Asymmetric Synthesis of (−)-Anatoxin-a via an Asymmetric Cyclization Using a New Ligand for Pd-Catalyzed Alkylations

Barry M. Trost* and Johan D. Oslob

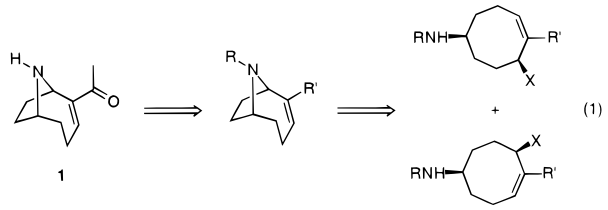
Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received October 14, 1998

Abstract: Palladium-catalyzed asymmetric allylic alkylations have been explored in the context of medium-sized ring substrates, intramolecular vs intermolecular processes involving attack on a formally meso π-allyl intermediate in the desymmetrization, and the presence of electron-withdrawing groups on the cationic π-allylpalladium intermediate. The synthesis of anatoxin-a, also known as the "very fast death factor", raises all of these questions. Ligands derived from *trans*-1,2-diaminocyclohexane and 2-diphenylphosphinobenzoic acid effect asymmetric alkylations with an allyl substrate bearing an electron-withdrawing group. On the other hand, a new type of ligand wherein the diamine is derivatized with both 2-diphenylphosphinobenzoic acid and 2-picolinic acid was required to effect asymmetric cyclization to form the 9-azabicyclo[4.2.1]non-2-ene system. A total synthesis of anatoxin-a from 5-hydroxy-1,8-nonadiene employing a metathesis reaction to form the cycloheptene and a palladium-catalyzed asymmetric cyclization to form the bicyclic ring system is achieved in 15% overall yield.

As a result of its potency to induce respiratory paralysis, the naturally occurring alkaloid anatoxin-a (**1**) is often referred to as "very fast death factor". Its isolation was originally reported in 1977[1] and the structure established by X-ray crystallographic analysis.[2] It exerts its action by depolarizing the postsynaptic acetylcholine receptors.[3] Owing to its biological activity and unusual 9-azabicyclo[4.2.1]nonane skeleton, a number of synthetic routes has been devised.[4] Of the routes that provide an asymmetric synthesis, almost all utilize a starting material from the "chiral pool". A de novo asymmetric synthesis provides greater flexibility by providing equivalent access to either enantiomer for exploration of biological activity. The one route that constitutes a de novo asymmetric synthesis involved the use of a stoichiometric amount of a chiral base in the enantioselective step.[5] To our knowledge, a synthesis of anatoxin-a introducing the chirality by an asymmetric catalytic process has not yet been recorded.

Our interest in asymmetric metal-catalyzed allylic alkylations led us to consider the cyclization shown in eq 1, a type of cyclization previously explored by Danheiser et al. in their synthesis of racemic anatoxin-a.[6] The attractiveness of this strategy for us stemmed, in large part, from the numerous questions it would answer with respect to asymmetric metal-catalyzed allylic alkylations.[7,8] Could eight-membered rings be employed as suitable substrates? Medium-sized rings have generally proven to be poor substrates in achiral metal-catalyzed allylic alkylations for conformational reasons. Could cyclizations be accomplished asymmetrically since all previous analogous deracemizations performed were intermolecular? What type of R and R′ groups could be tolerated? If R′ were to be a carbonyl substituent, conjugate addition−elimination might be anticipated to dominate. To answer these questions, we chose to undertake a synthesis of anatoxin-a. In this exercise, we developed a new ligand for asymmetric palladium-catalyzed reactions that complements our bidentate bis-phosphine ligands,[7] which proved pivotal to the success of this strategy.



(1)

Model Study

In considering the asymmetric cyclization of eq 1, two R′ groups appeared most likely, Br and COR. The vinyl bromide-allylic ester **3** was initially tested with a variety of nitrogen nucleophiles.[9] No desired alkylation occurred under a variety of conditions. In considering a carbonyl substituent, the high reactivity of vinyl ketones, such as **4a**, toward Michael additions of nitrogen nucleophiles led us to focus on the ester **4b** as a

(1) Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Starvik, B. *Can. J. Chem.* **1977**, *55*, 1367.

(2) (a) Huber C. S *Acta Crystallogr., Sect. B* **1972**, *78*, 2577. (b) Koskinen, A. M. P.; Rapaport, H. *J. Med. Chem.* **1985**, *28*, 1301.

(3) (a) Aronstam, R. S.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4639. (b) Swanson, K. L.; Allen, C. N.; Aronstam, R. S.; Rapoport, H.; Albuquerque, E. X. *Mol. Pharmacol.* **1986**, *29*, 250.

(4) For a recent review of synthetic routes to **1**, see: Mansell, H. L. *Tetrahedron* **1996**, *52*, 6025. For most recent syntheses, see: Oh, C.-Y.; Kim, K.-S.; Ham, W.-A. *Tetrahedron Lett.* **1998**, *39*, 2133. Parsons, P. J.; Camp, N. P.; Underwood, J. M.; Harvey, D. M. *Tetrahedron* **1996**, *52*, 11637.

(5) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1995**, 831.

(6) Danheiser, R. L.; Morin, J. M., Jr.; Salaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066.

(7) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(8) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(9) For comparison, see: Organ, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283. Organ, M. G.; Miller, M. *Tetrahedron Lett.* **1997**, *38*, 8181. Moreno-Manas, M. Pleixats, R.; Roglans, A. *Liebigs Ann.* **1995**, 1807. Nwokogu, G. C. *Tetrahedron Lett.* **1984**, *25*, 3263.

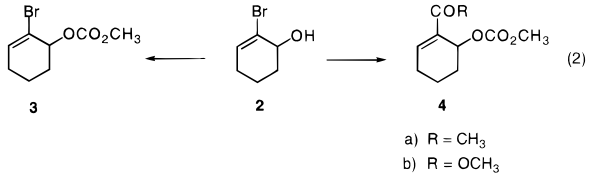
10.1021/ja983617d CCC: $18.00
Published on Web 03/19/1999

Table 1. Pd-Catalyzed Alkylations with Diester **4b**

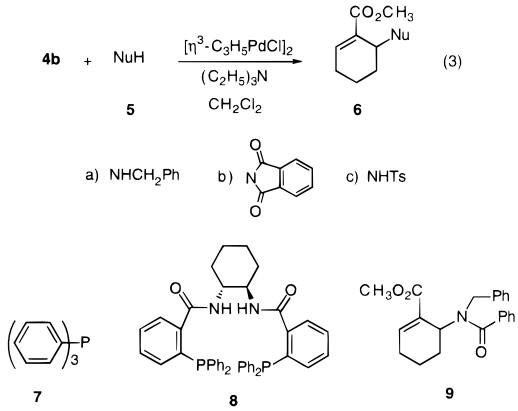
entry	catalyst	NuH	yield (%)[a]	ee (%)[b]
1[c]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**7**)	**5a**	85	na
2[d]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**8**)	**5a**	97	58[e]
3[f]	none	**5a**	60	na
4[c]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**7**)	**5b**	87	na
5[d]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**8**)	**5b**	93	97
6[f]	none	**5b**	nr	na
7[c]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**7**)	**5c**	85	na
8[d]	$[\eta^3\text{-}C_3H_5PdCl]_2$ (**8**)	**5c**	93	97[g]
9[f]	none	**5c**	nr	na

[a] Isolated yields; nr = no reaction. [b] na = not applicable. [c] 2.5 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, 15 mol % **7**, 200 mol % NuH, 200 mol % $(C_2H_5)_3N$, CH_2Cl_2, room temperature. [d] 2.5 mol % $[\eta^3\text{-}C_3H_5PdCl_3]_2$, 7.5 mol % **8**, 200 mol % NuH, 200 mol % $(C_2H_5)_3N$, CH_2Cl_2, room temperature. [e] Determined by chiral HPLC of *N*-benzoyl derivative **9**. [f] 200 mol % $(C_2H_5)_3N$, CH_2Cl_2, room temperature. [g] Determined by chiral HPLC.

poorer Michael acceptor.[10] It was available from the alcohol **2**[11] in one step by first converting the alcohol to its alkoxide with sodium hydride, and then performing metal−halogen exchange with *sec*-butyllithium, followed by quenching the dianion with methyl chloroformate (eq 2).



The reaction of **4b** with a variety of nitrogen nucleophiles was explored as summarized in eq 3 and Table 1. In stark contrast with vinyl bromide **3**, the ester **4b** reacted without complications with both achiral (i.e., **7**) and chiral (i.e., **8**) ligands (Table 1). With benzylamine as the nucleophile, the

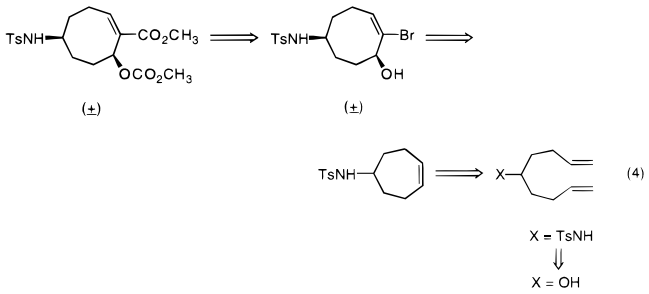


reaction proceeds at room temperature with excellent yields. While the product was obtained nearly quantitatively with the chiral ligand, the ee was only 58%. To determine this ee by chiral HPLC, we had to derivatize the product with benzoyl chloride (DMAP, C_5H_5N, CH_2Cl_2) and analyze this derivative **9**. Two pathways exist for reaction with benzylamine in the absence of a metal catalyst: (1) direct S_N2 substitution and (2) Michael addition followed by elimination. While direct substitution of an allylic carbonate seemed unlikely, the facility of Michael additions made the latter possibility worrisome. To check the background reactions, which would lead to racemic product, we exposed substrate **4b** to benzylamine under identical conditions save for the catalyst. Not surprisingly, a 60% yield of the adduct **6a** was obtained—an observation suggesting that the ee of entry **2** was a reflection of the ee of the metal-catalyzed process superimposed upon the background reaction which produces racemic product.

Turning to phthalimide and *p*-tosylamide as pronucleophiles, we established that no reaction occurs in the absence of a catalyst (Table 1, entries 6 and 9). On the other hand, both react in the presence of a palladium catalyst with both an achiral (entries 4 and 7) and a chiral ligand (entries 5 and 8). Satisfyingly, the substitutions with the "standard" chiral ligand **8** gave an excellent ee in both cases (97%). Armed with this information, we chose the tosylamide as the nucleophile for the anatoxin-a synthesis. The fact that no detectable background reaction occurred in the intermolecular process does not guarantee that such a non-metal-catalyzed reaction would not occur intramolecularly, especially since it involves formation of a five-membered ring. The experimental test is required to resolve the question.

Synthesis of Cyclization Substrate

Our strategy for the synthesis of the cyclization substrate is depicted in eq 4. Scheme 1 outlines the synthesis. We chose to



utilize a metathesis strategy, starting from the known alcohol **10**[12] prepared in one step from the Grignard reagent derived from 4-bromo-1-butene and ethyl formate. The metathesis of the diene **11**, using Grubbs' catalyst[13] with the protected amide, proceeded uneventfully to give the cycloheptene **12**. Dibromocyclopropanation of cycloheptene **12**, under classical conditions, gave an inseparable 3.5:1 ratio of the dibromocyclopropanes, tentatively assigned as *exo*-**13** and *endo*-**13,**[14] in excellent yield. An attempt to effect this reaction on a substrate corresponding to **12** but lacking the *N*-tosyl group failed.

The solvolytic ring opening of the dibromocyclopropanes **13** should preferentially lead to the *trans*-cyclooctenes,[15] for which there can be eight isomers because of the presence of three stereogenic centers/planes (one of which is the *trans*-alkene since the two enantiomers of *trans*-cyclooctene are stable at ambient

(10) For reviews, see: *The Chemistry of Enones*; Patai, S., Rapporport, Z., Eds.; Wiley: New York, 1989; Part 1. Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, pp 1−67.

(11) Skell, P. S.; Sandler, S. R. *J. Am. Chem. Soc.* **1985**, *80*, 2024.

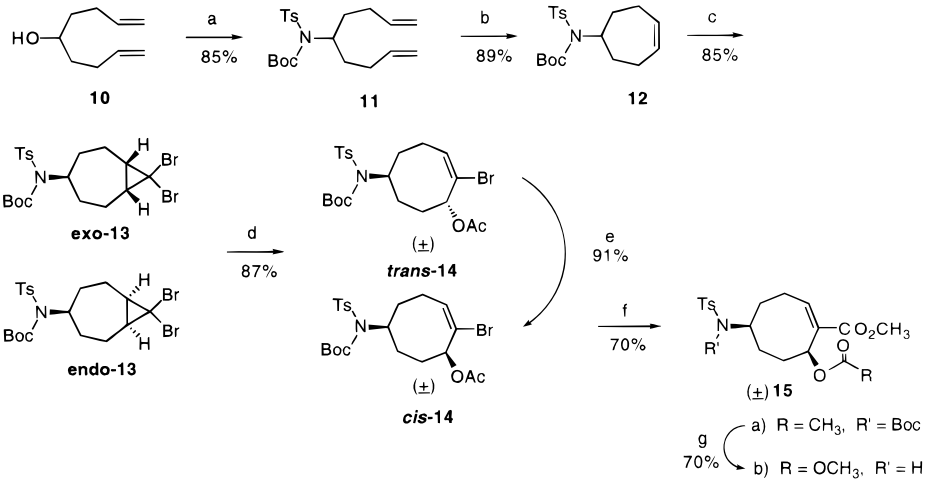
(12) Brown, H. C.; Negishi, E.; Dickason, W. C. *J. Org. Chem.* **1985**, *50*, 520.

(13) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. Grubbs, R. H.; Miller, S. J.; Fu, G. *Acc. Chem. Res.* **1995**, *28*, 446.

(14) The configurations of the two diastereomers were assigned by ^1H NMR. For the use of similar determinations of structures of closely related bicyclo[5.1.0]octane derivatives, see: (a) Cope, A. C.; Moon, S.; Park, C. H. *J. Am. Chem. Soc.* **1962**, *84*, 4843. (b) Taylor, M. D.; Minaskanian, G.; Winzernberg, K. N.; Satone, P.; Smith, A. B. *J. Org. Chem.* **1982**, *47*, 3960. See also ref 6.

(15) (a) De Puy, C. H.; Schnack, L. G.; Hausser, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 3343. (b) Reese, C. B.; Shaw, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2422. (c) Loozen, H. J.; Haan, J. W.; Buck, H. M. *J. Org. Chem.* **1977**, *42*, 418.

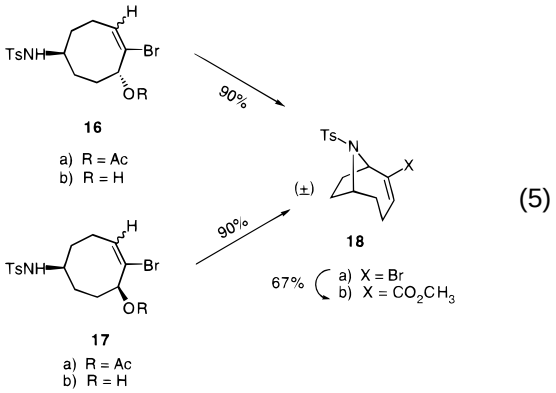
Scheme 1. Synthesis of Cyclization Substrate[a]



[a] Conditions: (a) TsNHBoc, Ph_3P, DIAD, PhH, room temperature. (b) $PhCH{=}Ru(Cl)_2[(C_6H_{11})_3P]_2$, $PhCH_3$, reflux. (c) $CHBr_3$, KOC_4H_9-t, pentane, −15 °C. (d) (i) AgOAc, HOAc, reflux; (ii) $(Boc)_2O$, DMAP, $(C_2H_5)_3N$, CH_2Cl_2. (e) (i) K_2CO_3, CH_3OH, room temperature; (ii) Ph_3P, HOAc, DIAD, PhH, room temperature. (f) CO, CH_3OH, 5% $(Ph_3P)_4Pd$, $(C_2H_5)_3N$, DMPU, 100 °C. (g) (i) K_2CO_3, CH_3OH, room temperature; (ii) n-C_4H_9Li, THF, −78 °C then $ClCO_2CH_3$; (iii) CF_3CO_2H, CH_2Cl_2, room temperature. <

conditions). In the Danheiser synthesis, opening with silver tosylate occurred only to form the *trans*-cyclooctenes, which subsequently had to be isomerized to the thermodynamically more stable *cis*-isomers. We were hopeful that solvolytic ring opening could be accompanied by trans−cis double bond isomerization in a silver-catalyzed process.

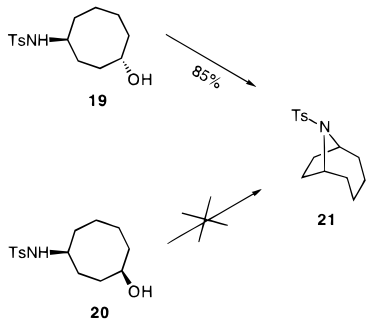
Exposure of the mixture of cyclopropanes **13** to silver acetate in refluxing acetic acid under normal laboratory light gave an 88% yield of a separable mixture of two acetates, **16a** (isolated in 73% yield) and **17a** (isolated in 15% yield), in a 5:1 ratio. To determine the alkene geometry, we subjected the alcohols **16b** and **17b** derived from both compounds to cyclization under Mitsunobu conditions (Ph_3P, DIAD, PhH, room temperature). Both did cyclize to the anatoxin skeleton **18a** (eq 5). The vinyl



(5)

bromide was carbonylated as for *cis*-**14** to generate the ester **18b**, which provides a route to racemic anatoxin-a. Since the *trans*-cyclooctenes cannot cyclize to the bicyclic compound **18a**, this result suggests both isomers have a *cis*-alkene geometry. The fact that both cis and trans amide alcohols cyclize suggests that cyclization is proceeding by both an S_N2 and an S_N2' mechanism, the latter making possible a displacement on the same face of the allyl unit from which the leaving group departs.[16]

This interpretation is reinforced by performing the Mitsunobu cyclization on the saturated alcohols **19** and **20** derived from catalytic hydrogenolysis and hydrogenation of alcohols **16b** and **17b**. Subjecting alcohol **19** derived from the major solvolysis product **16a** to the same Mitsunobu conditions smoothly gave the known 9-azabicyclo[4.2.1]nonane **21**[17] (eq 6). On the other



(6)

hand, the alcohol **20** derived from the minor solvolysis product **17a** gave no cyclization product. These results confirm the trans and cis relationships for **19** and **20,** respectively, as depicted.

Thus, the major solvolysis product, after reinstalling the Boc group,[18] was isolated in 72% yield and can be assigned as the *cis*-alkene *trans*-acetoxy amido stereochemistry depicted in *trans*-**14**. The minor solvolysis product, after reinstalling the Boc group, was isolated in 15% yield and can be assigned as depicted in *cis*-**14**. For the palladium-catalyzed cyclization, the *cis*-acetoxy amido relationship is required. Thus, the major diastereomer *trans*-**14** was inverted to give *cis*-**14**. Interestingly, palladium-catalyzed carbonylation[19] of *cis*-**14** proceeded without involvement of the allylic ester to give **15a**. The lack of reactivity of the allylic ester may be taken as an omen of things to come in terms of our subsequent cyclization efforts. In any event, the desired functionalized cyclooctane was efficiently available in 35% overall yield from the known alcohol **10**. In anticipation of the sluggish reactivity of an allylic acetate, the carbonate leaving group was installed to give the cyclization substrate in 70% yield from **15** and 25% overall yield from **10**.

(16) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1.

(17) Barleunga, J.; Jimenez, C.; Najera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 721.

(18) The Boc group is necessary later in the synthesis, for example, in the metal-catalyzed carbonylation reaction, in the conversion of *trans*-**14** to *cis*-**14** and when the carbonate is introduced.

(19) Tsuji, J. *Palladium Reagents and Catalysis. Innovations in Organic Synthesis*; Wiley: New York, 1995; p 341.

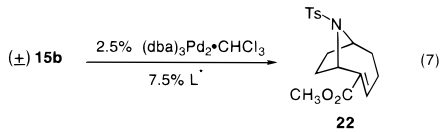
Table 2. Enantioselective Cyclization To Form 9-Azabicyclo[4.2.1]nonane Skeleton[a]

entry	ligand	solvent	temp	yield (%)	ee (%)
1	**8**	DMF	rt	nr[b]	
2	**8**	DMF	80 °C	65	13
3	**8**	DMF	100 °C	88	11
4	**8**	$PhCH_3$	100 °C	90	9
5	**23**	DMF	100 °C	75	0
6	**24**	DMF	100 °C	96	23
7	**24**	DMF	rt	96	63
8[c]	**24**	DMF	rt	92	56
9	**24**	DMF	0 °C	88	73
10	**24**	CH_2Cl_2	rt	96	83
11	**24**	CH_2Cl_2	0 °C	90	88
12	**27**	CH_2Cl_2	rt	45	0

[a] All reactions were run with 2.5 mol % $(dba)_3Pd_2CHCl_3$ and 7.5 mol % ligand at 0.067 M in substrate unless otherwise noted. [b] Isolated yields; nr = no reaction. [c] This run performed with 2.5 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$ and 5 mol % *N*-methylbenzylamine

Cyclization Studies

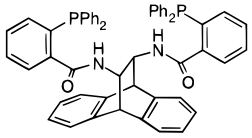
In contrast to our model studies, subjecting amido carbonate **15b** to a catalyst derived from our "standard" ligand **8** in DMF at room temperature led to no reaction (see eq 7 and Table 2, entry 1). Raising the temperature to 80 °C (entry 2), or better,



(7)

22

100 °C (entry 3), allowed reaction to proceed but with low ee. To establish whether the low ee derived from a noncatalytic background reaction, the substrate **15b** was heated in DMF at 100 °C, but no reaction was observed. To see if DMF was playing some role that reduced the ee, the reaction was performed in toluene (entry 4); however, very similar results were obtained. Switching to our larger bite angle ligand **23** led to even poorer ee (entry 5).



23

In surmising that the high temperature required for the cyclization might mean that our chiral pocket was too small to accommodate the substrate and therefore may be destroyed, we considered redesigning the pocket in order to accommodate more hindered substrates. Figure 1 depicts our working model. As this model suggests, increasing the size of R may lead to substrates that would not be readily accommodated by the chiral pocket. In fact, the 1,3-diphenylallyl system does *not* work well with this family of ligands. We therefore chose this substrate

(20) For some more recent P,N-ligands for asymmetric palladium-catalyzed reactions, see: Glaser, B.; Kunz, H. *Synlett* **1998**, *53*. Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073. Vasconcelos, I. C. F.; Rath, N. P.; Spilling, C. D. *Tetrahedron: Asymmetry* **1998**, *9*, 937. Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343. Saitoh, A.; Achiwa, K.; Morimoto, T. *Tetrahedron: Asymmetry* **1998**, *9*, 741. Sudo, A.; Saigo, K. *J. Org. Chem.* **1997**, *62*, 5508. Gilbertson, S. R.; Chang, C. W. T. *Chem. Commun.* **1997**, 975. Burckhardt, U.; Baumann, M.; Trabesinger, G.; Gramlich, V.; Togni, A. *Organometallics* **1997**, *16*, 5252. For some recent mechanistic work, see: Steinhagen, H.; Reggelin, M.; Helmchen, G. *Ang. Chem., Int. Ed. Engl.* **1997**, *36*, 2108. Liu, S.; Müller, J. F. K.; Neuberger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283.

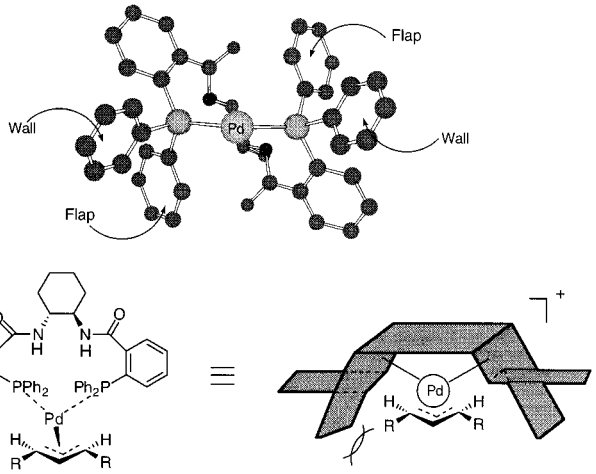


Figure 1. Model of chiral pocket and cartoon representation.

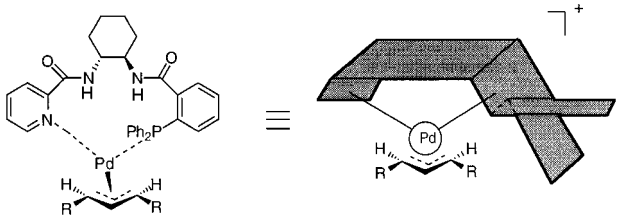
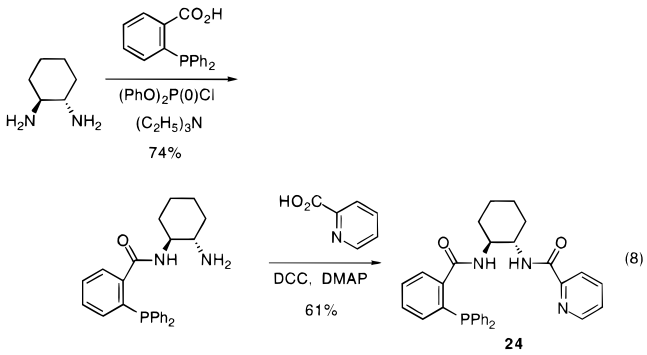


Figure 2. Model of modified pocket.

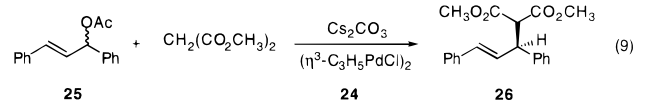
to explore a modified ligand design in which the steric hindrance on one side of the chiral pocket was removed, as depicted in Figure 2, to alleviate the unfavorable steric interaction between the R group and the "wall". The ligand **24** is easily accessed, as shown in eq 8. In complete contrast with the reactions of



(8)

24

1,3-diphenylallyl acetate **25** using a chiral palladium complex derived from ligand **8**, the palladium complex formed in situ from π-allylpalladium chloride dimer and ligand **24** reacted completely within 1 h at room temperature to give an 82% yield of alkylated product **26** (eq 9). Chiral HPLC established the ee



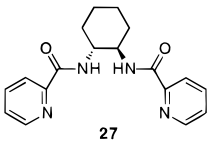
(9)

25 **24** **26**

as 86%, and the rotation established the configuration as *S*. Interestingly, this absolute configuration corresponds to that which would be expected from the *S,S*-ligand corresponding to **8**.[7] If this model is valid, then nucleophilic attack occurred anti to the nitrogen ligand, in contrast to other P,N-bidentate ligands, where attack is normally favored trans to phosphorus.[8,20]

Extension of this new ligand for the cyclization immediately showed a positive effect. The speed with which the reaction

occurred at 100 °C (Table 2, entry 6), wherein nearly a quantitative yield of cyclized product formed within 0.5 h, encouraged us to examine the reaction at room temperature (Table 2, entry 7). The reaction took only 3 h to go to completion and gave a 63% ee. Switching to π-allylpalladium chloride dimer as the Pd(0) source had no appreciable effect (entry 8). Lowering the temperature to 0 °C further enhanced the ee (entry 9). The best results were obtained by switching to methylene chloride (entries 10 and 11), wherein the cyclized product of 88% ee was isolated in 90% yield (entry 11). The requirement for one phosphine in the ligand was verified by the use of the diamine ligand **27**.[21] Cyclization proceeded at ambient temperature albeit more slowly (entry 12). However, no ee was detected in the product.



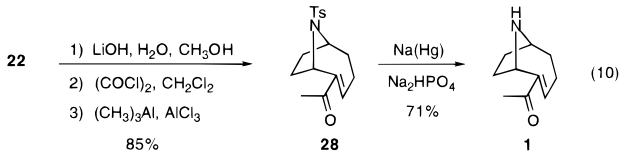
27

At this point, the absolute configuration of the product could not be assigned. It is interesting to note that the product with ligand **24**, derived from the *S,S*-diamine, had the same absolute configuration as the product with ligand **8,** derived from the *R,R*-diamine. The significance of this unexpected observation is tempered by the low ee in the latter case.

The availability of the trans amido ester *trans*-**14** as the major product of the solvolytic ring opening led us to consider the trans analogue of **15b** as a cyclization substrate. While the normal course of palladium substitutions proceed with overall net retention of facial selectivity,[22] net inversion has been seen in special circumstances.[23] We therefore prepared this trans analogue by an identical sequence, but to no avail. No cyclization product was observed. Thus, the usual requirement for substitution with net retention of facial selectivity holds in this case.

Final Stage of Synthesis

The synthesis of anatoxin-a from **22** proceeded straightforwardly as shown in eq 10. The ester was converted to the methyl



(10)

ketone via the acid chloride with trimethylaluminum in the presence of aluminum chloride.[25] Reductive desulfonylation[24,26] generated anatoxin-a. The sign of the rotation for both **28** and **1** indicated the absolute stereochemistry as depicted, which corresponds to the enantiomer of the natural product.[2] Obviously, simply switching the chirality of the ligand **24** to the *R,R*-enatiomer will provide the absolute configuration of the natural product. Our observed rotations of $[\alpha]^{25}_D = +14.7$ (*c* 1.40, $CHCl_3$) for **28** and $[\alpha]^{25}_D = -39.0$ (*c* 0.55, C_2H_2, OH) for **1** correspond to 89%[24] and 90% ee,[27] respectively, in excellent agreement with that determined by chiral HPLC of **22** (88% ee).

The observed absolute configuration of this cyclization does not correspond to the same sense of chirality as that seen in the intermolecular reaction of eq 9. In this case, if the model as depicted in Figure 2 is followed, nucleophilic attack occurs anti to phosphorus. However, any further discussion of this point must await considerably more study of this new ligand.

Conclusion

The synthesis of anatoxin-a has proven to be quite instructive. The rigidity of the chiral space created by our standard ligands proved to be too restrictive for the steric demands of the cyclooctenyl substrate **15b**. In this respect, this substrate behaved similarly to sterically demanding acyclic substrates. Examination of the model suggested a solution to this issue whereby the chiral space could be modified so it can better accommodate sterically demanding substrates. This proved to be exceptionally successful in the cyclization, whereby both a considerable rate enhancement (0 rather than 100 °C) and a good ee were observed. This new ligand differentiates itself from previously disclosed P,N-bidentate chiral ligands[8,20] by the length of the tether. In this case, bidentate coordination to palladium of **24** creates a 12-membered ring, in contrast to the more common 5−7-membered rings. As described for the bis-phosphine ligands, which also create macropalladacycles,[28] such large rings are anticipated to open the N−Pd−P bite angle, thereby deepening the chiral pocket. Thus, with these ligands, the enantiodifferentiation observed will be the result of the nature of the chiral space and the electronic influence of nitrogen vs phosphorus. A maximum enantioselectivity would derive if these two effects work in concert. Thus, medium-sized rings can be substrates for these asymmetric palladium-catalyzed reactions.

Previous work showed that the ionization of cyclic allylic esters that could generate meso π-allyl complexes do not form such symmetric structures initially—a phenomenon that leads to a memory effect.[29] The kinetically formed intermediate must equilibrate faster than it undergoes nucleophilic attack to obtain good ee's. Tethering the nucleophile, which will have the effect of speeding up the rate of its attack on the π-allylpalladium intermediate, might capture the kinetic species faster than it equilibrates, especially if the ring to be formed is five-membered.[30] This might be the source of the low ee with our standard ligand **8**. Replacing a phosphorus by a nitrogen in the ligand should decrease the electrophilicity of the π-allylpalladium species. In so doing, the rate of nucleophilic attack would also be slowed and, therefore, permit the required equilibration. On the other hand, the better donor properties of the nitrogen compared to those of phosphorus would speed up the ionization, which is, most likely, the rate-determining step. The new ligand, then, facilitates the ionization, therefore allowing the reaction to proceed at room temperature, and slows nucleophilic attack, therefore enhancing ee.

(21) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023. Chapman, R. L.; Vagg, R. S.; Watton, E. C.; Barnes, D. J. *J. Chem. Eng. Data* **1978**, *23*, 349.

(22) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 4215.

(23) For recent examples, see: Farthing, C. N.; Kocovsky, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661. Kraft, M. E.; Wilson, A. M.; Fu, Z.; Procter, M. J.; Dasse, O. A. *J. Org. Chem.* **1998**, *63*, 1748.

(24) Somfai, P.; Åhman, J. *Tetrahedron Lett.* **1992**, 3791.

(25) Arisawa, M. Torisawa, Y.; Kawahara, M.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1997**, *62*, 4327.

(26) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(27) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.

(28) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817. Also see: Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2386.

(29) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.

(30) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297.

The sequence also constitutes an efficient synthesis of (−)-anatoxin-a. The enantiomer of the natural product (and, by simple exchange of ligand stereochemistry in the enantioselectivity-determining step, the natural enantiomer as well) is available in 15% overall yield, with most of the intermediates being crystalline. In addition to the reaction providing either enantiomeric series, analogues would also be easily accessed. The key cyclization and the model studies indicate the utility of the ester-substituted allyl system in the metal-catalyzed asymmetric alkylation, despite the potential facility of the Michael addition. The high ee obtained clearly shows that any background reaction involving a Michael addition−elimination sequence does not compete significantly if the nucleophile is chosen appropriately. The compatibility of such an electron-withdrawing group on the π-allyl intermediate, even though the latter is cationic, significantly expands the scope of the substrates possible for asymmetric alkylations.

Experimental Section

General. All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. Anhydrous solvents were transferred by oven-dried syringe or cannula. Glass equipment was flame-dried under a stream of nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. THF and diethyl ether were distilled from sodium benzophenone ketyl. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Optical rotations were determined using a JASCO DIP-360 in 5-mm cells. Solvents for chromatography are listed as volume/volume ratios. Flash chromatography employed E. Merck silica gel (Kieselgel 60, 230−400 mesh). Analytical TLC was performed on Merck glass plates coated with silica using UV light, 1% $KMnO_4$ in water, and 0.25% *p*-anisaldehyde in ethanol for visualization. Infrared spectra were recorded on a Perkin-Elmer FT-IR Paragon 500. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 300 (300, 75 MHz). Bis(η^3-allyl)di-μ-chlorodipalladium(II) ($[C_3H_5PdCl]_2$),[31] palladium(0) tetrakis(triphenylphosphine) ($Pd(PPh_3)_4$),[32] and tris(dibenzylideneacetone)-dipalladium(0)-chloroform[33] ($Pd_2(dba)_3CHCl_3$) were prepared using literature procedures. Enantiomeric excesses were determined by HPLC analysis using chiral stationary-phase columns (Chiralpak AD and Chiralcel OD columns) with mixtures of heptane and 2-propanol as eluting solvents. Microanalyses were performed by M-H-W Laboratories, Phoenix, AZ. Mass spectra were provided by the Mass Spectrometry Facility at the University of California−San Francisco.

Preparation of Methyl 6-Phthalidimido-1-cyclohexenyl Carboxylate (6b). A degassed solution of 21.4 mg (0.1 mmol) of carbonate **4b** and phthalimide (29.4 mg, 0.2 mmol) in 0.5 mL of anhydrous CH_2Cl_2 was added to the catalyst generated from bis(η^3-allyl)di-μ-chlorodipalladium(II) (0.9 mg, 0.0025 mmol), ligand **8** (5.2 mg, 0.075 mmol), and triethylamine (28 μL, 0.2 mmol) in degassed CH_2Cl_2 (0.5 mL). After 5 h, evaporation of the solvent and flash chromatography (0−40% EtOAc in hexanes) yielded 26.6 (93%) of a white solid, mp 111−112 °C, $[\alpha]^{25}_D = +229.8$ (*c* 1.0, CH_2Cl_2), ee 97% as determined by HPLC (Chiracel, OD column). Elution times (flow rate 1 mL/min, 10% isopropyl alcohol in heptane, $\lambda = 254$ nm): (+)-isomer, 9.4 min; (−)-isomer, 10.8 min. IR (neat film from $CDCl_3$): 1773, 1710, 1391 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81−7.78 (m, AA′BB′, 2 H), 7.69−7.66 (m, AA′BB′, 2 H), 7.30 (m, 1 H), 5.12 (app t, $J = 2.4$ Hz, 1 H), 3.58 (s, 3 H), 2.41 (m, 1 H), 2.31 (m, 1 H), 2.07 (m, 1 H), 1.92 (m, 2 H), 1.68 (m, 2 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 169.9, 167.8, 146.1, 135.4, 133.7, 129.1, 124.7, 53.1, 18.8, 29.9, 27.1, 21.1. HRMS: calcd for $C_{16}H_{15}NO_4$, 285.1001; found, 285.1000.

Preparation of Methyl 6-Tosylamido-1-cyclohexenyl Carboxylate (6c). A degassed solution of 100 mg (0.467 mmol) of the carbonate **4b** and tosylamide (160 mg, 0.934 mmol) in 2.5 mL of anhydrous CH_2Cl_2 was added to the catalyst generated from bis(η^3-allyl)di-μ-chlorodipalladium(II) (4.3 mg, 0.0117 mmol), ligand **8** (24.0 mg, 0.035 mmol), and triethylamine (65 μL, 0.934 mmol) in degassed CH_2Cl_2 (2 mL). After 3 h, evaporation of the solvent in vacuo and flash chromatography (0−20% EtOAc in hexanes) yielded 137 mg (95%) of a white solid, mp 155−156 °C, R_f 0.38 (50% EtOAc in hexanes), $[\alpha]^{25}_D = +50.4$ (*c* 0.23, CH_2Cl_2), ee 97% as determined by HPLC (Chiracel, OD column). Elution times (flow rate 1 mL/min, 10% isopropyl alcohol in heptane, $\lambda = 254$ nm): (−)-isomer, 25.4 min; (+)-isomer, 27.5 min. IR (neat from $CDCl_3$): 3274, 1702, 1269, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, $J = 8.2$ Hz, 2 H), 7.32 (d, $J = 8.0$ Hz, 2 H), 7.13 (app t, $J = 3.1$ Hz, 1 H), 4.63 (d, $J = 5.4$ Hz, 1 H) 3.42 (s, 3 H), 2.43 (s, 3 H), 2.35−2.05 (m, 3 H), 1.65 (m, 2 H), 1.46 (m, 1 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 161.5, 140.9, 138.4, 132.7, 124.7, 124.2, 122.7, 46.8, 42.1, 23.6, 20.9, 16.7, 10.9. Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19. Found: C, 58.00; H, 6.02.

Preparation of 5-(*N*-Tosyl-*N*-boc-amido)-1,8-nonadiene (11). Diisopropyl azodicarboxylate (13.26 mL, 68.6 mmol) was added dropwise to a solution of dienol **10**[12] (7.70 g, 54.9 mmol), triphenylphosphine (21.61 g, 82.4 mmol), and TsNHBOC (20.87 g, 76.9 mmol) in anhydrous benzene (200 mL) under nitrogen at room temperature. After the solution was left to stand overnight, silica gel was added to the reaction mixture, and the solvent was removed in vacuo. Flash chromatography (0−10% EtOAc in hexanes) yielded 18.4 g (85%) of a colorless oil, R_f 0.63 (10% EtOAc in hexanes). IR (neat film from $CDCl_3$): 1726, 1355, 1279, 1254, 1153, 1088 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, $J = 8.3$ Hz, 2 H), 7.29 (d, $J = 8.0$ Hz, 2 H), 5.82 (m, 2 H), 5.04 (d, $J = 18.8$ Hz, 2 H), 4.99 (d, $J = 11.0$ Hz, 2 H), 4.43 (m, 1 H), 2.43 (s, 3 H), 2.09 (br m, 6 H), 1.81 (m, 2 H), 1.37 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 152.6, 145.6, 139.4, 139.2, 130.6, 129.9, 116.6, 85.5, 60.7, 34.4, 32.5, 29.4, 23.0. Anal. Calcd for $C_{21}H_{31}NO_4S$: C, 64.09; H, 7.94. Found: C, 64.22; H, 8.05.

Preparation of 5-(*N*-Tosyl-*N*-boc-imido)-1-cycloheptene (12). Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride[13] (305 mg, 0.388 mmol) in anhydrous degassed toluene (20 mL) was added to a solution of diene **11** (7.63 g, 4.73 mmol) in toluene (630 mL). The resulting mixture was stirred at reflux under nitrogen for 2 h, the solvent evaporated, and the residue purified by flash chromatography (0−20% EtOAc in hexanes) to yield 6.31 g (89%) of a white solid, mp 95−97 °C, R_f 0.63 (10% EtOAc in hexanes). IR (neat film from $CDCl_3$): 1727, 1356, 1279, 1256, 1153, 1090 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (m, 4 H), 7.29 (d, $J = 8.5$ Hz, 2 H), 5.82 (m, 2 H), 4.44 (m, 1 H), 2.43 (s, 3 H), 2.25 (m, 2 H), 2.10 (m, 4H), 1.89 (m, 2 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 152.5, 15.4, 139.8, 133.2, 130.8, 129.2, 85.5, 65.1, 34.1, 29.4, 27.4, 23.0. Anal. Calcd for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.45. Found: C, 62.61; H, 7.55.

Preparation of 4-(*N*-Tosyl-*N*-boc-imido)-8,8-dibromobicyclo-[5.1.0]octane (13). A cold (−15 °C) solution of bromoform (8.66 mL, 9.902 mmol) in pentane (20 mL) was added dropwise during 1 h to a −15 °C suspension of alkene **12** (3.62 g, 9.90 mmol) and potassium *tert*-butoxide (14.04 g, 118.82 mmol) in pentane (80 mL). After the addition, the reaction mixture was allowed to reach ambient temperature and the quenched with water. After the organic phase was dried ($MgSO_4$) and concentrated in vacuo, evaporation of the solvent and flash chromatography (0−20% EtOAc in hexanes) yielded 4.52 g (85%) of an inseparable 3.5:1 mixture of *exo*-**13** and *endo*-**13** as a white solid, mp 155−157 °C. IR (neat film from $CDCl_3$): 1732, 1459, 1360, 1281, 1152, 1089 cm^{-1}. ^{1}H NMR (selected signals, 300 MHz, $CDCl_3$): δ 7.78 (d, $J = 8.5$ Hz, 2 H, *endo*-**13**), 7.74 (d, $J = 8.5$ Hz, 2 H, *exo*-**13**), 7.29 (d, $J = 8.0$ Hz, 2 H, *endo*-**13** and *exo*-**13**), 4.69 (m, 1 H, *endo*-**13**), 4.29 (app tt, $J = 11.9$ Hz, $J = 3.3$ Hz, 1 H, *exo*-**13**), 2.43 (s, 3 H, *endo*-**13** and *exo*-**13**), 1.33 (s, 9 H, *endo*-**13** and *exo*-**13**). ^{13}C NMR (75.46 MHz, $CDCl_3$) for *endo*-**13**: δ 152.5, 145.8, 140.0, 130.9, 129.2, 85.9, 55.8, 40.5, 34.0, 31.8, 30.8, 29.3, 24.8. ^{13}C NMR (75.46 MHz, $CDCl_3$) for *exo*-**13**: δ 152.4, 145.6, 139.6, 130.9, 129.1, 85.9, 64.1, 39.6, 34.8, 33.9, 29.3, 26.8, 23.0. Anal. Calcd for $C_{20}H_{27}Br_2NO_4S$: C, 44.71; H, 5.06. Found: C, 44.87; H, 4.83.

Preparation of *cis* (17) and *trans* (16)-1-Bromo-5-(*N*-tosylamido)-8-acetoxy-(*E*)-cyclooctene. A 3.5:1 mixture of *gem*-dibromocyclopropyl derivatives *exo*-**13** and *endo*-**13** (4.00 g, 6.98 mmol) and silver

(31) Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 342.
(32) Colson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
(33) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.

acetate (2.33 g, 14.0 mmol) in 8 mL of acetic acid was stirred at reflux overnight. After cooling, the reaction was cautiously added to a saturated sodium bicarbonate solution and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (0−30% EtOAc in hexanes) yielded 2.13 g (73%) of **16** and 0.43 g (15%) of **17** as white solids.

Characterization Data for 16. R_f 0.50 (50% EtOAc in hexanes), mp 133−135 °C. IR (neat film from $CDCl_3$): 3278, 1741, 1238, 1160, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.43 (m, 1 H), 5.11 (d, J = 7.4 Hz, 2 H), 2.38 (m, 1 H), 2.42 (s, 3 H), 2.36 (m, 1 H), 2.08 (s, 3 H), 2.03 (m, 1 H), 1.71 (br m, 4 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 171.6, 145.1, 139.0, 133.1, 131.4, 128.7, 126.7, 72.8, 53.4, 37.3, 32.0, 31.0, 26.1, 23.0, 22.3. Anal. Calcd for $C_{17}H_{22}BrNO_4S$: C, 49.09; H, 5.33. Found: C, 49.26; H, 5.21.

Characterization Data for 17. R_f 0.63 (50% EtOAc in hexanes), mp 152−153 °C. IR (neat): 3279, 1741, 1445, 1318, 1236, 1160, 1094, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 6.16 (app t, J = 8.7 Hz, 1 H), 5.41 (m, 1 H), 4.54 (d, J = 8.0 Hz, 1 H), 3.21 (m, 1 H), 2.43 (s, 3 H), 2.10 (s, 3 H), 1.75 (br m, 5 H), 1.42 (m, 1 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 171.6, 145.2, 139.5, 133.8, 131.5, 128.6, 125.3, 71.8, 56.1, 38.7, 34.0, 30.2, 28.0, 23.0, 22.3. Anal. Calcd for $C_{17}H_{22}BrNO_4S$: C, 49.09; H, 5.33. Found: C, 49.12; H, 5.51.

Preparation of *cis*- and *trans*-1−5-(*N*-Tosyl-*N*-boc-imido)-8-acetoxy-(*E*)-cyclooctene (14). A crude 5:1 mixture of **16** and **17** obtained from a thermal electrocyclic ring opening of 2.0 g (3.72 mmol) of a 3.5:1 mixture of *exo*-**13** and *endo*-**13** (vide supra) was dissolved in CH_2Cl_2 (20 mL). Triethylamine (1.04 mL, 7.44 mmol), DMAP (128 mg, 1.05 mmol), and di-*tert*-butyl-dicarbonate (1.62 g, 7.44 mmol) were added, and the mixture was stirred at room temperature under nitrogen for 4 h. Evaporation of the solvent and flash chromatography (0−40% EtOAc in hexanes) yielded 1.38 g (72%) of *trans*-**14** and 288 mg (15%) of *cis*-**14** as white solids.

Characterization Data for *trans*-14. Mp 138−140 °C. IR (neat film from $CDCl_3$): 1728, 1357, 1281, 1237, 1154, 1089, 1047 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 6.15 (dd, J = 3.6 Hz, J = 3.0 Hz, 1 H), 5.41 (d, J = 10.4 Hz, 1 H), 4.50 (m, 1 H), 2.48 (m, 1 H), 2.43 (s, 3 H), 2.12 (s, 3 H), 1.91 (m, 2 H), 1.81 (m, 3 H), 1.36 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 169.7, 150.6, 144.0, 137.6, 130.6, 129.3, 127.6, 126.2, 84.3, 72.1, 57.2, 33.2, 32.8, 31.8, 27.9, 25.7, 21.6, 20.9. Anal. Calcd for $C_{22}H_{20}BrNO_6S$: C, 51.16; H, 3.90. Found: C, 51.39; H, 5.78.

Characterization Data for *cis*-14. Mp 144−146 °C. IR (neat): 1732, 1455, 1360, 1235, 1151, 1089, 1046 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.23 (app t, J = 8.7 Hz, 1 H), 5.59 (m, 1 H), 4.35 (m, 1 H), 2.43 (s, 3 H), 2.33 (m, 2 H), 2.11 (s, 3 H), 2.05 (m, 1 H), 1.85 (m, 5 H), 1.34 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 171.6, 152.3, 145.7, 139.3, 134.1, 130.9, 129.2, 125.3, 86.0, 71.5, 61.0, 36.7, 34.1, 30.6, 29.4, 29.0, 23.0, 22.3. Anal. Calcd for $C_{22}H_{20}BrNO_6S$: C, 51.16; H, 5.90. Found: C, 51.42; H, 6.04.

Conversion of *trans*-14 to *cis*-14. Potassium carbonate (0.739 g, 5.35 mmol) was added to 1.38 g (2.67 mmol) of *trans*-**14** in methanol (40 mL). After 1 h at room temperature, the reaction mixture was filtered through a plug of silica gel, and the solvent was removed in vacuo, yielding 1.27 g (quantitative) of the intermediate alcohol. IR (KBr): 1727, 1670, 1572, 1406, 1350, 1153, 1088 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.5 Hz, 2 H), 6.14 (m, 1 H), 5.59 (m, 1 H), 4.50 (m, 2 H), 2.43 (s, 3 H), 2.37−2.11 (m, 2 H), 1.96−1.69 (m, 6 H), 1.34 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 145.9, 139.6, 132.6, 127.4, 124.3, 124.1, 122.5, 79.1, 64.7, 52.3, 29.4, 28.5, 28.0, 21.9, 20.0, 15.3. The alcohol was dissolved in 50 mL of anhydrous benzene, and triphenylphosphine (2.10 g, 8.01 mmol) and acetic acid (0.459 mL, 8.01 mmol) were added at room temperature. To the resulting mixture was added dropwise 1.03 mL (5.34 mmol) of diisopropyl azodicarboxylate, and the solution was stirred at ambient temperature for 3 h. Evaporation of solvent and flash chromatography (0−30% EtOAc in hexanes) yielded another 1.25 g of *cis*-**14** (overall yield from *exo*-**13** and *endo*-**13**, 80%). The same protocol could be used to convert *cis*-**14** to *trans*-**14**.

Preparation of Methyl *cis*-5-(*N*-Tosyl-*N*-boc)-8-acetoxy-1-cyclooctenyl Carboxylate (15a). A stainless steel autoclave was charged with a solution of *cis*-**14** (1 g, 1.94 mmol), $Pd(PPh_3)_4$ (112 mg, 0.097 mmol), triethylamine (405 μL, 2.90 mmol), and 1.66 mL of methanol in 6 mL of DMPU. The autoclave was purged and pressurized with CO at 600 psi. After the solution was stirred at 100 °C for 14 h, the pressure was released, and the reaction mixture was diluted with water and extracted three times with ether. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (0−30% EtOAc in hexanes) yielded 671 mg (70%) of a white solid, mp 62−64 °C, R_f 0.32 (30% EtOAc in hexanes). IR (neat film from $CDCl_3$): 2981, 2953, 1732, 1360, 1235, 1154, 673 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.99 (dd, J = 10.2 Hz, J = 8.0 Hz, 1 H), 5.91 (dd, J = 7.8 Hz, J = 3.3 Hz, 1 H), 4.39 (m, 1 H), 3.75 (s, 3 H), 2.86 (m, 1 H), 2.42 (s, 3 H), 2.37 (m, 2 H), 2.15 (m, 1 H), 2.02 (s, 3 H), 1.83 (m, 4 H), 1.32 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 171.6, 167.9,152.3, 145.7, 144.6, 139.4, 134.4, 130.9, 129.2, 85.9, 70.5, 60.4, 53.5, 34.3, 33.2, 32.5, 29.3, 25.8, 23.0, 22.4. Anal. Calcd for $C_{24}H_{33}NO_8S$: C, 58.17; H, 6.71. Found: C, 58.18; H, 6.90.

Preparation of Methyl *cis*-5-(*N*-Tosyl-*N*-boc-imido)-8-methoxycarbonyl-1-cyclooctenyl Carboxylate (15b). To a solution of **15a** (287 mg, 0.580 mmol) in 2.4 mL of anhydrous methanol was added 76 mg (0.551 mmol) of potassium carbonate. After 20 min, the reaction mixture was filtered through a plug of silica gel, and the solvent was removed in vacuo, yielding 254 mg (quantitative) of the desired alcohol as a white solid. IR (neat film from $CDCl_3$): 3526, 1732, 1694, 1644, 1598, 1435, 1360 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.04 (app t, J = 8.2 Hz, 1 H), 4.78 (m, 1 H), 4.30 (m, 1 H), 3.85 (d, J = 10.7 Hz, 1 H), 3.76 (s, 3 H), 2.44 (s, 3 H), 2.35 (m, 2 H), 2.13 (m, 1 H), 1.98 (m, 1 H), 1.75 (m, 4 H), 1.34 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 162.2, 145.8, 139.3, 137.4, 132.9, 128.1, 124.5, 122.8, 79.6, 62.7, 55.1, 47.0, 30.5, 30.1, 28.7, 23.1, 20.9, 16.8.

To a solution of the above alcohol (245 mg, 0.56 mmol) in freshly distilled THF at −78 °C was added dropwise 350 μL of *n*-butyllithium (1.6 M, 0.56 mmol) in hexanes. After 30 s, 87 μL (1.12 mmol) of methyl chloroformate was added rapidly, and the reaction mixture was allowed to reach ambient temperature. Evaporation of the solvent followed by flash chromatography (0−30% EtOAc in hexanes) gave 253 mg (91%) of a white solid. IR (neat film from $CDCl_3$): 1732, 1650, 1598, 1442, 1360 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.06 (dd, J = 10.3 Hz, J = 8.1 Hz, 1 H), 4.40 (m, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 2.88 (m, 1 H), 2.43 (s, 3 H), 2.31 (m, 3 H), 1.85 (m, 4 H), 1.33 (s, 9 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 161.1, 150.2, 145.8, 139.3, 138.9, 132.9, 127.5, 124.5, 122.8, 79.6, 67.9, 53.9, 50.0, 47.3, 28.0, 27.1, 26.1, 23.1, 19.6, 16.8.

To a solution of 253 mg (0.519 mmol) of the above carbonate in 0.66 mL of CH_2Cl_2 was added 0.33 mL of TFA. After 1 h, the solvent was evaporated, and the product was purified by flash chromatography (0−30% EtOAc in hexanes), yielding 203 mg (95%) of a white solid, mp 43−44 °C. IR (neat film from $CDCl_3$): 3568, 3286, 1749, 1713, 1442 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.2 Hz, 2 H), 6.96 (dd, J = 10.1 Hz, J = 8.0 Hz, 1 H), 5.71 (dd, J = 6.6 Hz, J = 3.3 Hz, 1 H), 4.78 (d, J = 8.5 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.27 (m, 1 H), 3.22 (m, 1 H), 2.79 (m, 1 H), 2.42 (s, 3 H), 2.15 (m, 1 H), 2.02 (m, 1 H), 1.90−1.50 (m, 4 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 161.3, 150.0, 139.0, 138.7, 133.2, 127.3, 125.0, 122.1, 68.1, 50.1, 48.5, 47.4, 30.5, 26.1, 26.0, 18.6, 16.7. Anal. Calcd for $C_{19}H_{25}NO_7S$: C, 55.46; H, 6.12. Found: C, 55.62; H, 6.34.

Preparation of 9-Tosyl-9-aza-1-methoxycarbonylbicyclo[4.2.1]-non-1-ene (22). To a neat mixture of 4.6 mg (0.009 mmol, 7.5 mol %) of *S*,*S*-**24** and 3.1 mg (0.003 mmol, 2.5 mol %) of $Pd_2(dba)_3CHCl_3$ was added 1.2 mL of freshly distilled CH_2Cl_2 (thoroughly degassed by bubbling nitrogen through it for at least 0.5 h). *Note: Failure to degas thoroughly might lead to irreproducible results. Degassing by applying freeze−pump−thaw cycles or bubbling nitrogen through the solvent should be done even though it is has been freshly distilled.* After 20 min, the temperature was lowered to 0 °C, and a solution of **15b** (50 mg, 0.121 mmol) in thoroughly degassed CH_2Cl_2 (0.7 mL) was added.

The reaction was stirred at 0 °C under nitrogen for 14 h. Flash chromatography (0−30% EtOAc in hexanes) yielded 38.0 mg (94%) of a white solid, mp 135−137 °C, $[\alpha]^{25}_D = +42.0$ (*c* 1.90, CH_2Cl_2), ee 88% as determined by HPLC (Chiralpak AD column). Elution times (flow rate 1 mL/min, 10% isopropyl alcohol in heptane, $\lambda = 254$ nm): (−)-isomer, 15.7 min; (+)-isomer, 19.6 min. IR (neat film from $CDCl_3$): 3450, 1707, 1633, 1527, 1438, 1342, 1318 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, $J = 8.2$ Hz, 2 H), 7.26 (d, $J = 7.9$ Hz, 2 H), 7.00 (app t, $J = 6.0$ Hz, 1 H), 5.12 (dd, $J = 5.9$ Hz, 1 H), 4.41 (s, 1 H), 3.72 (s, 3 H), 2.55 (m, 1 H), 2.40 (s, 3 H), 2.30 (m, 1 H), 2.11 (m, 1 H), 1.68 (m, 5 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 168.2, 144.9, 144.4, 144.3, 138.9, 131.3, 128.6, 60.2, 59.6, 53.5, 35.0, 33.5, 31.3, 25.5, 22.9. Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31. Found: C, 60.62; H, 6.07.

Preparation of (+)-*N*-Tosylanatoxin-a (28). A solution of **22** (32 mg, 0.095 mmol) and aqueous LiOH (48 μL, 2 N) in 0.5 mL of THF was stirred for 4 h. After acidification (10% aqueous HCl), the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was then diluted with 0.7 mL of CH_2Cl_2 and 3.8 mg (60%, 0.095 mmol) of sodium hydride, followed by 80 μL (0.95 mmol) of oxalyl chloride at 0 °C. The solution was allowed to reach ambient temperature, and after 1.5 h the solvent was removed in vacuo. The residue was taken up in 0.1 mL of CH_2Cl_2 and added to a cold (−50 °C) suspension of $AlCl_3$ (13 mg, 0.095 mmol) in 0.1 mL of CH_2Cl_2. After 1 h, a solution of trimethylaluminum (2.0 M in toluene, 19 μL) was added dropwise at −30 °C. The mixture was allowed to reach ambient temperature, stirred for 2 h, and then recooled to 0 °C and quenched with ice. The aqueous phase was extracted three times with CH_2Cl_2. The organic phases were combined, extracted with 5% aqueous sodium bicarbonate, and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography (0−40% EtOAc in hexanes) to yield 28 mg (85%) of a white solid, $[\alpha]^{25}_D = +14.7$ (*c* 1.40, $CHCl_3$), R_f 0.50 (50% EtOAc in hexanes). Spectroscopic data are in full accordance with those reported in the literature for the (−) enantiomer.[24] IR (neat film from $CDCl_3$): 1662, 1635, 1598, 1343 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, $J = 8.2$ Hz, 2 H), 7.26 (d, $J = 8.1$ Hz, 2 H), 6.88 (app t, $J = 6.1$ Hz, 1 H), 5.21 (d, $J = 8.0$ Hz, 1 H), 4.45 (m, 1 H), 2.68 (m, 1 H), 2.43 (s, 3 H), 2.29 (s, 3 H), 2.19 (m, 1 H), 1.81−1.62 (m, 4 H), 1.60−1.46 (m, 3 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 197.7, 147.5, 143.3, 137.3, 129.8, 127.0, 58.8, 56.4, 33.5, 31.9, 29.8, 25.3, 24.3, 21.5.

Preparation of (−)-Anatoxin-a (1). To a cold (−40 °C) solution of (+)-**28** (26 mg, 0.0814 mmol) and Na_2HPO_4 (46 mg, 0.326 mmol) in 0.5 mL of MeOH (freshly distilled from magnesium methoxide) was added 37 mg of 5% sodium amalgam. After 10 min at −40 °C, another 37 mg of sodium amalgam was added. After an additional 5 min, 5 mL of water was added, and the resulting mixture was extracted four times with CH_2Cl_2. The extracts were dried ($NaSO_4$) and concentrated, giving 9.4 mg (70%) of **(−)-1**. The HCl salt of **(−)-1**, $[\alpha]^{25}_D = -39.0$ (*c* 0.55, EtOH), was prepared by bubbling HCl through a solution of **(−)-1** in $CDCl_3$, followed by evaporation of the solvent. Infrared data for the hydrochloride salt[6] and ^1H and ^{13}C NMR data for the free base[34] are in full accordance with those reported in the literature. IR (neat film, HCl salt): 3408, 1670, 1640, 1360 cm^{-1}. ^1H NMR (free base) (300 MHz, $CDCl_3$): δ 6.93 (m, 1 H), 4.71 (d, $J = 8.8$ Hz, 1 H), 3.40 (m, 1 H), 2.46 (m, 2 H), 2.30 (s, 3 H), 2.30−1.45 (m, 7 H). ^{13}C NMR (free base) (75.46 MHz, $CDCl_3$): δ 198.7, 152.8, 143.2, 57.7, 54.2, 33.8, 32.8, 30.4, 25.6, 25.0.

Preparation of *S,S*-1-(2-Diphenylphosphinobenzamido)-2-(2-picolinamido)cyclohexane (24). *S,S*-1-(2-Diphenylphosphinobenzamido)-2-aminocyclohexane[28] (540 mg, 1.49 mmol), DMAP (9.1 mg, 0.075 mmol), DCC (277 mg, 1.49 mmol), and picolinic acid (202 mg, 1.64 mmol) were stirred in anhydrous CH_2Cl_2 (10 mL) at ambient temperature under nitrogen overnight. Evaporation of the solvent and flash chromatography (30−60% EtOAc in hexanes) yielded 462 mg (61%) of a white solid, mp 194−196 °C, $[\alpha]^{25}_D = -25.8$ (*c* 1.00, CH_2Cl_2), R_f 0.43 (silica, 5% MeOH in CH_2Cl_2). IR (neat film from $CDCl_3$): 3300, 1649, 1587, 1526, 1464, 1434, 1325 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (dd, $J = 3.2$ Hz, $J = 0.9$ Hz, 1 H), 8.33 (d, $J = 6.3$ Hz, 1 H), 8.18 (d, $J = 7.8$ Hz, 1 H), 7.83 (app t d, $J = 7.8$ Hz, $J = 1.7$ Hz, 1 H), 7.45−7.40 (br m, 2 H), 7.32−7.13 (br m, 12 H), (app, $J = 5.6$ Hz, 1 H), 6.60 (br s, 1 H), 3.94−3.87 (br m, 2 H), 2.09 (d, $J = 12.9$ Hz, 1 H), 1.99 (d, $J = 12.9$ Hz, 1 H), 1.80−1.68 (br m, 2 H), 1.46−1.30 (br m, 3 H), 1.98 (m, 1 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.6, 166.8, 151.3, 149.9, 139.5, 139.4, 138.7, 138.1, 135.7, 135.6, 135.5, 135.3, 135.2, 131.5, 130.1, 130.0, 129.9, 129.9, 129.8, 128.8, 127.7, 123.7, 56.2, 54.3, 33.8, 33.6, 26.3, 26.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ −9.05. HRMS: calcd for $C_{31}H_{30}N_3O_2P$, 507.2076; found, 507.2071.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their generous support of our programs. J.D.O. thanks the Wallenberg Foundation for a postdoctoral fellowship. Mass spectra were provided by the Mass Spectrometry Facility of the University of California−San Francisco.

Supporting Information Available: Experimental procedures for **4b**, **6a**, **9**, **16b**, **17b**, **18a**, **19**, **20**, and **21** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA983617D

(34) Skrinjar, M.; Nilsson, C.; Wistrand, L.-G. *Tetrahedron: Asymmetry* **1992**, *3*, 1263.