Total Synthesis of (−)-Grayanotoxin III†

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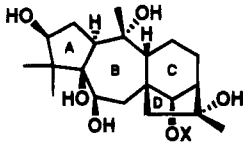
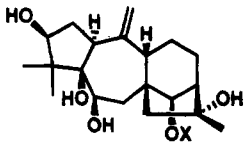
Summary: Total synthesis of (−)-grayanotoxin III (**3**), a unique tetracyclic diterpene isolated from the leaves of various plants of the family *Ericaceae*, has been successfully accomplished featuring the highly stereoselective cyclization reactions induced by SmI_2.

Grayanotoxins such as grayanotoxin I–IV (**1**–**4**) are a unique class of toxic diterpenoids that occur in leaves of various plants belonging to the family *Ericaceae*.[1] Because these toxins exert their effects by modification of the sodium channel, grayanotoxins are potential candidates as a pharmacological tool for examining the sodium channel. Grayanotoxins are characterized by the A-*nor*-B-*homo*-kaurane skeleton, an unusual tetracyclic carbon framework and by the dense arrangement of hydroxyl groups. Their remarkable physiological activity and complicated structure distinguish these molecules as very interesting targets for total synthesis.[2] We started the program directed toward the total synthesis of grayanotoxins with the aim of exploring a general and flexible synthetic route to these novel diterpenes. Eventually, our effort culminated in the first total synthesis of (−)-grayanotoxin III (**3**), featuring new types of highly stereoselective cyclization reactions induced by SmI_2. In this paper, we report the completely stereocontrolled total synthesis of (−)-**3**.



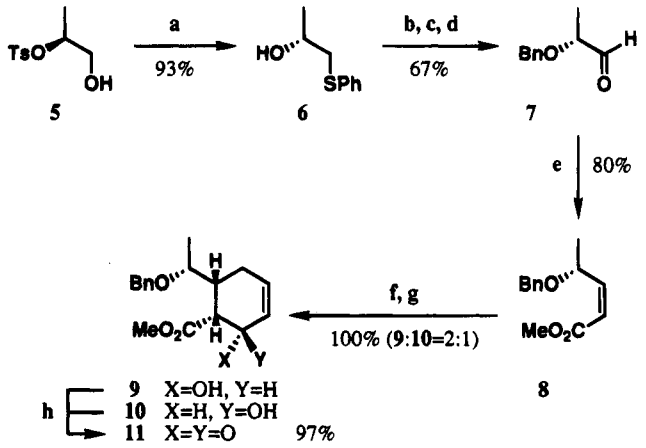
Grayanotoxin I (**1**) X=Ac
Grayanotoxin III (**3**) X=H



Grayanotoxin II (**2**) X=H
Grayanotoxin IV (**4**) X=Ac

The total synthesis of (−)-grayanotoxin III (**3**) originated from (*R*)-2-(benzyloxy)propionaldehyde (**7**).[3] A practical synthetic scheme for **7** starting from (*S*)-2-((*p*-toluenesulfonyl)oxy)-1-propanol (**5**)[4] was developed (Scheme 1). The phenyl sulfide **6** was obtained by treating **5** with NaSPh through *in situ* formation of (*R*)-propylene oxide[4] and successive opening of the epoxide ring. After protection of the hydroxyl group of **6** as its benzyl ether, oxidation of the phenylthio ether group, followed by Pummerer rearrangement of the resulting

Scheme 1[a]



[a] Key: (a) NaSPh, MeOH, rt; (b) (1) NaH, DMF, 0 °C; (2) BnCl, rt; (c) $NaIO_4$, H_2O–MeOH, rt; (d) $(CF_3CO)_2O$, Py-CH_2Cl_2, 0 °C → rt, then saturated $NaHCO_3$; (e) $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C; (f) 1-((trimethylsilyl)oxy)-1,3-butadiene, *p*-hydroquinone, 160 °C; (g) 10% HF, MeCN, rt; (h) PDC, MS-4A, CH_2Cl_2, rt.

sulfoxide, afforded **7**. The Wittig reaction of **7** in MeOH[5] gave rise to the 10:1 mixture of methyl (2*Z*,4*R*)-4-(benzyloxy)-2-pentenoate (**8**) and its (2*E*,4*R*)-isomer, which was further purified by vacuum distillation affording geometrically pure **8**. The Diels–Alder reaction of **8** with 1-((trimethylsilyl)oxy)-1,3-butadiene took place with complete diastereofacial selectivity to give the epimeric mixture of **9** and **10** (2:1) in almost quantitative yield (based on consumed **8**).[6] Oxidation of the 2:1 mixture yielded the C-ring system precursor **11**.

In order to construct the D-ring, stereoselective introduction of the C_3-carbon chain into the C-8 position (grayanotoxin numbering) of the C-ring system precursor **11** was achieved by performing stereocontrolled alkylation of **11** with propargyl bromide to afford the keto ester **12** as the sole product (Scheme 2). Cleavage of the benzyl ether group of **12** with $FeCl_3$[7] accompanied with simultaneous lactone closure gave rise to the keto lactone **13**. Reduction of **13** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ took place in a completely regioselective and stereose-

† This paper is dedicated to the memory of the late Dr. Mitsutoshi Yanagiya.

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(6) On the other hand, the (2*E*,4*R*)-isomer gave the mixture containing the four cycloadducts by performing the reaction under the same conditions. It is noteworthy that the diastereoselectivity of this pair of Diels–Alder reactions is similar to that of the [4 + 2] and [3 + 2] cycloadditions of methyl (2*Z*,4*S*)-4,5-(isopropylidenedioxy)-2-pentenoate and methyl (2*E*,4*S*)-4,5-(isopropylidenedioxy)-2-pentenoate; see: (a) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Tetrahedron Lett.* **1985**, *26*, 1631. (b) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284. (c) Trost, B. M.; Mignani, S. M. *Tetrahedron Lett.* **1986**, *27*, 4137. (d) Nagaoka, H.; Kobayashi, K.; Okamura, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 6641.

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(8) In contrast, **12** was reduced with $NaBH_4$ under the same conditions to give the corresponding α-alcohol.

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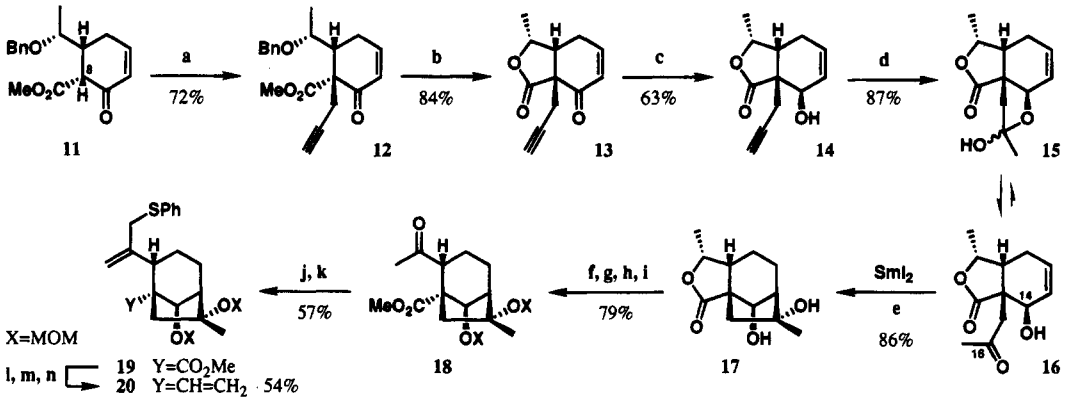
Scheme 2[a]



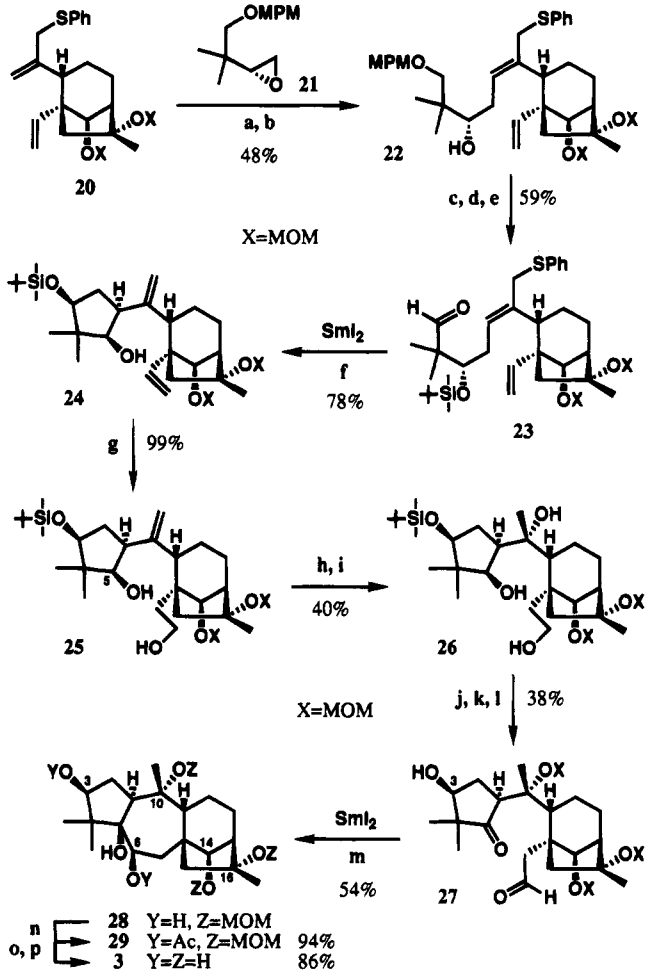
[a] Key: (a) (1) NaH, DMF, 0 °C; (2) HC≡CHCH$_2$Br, 0 °C; (b) FeCl$_3$, CH$_2$Cl$_2$, rt; (c) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, −78 °C → rt; (d) NaAuCl$_4$·H$_2$O, H$_2$O−THF, 60 °C; (e) SmI$_2$, HMPA−THF, −78 → 0 °C; (f) MOMCl, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, rt; (g) 1 N KOH, MeOH, 80 °C, then 1 N HCl; (h) CH$_2$N$_2$, ether, rt; (i) Jones reagent, acetone, 0 °C; (j) (1) LiN(SiMe$_3$)$_2$, THF, −78 °C; (2) Tf$_2$NPh, −78 °C; (k) Li$_2$CuCN(CH$_2$SPh)$_2$, THF, −20 °C; (l) DIBAL, CH$_2$Cl$_2$, −78 °C; (m) Dess−Martin reagent, CH$_2$Cl$_2$, rt; (n) Ph$_3$P=CH$_2$, THF, rt.

lective manner to yield the β-alcohol **14**.[8] The ketol **15** was cleanly derived from **14** using NaAuCl$_4$.[9]

Recently, we demonstrated that the stereochemical course of the reductive cyclizations mediated by SmI$_2$ is completely stereocontrolled by chelation of the Sm(III) cations generated in the initial reduction with the hydroxyl groups incorporated within the starting materials.[10] As expected, the CD-ring system **17** was obtained exclusively *via* the SmI$_2$-induced cyclization of **15**.[11] The hydroxy ketone **16** must be generated in an equilibrium process before the ketone−olefin coupling. In contrast, the SmI$_2$-mediated cyclization of the 14-*O*-MOM derivative of **16** gave a 5:1 mixture of the 14-*O*-MOM derivative of **17** and its epimer. Obviously, the observed stereochemistry of **17** is established by chelation between the C-14 hydroxyl group and the resulting Sm(III) cation generated after single electron transfer from SmI$_2$ to the C-16 ketone functionality of **16**.

All attempts to attach the 5-membered precursors of the A-ring to the CD-ring systems led to failure, probably due to steric hindrance. As described previously,[12] an efficient method of cyclizing the A-ring system was successfully explored based on the SmI$_2$-mediated cyclization using allyl sulfides as a ketyl radical acceptor. Thus, the alkylation reaction[13] of an anion generated from an allyl sulfide with an epoxide was applied to the connection of the acyclic precursor of the A-ring and the CD-ring system. For this purpose, we prepared the allyl sulfide **20** from **17** (Scheme 2). At first, the allyl sulfide functionality was constructed by (1) protection of the two hydroxyl groups of **17**, (2) subsequent hydrolysis of the γ-lactone ring and esterification, (3) Jones oxidation, (4)

Scheme 3[a]



[a] Key: (a) **21**, ^{n}BuLi, TMEDA, HMPA, THF, −78 → 0 °C; (b) (PhS)$_2$, xylene, 160 °C; (c) ^{t}BuMe$_2$SiOTf, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C; (d) DDQ, H$_2$O−CH$_2$Cl$_2$, rt; (e) Dess−Martin reagent, CH$_2$Cl$_2$, rt; (f) SmI$_2$, HMPA−THF, −78 °C; (g) (1) 9-BBN, THF, rt, then H$_2$O, (2) 30% H$_2$O$_2$, 2 N NaOH, rt; (h) *m*CPBA, CH$_2$Cl$_2$, rt; (i) DIBAL, CH$_2$Cl$_2$, 0 °C; (j) Dess−Martin reagent, CH$_2$Cl$_2$, rt; (k) MOMCl, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, rt; (l) ^{n}Bu$_4$N·F, THF, 0 °C; (m) SmI$_2$, HMPA−THF, −78 → 0 °C; (n) Ac$_2$O, DMAP, Py, rt; (o) RuCl$_3$·nH$_2$O, NaIO$_4$, H$_2$O−MeCN−CCl$_4$, rt; (p) 1 N KOH, MeOH, 80 °C.

vinyl triflate formation[14b] by trapping the Li enolate of the methyl ketone **18**, and (5) the coupling reaction[14] of the triflate with Li$_2$CuCN(CH$_2$SPh)$_2$ prepared from LiCH$_2$-

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SPh and CuCN.[15] Reduction of the ester moiety of the allyl sulfide **19**, Dess–Martin oxidation, and Wittig olefination provided **20**. Coupling of the Li anion generated from **20** with the (*R*)-epoxide **21**[16] occurred cleanly (Scheme 3), and the coupling adduct was further subjected to the facile 1,3-sulfide shift accelerated by $(PhS)_2$[17] to furnish the (*E*)-allyl sulfide **22**. Protection of the hydroxyl group of **22**, oxidative removal of the MPM ether group, and Dess–Martin oxidation produced the aldehyde **23**. As anticipated from the model study,[12] the SmI_2-mediated cyclization of **23** proceeded with excellent stereochemical control, exclusively affording the *homo*-allyl alcohol **24**.

After regioselective hydroboration–oxidation of the monosubstituted olefin of **24**, epoxidation of the diol **25** stereocontrolled by the C-5 hydroxyl group and immediate reduction of the unstable α-epoxide generated the triol **26** as the sole product. Oxidation of the primary and secondary hydroxyl groups of **26**, protection of the tertiary hydroxyl group, and removal of the silyl ether group led to the keto aldehyde **27**. In the hydroxyl group (C-3 hydroxyl group) directed pinacol coupling of **27** promoted by SmI_2 (construction of the B-ring), complete diastereoselectivity was achieved at the *cis*-1,2-diol part of the triol **28** as previously mentioned.[10a] Deprotection of **28** was carried out in a stepwise manner.[18] Acetylation of the two secondary hydroxyl groups of **28**, oxidation of the methylene moieties of the MOM ether groups of the diacetate **29** with RuO_4,[19] and basic hydrolysis of 3,6-di-*O*-acetyl-10,14,16-tris-*O*-(methoxycarbonyl)grayanotoxin III provided (−)-**3**. The synthetic sample was found to be identical with natural (−)-**3** in all respects.

As described in this paper, the authors were able to complete the efficient total synthesis of (−)-grayanotoxin III (**3**). The characteristic points of the total synthesis are the new types of stereocontrolled cyclizations induced by SmI_2. Obviously, these cyclization reactions provide efficient entries into powerful methods for control over various types of reductive coupling reactions promoted by SmI_2.[20]

Supplementary Material Available: Physical and spectroscopic data for compounds **6**–**15**, **17**–**29**, and **3** (9 pages). This material is contained in 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.

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