Stereocontrolled Synthesis of (–)-Hapalindole G

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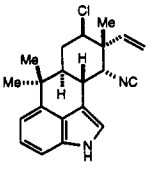
Received December 16, 1993

The hapalindoles were recently isolated by Moore and coworkers from the terrestrial blue-green alga *Hapalosiphon fontinalis* (Ag.) Bornet (Stigonemataceae) and have been shown to be responsible for most of the antibacterial, antimycotic, and antialgal activity associated with the alga.[1-3] A series of related natural products have more recently been reported which include hapalonamides,[4] ambiguine isonitriles,[5] and Fischerindole L.[6] A majority of these novel alkaloids, including hapalindole G (**1**), have in common a hitherto unknown tetracyclic indoloterpene framework of presumed tryptophan–monoterpene origin. Al-



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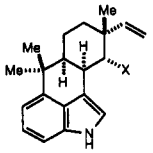
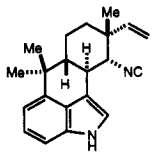


2: X = NC
3: X = NCS



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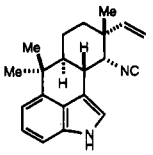

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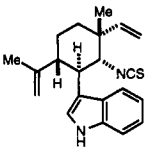

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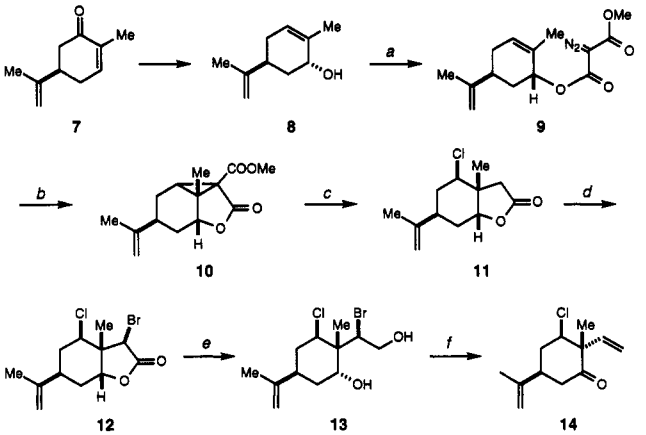
though the total syntheses of racemic hapalindoles J (**2**), M (**3**), H (**4**), and U (**5**)[7] as well as the enantiospecific synthesis of (+)-hapalindole Q (**6**)[8] have been reported to date, the more challenging hapalindoles containing chlorine adjacent to a quaternary center remain elusive. In this communication we report the first enantiospecific synthesis of (–)-hapalindole G (**1**).

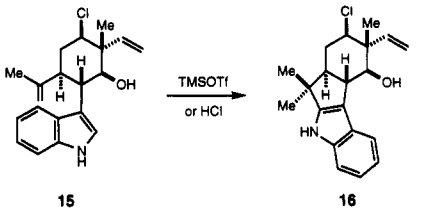
(–)-Carvone (**7**) was chosen as our starting material and was converted to (–)-*trans*-carveol (**8**) in two steps (Scheme 1).[9] Condensation of the carveol with methyl (chloroformyl)acetate followed by a diazo transfer under standard conditions[10] furnished the diazomalonate **9**. Intramolecular cyclopropanation of **9**, catalyzed by copper(II) bis(salicylidene-*tert*-butylamine)[11] in

Scheme 1[a]



[a] MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, –30 °C, (97%); *p*-AcNHC$_6$H$_4$SO$_2$N$_3$, DBU, CH_3CN, 23 °C (98%). [b] Copper(II) bis(salicylidene-*tert*-butylamine), CH_2Cl_2, 70 °C, 8 h (60%). [c] LiCl, CSA, DMF, 140 °C (71%). [d] LDA, –78 °C, THF, then CBr_4, –78 → 23 °C (81%). [e] DIBAL, –78 °C, CH_2Cl_2, then EtOH, $NaBH_4$, 23 °C (71%). [f] Zn–Cu couple, EtOH, reflux (95%); Jones reagent, acetone, 23 °C (99%).

Scheme 2



CH_2Cl_2, provided the desired cyclopropyl ester **10** in 60% yield. Among a variety of catalysts we tried, this was practically the only one that gave a satisfactory yield for the cyclopropanation. The critical, stereospecific introduction of chlorine to the hindered C-13 position (hapalindole numbering) was achieved by heating the activated cyclopropane ester **10** with lithium chloride and camphorsulfonic acid (CSA) in DMF at 140 °C, giving **11** in 71% yield as a result of the concomitant decarbomethoxylation. The lactone **11** was converted to the desired vinyl ketone **14** in an efficient four-step sequence involving bromination of the lactone, a one-pot, two-stage reduction of the α-bromo lactone **12** to the bromohydrin **13**,[12] reduction of **13** to the olefin **14** with zinc–copper couple, and subsequent Jones oxidation.

Our initial approach was to form the tetracyclic framework of the hapalindoles by cationic cyclization of the indole **15**[13] according to the reported procedure.[14] Unfortunately, the attempted cyclization of **15** under acidic conditions resulted in the exclusive formation of the undesired 2-substituted indole **16** (Scheme 2). Accordingly the following alternative approach has been developed to alleviate this cyclization problem. Aldol reaction of the ketone **14** was effected by addition of 1 equiv of lithium diisopropylamide (LDA) followed by addition of 0.1 equiv of Ti(O-*i*-Pr)$_4$ and *o*-iodobenzaldehyde to give an epimeric mixture of the hydroxy ketone **17** (Scheme 3).[15] While treatment of **15** with neat trifluoroacetic acid (TFA) yielded the desired tricyclic enone **18** directly, a higher and more reproducible yield was obtained in a three-step sequence ((1) acetylation; (2) elimination of the

(1) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.
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(12) In order to minimize the undesired debromination, it was essential to first reduce the lactone with DIBAL at –78 °C to the corresponding lactol followed by addition of ethanol and $NaBH_4$ to complete the reduction.
(13) This compound was prepared in three steps from **14**: (1) LDA, –78 °C, THF, then *o*,β-dinitrostyrene; (2) $NaBH_4$, MeOH; (3) Fe, AcOH, EtOH, reflux.
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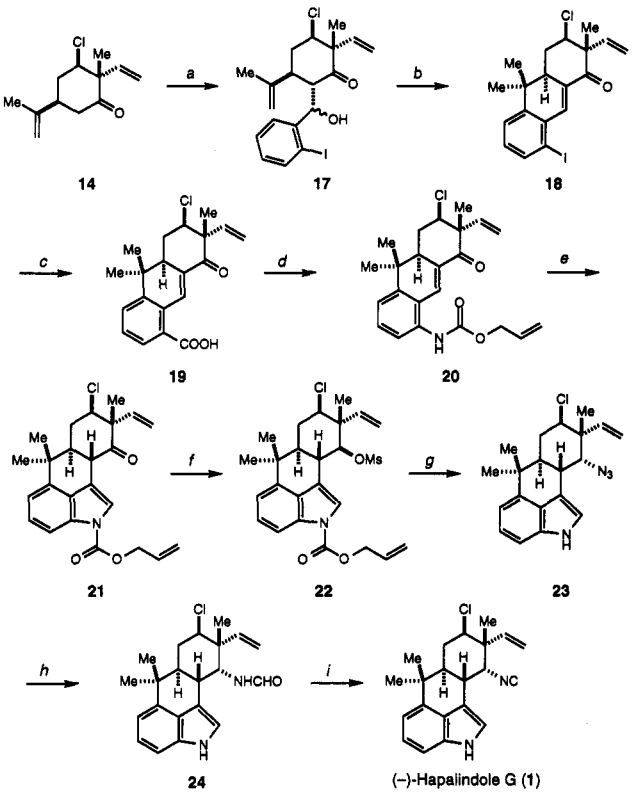
Scheme 3[a]



[a] LDA, −78 °C, THF, (*i*-PrO)$_4$Ti, then *o*-IC$_6$H$_4$CHO (68%). [b] Ac$_2$O, pyridine, 60 °C; DBU, C$_6$H$_6$, reflux; TFA–CH$_3$SO$_3$H (10:1), 23 °C (88% from **17**). [c] Pd(OAc)$_2$, Ph$_3$P, Et$_3$N, CO (1 atm), CH$_3$CN–H$_2$O (8:1), 80 °C (80%). [d] DPPA, Et$_3$N, allyl alcohol, toluene, 110 °C (90%). [e] LiCHSMe(SOMe), −78 °C, THF, then H$_2$O, HgCl$_2$, HClO$_4$, 80 °C (69%). [f] NaBH$_4$, MeOH, 23 °C (91%); Ms$_2$O, pyridine, 65 °C (82%). [g] LiN$_3$, 2% H$_2$O–DMF, 100 °C, 36 h (96%). [h] Na/Hg, EtOH, reflux; HCO$_2$H, Ac$_2$O, pyridine, CH$_2$Cl$_2$, 23 °C (84% from **23**). [i] COCl$_2$, Et$_3$N, CH$_2$Cl$_2$, 0 °C (90%).

resultant acetate by DBU; (3) treatment with TFA and methanesulfonic acid (10:1) (88% overall yield)).[16] Construction of the requisite indole was performed by first converting the aryl iodide **18** to the carboxylic acid **19** by a palladium-mediated carbonylation[17] and then transforming **19** to the allyl urethane **20** according to the Shioiri–Yamada procedure.[18] Conjugate addition of lithiated methyl (methylthio)methyl sulfoxide to the enone **20** followed by acid treatment in the presence of mercuric chloride furnished the indole **21** as a single stereoisomer in 50% overall yield from **18**.[19] Reduction of the ketone **21** with NaBH$_4$ gave exclusively the β-alcohol, which was converted to the mesylate **22** using methanesulfonic anhydride. The highly hindered mesylate **22** was treated with lithium azide in wet DMF at 100 °C for 36 h, giving the desired α-azide **23** in 96% yield with concomitant deprotection of the allyl urethane. While the hindered azide **23** resisted the attempted reduction with Zn–AcOH, Ph$_3$P, *n*-Bu$_3$P, or H$_2$S–Py, it was smoothly reduced to the corresponding amine by heating with sodium amalgam in ethanol, which was subsequently formylated in a conventional manner to provide the formamide **24**. Finally, dehydration of the formamide **24** with phosgene and triethylamine gave (−)-hapalindole G (**1**) in 90% yield ($[\alpha]_D^{25}$ −45.0° (*c* = 0.037, CH$_2$Cl$_2$), lit.[2] $[\alpha]_D^{23}$ −43.9° (*c* = 0.28, CH$_2$Cl$_2$)). The synthetic (−)-hapalindole G was identical to an authentic sample by spectroscopic comparison (^{1}H NMR, ^{13}C NMR, MS, IR, CD).[20]

Acknowledgment. Financial assistance from the Robert A. Welch Foundation is gratefully acknowledged.

Supplementary Material Available: Spectroscopic data of the key intermediates (**9–14** and **17–24**) and synthetic (−)-hapalindole G (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) No cyclization products were obtained when the compounds with a range of protected amino functionalities, such as acetamide, azide, and nitro in place of the iodide, were subjected to the same acidic conditions.

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(19) The stereochemistry of **21** was assigned as shown on the basis of the ^{1}H coupling constant of H-9 and H-10 (J = 12.7 Hz).

(20) We are indebted to Professor Richard E. Moore of the University of Hawaii for direct comparison of our synthetic sample with the natural hapalindole G.