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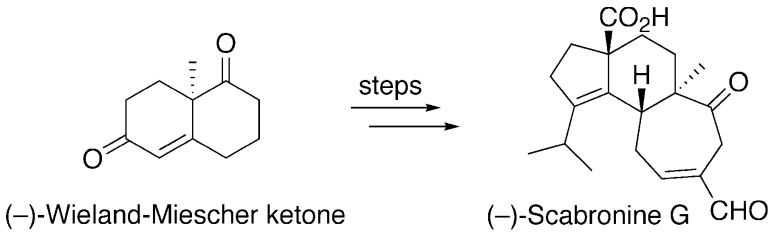

(–)-Wieland-Miescher ketone (–)-Scabronine G

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Total Synthesis of (−)-Scabronine G, an Inducer of Neurotrophic Factor Production

Stephen P. Waters, Yuan Tian, Yue-Ming Li, and Samuel J. Danishefsky*

Laboratory for Bioorganic Chemistry and Laboratory of Biochemistry and Pharmacology, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

Received August 1, 2005; E-mail: s-danishefsky@mskcc.org

The scabronines, metabolites from the bitter mushroom *Sarcodon scabrosus*, are related to a broader class of angularly fused tricyclic diterpenoids known as cyathanes.[1] Our interest in scabronine G (**1**) followed a report by Ohta which disclosed it to induce the production and excretion of nerve growth factor (NGF) in 1321N1 human astroglial cells.[2] Its methyl ester derivative (**2**) is even more active in promoting excretion of NGF and an additional neurotrophin, interleukin 6 (IL-6). Consistent with these biochemical markers, dramatic neuronal differentiation of rat pheochromocytoma cells (PC-12) was also observed. Accordingly, compounds **1** and **2** fall in to a class of nonpeptidyl structures exhibiting neurotrophic properties.[3]

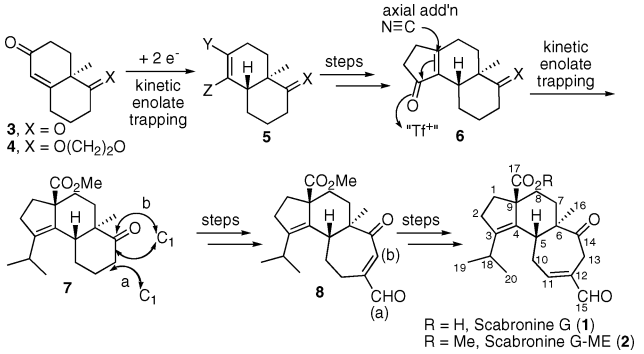
Naturally occurring polypeptidyl neurotrophic factors play a central role in mediating neuronal growth and survival.[4] The study of the mechanism of action of these factors (cf. NGF and BDNF) is one of the central challenges to the neurosciences. The clinical application of naturally occurring polypeptidyl neurotrophic factors in reversal of neurodegenerative disorders (cf. Parkinson's, Alzheimer's Diseases) has been investigated. However, unfavorable pharmacokinetics require their direct infusion into appropriate sectors of the brain, thus seriously complicating their progression to medical application.[5]

One of the goals of our laboratory is that of identifying promising small molecules with neurotrophic activity. Toward this end, we are drawn to natural products which exhibit such activity and whose structures invite new possibilities in chemical synthesis. Earlier in our program, we reported total syntheses of the extensively oxidized neurotrophic agents tricycloillicinone, merrilactone A, and jiadefenin.[6] The scabronines struck us even more important in light of the data reported above. Herein we describe the first total synthesis of scabronine G.[7]

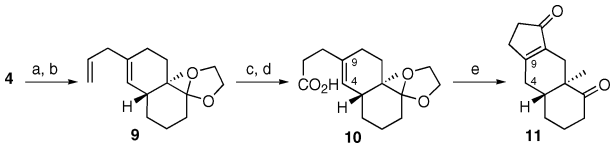
*We operated from the pleasingly simple idea that scabronine G can be viewed as an annulated (ring A) one-carbon ring-expanded (ring C) version of the (−)-Wieland−Miescher ketone (**3**).*[8] Trapping of the reductively generated *trans* BC fused kinetic enolate derived from **4** would provide the as-yet undefined **5** (Scheme 1). The condition placed on the Y and Z functions of **5** is that they be integratable to afford **6**. Anticipating conjugate attack of a cyano nucleophile on the 4,9-enone,[9] the remote C6−C9 backbone relationship would be solved through sound stereoelectronic principles rather than through ad hoc steric hindrance based selectivities. In the concluding phases, sequential interpolation of two C_1 fragments, which emerge as C15 and C13, respectively, would lead to **8** and thence to **1** and **2**.

We first describe an initiative which, while unsuccessful from the perspective of our proposed total synthesis, provided a valuable teaching in structuring our later work. From **4**,[10] kinetically controlled enol triflation[11] followed by Stille cross-coupling gave diene **9** in the expected stereo- and regiocontrolled manner (Scheme 2). Chemoselective hydroboration of the terminal olefin and further oxidation provided carboxylic acid **10**. Interestingly, acid-mediated Friedel−Crafts-type annulation of **10** provided **11** rather than the expected **6**.

Scheme 1. Synthetic Strategy toward Scabronine G



Scheme 2. Attempted Synthesis of Cyclopentenone **6**[a]



[a] Key: (a) Li/NH_3, $PhNTf_2$, THF, −78 °C, 73%; (b) allylSn(Bu)$_3$, Pd(PPh$_3$)$_4$, LiCl, THF, 55 °C, 96%; (c) 9-BBN, THF; NaOH, H_2O_2, 0 °C, 92%; (d) Jones reagent, acetone, 82%; (e) PPA, CH_2Cl_2, 75 °C, 60%.

We took this then disappointing outcome to presage potential problems in fashioning the cyclopentenone moiety of **6** by cyclization of a three-carbon fragment based at C9 (see **5**). Such a modality would require an attack at C4, which is 1,3-diaxial to the angular methyl group and *ortho* to the hindered C ring. The take-home lesson for us, still keeping within the spirit of Scheme 1, was to securely install the substitution at C4 via the Z group, leaving the cyclization event to occur at C9. Reduction of **4** and acylation with Mander's reagent afforded the known ketoester **12** (Scheme 3).[12] Conversion of the ketone to its enol triflate followed by hydride reduction gave unsaturated ester **13**.[13] Transformation of the ester in **13** to the corresponding Weinreb amide[14] and subsequent addition of vinylmagnesium bromide provided the divinyl ketone, **14**. Lewis acid-mediated Nazarov cyclization provided the requisite cyclopentenone **6** as a single olefin isomer.[15] Indeed, conjugate addition of Nagata's reagent[9] to the enone in **6** and trapping of its derived aluminum enolate with TMSCl gave a silyl enol ether which was converted to **15** as shown.[16] Installation of the isopropyl group via Negishi coupling (notably, to a secondary sp^3 center) afforded **16**.[17] The orchestration of stereocontrolled Nagata addition with enolate trapping and cross-coupling has apparently not been widely

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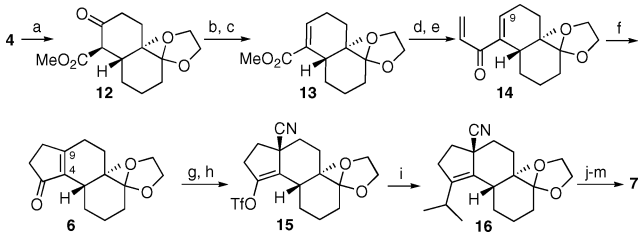
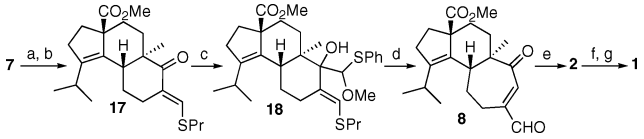
Scheme 3. Synthesis of Intermediate **7**[a]



[a] Key: (a) Li/NH_3, *t*-BuOH, THF, −78 °C; $NCCO_2Me$, 72%; (b) NaH, $PhNTf_2$, DME, 98%; (c) $Pd(PPh)_3$, Bu_3SnH, LiCl, THF, 55 °C, 91%; (d) LHMDS, Me(OMe)NH·HCl, THF, −10 °C, 79%; (e) vinylMgBr, THF, −10 °C, 84%; (f) $FeCl_3$, CH_2Cl_2, 72%; (g) Et_2AlCN, THF, Et_3N, TMSCl; (h) *t*-BuOK, THF, −78 °C, *N*-(5-chloro-2-pyridyl)triflimide, 86% over two steps; (i) *i*-PrMgCl, $ZnCl_2$, LiCl, $(dppf)PdCl_2$, THF, 55 °C, 75%; (j) DIBAL-H, CH_2Cl_2, −78 °C, 88%; (k) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O; (l) MeI, K_2CO_3, DMF; (m) THF, HCl/H_2O; 92% over three steps.

Scheme 4. Synthesis of Scabronine G[a]



[a] Key: (a) NaH, HCO_2Me, DME, 97%; (b) *n*-PrSH, TsOH, PhH, 50 °C, 93%; (c) *n*-BuLi/$MeOCH_2SPh$, THF, −78 °C; (d) $HgCl_2$, HCl/MeCN, 80 °C, 86% over two steps; (e) DBU, benzene, 75 °C, quant; (f) TsOH, $HO(CH_2)_2OH$, PhH, 89%; (g) aq. NaOH, MeOH, 55 °C, then HCl, 87%.

practiced. Conversion of the nitrile to the corresponding methyl ester and deketalization provided cyclohexanone **7**.

The stage was now set for further elaboration to scabronine G. Ketone **7** was converted to thiopropylmethylidene intermediate **17** in two steps (Scheme 4). Addition of lithiated methoxymethyl phenyl sulfide afforded diastereomeric alcohols **18**, which, upon treatment with $HgCl_2$ in acidic medium, underwent ring expansion to afford the cross-conjugated cycloheptenone **8**.[18] Thermodynamically favored isomerization of the olefin in **8** (cf. ref 7b) afforded scabronine G methyl ester (**2**), whose spectral data were identical to those derived from natural sources. The natural product itself (**1**) was accessed, after chemoselective protection of the aldehyde function, by saponification of the ester and subsequent hydrolysis of the dioxolane moiety.

Fully synthetic scabronine G methyl ester (**2**) effectively enhanced the biosynthesis and secretion of neurotrophic factors from 1321N1 human glial cells. In turn, significant neurite outgrowth of PC-12 cells was observed after treatment with the conditioned 1321N1 cell culture medium (Figure 1). To our delight, synthetic intermediate **8**, a cross-conjugated analogue of **2**, displayed greater activity as evidenced by increased neurite length. These effects were comparable to those produced by direct exposure of PC-12 cells to purified NGF (50 ng/mL, see graph). Very small differences in neurite outgrowth may enable otherwise failed synapses to be fruitful. The ability of **2** and, particularly **8**, to extend the length of pre-existing neurites invites the study of their applicability in neurodegenerative disorders.

In summary, the first total synthesis of scabronine G, in optically pure form, has been achieved in a high-yielding sequence from readily available materials. We emphasize that this sequence, which borrows primarily from the more classical canons of organic synthesis, lends itself to both multigram scale-up and to molecular modification. Moreover, it was demonstrated that an olefin isomer showed a more efficacious activity profile. Improved activity through a subtle movement in olefin position provides a point of entry for further total synthesis enabled SAR studies, which are currently underway.

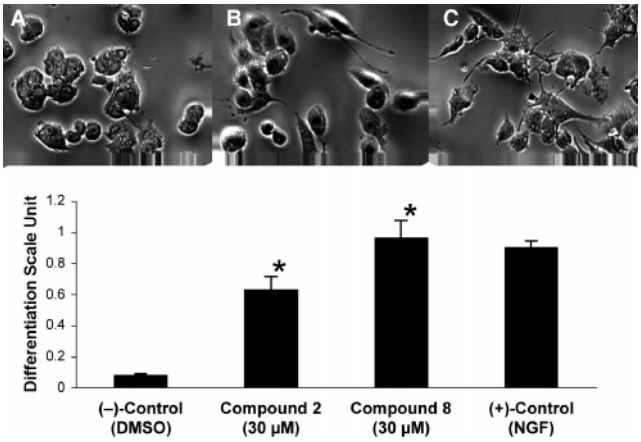


Figure 1. Images of differentiation and neurite outgrowth of PC-12 cells after treatment with the 1321N1 cell culture medium conditioned by: (A) DMSO (negative control), (B) scabronine G methyl ester (**2**, 30 μM), and (C) compound **8** (30 μM), and graphical evaluation of neurite outgrowth of PC-12 cells (*P < 0.001 relative to DMSO control).

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Supporting Information Available: Experimental procedures, characterization data, assay protocols, and a further discussion on cyclopentenone intermediate **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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