Natural Products Synthesis

Fully Stereocontrolled Total Syntheses of (−)-Cylindricine C and (−)-2-Epicylindricine C: A Departure in Sulfonamide Chemistry**

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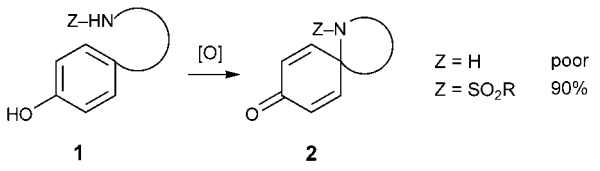
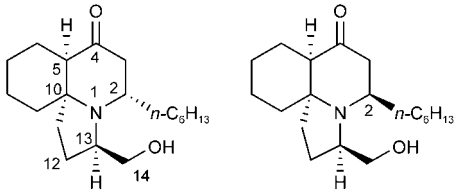
The oxidative spirocyclization of phenolic primary amines (**1**→**2**; Z = H) holds considerable potential in the chemical syntheses of spirocyclic natural products and pharmaceutically interesting molecules. We recently disclosed that this hitherto problematic transformation may be carried out through the oxidation of sulfonamide derivatives of primary amines with $PhI(OAc)_2$ ((diacetoxyiodo)benzene, DIB) in excellent yield.[1] Further studies have revealed that the sulfonamide unit may function not only as a modulator of the reactivity of the primary amino group to allow an otherwise "impossible" transformation, but also (and especially so) as a useful implement for the subsequent elaboration of spirocycles **2** (Z = SO_2R) into more-complex synthetic goals. Herein, we describe the fully stereocontrolled total syntheses of (−)-cylindricine C (**3**) and its stereoisomer (−)-2-epicylindricine C (**4**), which has not yet been observed as a natural product, from a common precursor **14**, to illustrate some possibilities inherent to the combination of oxidative spirocyclization technology with such sulfonamide-based transformations.



1 **2**



3

4

Cylindricines are structurally unique alkaloids produced by the ascidian, *Clavelina cylindric*a.[2] Their unusual architecture and (moderate) cytotoxic activity have elicited substantial interest in the synthetic arena.[3,4] Research in this domain has shown that the series of 2-epi derivatives may result from a Michael-[5] or Mannich-type[3e] cyclization of suitable precursors. A synthesis capable of providing *either* **3** or **4** from a common intermediate, such as **14** in the present case, is clearly not subject to any stereochemical uncertainty.

Commercial D-homotyrosine[6] was elaborated into the sulfonamide **5** in a conventional fashion.[7] Subsequent oxidation of **5** by DIB in hexafluoro-2-propanol induced cyclization into **6** in excellent yield. The primary OH group was then protected as a bulky *tert*-butyldiphenylsilyl (TBDPS) ether prior to the desymmetrization of the locally symmetrical dienone in **7** through the regioselective base-promoted 1,4-addition of the anion of the sulfonamide group. It is apparent that the methyl group of the mesylamide is poised to become the carbonyl group of **3** and **4**. Conversion of **7** into **8** occurred with satisfactory diastereoselectivity (d.r. = 7:1) upon treatment of **7** with KHMDS at −100 °C.[8] The two regioisomers thus produced were not separable at this point, but the minor isomer was readily removed at the stage of compound **10**, which resulted upon treatment of **8** with PhSH and $BF_3{\cdot}OEt_2$ to form **9** diastereoselectively,[9] followed by the desulfurization of the latter with Raney Ni[10] (Scheme 1).

The importance of the sulfonamide function in the construction of the third and final ring of the molecule becomes fully apparent at this juncture. Deprotonation of **10** with *t*BuLi[11] and capture of the anion with racemic octene oxide activated by $BF_3{\cdot}OEt_2$[12] resulted in the formation of **11**,

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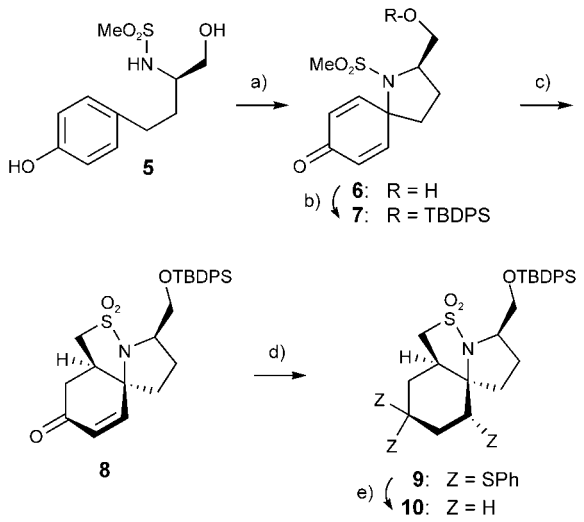
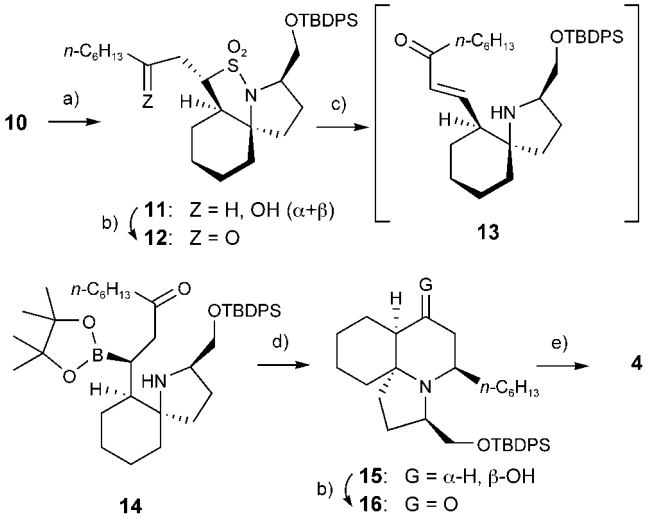


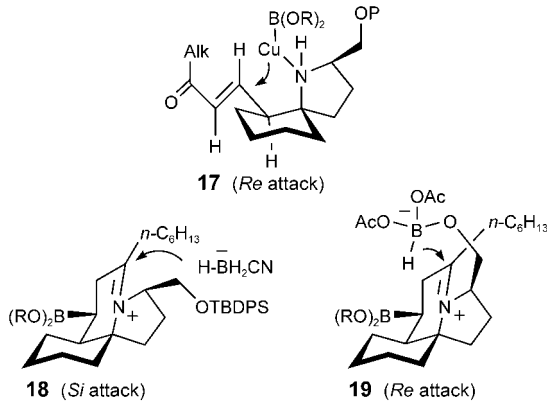
Scheme 1. a) $PhI(OAc)_2$, $(CF_3)_2CHOH$, room temperature; b) $tBuPh_2SiCl$, imidazole, DMF, room temperature, 82% over two steps; c) KHMDS, THF, −100°C, 89% (d.r. = 7:1); d) PhSH, $BF_3{\cdot}OEt_2$ (cat.), CH_2Cl_2, 0°C, 77%; e) Raney Ni, EtOH/THF, 77%. DMF = *N*,*N*-dimethylformamide, KHMDS = potassium hexamethyldisilazide

which was then subjected to a Dess–Martin oxidation[13] to give **12**. A one-pot sequence, which involved sequential β-elimination and Miyaura borylation[14] of the isolable intermediate **13**, resulted in the extremely rapid (20 min; the reaction normally requires > 15 h) and highly diastereoselective[15] formation of the boronic ester **14** (Scheme 2). Several pieces of evidence suggest that the unusually fast rate and the high degree of diastereoselectivity observed in the Miyaura reaction of **13** may be ascribed to a directing effect of



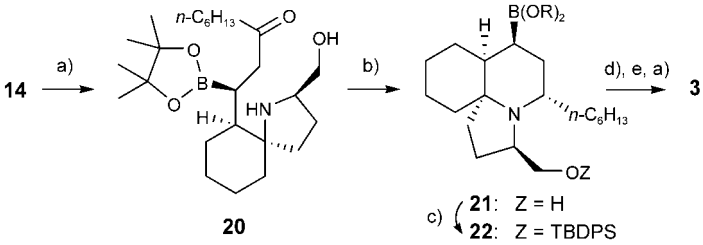
Scheme 2. a) *t*BuLi, THF, −78°C, (±)-1-octene oxide, BF_3OEt_2; b) Dess–Martin periodinane, CH_2Cl_2, room temperature, 88% over two steps for **12**; 94% for **16**; c) 1. DBU, DMF, then 2. bis(pinacolyl)diboronate, CuCl, KOAc, room temperature, 86%; d) 1. $NaBH_3CN$, AcOH, MeOH, 0°C, then 2. H_2O_2, NaOH, 80%; e) TBAF, THF, 96%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBAF = tetra-*n*-butylammonium fluoride

the nitrogen atom. We thus envision that the selective delivery of the copper(I) agent to the *Re* face of the double bond occurs from a complex such as **17**. Similar directed organocopper additions are documented.[16]



Intermediate **14** is then readily and diastereoselectively elaborated into either cylindricine C or into 2-epicylindricine C (Scheme 2). Compound (−)-**4** was prepared through an initial one-pot, sequential intramolecular reductive amination reaction (AcOH, $NaBH_3CN$)[17] and borane oxidation process (H_2O_2, NaOH). This resulted in the highly stereoselective[15] formation of **15**. A rationale for this elevated diastereoselectivity is proposed as follows: A MM+ force field study suggests that the configuration of the borylated stereogenic carbon center defines **18** as the most stable conformer of the presumed iminium ion intermediate. Reduction of **18** under stereoelectronic control (axial delivery of hydride)[18] yields **15**. Dess–Martin oxidation[13] of **15** and deprotection led to **4**.[19]

The total synthesis of (−)-cylindricine (Scheme 3) started with the desilylation of **14** followed by treatment of the



Scheme 3. a) TBAF, THF, 95% for **20**, 96% for **3**; b) $NaBH(OAc)_3$, AcOH (cat.), CH_2Cl_2, −78°C, 73%; c) $tBuPh_2SiCl$, imidazole, DMF, 95%; d) H_2O_2, NaOH, THF, 0°C 97%; e) Dess-Martin periodinane, CH_2Cl_2, room temperature, 94%.

resultant product **20** with $NaBH(OAc)_3$ and a catalytic quantity of AcOH. This induced a highly stereoselective[15] Evans-type directed reduction[20] of a presumed iminium ion intermediate **19**. Such a directed reduction of an iminium ion appears to be undocumented. The emerging product **21** was readily transformed into **3** as shown in Scheme 3.[21]

The applicability of the new technology to other synthetic problems is currently under study and will constitute the subject of future reports.

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Keywords: antitumor agents · cyclization · spiro compounds · sulfonamides · total synthesis

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[5] Unpublished results from these laboratories; details will be provided in a forthcoming full paper.

[6] The absolute configuration of cylindricine C is unknown.[2] We chose to prepare (−)-**4** from D-homotyrosine for comparison purposes because at the beginning of our investigations the only enantioselective synthesis of (−)-**4** reported in the literature was that by Molander and Roenn.[3a]

[7] a) $SOCl_2$/MeOH; b) MsCl/TEA (excess), CH_2Cl_2, 0 °C, (formation of the *N*,*O*-dimesyl derivative), 91% over two steps; c) $NaBH_4$/EtOH/THF, 94%; d) NaOH/dioxane, 80 °C, 90%. Ms = methanesulfonyl, TEA = triethylamine.

[8] Under identical conditions, cyclization of the corresponding methyl ether proceeded with d.r. = 3.5:1 and that of the TBDMS ether with d.r. = 4.5:1.

[9] The structure of this material was confirmed by an X-ray crystallographic study of its desilylated analogue. The selectivity of the 1,4-addition of PhSH to **8** appears to be due to a Felkin–Anh-type stereoelectronic effect created by the strongly electronegative sulfonamide nitrogen atom. For examples, see: a) E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 875; b) S. Bennabi, K. Narkunan, L. Rousset, D. Bouchu, M. A. Ciufolini, *Tetrahedron Lett.* **2000**, *41*, 8873, and references therein.

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[15] Only one stereoisomer of the product was apparent within the limits of ^{1}H- (300 MHz) and ^{13}C NMR (75 MHz) spectrometry.

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[17] For related processes, see reference [3g].

[18] For a discussion, see: R. V. Stevens, *Acc. Chem. Res.* **1984**, *17*, 289.

[19] The ^{1}H NMR spectra of (−)-**4** synthesized herein ($[\alpha]_D^{25} = -39°$; $c = 0.5$ in CH_2Cl_2), could be superimposed on those of (±)-2-epicylindricine C published by Weinreb and co-workers[3e] (see Supporting Information).

[20] D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, G. S. Sheppard, *J. Am. Chem. Soc.* **1990**, *112*, 866.

[21] The ^{1}H NMR spectra of (−)-**3** synthesized herein could be superimposed on those of (−)-cylindricine C reported by Molander and Roenn[3a] (see Supporting Information), and the specific rotations were also essentially identical: $[\alpha]_D^{25} = -66°$ ($c = 0.5$ in CH_2Cl_2) for **3** versus $[\alpha]_D^{25} = -64°$ ($c = 0.2$ in CH_2Cl_2) for reference [3a].

