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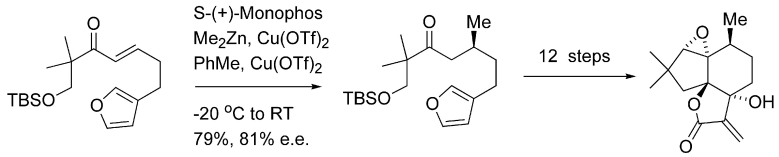
J. Am. Chem. Soc., **2004**, 126 (29), 9106-9111• DOI: 10.1021/ja048085h • Publication Date (Web): 03 July 2004



(-)-Alliacol A

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Oxidative Cyclizations: The Asymmetric Synthesis of (−)-Alliacol A

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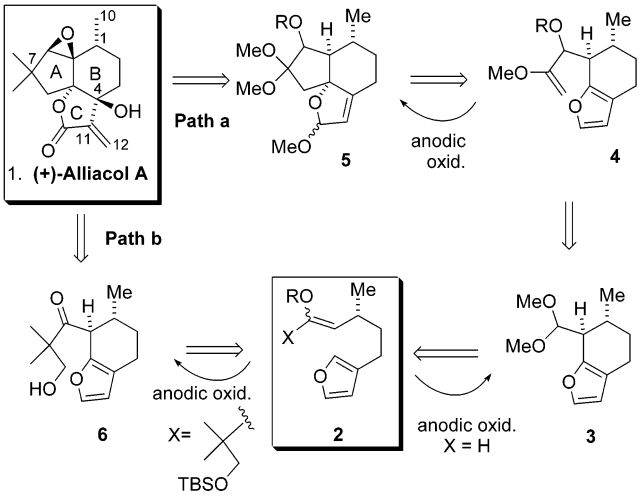
Abstract: A tandem anodic coupling−Friedel−Crafts alkylation strategy has been used to rapidly complete the asymmetric synthesis of alliacol A. The anodic oxidation reaction allowed for the generation of a new bond between two nucleophiles. In the synthesis, the absolute stereochemistry of the final natural product is set relative to a methyl group that is incorporated early in the sequence using an asymmetric Michael reaction.

Our interest in determining the synthetic utility of oxidative cyclization reactions[1] led us to explore new, potentially efficient routes to (+)-alliacol A (**1**).[2] Alliacol A is a sesquiterpene that was first isolated in Europe from the culture broth of the fungus *Marasmius alliaceus*.[3] The molecule displays moderate antimicrobial activity and inhibits DNA synthesis in the ascetic form of Ehrlich carcinoma at concentrations less than 10 μg/mL.[4] Studies indicate that the α,β-unsaturated lactone present in the C-ring serves as a Michael acceptor for sulfur-containing residues present in enzymes.[4,5] The molecule's angulary fused tricyclic skeleton, five contiguous stereogenic atoms, and three contiguous tetrasubstituted carbons make it a challenging and attractive target for synthesis. It has previously been made in racemic form by the Lansbury group.[6] This very nice approach to the molecule utilized an intramolecular S_N2 displacement to construct the C-ring late in the synthesis. For our part, we hoped to demonstrate that an anodic cyclization reaction could lead to a unique, very direct synthesis of the natural product in a manner that would readily allow for the asymmetric synthesis of the molecule.

Two such strategies appeared feasible (Scheme 1). Both strategies would originate from an intramolecular cyclization substrate having the overall form of **2**. In the first (path a), the intramolecular cyclization of a simple substrate (X = H) would afford a bicyclic product[7,8] that would then be converted to a second oxidative cyclization substrate (**4**). A second oxidative cyclization reaction would then be used to construct the tetrasubstituted carbon at the core of the natural product and a tricyclic ring system (**5**) that would be converted into the natural product. This pathway was intriguing because it offered the opportunity to probe the ability of the intramolecular cyclizations to overcome the barriers associated with a formal 5-endo-type cyclization. However, from a synthetic perspective, the second approach (path b) appeared much more attractive. In this scenario, a more complex initial substrate having all of the carbons needed to complete the synthesis would be synthesized and then oxidized to afford bicyclic intermediate **6**. The alcohol functional group in **6** would then be used to set up either an intramolecular Friedel−Crafts cyclization, a radical cyclization reaction, or a second anodic cyclization. The approach selected would be the one that allowed for construction of the tetrasubstituted carbon at the core of alliacol A while enabling the most efficient pathway for completing the synthesis of the natural

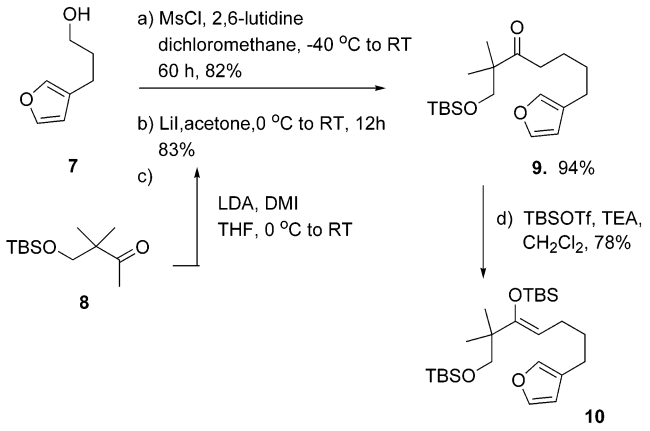
Scheme 1



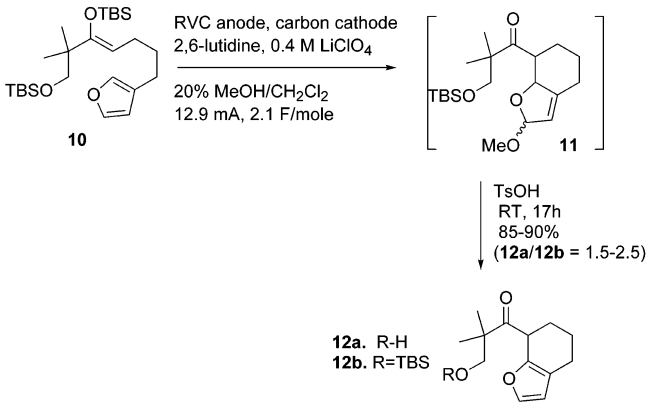
(1) For reviews, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527−9554. (b) Moeller, K. D. *Top. Curr. Chem.* **1997**, *185*, 50−86.
(2) For a preliminary report on the racemic synthesis, see: Mihelcic, J. M.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36−37.
(3) King, T.; Farrell, K.; Halsall, T.; Thaller, V. *J. Chem. Soc., Chem. Commun.* **1977**, *20*, 727−728.
(4) Anke, T.; Watson, W.; Giannetti, B.; Steglich, W. *J. Antibiot.* **1981**, *34*, 1271−1277.
(5) Hoffman, H.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94−110.
(6) (a) Lansbury P.; Zhi, B. *Tetrahedron Lett.* **1988**, *29*, 5735−5738. (b) Lansbury, P.; La Clair, J. *Tetrahedron Lett.* **1993**, *34*, 4431−4434. (c) La Clair, J.; Lansbury, P.; Zhi, B.; Hoogsteen, K. *J. Org. Chem.* **1995**, *60*, 4822−4833. For a related synthesis of (±)-alliacolide, see: (d) Ladlow, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1107−1118.
(7) (a) For a general discussion of enol ether/furan coupling reactions, see: New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578−1598. (b) For a review, see ref 1a.
(8) For a very nice example of anodic cyclizations using furans, see: Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright, D. L. *Org. Lett.* **2002**, *4*, 3763−3765.

10.1021/ja048085h CCC: $27.50

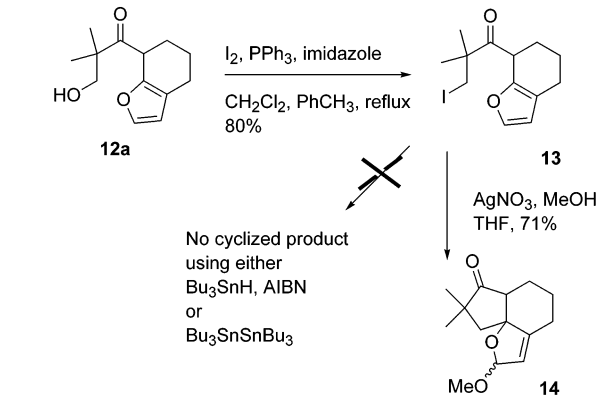
Scheme 2



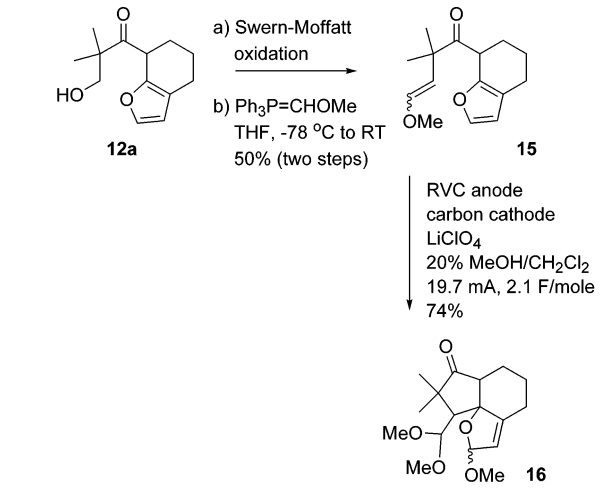
Scheme 3



Scheme 4



Scheme 5



product. In each of the pathways, the initial oxidative cyclization reaction would be used to construct an advanced intermediate with all of the functionality needed to complete the synthesis.

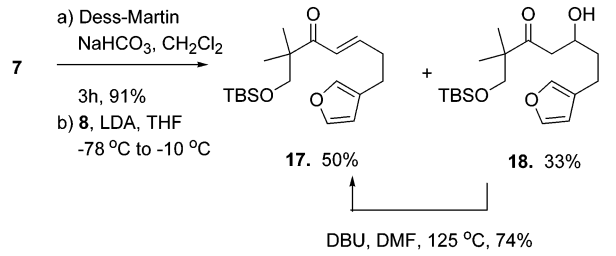
Initial Model Studies. With this in mind, we set out to determine if this approach to the key tetrasubstituted center and the tricyclic ring skeleton of alliacol A was feasible. Because of the ready availability of known starting materials **7**[7] and **8**,[9] this work commenced with the construction of model substrate **10** (Scheme 2). To this end, compound **7** was converted into the corresponding iodide,[10] compound **8** deprotonated to generate an enolate, and then the two molecules combined to form ketone **9**. In this reaction, the yield of the product was optimized by slowly adding the iodide to 5 equiv of the enolate. This minimized the formation of overalkylated enolate. Finally, conversion of the ketone into a silyl enol ether provided substrate **10** for the initial electrolysis reaction.

The electrolysis reaction was performed in a three neck flask using constant current conditions of 12.9 mA, a reticulated vitreous carbon (RVC) anode, a carbon rod cathode, a 0.4 M lithium perchlorate in 20% methanol/dichloromethane electrolyte solution, and 2,6-lutidine as a proton scavenger. The electrolysis was continued until 2.1 F/mol of charge had been passed (Scheme 3). When complete, the crude reaction mixture was treated with 5 equiv of *p*-toluenesulfonic acid, and the reaction was stirred at room temperature for 17 h. As in previous cyclizations using furans,[7] this final acid step was done to ensure regeneration of the furan from the initially formed product **11**. The reaction typically afforded the cyclized product in an 85−90% yield as a 1.5:1 to 2.5:1 ratio of deprotected alcohol to silyl ether products. Clearly, the electrochemical reaction was compatible with the full side chain needed for the synthesis.

With the formation of the bicyclic molecule complete, attention was turned toward finishing the tricyclic core of the natural product. To this end, the alcohol in **12a** was converted to the corresponding iodide (Scheme 4), which would in turn be used for either the planned Friedel−Crafts alkylation or radical cyclization approach to construction of the A-ring. For the Friedel−Crafts approach, treatment of the iodide with silver nitrate in methanol then afforded a 71% yield of the desired tricyclic product **14** (along with 16% of recovered starting material). Interestingly, attempts to form the tricyclic product using a radical cyclization reaction failed.[11] These reactions led to either the recovery starting material or reduction of the iodide. The failure of the radical reaction was interesting because the anodic cyclization pathway to formation of the A-ring using a radical cation intermediate was successful (Scheme 5). In this approach, the alcohol in **12a** was converted into an enol ether, forming the anodic oxidation substrate **15**. Oxidation of **15** using the same conditions employed in the first cyclization led to a 74% isolated yield of the tricyclic product **16**. The success of the anodic cyclization suggested that the radical cation inter-

(9) Boeykens, M.; Di Kimpe, N.; Tehrani, K. *J. Org. Chem.* **1994**, *59*, 6973−6985.
(10) Cebula, R.; Blanchard, J.; Boisclair, M.; Pal, K.; Bockovich, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2015−2020.
(11) For radical cyclization reactions involving furan rings, see: (a) Parsons, P. J.; Penverne, M.; Pinto, I. L. *Synlett* **1994**, 721−722. (b) Demircan, A.; Parsons, P. J. *Eur. J. Org. Chem.* **2003**, 1729−1732.

Scheme 6



mediate was more reactive toward cyclization than the radical, an observation that was consistent with earlier studies by Newcomb and co-workers demonstrating that enol ether radical cation intermediates are more reactive participants in cyclizations with olefin trapping groups than are the corresponding radical intermediates.[12]

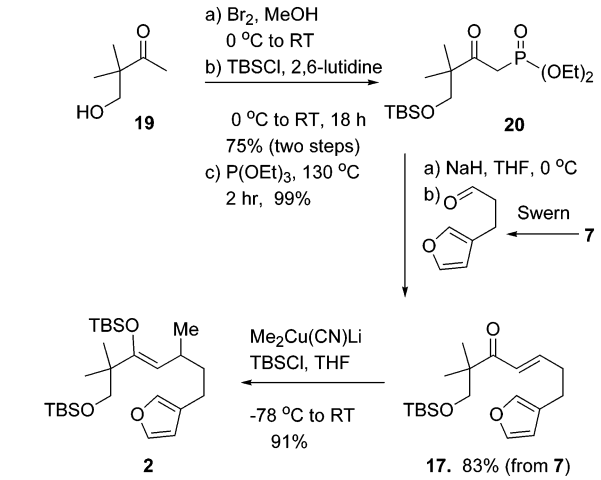
While the second electrochemical cyclization was successful, it was clear that it would not be the method of choice for completing the synthesis of alliacol A because it led to the presence of a formyl group equivalent on the A-ring. This group would need to be removed in a subsequent reaction. Since the Friedel−Crafts cyclization led to formation of both the A-ring and the tetrasubstituted carbon without this added complication, the tandem electrochemical cyclization−Friedel−Crafts approach was chosen for the natural product synthesis.

Developing a Racemic Synthesis.[2] With a strategy for making the ring skeleton in place, attention was turned toward assembling substrate **2** having the B ring methyl group of alliacol A in place. Initial plans for this synthesis called for construction of enone **17** from an aldol condensation involving **8** and the aldehyde generated from **7**. A Michael reaction would then be used to introduce the B-ring methyl group. Accordingly, alcohol **7** was oxidized using the Dess−Martin reagent and then treated with the enolate derived from **8** (Scheme 6). The aldol reaction led to a mixture of the desired enone **17** and aldol product **18**. Treatment of **18** with DBU effected the elimination and generated the enone in a 74% yield. However, the yield of the aldol reaction was inconsistent. For this reason, a Horner−Emmons−Wadsworth strategy was undertaken by first converting keto alcohol **19** to a phosphonate and then performing the net condensation reaction. Using this method, we could generate an 83% yield of enone **17** (two steps from alcohol **7**) in a consistent fashion (Scheme 7). For larger scale applications of this sequence, it proved useful to employ a Swern oxidation for the oxidation of **7** in place of the initial Dess−Martin oxidation (Scheme 6). This avoided the need for purification of the aldehyde prior to the Horner−Emmons−Wadsworth reaction. Once the enone was in hand, the Michael reaction was accomplished using a higher order cuprate reagent in the presence of TBSCl to directly afford substrate **2** in a 91% isolated yield.

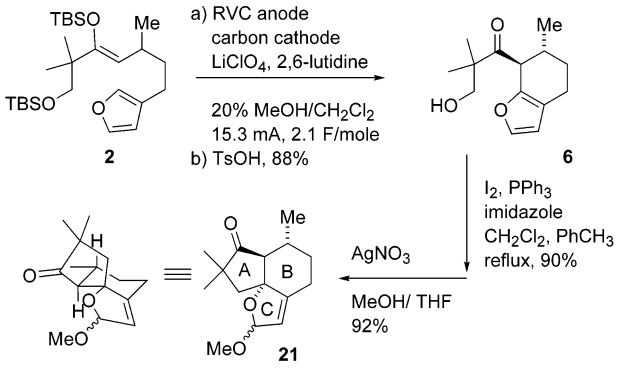
Electrolysis substrate **2** was then oxidized using conditions that were again directly analogous to those described above for the electrolysis of substrate **10**. In this manner, an 88% isolated yield of the bicyclic product **6** was generated (Scheme 8).

As in other anodic cyclization reactions, specialized electrochemical equipment was not needed for generating good yields of the desired product. For example, the electrolysis reaction

Scheme 7



Scheme 8



could also be performed using a 6 V lantern battery as a power supply.[13] Everything other than the power supply for the reaction remained exactly as described above. The reaction was monitored by TLC until complete and then worked up with acid as described previously to afford an 82% isolated yield of product.

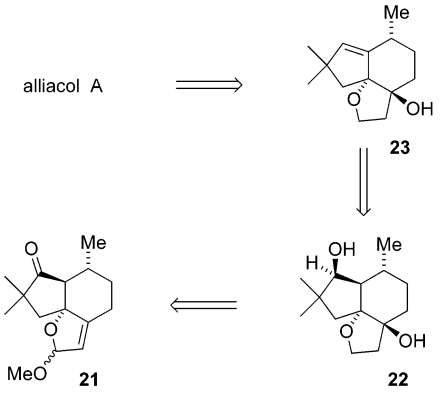
With the bicyclic product in hand, the alcohol was converted into an iodide and the Friedel−Crafts cyclization was completed using the same conditions employed in the initial model study. A 92% isolated yield of the tricyclic product **21** was obtained from the Friedel−Crafts reaction. The structure of the tricyclic compound was assigned with the use of COSY and HMQC NMR spectra. In addition, the stereochemistry of the two methine protons on the B-ring was assigned with the use of coupling constants. The *J* value for the coupling of these two protons was 13 Hz, indicating a dihedral angle approaching 180° for the two C−H bonds and a trans-diaxial relationship between the protons. At this point, the Friedel−Crafts annulation was assumed to provide a cis-product with respect to the A,B-ring juncture.

Initial efforts to complete the racemic synthesis of alliacol A focused on strategies that would preserve the protected lactol while converting the A-ring ketone in **21** into the double bond needed for introducing the epoxide found in the natural product. All such efforts met with failure for two main reasons. First, the protected lactol was sensitive to a variety of reaction conditions. Even when the C-ring lactol ether was deprotected and oxidized to the unsaturated lactone, all efforts to manipulate

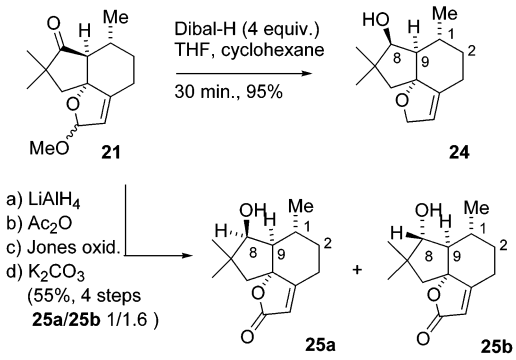
(12) Horner, J.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402−5410.

(13) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317−8320.

Scheme 9



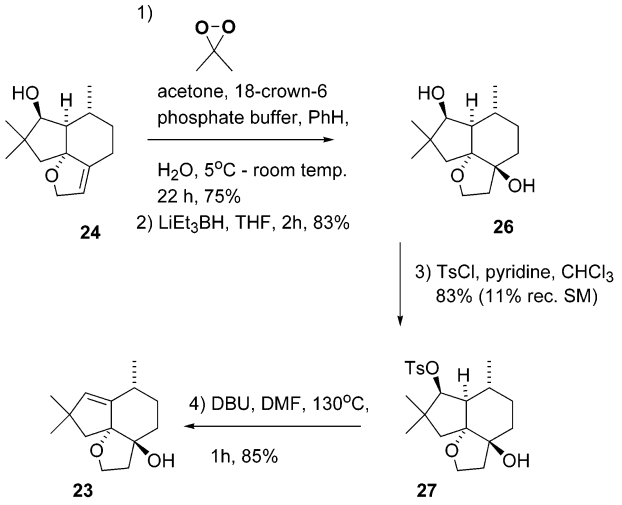
Scheme 10



the A-ring functionality of the intermediate led to a complex mixture of products. With this in mind, it was decided that the lactol ether in the C-ring ether of **21** should be removed and then reintroduced later. Such an approach would not lengthen the overall synthesis since reintroduction of the lactone carbonyl could be accomplished in a single oxidation step. Even in an approach that retained the C-ring functionality from the electrolysis, an oxidation reaction would eventually be required to generate the lactone group needed for the final product. Second, all attempts to effect the elimination reaction needed to introduce the A-ring double bond failed as long as the C-ring double bond was present. Presumably, the increase in ring strain associated with placing a second double bond into the tricyclic ring skeleton was simply too large. With this in mind, the alternative strategy outlined in Scheme 9 was undertaken. In this approach, a simultaneous reduction of the carbonyl and removal of the lactol functionality in **21** would be followed by conversion of the C-ring double bond into the bridgehead alcohol needed for the total synthesis. At this point, a double bond could be introduced into the A-ring. In this way, there would be no need to introduce a second double bond and the associated additional ring strain into the tricyclic skeleton. Such a sequence would afford an intermediate (**23**) that had been previously converted into (±)-alliacol A.[6c]

The overall transformation started by treating **21** with Dibal-H to reduce the ketone and remove the C-ring lactol functionality (Scheme 10). The reduction led to a single alcohol product **24**. Assignment of the stereochemistry in **24** was difficult because of the overlap of the resonances for the protons at C_2, C_1, and C_9. For this reason, the stereochemistry of the alcohol was tentatively assigned as anti to the bridgehead proton since it was thought that the Dibal-H reagent would approach from the

Scheme 11

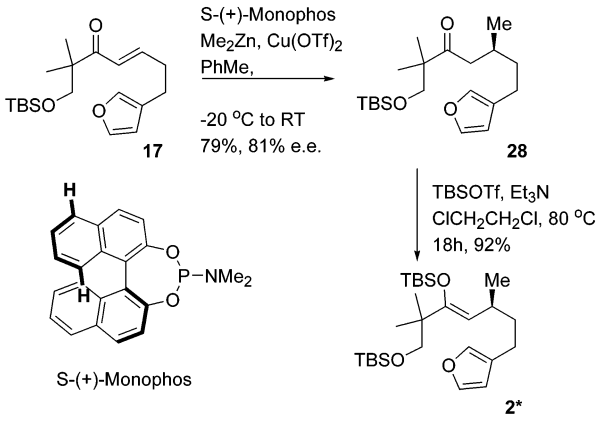


least hindered convex face of the molecule. Some support for this assignment was gathered by comparing the H^1 NMR of **24** to the earlier synthesized lactone analogues **25a** and **25b**. In this case, the stereochemistry of **25b** had been assigned as having the alcohol cis to the bridgehead proton at C_9 because of the lack of a coupling interaction between the methine protons at C_9 and C_8 in the COSY spectrum. The absence of this coupling interaction suggested that the methine protons had a dihedral angle of 90°. Once the two stereochemical isomers were assigned, they could be readily distinguished because the chemical shift of the C_8 methine proton was at 4.5 ppm in **25a** and 3.8 ppm in **25b**. For **24**, the C_8 methine had a chemical shift of 4.34 ppm. On the basis of this comparison, the hydroxyl group **24** appeared to have the same relationship to the ring skeleton as the hydroxyl group in **25a**. On the basis of the tentative assignment of stereochemistry in **24**, plans were made to set up an anti-elimination of the hydroxyl group, knowing that if the assignment was wrong an alternative syn-elimination could be used.

Initially, the reduced product **24** was protected as a TBS ether, and then the C-ring olefin epoxidized with m-CPBA. However, the epoxidation reaction in this sequence led to a 1.3:1 mixture of stereoisomers. While the isomers could be separated, clearly a strategy that avoided such a mixture was preferred.

To this end, we found that treatment of alcohol olefin **24** with DMDO led to a single epoxide product that could be reductively opened to form diol **26** (Scheme 11). On the basis of NMR chemical shift data and molecular models of the intermediate epoxide, the stereochemistry of **26** was tentatively assigned as shown. However, the proof of stereochemistry was only accomplished after converting the diol into the known intermediate **23**. To effect this transformation, the diol was first converted into the monotosylate using *p*-toluenesulfonyl chloride and pyridine. This reaction could not be forced to completion. When the temperature was raised above 5 °C or excess TsCl was employed, the reaction led to tosylation and elimination of the tertiary alcohol. For this reason, the reaction was run to partial conversion, the product and starting material were separated, and then the recovered starting material was recycled. After four such cycles, an 83% isolated yield of the desired monotosylated product was obtained. This material was then treated with DBU in DMF at 130 °C to form **23** in an 85%

Scheme 12



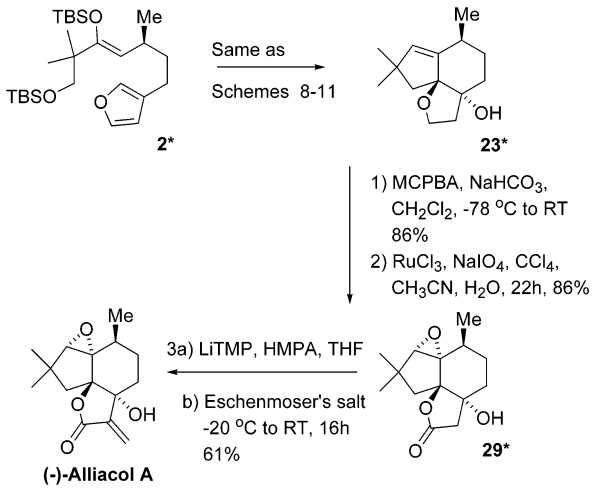
yield and complete the formal racemic synthesis of alliacol A. The success of the elimination reaction suggested that the earlier tentative assignment of stereochemistry in **24** had been correct.

Overall, the yield for the formal synthesis (±)-alliacol A was 18% over 13 steps (88% per step) starting from the known compounds.

Completing the Asymmetric Synthesis. In the synthesis described above, the stereocenters in the final product are all set relative to the initial methyl group in intermediate **2**. Hence, it appeared that if the methyl group in **2** could be introduced in an asymmetric fashion, then the route developed would provide a convenient means for completing the asymmetric synthesis of alliacol A. With this in mind, attention was focused on asymmetric variants of the Michael reaction used to introduce the methyl group into substrate **2**. Of immediate concern in these deliberations was the observation that the direction and magnitude of the asymmetric induction in such reactions were difficult to predict.[14] In fact, changes in a substrate for such a reaction can completely change the direction of asymmetric induction for even a single catalyst system. How would the use of a more complex enone such as **17** alter the reaction, and would a commercially available ligand lead to a high degree of asymmetric induction? If so, then what enantiomer of the product would be formed?

To address these questions, substrate **17** was treated with dimethylzinc in the presence of copper triflate and the commercially available asymmetric ligand *S*-(+)-monophos (Scheme 12).[15] Initial trials were conducted using 1 to 1.5 equiv of dimethylzinc at 5−10% catalyst loading at low temperature (−20 to −10 °C). Under these conditions, none of the desired product was formed. Raising the temperature of the reaction did lead to some product, but it was only after dramatically increasing the amount of catalyst used that the reaction afforded synthetically useful amounts of material. To this end, 3 equiv of dimethylzinc were employed along with 30 mol % of the copper catalyst at the start of the reaction. Initially, the reagents were added at −20 °C. The reaction was allowed to warm to room temperature over a period of 5 h, and then an additional 25 mol % of the $Cu(OTf)_2$ was added. Using these conditions,

Scheme 13



the reaction afforded a 79% yield of product with an 81% ee. The magnitude of the asymmetric induction was established with the use of a chiral HPLC column in comparison with the racemic material. As for the direction of the asymmetric induction, it was determined that the easiest method for making the assignment was to convert the material into the natural product (the enantiomer illustrated in Scheme 12 is the correct one based on the assignment made below). Hence, the ketone was treated with TBSOTf and triethylamine to form the silyl enol ether substrate **2***, which was then transformed into the mono-alcohol olefin product **23*** using the exact same procedure described above for the racemic material.

Once in hand, **23*** was converted into alliacol A using the procedure developed by Landsbury (Scheme 13).[6c] This sequence started with the m-CPBA epoxidation of **23*** and the subsequent oxidation of the C-ring to reintroduce the lactone carbonyl with ruthenium tetraoxide. In the final step, the exocyclic methylene of the natural product was introduced using Eschenmoser's salt.

Analysis of the synthesized alliacol A by optical rotation ($[\alpha]^{23}_D$ −9.6 °C) indicated that the material was the opposite enantiomer relative to the natural product ($[\alpha]^{23}_D$ +10.2 °C).[5,16] Hence, (−)-alliacol A was synthesized. For construction of the natural (+)-enantiomer, the *R*-(+)-monophos ligand would be required for the Michael reaction.

Conclusion

The anodic coupling of two nucleophiles has been used as the key step in an efficient synthesis of alliacol A. The electrochemical reaction proceeds in high yield and can be accomplished using a simple battery power supply. No specialized equipment is needed. The overall synthetic route utilizes a single stereocenter established early in the synthesis to control the relative stereochemistry of all the stereogenic atoms in the final natural product. In this way, construction of the initial stereocenter with control over absolute stereochemistry has enabled the first asymmetric synthesis of alliacol A. The overall strategy taken would appear to provide a general route to

(14) Alexakis, A.; Benhaim, C.; Fournioux, X.; Van den Heuvel, A.; Leveque, J.; March, S.; Rosset, S. *Synlett* **1999**, *11*, 1811−1813.

(15) The conditions developed by Feringa and co-workers were used. Feringa, B.; de Vries, A.; Meetsma, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374−2376. *R*- and *S*-monophos are available from Strem Chemicals.

(16) The absolute stereochemistry of (+)-alliacol A was assigned by chemical correlation to the structure of alliacolide. For the assignment of alliacolides absolute stereochemistry by CD, see: Bradshaw, A. P. W.; Hanson, J. R.; Kirk, D. N.; Scopes, P. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, *6*, 1794−1795.

angularly fused tricyclic natural products. Efforts to establish the scope of this approach are currently underway.

Acknowledgment. We thank the National Science Foundation (CHE-9023698) for their generous support of this work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH Grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: Full experimental details are included for the asymmetric synthesis along with both proton and carbon spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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