

Total Synthesis of (–)-Ascochlorin via a Cyclobutenone-Based Benzannulation Strategy

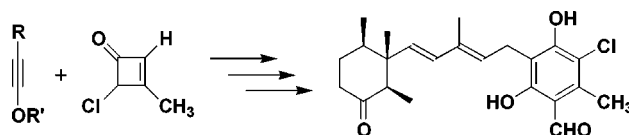
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ABSTRACT



The application of a convergent benzannulation strategy in an efficient synthesis of (–)-ascochlorin is described.

The fungal metabolite (–)-ascochlorin (**1**) was first isolated in the late 1960s by groups at the Chugai Pharmaceutical Co.^{1a} and Lederle Laboratories.^{1b} Ascochlorin exhibits antiviral, antibiotic, and antitumor activity, and certain *O*-alkyl derivatives have attracted attention as potential drugs for the treatment of hyperlipidemia and diabetes.² The cylindrols constitute a class of Ras farnesyl-protein transferase inhibitors recently isolated by researchers at Merck³ and, together with other members of the ascochlorin family, represent potential lead compounds for the development of new anticancer agents (Figure 1).

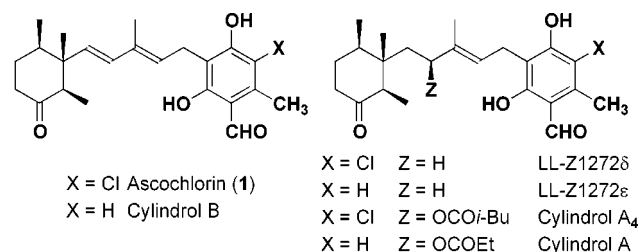


Figure 1. Representative members of the ascochlorin family of sesquiterpenyl phenol natural products.

Previous synthetic approaches to the aromatic moiety of ascochlorin⁴ involved the synthetic elaboration of orcinol

derivatives and relied on alkylation and electrophilic substitution reactions to append additional substituents to the aromatic ring. Herein we report an efficient route to the aromatic system of the ascochlorin family of sesquiterpenyl phenols which is based on the benzannulation strategy previously developed in our laboratory.^{5,6} Our convergent synthesis of (–)-ascochlorin is considerably more efficient than the previous enantioselective synthesis of this natural product^{4a} and avoids regiochemical problems that arose in the other prior route.^{4b} As detailed below, our approach

(1) (a) Tamura, G.; Suzuki, S.; Takatsuki, A.; Ando, K.; Arima, K. *J. Antibiot.* **1968**, *11*, 539. (b) Ellestad, G. A.; Evans, R. H., Jr.; Kunstmann, M. P. *Tetrahedron* **1969**, *25*, 1323.

(2) See: Hosokawa, T.; Ando, K.; Tamura, G. *Diabetes* **1985**, *34*, 267 and references therein.

(3) Singh, S. B.; Ball, R. G.; Bills, G. F.; Cascales, C.; Gibbs, J. B.; Goetz, M. A.; Hoogsteen, K.; Jenkins, R. G.; Liesch, J. M.; Lingham, R. B.; Silverman, K. C. *J. Org. Chem.* **1996**, *61*, 7727.

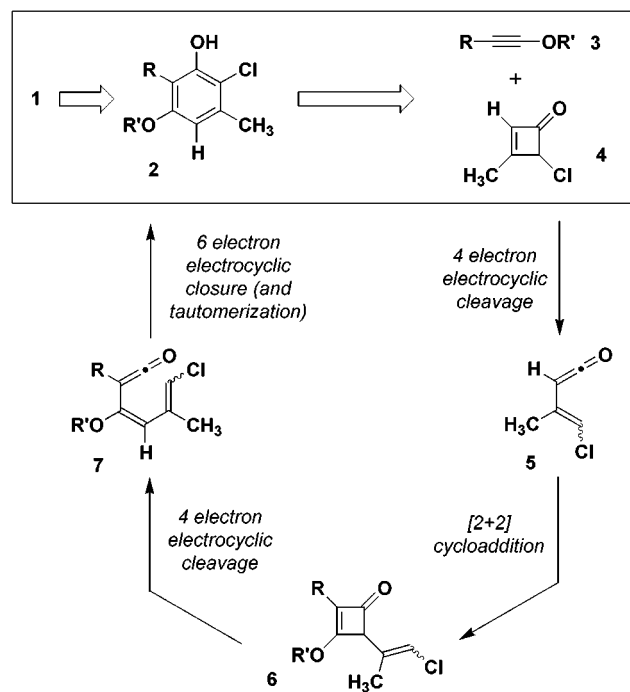
(4) (a) Total synthesis of (–)-ascochlorin: Mori, K.; Takechi, S. *Tetrahedron* **1985**, *41*, 3049. (b) Total synthesis of (±)-ascochlorin: Safaryn, J. E.; Chiarello, J.; Chen, K. M.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 2635.

(5) (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

(6) Previous natural product syntheses based on this benzannulation strategy: (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (b) Danheiser, R. L.; Cha, D. C. *Tetrahedron Lett.* **1990**, *31*, 1527. (c) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149. (d) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844. (e) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471. (f) Danheiser, R. L.; Trova, M. P. *Synlett* **1995**, 573. (g) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341.

proceeds via a key intermediate of type **2** and then employs a Casnati reaction to introduce a formyl group at the remaining unsubstituted position of the aromatic ring. The pivotal step in the synthesis involves the assembly of key intermediate **2** via an aromatic annulation employing cyclobutenone **4** and acetylene **3**. Scheme 1 outlines the mecha-

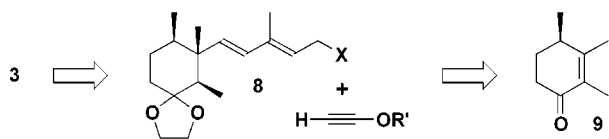
Scheme 1



nistic course of this key benzannulation reaction. Irradiation of the cyclobutenone triggers four-electron electrocyclic ring opening to the vinylketene **5**, which combines with acetylene **3** in a regioselective [2 + 2] cycloaddition to form **6**. Further irradiation (or warming) then induces a second four-electron electrocyclic ring opening reaction to generate dienylyketene **7**, which undergoes rapid 6π electrocyclization. Tautomerization affords the desired pentasubstituted benzene.

Our retrosynthetic plan for the synthesis of key acetylene intermediate **3** involved the alkylation of an appropriate alkoxyacetylene with the sesquiterpenyl building block **8** (Scheme 2). Access to this intermediate would be obtained

Scheme 2



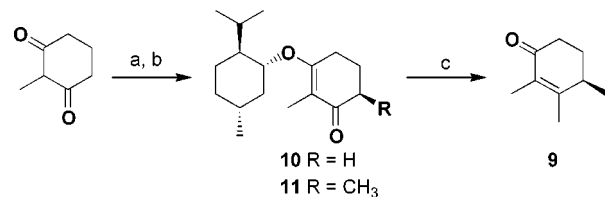
via a stereoselective organocuprate addition to (4*R*)-2,3,4-trimethylcyclohexenone (**9**).⁷

Cyclohexenone **9** has previously been prepared in racemic form by Cory,⁸ employing Stork's alkoxy enone alkylation

strategy,⁹ and initially we believed that the application of this method in conjunction with classical resolution would provide the most expeditious means of obtaining enone **9** in enantiomerically pure form. On further consideration, however, we realized that the Cory route could be easily modified to provide the desired enantiopure enone *without the introduction of the additional steps usually required in classical resolutions*.

Thus, as shown in Scheme 3, by substituting (–)-menthol for the achiral alcohol normally employed in the Stork

Scheme 3^a



^a Key: (a) 1.0 equiv of (–)-menthol, cat. (+)-CSA, 4:1 toluene-diglyme, reflux, (–H₂O), 20 h, 74%; (b) (i) 1.03 equiv of LDA, 1.2 equiv of MeI, THF, –78 °C to rt, 14 h; (ii) recrystallize and recycle, 51% overall; (c) 1.4 equiv of MeLi, THF, 0 °C, 1 h; then 1 M HCl, 0 °C, 10 min, 100%.

alkylation we obtained methylation product **11** as a 1:1 mixture of separable diastereomers (rather than enantiomers). Addition of methyllithium to the desired diastereomer (obtained by recrystallization from hexanes) followed by hydrolysis then provided **9** in excellent yield and enantiomeric purity (200:1 er).¹⁰

An added benefit of this approach is that the undesired diastereomer of **11** is easily recycled: exposure of the mother liquors from the recrystallization of **11** to 0.5 equiv of KO*t*-Bu in *t*-BuOH–THF (rt, 4 h) regenerates a 1:1 mixture of diastereomers from which additional **11** can be obtained by recrystallization.

Two routes have been developed for the elaboration of enone **9** to the key sesquiterpenyl alcohol intermediate **16**. The first approach, outlined in Scheme 4, exploits the ready availability of dienylystannane **12**¹¹ and features the BF₃·Et₂O-promoted conjugate addition¹² of the mixed cuprate reagent¹³ derived from **13** to cyclohexenone **9**. Exposure of the product

(7) Conjugate addition of organocuprate reagents to 3,4-disubstituted cyclohexenones is well documented to proceed with the required stereochemistry. For examples, see refs 4b, 8, and Ziegler, F. E.; Wender, P. A. *Tetrahedron Lett.* **1974**, 449.

(8) Cory, R. M.; Burton, L. P. J.; Chan, D. M. T.; McLaren, F. R.; Rastall, M. H.; Renneboog, R. M. *Can. J. Chem.* **1984**, *62*, 1908.

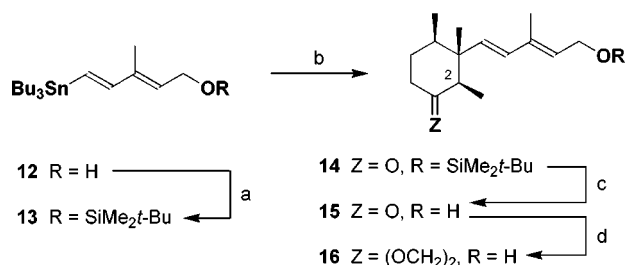
(9) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(10) The absolute configuration of **11** was established by X-ray crystallographic analysis, and the enantiomeric purity of enone **9** was determined by gas chromatography on an HP19091G-B133 chiral 10% permethylated cyclodextrin column.

(11) Prepared by stannylcupration of *trans*-3-methylpent-2-en-4-yn-1-ol ("1"-pentol", an intermediate in the industrial synthesis of vitamin A). See: Betzer, J. F.; Delalogue, F.; Muller, B.; Pancrazi, A.; Prunet, J. J. *Org. Chem.* **1997**, *62*, 7768.

(12) Reviewed in: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

(13) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

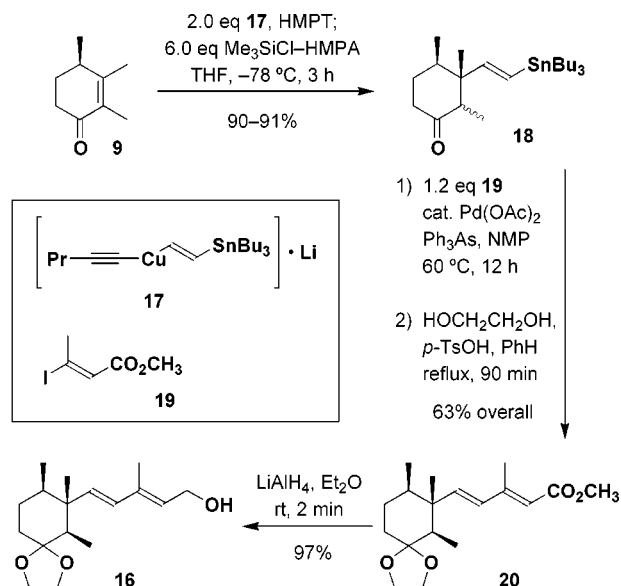
Scheme 4^a

^a Key: (a) 1.3 equiv of *t*-BuMe₂SiCl, 1.4 equiv of Et₃N, 0.04 equiv of DMAP, CH₂Cl₂, rt, 2.5 h, 98%; (b) 2.5 equiv of **13**, 2.5 equiv of *n*-BuLi, -78 °C, 90 min; then 2.5 equiv of 1-pentynyl-copper, 5.0 equiv of HMPT, -50 °C, 3 h; then 2.5 equiv of BF₃·Et₂O, 1.0 equiv of **9**, -78 °C to rt, THF, 14 h, 75–78%; (c) 1.2 equiv of TBAF, DMF, 0 °C, 3.5 h, 83–90%; (d) 0.2 equiv of *p*-TsOH·H₂O, 6.0 equiv of CaSO₄, 5:1 cyclohexane–HOCH₂CH₂OH, rt, 3.5 h, 76%. ^b Reactions performed beginning with racemic **9**.

(**14**, ca. 85:15 mixture of C-2 epimers) to *n*-Bu₄NF in dimethylformamide resulted in desilylation with concomitant equilibration at C-2 to afford **15** and its epimer in a ratio of 93:7. Protection of the ketone carbonyl group with ethylene glycol under standard conditions was complicated by competing substitution reactions at the dienyl side chain but was eventually achieved in good yield via the indicated protocol.

An alternative route to key intermediate **16**, outlined in Scheme 5, employs bis(tributylstannyl)ethylene¹⁴ as a syn-

Scheme 5



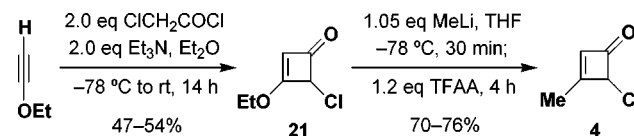
thetic linchpin for the assembly of the sesquiterpenyl section of ascochlorin. Conjugate addition of the mixed cuprate

(14) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, 96, 5581. (b) Renaldo, A. F.; Labadie, J. W.; Stille, J. K. In *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, pp 268–274.

reagent **17**^{14a,15} furnished vinylstannane **18**, which we employed in a Stille coupling reaction¹⁶ with vinyl iodide **19**^{17,18} to provide **20** after ketalization under standard conditions. LiAlH₄ reduction then gave **16** in nearly quantitative yield.

The synthesis of 4-chloro-3-methylcyclobutenone, the vinylketene precursor required for the key benzannulation step, is outlined in Scheme 6. Reaction of monochloro-

Scheme 6



ketene¹⁹ with ethoxyacetylene furnished the desired cycloadduct (**21**), but subsequent addition of CH₃Li and hydrolysis under standard acidic conditions produced a complex mixture of products. Conversion of **21** to **4** was ultimately realized via a modified protocol in which the CH₃Li adduct is first acylated, after which hydrolysis is conducted under mild alkaline conditions.²⁰

Our initial studies of the key aromatic annulation step focused on the reaction of **4** and other cyclobutenones with methoxyacetylene derivatives. Although the desired benzannulation product was obtained in good yield, cleavage of the resultant aryl methyl ether to reveal the desired resorcinol failed to take place under a variety of conditions.²¹ Attention was then turned to the application of various acetal and silyl ether derivatives, but these approaches were frustrated by our inability to develop efficient synthetic routes to the requisite alkyne annulation components. Success was ultimately realized through the application of benzyloxyalkyne **25**. Initially we had avoided the use of benzyloxyacetylenes as annulation components due to their propensity to undergo [3,3] sigmatropic rearrangement on mild heating.²² On further consideration, however, we felt that these alkynyl ethers

(15) Me₃SiCl was used to promote this reaction. For a discussion, see: Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, 122, 3288 and references therein.

(16) Reviewed in: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50, 1.

(17) Previous synthesis: Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, 56, 5834.

(18) We prepared **19** by a modification of the method previously employed by Ohba et al. for the corresponding ethyl ester (Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, 118, 8250). Attempts to achieve Stille coupling to allylic alcohol derivatives (both vinyl bromides and iodides) were unsatisfactory under a variety of conditions.

(19) Reviewed in: (a) Brady, W. T. *Tetrahedron* **1981**, 37, 2949. (b) Tidwell, T. *Ketenes*; Wiley & Sons: New York, 1995; pp 336–348.

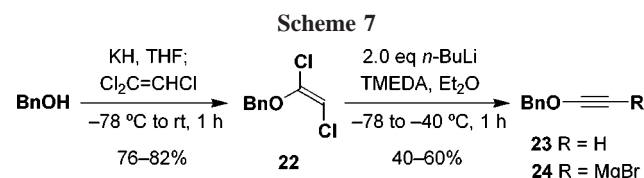
(20) For previous examples of the hydrolysis of vinylogous hemiketals under alkaline conditions, see: (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 8031. (b) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, 55, 5350.

(21) Reactions with basic and nucleophilic reagents were too sluggish to be useful, and exposure to acidic (and Lewis acidic) conditions resulted in cyclization to form chromanes.

(22) (a) Wunderli, A.; Zsindely, J.; Hansen, H. J.; Schmid, H. *Chimia* **1972**, 26, 643. (b) Katzenellenbogen, J. A.; Utawanit, T. *Tetrahedron Lett.* **1975**, 38, 3275 and references therein.

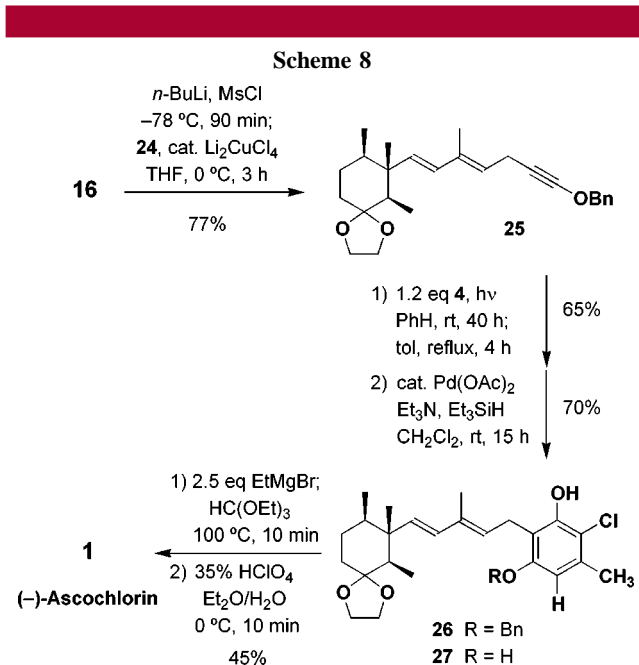
might be successfully deployed in our benzannulation strategy by utilizing a *photochemical* variant of the process.²³

Benzyloxyacetylene (**23**) was prepared by application of the general method of Greene²⁴ (Scheme 7) and then was



coupled to the mesylate derivative of sesquiterpenyl alcohol intermediate **16** according to our previously described protocol.^{5a,6a} The stage was now set for us to examine the feasibility of the pivotal benzannulation step. The target compound **26** constituted the most highly functionalized system we had yet attempted to synthesize by employing the cyclobutenone-based benzannulation strategy. In the event, this key reaction proceeded smoothly and in good yield when a solution of alkynyl ether **25** and 1.2 equiv of **4** was irradiated for 40 h (450 W Hanovia mercury lamp, Pyrex filter). The initial product, which contained some cyclobutenone intermediate of type **6** (Scheme 1), was briefly heated to complete conversion to the desired aromatic product.²⁵ Finally, chemoselective hydrogenolysis of the benzyl ether group in the presence of the conjugated diene was achieved by exposure to triethylsilane and catalytic palladium acetate²⁶ to afford resorcinol **27** in good yield (Scheme 8).

Completion of the total synthesis of (–)-ascochlorin was achieved by formylation of **27** according to the method of Casnati²⁷ as previously reported by Mori.^{4a} Hydrolysis of



the ketal produced (–)-ascochlorin [mp 172–174 °C (lit.^{1b} mp 172–173 °C), $[\alpha]^{20}_{\text{D}} -31^\circ$ ($c = 0.49$, MeOH) (lit.^{1b} $[\alpha]^{25}_{\text{D}} -31^\circ$ ($c = 0.99$, MeOH))] with spectral characteristics identical with those reported for the natural product.^{1b,4a}

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Supporting Information Available: Experimental procedures and characterization data for all compounds and crystallographic data for **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(23) Pal, K. Ph.D. Thesis, Massachusetts Institute of Technology, 1987.
 (24) (a) Kann, N.; Bernardes, V.; Greene, A. E. In *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. IX, pp 533–538. (b) For the previous synthesis of **23**, see ref 22a.

(25) The crude annulation product was treated with KOH in THF–aq MeOH to saponify a small amount of ester formed by reaction of the phenolic product with the vinylketene intermediate.

(26) (a) Birkofer, L.; Bierwirth, E.; Ritter, A. *Chem. Ber.* **1961**, *94*, 821. (b) Coleman, R. S.; Shah, J. A. *Synthesis* **1999**, 1399.

(27) Casnati, G.; Crisafulli, M.; Ricca, A. *Tetrahedron Lett.* **1965**, 243.