First Enantioselective Total Synthesis of a Naturally Occurring Dolabellane. Revision of Absolute Configuration

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Reported herein is the first enantioselective synthesis of **1**, 1(*R*),11(*S*)-dolabella-3(*E*),7(*E*),12(18)-trien-13-one (dolabellatrienone), a naturally occurring member[1] of the widely distributed dolabellane class of marine diterpenoids[1c,2] which is characterized by the unusual *trans*-bicyclo[9.3.0]tetradecane nucleus. This synthesis is based on a novel strategy for simultaneously creating the 11-membered ring and the stereogenic centers of the dolabellane system by an unprecedented enantioselective Claisen rearrangement of an achiral 15-membered macrocyclic lactone (**8**). Since the enantioselectivity of this key step is remarkably high (>98%), both of the dolabellatrienones **1** and *ent*-**1** were obtained in enantiomerically pure form from the common intermediate **8**, allowing the unambiguous determination of the absolute configuration **1** for the natural product, dolabellatrienone, a revision of the previous assignment.[1] Three other noteworthy approaches to the synthesis of the dolabellane system have recently been demonstrated.[3]

The total synthesis of **1** commenced from two readily available intermediates, *tert*-butyldiphenylsilyl (TBDPS) ether **2**[4] and epoxy-(*E*,*E*)-farnesyl chloride **4**.[5] Lithiation of **2** (2 equiv of *t*-BuLi, THF, −78 °C) and coupling with **4** in THF−HMPA at −94 °C afforded **5** in good yield. The use of low temperature and of HMPA as cosolvent is critical to the success of this not so common 1,4-diene construction. Acidic periodate induced hydrolytic cleavage of the epoxide **5** followed by reduction furnished the primary alcohol **6**, which was homologated to the acid **7** in excellent overall yield. Cyclization of **7** to the macrolactone **8** occurred cleanly by reaction with 2,4,6-trichlorobenzoyl chloride−Et_3N−THF at 0 °C for 45 min to form the mixed anhydride and subsequent slow addition to a solution of 10 equiv of 4-(*N*,*N*-dimethylamino)pyridine in toluene at 85 °C.[6]

The crucial Claisen rearrangement of **8** to form **9** was based on recently described methodology involving boron enolates of esters with the chiral diazaborolidine L_2BBr (Scheme 1).[7,8] However, the applicability of the enantioselective Claisen rearrangement to lactones had not previously been demonstrated. Nor was it obvious that the required (*E*)-form of the boron enolate could be generated selectively. On the basis of previous studies, it was expected that the (*S*,*S*)-form of the diazaborolidine reagent L_2BBr (shown in Scheme 1) would lead to Claisen product **9** and that the (*R*,*R*)-form would produce *ent*-**9**. Accordingly, the lactone **8** was treated with the (*S*,*S*)-form of L_2BBr (1 equiv) and *i*-Pr_2NEt (5 equiv) at −78 °C for 8 h to form the boron enolate, which was then kept at 4 °C for 48 h to effect the Claisen rearrangement. The desired monocyclic acid **9** was produced with excellent diastereoselectivity (>97:3 *trans* CH_3/H) and enantioselectivity (>99:1) but in only 31% yield. The major byproducts were carboxylic acids which appeared to result from Lewis acid catalyzed heterolysis of the allylic C−O bond of the lactone **8** to form an intermediate allylic carbocation. Since more rapid deprotonation of the complex between **8** and the chiral L_2BBr reagent was clearly desirable, the stronger hindered base pentaisopropylguanidine (Barton's base)[9] was then used. The result was a substantial increase in the yield of **9** (86%) (dextrorotatory) with no loss of the excellent degree of diastereo- and enantioselectivity.[10] The dramatic effectiveness of this conversion of **8** to **9** emphasizes the great potential for enantioselective Claisen rearrangements in synthesis.[7b,11]

The triene acid **9** was transformed into tetraene **10** (75% overall) (dextrorotatory) by hydride reduction, Dess-Martin oxidation[12] ($RCH_2OH \rightarrow RCHO$), and Wittig olefination ($RCHO \rightarrow RCH{=}CMe_2$). The next step in the projected synthesis, **10** → **11**, which we had expected to be routine, involved formidable difficulties. Hydroboration using 1 equiv of either 9-borobicyclo[3.3.1]nonane or disiamylborane was unsatisfactory due to preferential reaction with the endocyclic olefinic groups. This surprising result may be a consequence of unusually high reactivity of the trisubstituted endocyclic double bonds in **10** due to strain in the 11-membered ring. Zirconocene chloride hydride (Schwartz's reagent) in benzene at 60 °C afforded no hydrozirconation product but simply Cp_2ZrCl_2 from disproportionation. However, reaction of **10** with Cp_2HfHCl[13] in benzene at 50 °C for 10 h effected hydrometalation selectively at the vinyl appendage, as desired, to form an intermediate which upon treatment with *tert*-butyl hydroperoxide at 23 °C for 45 min produced the primary alcohol **11** in 68% yield. Two-step oxidation[12,14] converted **11** to carboxylic acid **12**, which was transformed into the corresponding acid chloride

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(3) (a) Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654. (b) Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 35. (c) Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761. (d) Kato, N.; Higo, A.; Nakanishi, K.; Wu, X.; Takeshita, H. *Chem. Lett.* **1994**, 1967.

(4) The *tert*-butyldiphenylsilyl ether **2** was prepared in 99% yield by reaction in DMF of TBDPSCl and imidazole with the corresponding bromo alcohol, which was made according to Corey et al.: Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *12*, 1051.

(5) Chloride **4** was prepared from (*E*,*E*)-farnesol (Aldrich Co.) by sequential reaction with (a) acetic anhydride, (b) NBS−H_2O−THF, (c) K_2CO_3−CH_3OH, and (d) MsCl−LiCl (71% overall).

(6) See: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(7) (a) Corey, E. J.; Lee, D-Y. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (b) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.

(8) For the use of boron enolates derived from L_2BBr in enantioselective *syn* and *anti* aldol reactions, see: Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

(9) Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085. The use of a *hindered* strong base is necessary to avoid coordination with the L_2BBr reagent.

(10) The diastereomeric purity of the Claisen rearrangement product **9** was determined by 500 MHz ^1H NMR analysis. The enantiopurity of **9** was determined by HPLC analysis using a Chiralcel OD column (Chiral Technologies). Details may be found in the supporting information.

(11) For a number of recent examples of *non-enantioselective* syntheses of medium rings from lactones by Claisen rearrangement, see: (a) Wipf, P. In *Compr. Org. Synth.* **1991**, *5*, 827 (review). (b) Magriotis, P. A.; Kim, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2972. (c) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (d) Knight, D. W.; Cameron, A. G. *Tetrahedron Lett.* **1982**, *51*, 5455.

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(13) For preparation, see: Tolstikov, G. A.; Miftakhov, M. S.; Valeev, F. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1979**, *28*, 2392.

(14) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574.

(15) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

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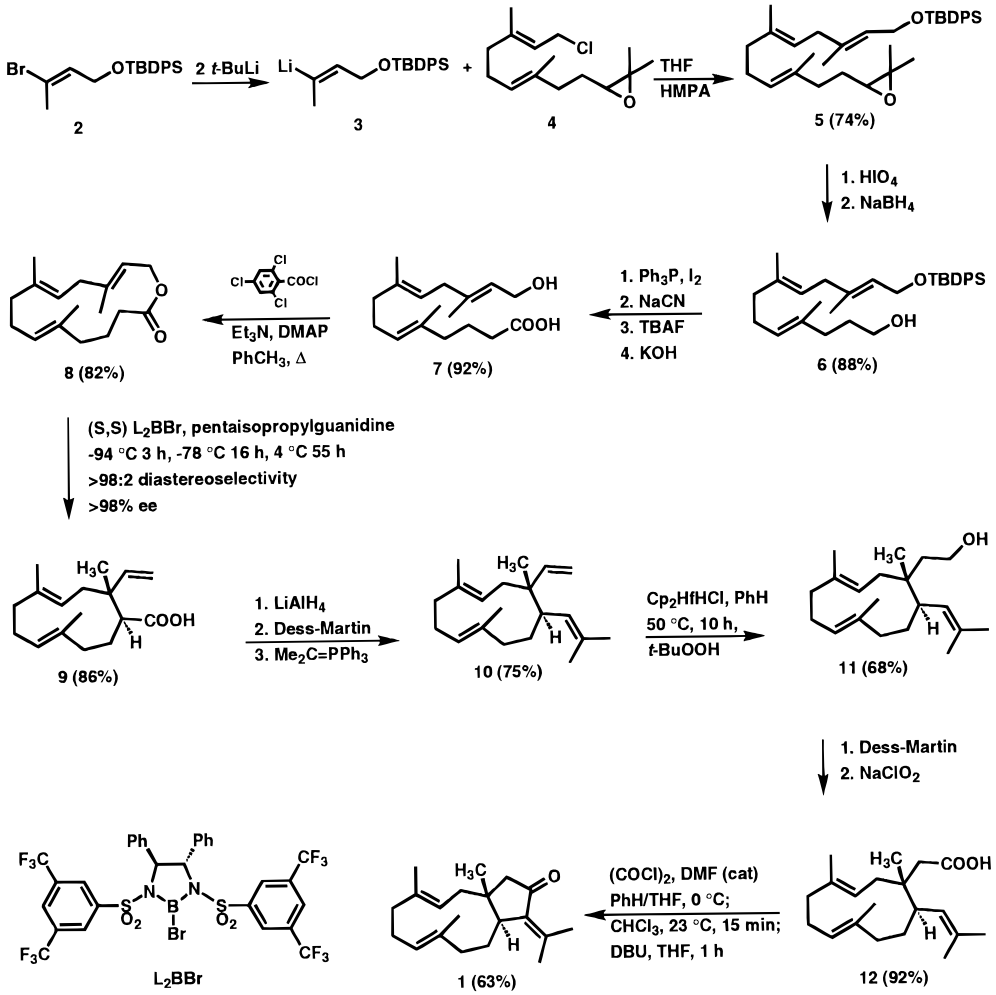
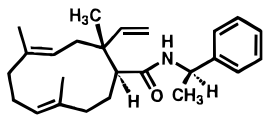
Scheme 1. Enantioselective Synthesis of Dolabellatrienone



by oxalyl chloride. The acid chloride underwent spontaneous cyclization upon storage in $CHCl_3$ solution for 15 min at room temperature to a mixture of bicyclic products (α,β- and β,γ-unsaturated and β-chloro ketones), which gave pure **1** upon treatment with 1,3-diazabicyclo[5.4.0]undec-7-ene (DBU) and chromatography on silica gel (63% from **12**). Synthetic dolabellatrienone (**1**) (colorless oil) was dextrorotatory as reported for the natural product. Although we observed a somewhat lower positive rotation, $[\alpha]^{23}_D$ +25° (c = 0.5, $CHCl_3$), than that previously reported (+31),[1a] we are confident of our value since synthetic **1** was determined to be pure by 500 MHz ^{1}H NMR, ^{13}C NMR, and HPLC analysis and since the enantiomeric purity (HPLC, Whelk-O1 column (Regis Co.)) was >99%.[16]

The absolute configuration for dolabellatrienone (**1**) is opposite to that previously assigned[1a] on the basis of NMR studies using Mosher's ^{19}F NMR method.[1a,15] Since our assignment based upon the expected absolute stereochemical course of the enantioselective Claisen rearrangement controlled by the (*S,S*)-form of L_2BBr and the literature assignment[1a] were in conflict, we have obtained additional unambiguous evidence of absolute configuration. The carboxylic acid **9** was converted to the corresponding amide with (*R*)-(+)-α-methylbenzylamine, and the resulting crystalline material (mp 202 °C) was subjected to X-ray single-crystal analysis, which showed the structure of this derivative to be **13**.[17] This result establishes beyond doubt the absolute configuration of dolabellatrienone as shown in **1** and would seem to require a revision of the absolute configuration previously accepted for at least some of the naturally occurring dolabellanes.[1,2]



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In summary, the synthesis described above demonstrates an entirely new approach to the enantioselective synthesis of chiral strained, medium-ring-containing structures from achiral precursors and emphasizes a new field of application of the venerable Claisen rearrangement. It is interesting that we were able to use the achiral intermediate **8** for the synthesis not only of **1** but also of *ent*-**1** and (±)-**1** (solid, mp 87−89 °C).

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Supporting Information Available: Experimental procedures and physical data for the synthesis of **1** from **2** and farnesol and for **13** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) The ^{1}H NMR, ^{13}C NMR, UV, IR, and MS data obtained for synthetic **1** were identical with those obtained for natural dolabellatrienone. We are grateful to Dr. William Fenical for providing copies of the spectra of natural **1**.

(17) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.