**[7] and (−)-picrotin[8] by Corey and Pearce was reported in 1979 and in 1980, respectively, and that of racemic **2**[9] by Inubushi et al. in 1982.



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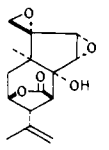

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