Natural Product Synthesis

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Total Syntheses of (−)-Scabronines G and A, and (−)-Episcabronine A**

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(−)-Scabronines A–G (Figure 1) and (−)-episcabronine A (**2**) were isolated from the bitter mushroom, *Sarcodon scabrosus*, and characterized by Ohta et al.[1] (−)-Scabronine A (**1**) contains six contiguous stereogenic centers in its seven-membered ring, thus distinguishing it as the most

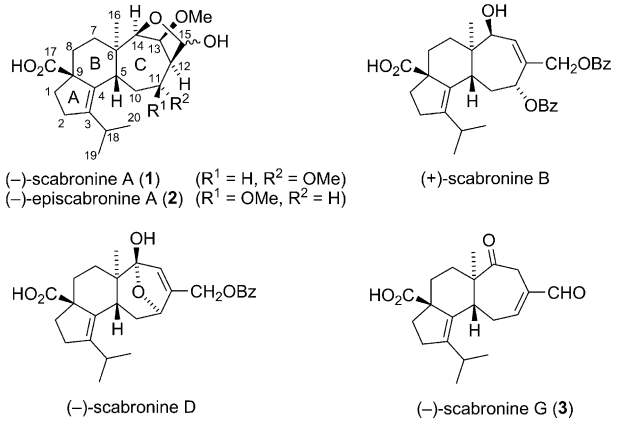

Figure 1. Selected members of the scabronines.

complex structure in the scabronine family. (−)-Scabronine G (**3**) possesses the least oxidized seven-membered ring of known scabronines, which range in oxidation state between **1** and **3**. Biogenetic deviation of **1** from **3** through various oxidation processes is inferred by the array of isolated natural products.

The compounds **1** and **3** demonstrate a potent induction effect upon the production and excretion of neurotrophic factors, including nerve growth factor (NGF) in 1321N1 human astroglial cells.[1a,c,2] NGF is a member of a family of small secreted proteins known as neurotrophins, which are important signaling molecules for the growth, maintenance, and survival of neural cells.[3] It has been suggested that administration of exogenous NGF could result in cytoprotection and stimulate the outgrowth of neuritic projections.[4] Consequently, direct administration of NGF to the brain has potential applicability in the treatment of neurodegenerative disorders such as Alzheimer, Parkinson, and Huntington diseases.[5] However, this approach is clinically problematic because NGF does not cross the blood-brain barrier (BBB) and is rapidly metabolized in vivo.[4]

Hence, the search for compounds able to stimulate the endogenous production of NGF has led to the isolation of structurally unique natural products with this property.[6] Owing to their lipophilic nature and small size, cyathane diterpenoids present promising characteristics amenable to crossing of the BBB. Accordingly, their therapeutic relevance and synthetic challenges have evoked intense investigation by a number of research groups since their description in the literature.

But while a large number of synthetic studies involving cyathane diterpenoids were performed over the last decade,[7–9] only two total syntheses of scabronines have been reported.[10] Lack of literature precedent may be attributable to their highly oxygenated structures. Thus, the C9-methyl group and C3-isopropyl group are oxidized in scabronines, thus distinguishing them as difficult synthetic targets. Although (−)-scabronine A (**1**) is one of the most potent NGF synthesis stimulators, its total synthesis has not been achieved to date.[11] Herein we report the enantioselective total syntheses of (−)-scabronines G and A, and (−)-episcabronine A.

Scheme 1 displays the retrosynthetic analysis of **1**–**3** through the key intermediate **6**. Considering the same relative configurations of C11 and C14 in **1** and (+)-scabronine B (Figure 1), we surmised that the latter compound is a biosynthetic intermediate. Hence, we envisioned a biomimetic approach from **4** and **5** to **1** and **2**, respectively. The oxa-Michael reaction may take place at C13 from the less-hindered β face of **4** to form an enolate with a subsequent protonation/acetalization cascade, thus affording a hemiacetal with C12 and C13 stereogenic centers. The C11-hydroxy group in **4** was expected to resist β elimination because of its poor leaving ability. In contrast, β elimination of the C11 benzoate in **5** could follow the oxa-Michael reaction of **5**, thus allowing the resultant enal to undergo a second oxa-Michael reaction with sodium methoxide at the C11-position with a subsequent protonation/acetalization cascade to give a hemiacetal with three (C11–C13) contiguous stereogenic centers in **2**.

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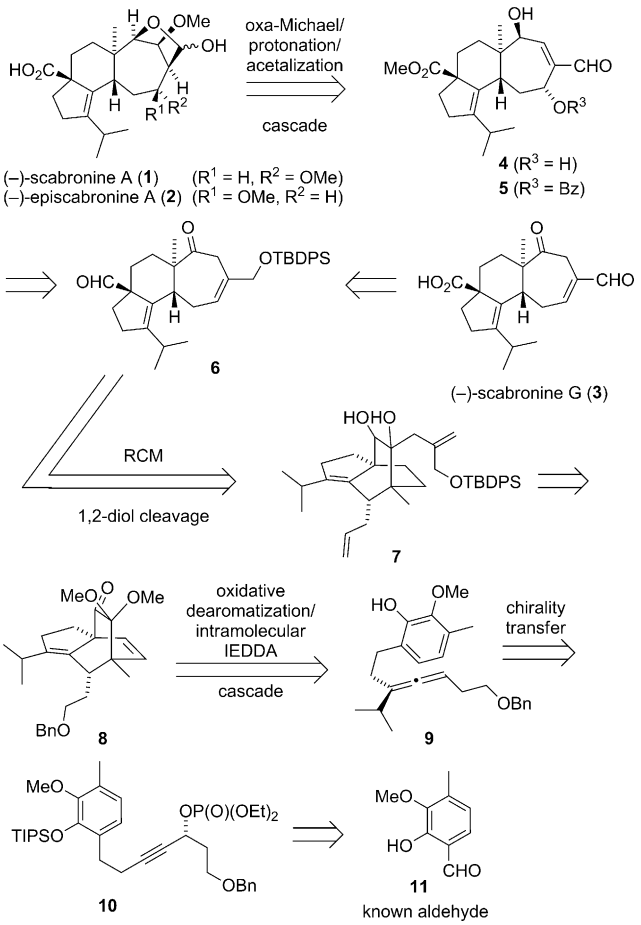
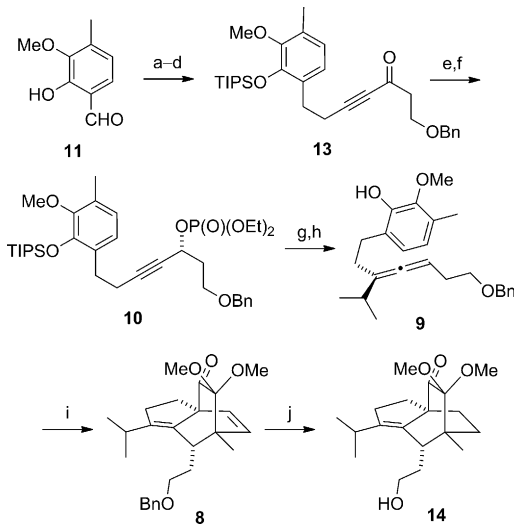


Scheme 1. Retrosynthetic analysis of (−)-scabronine A, (−)-episcabronine A, and (−)-scabronine G.



Scheme 2. Highly stereoselective preparation of **14**. Reagents and conditions: a) TIPSCl, imidazole, DMF, 40 °C, 83 %. b) propargyl bromide, Zn, $TiCl_4$ (5 mol %), THF, 0 °C. c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 84 % (2 steps). d) *n*BuLi, $BnO(CH_2)_2CON(OMe)Me$ (**12**), THF, −78 °C to RT, 89 %. e) Ru[(*R*,*R*)-Tsdpen](*p*-cymene) (6 mol %), *i*PrOH, RT, 92 % (95 % *ee*); f) $(EtO)_2P(O)Cl$, DMAP, Et_3N, CH_2Cl_2, RT, 97 %. g) *i*PrMgCl, CuCN·2 LiCl, THF, −78 °C, quant. h) TBAF, THF, 0 °C, 97 % (95 % *ee*). i) PIDA, MeOH, RT, 7 days, 97 %. j) H_2, Pd/C (5 mol %), EtOAc, RT, 92 % [95 % *ee*, >99 % *ee* (recryst)]. DMAP = 4-(*N*,*N*-dimethyl)pyridine, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, TIPS = triisopropylsilyl, Tsdpen = *N*-*p*-tosyl-1,2-diphenylethylenediamine.

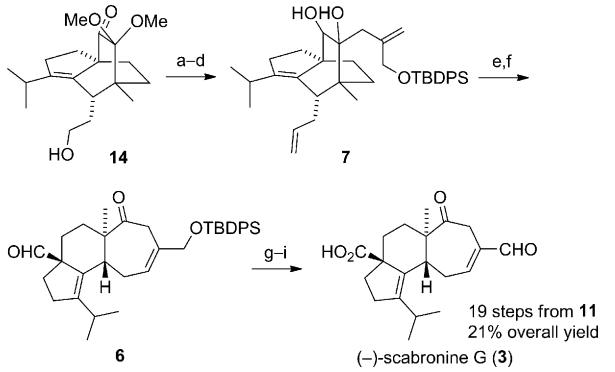
The compound **6** is a rational intermediate for **3**, **4**, and **5**, given our previous reports of the total syntheses of cyathanes in which requisite stereoselective transformations from **6** into both **4** and **5** were achieved.[9g,k,m] The compound **6** was deemed accessible from **7** by a 1,2-diol cleavage and subsequent ring-closing metathesis (RCM). The compound **7** could be prepared from **8**, which could itself be generated by the oxidative dearomatization[12] of **9** and an intramolecular inverse-electron-demand Diels–Alder (IEDDA) reaction.[13] The intramolecular IEDDA reaction offered an appealing method for simultaneous generation of the two C6 and C9 stereogenic centers and the C3-C4 tetrasubstituted alkene. As the chiral allene **9** could be prepared by a chirality-transfer reaction of **10**, total syntheses of **1**–**3** commenced with the preparation of **10**.

Propargylation[14] of the TIPS ether of **11**[15] and reductive removal of the benzylic hydroxy group with triethylsilane gave an alkyne (Scheme 2). Lithiation of the terminal alkyne and subsequent reaction with the Weinreb amide **12**[16] provided **13**. Noyori reduction[17] of **13** afforded the desired alcohol (95 % *ee*), which was converted into the phosphate **10**. The reaction of **10** with isopropylmagnesium chloride and CuCN·2 LiCl[18] quantitatively afforded a chiral allene with subsequent removal of the TIPS group to afford **9**. HPLC analysis of **9** confirmed complete chirality transfer from **10** to the chiral allene.

The reaction of **9** with phenyliodine(III) diacetate (PIDA) afforded an *o*-benzoquinone mono-dimethylacetal at 0 °C within 15 minutes. Subsequent intramolecular IEDDA proceeded slowly at room temperature[19] and required seven days to give a single product with 95 % *ee*, a product which was structurally confirmed by X-ray crystallographic analysis of **14**.[20] The high stereoselectivity of this reaction is attributed to the IEDDA transition state which avoids steric repulsion between the dimethyl acetal and 2-benzyloxyethyl groups.

Swern oxidation of **14** (Scheme 3), Wittig reaction, and subsequent reduction and acidic work-up generated a hydroxyketone, which was treated with an organozinc reagent prepared from **15**,[21] to afford **7** as a single isomer. NOESY analysis of a derivative of **7** supported the structure in Scheme 3. The *cis*-1,2-diol of **7** resisted oxidative cleavage by $NaIO_4$, probably as a result of steric hindrance. However, the reaction with PIDA[22] successfully afforded a ketoaldehyde, which underwent RCM with the Grubbs II catalyst[23] to produce **6** in excellent yield. Removal of the TBDPS group and subsequent Pinnick and Dess–Martin oxidations afforded pure (−)-scabronine G (**3**; 9 steps from **11**; 21 % overall yield).

Subsequently we examined the total synthesis of (−)-scabronine A and its methyl ester from **6** (Scheme 4). An attempt was made to epoxidize the C11-C12 alkene of **6** and its derivative but without success. However, the corre-



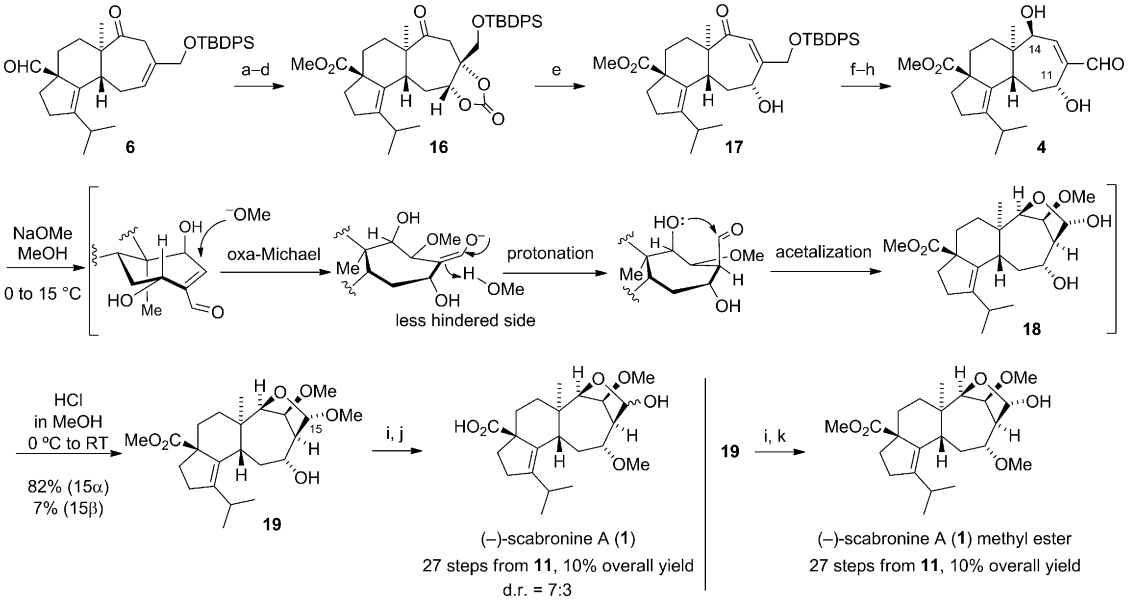
Scheme 3. Total synthesis of (−)-scabronine G. Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 98%. b) Ph_3PCH_3Br, *t*BuOK, THF, 0 °C, 99%. c) $NaBH_4$, MeOH, 0 °C; then, 3 N HCl (aq.), 95%. d) $H_2C{=}C(CH_2Br)(CH_2OTBDPS)$ (**15**), Zn, THF, RT, 91%. e) PIDA, CH_2Cl_2, RT, 90%. f) Grubbs II (2.5 mol%), CH_2Cl_2, reflux, 98%. g) TBAF, AcOH, THF, RT, 70%. h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*BuOH, H_2O, RT, 97%. i) DMP, CH_2Cl_2, 0 °C, 89%. DMP = Dess–Martin periodinane, DMSO = dimethyl sulfoxide, TBDPS = *tert*-butyldiphenylsilyl.

sponding methyl ester, which was prepared from **6**, was successfully converted into **16** (d.r. = 3.3:1) by dihydroxylation and carbonate formation. Treatment of **16** with DBU cleanly gave **17**, followed by CBS reduction,[9k,24] removal of the TBDPS ether, and selective oxidation of the primary hydroxy group with TEMPO and PIDA to give **4** as a single isomer.

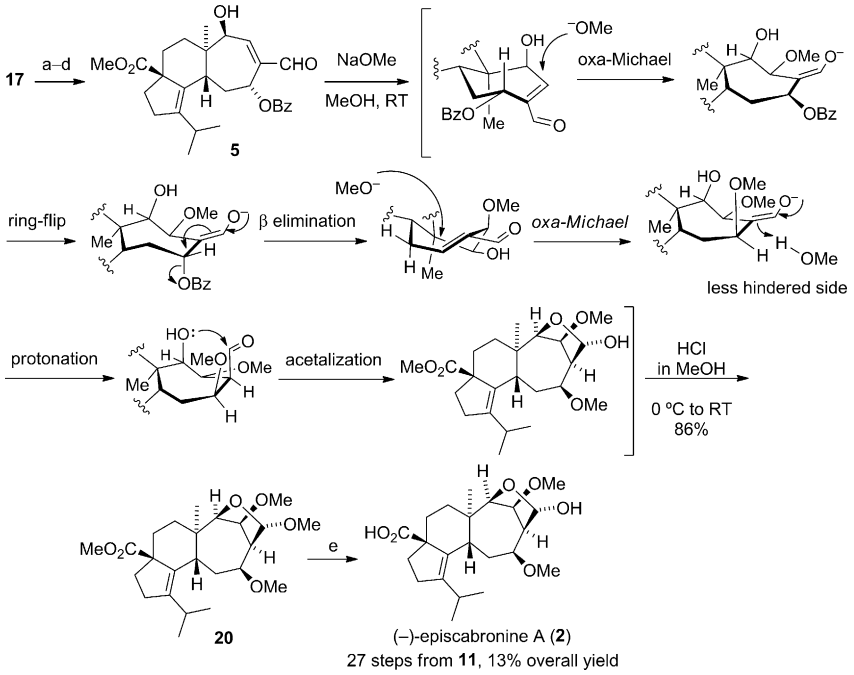
Armed with the necessary precursor, we examined an oxa-Michael/acetalization cascade. The reaction of **4** with sodium methoxide in methanol produced **18**, which could be treated directly with acidic methanol to afford **19** as a mixture of C15 isomers.[25] No side-products were observed in this cascade reaction. The stereoselectivity of the oxa-Michael reaction and subsequent protonation of the enolate is attributed to the conformational bias and directing effect by the C14- and the C11-hydroxy groups, respectively. The C11-hydroxy group of **19** was methylated and the product converted into either (−)-scabronine A or its methyl ester, which proved to be identical to the naturally occurring compounds.[26]

In an analogous cascade reaction, the reaction of **5** with sodium methoxide afforded **20** as a single product (Scheme 5). The stereoselective transformations may be explained as follows: the oxa-Michael reaction of **5** with sodium methoxide installed the β-methoxy group at the C13-position to form the enolate, with subsequent β elimination of the C11 benzoate to generate an enal which underwent a second oxa-Michael reaction to incorporate the β-methoxy group at the C11-position with final protonation at the C12-position from the less-hindered α face. A final acetalization furnished **20**. The C11 benzoate of **5** is converted into a methoxy group with inversion of the configuration during the cascade reaction. Hydrolysis of the methyl ester **20** afforded the corresponding carboxylic acid, which proved to be identical to (−)-episcabronine A (**2**) in all respects.

In conclusion, the enantioselective total syntheses of (−)-scabronines G and A, and (−)-episcabronine A were achieved. The syntheses feature stereoselective construction of the AB ring of the scabronines by an oxidative dearomatization/intramolecular IEDDA reaction cascade. This



Scheme 4. Total synthesis of (−)-scabronine A and its methyl ester. Reagents and conditions: a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*BuOH, H_2O, RT. b) MeI, K_2CO_3, DMF, RT, 74% (2 steps). c) OsO_4 (2.5 mol%), NMO, THF, *t*BuOH, H_2O, RT. d) triphosgene, pyridine, DMAP, CH_2Cl_2, 0 °C to RT, 66% (α), 20% (β) (2 steps). e) DBU, PhH, RT, quant; f) (*R*)-CBS, $BH_3{\cdot}SMe_2$, THF, 0 °C. g) TBAF, THF, 0 °C to RT, 90% (2 steps). h) TEMPO (20 mol%), PIDA, CH_3CN, CH_2Cl_2, KPB7, 80%. i) MeI, NaH, THF, RT, 99%. j) 2 N NaOH (aq.), MeOH, 70 °C, then, 3 N HCl (aq.), 94%. k) 3 N HCl (aq.), THF, 60 °C, 95%. CBS = Corey–Bakshi–Shibata catalyst, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMP = 4-dimethylaminopyridine, KPB7 = potassium phosphate buffer (pH 7.0), NMO = *N*-methylmorpholin *N*-oxide, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.



Scheme 5. Total synthesis of (−)-episcabronine A. Reagents and conditions: a) BzCl, Et_3N, DMAP, CH_2Cl_2, RT, 97%. b) (*R*)-CBS, $BH_3{\cdot}SMe_2$, THF, 0°C. c) TBAF, NH_4Cl, THF, 0°C to RT, 93% (2 steps). d) TEMPO (20 mol%), PIDA, CH_3CN, CH_2Cl_2, KPB7, RT, 97%. e) 2 N NaOH (aq.), MeOH, 70°C; then, 3 N HCl (aq.), 99%. Bz = benzoyl.

approach enables the total synthesis of (−)-scabronine G in 19 steps and 21% overall yield. The highly stereoselective oxa-Michael/protonation/acetalization cascade, inspired by the biogenetic precedent for the scabronines, was realized by setting hydroxy groups, with the correct configurations, at suitable positions on the seven-membered C ring to accomplish the first total synthesis of (−)-scabronine A. Substitution of the C11-hydroxy group for a benzoate in **5** altered the cascade to involve a β-elimination/oxa-Michael cascade, thus leading to the first total synthesis of (−)-episcabronine A.[27] The high efficiency of this divergent synthetic approach, which includes time and space integration steps,[28] makes a valuable contribution to the synthesis of scabronine derivatives needed for structure–activity relationship studies.

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[26] The $[\alpha]_D$ value of synthesized **1** {$[\alpha]_D^{24} = -40.9$ ($c = 0.74$, MeOH)} is different from the reported value {$[\alpha]_D^{23} = -15.0$ ($c = 0.92$, MeOH)[1a]}. This difference may be attributed to varying $[\alpha]_D$ contributions by the C15 isomers of **1**, a characteristic which was similarly noted for **19** (see the Supporting information).

[27] The cascade reactions in this work could suggest that (−)-scabronine A and (−)-episcabronine A are artifacts because these compounds were isolated from the methanol extract of *Sarcodon scabrosus*. We are now investigating possibility of their formation during the isolation.

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