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Total Synthesis of the Cyathane Diterpenoid (±)-Sarcodonin G

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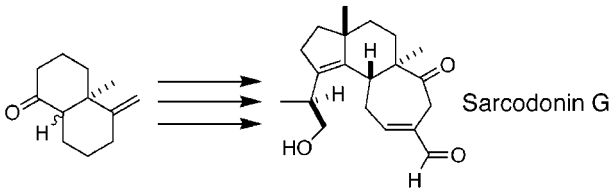
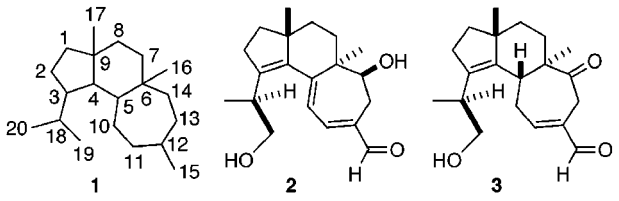
ABSTRACT



The total synthesis of (±)-sarcodonin G (3), a highly functionalized member of the cyathane family of diterpenoids, is described.

The cyathane family of diterpenoids share the tricyclic carbon skeleton **1**.[1] The first members of this structurally unique group of natural products were structurally characterized by Ayer and Taube in 1972.[2] In a series of papers[3] that followed this initial disclosure, Ayer and his group reported the structural elucidation of a number of additional cyathanes that had been isolated from several species of bird's nest fungi of the genus *Cyathus*. Subsequently, additional cyathanes were isolated and characterized by other groups.[4]



1 **2** **3**

Certain members of the cyathane diterpenoid family possess pronounced antibacterial and antifungal properties,[4f,5] while others exhibit the potentially important ability to stimulate the synthesis of nerve growth factor.[4b,c,e,f,6] The structural novelty and the diverse biological activities displayed by the cyathanes have made members of this family attractive targets for total synthesis.[7,8] The structures of most of the known cyathanes, including those that have been synthesized,[7] display at C-3 a nonfunctionalized isopropyl group. However, a small number of cyathanes (e.g., sarcodonin A (**2**)[4a] and sarcodonin G (**3**)[4a]) have a hydroxyl group at C-19, and therefore, in these substances, C-18 is a

(1) The numbering system shown in **1** is that proposed by Ayer and Taube (ref 2).

(2) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, 1917.

(3) Ayer, W. A.; Lee, S. P. *Can. J. Chem.* **1979**, *57*, 3332, and earlier publications in the series.

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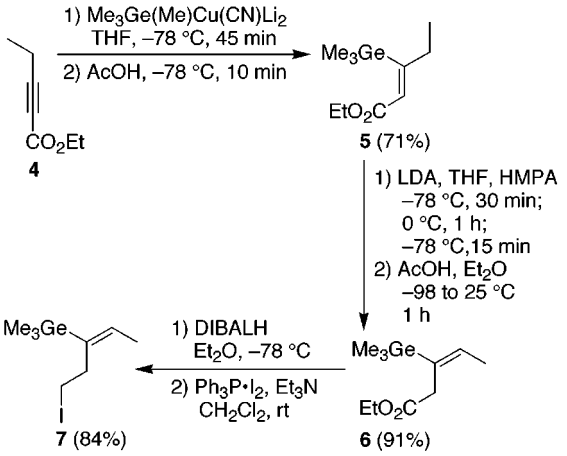
stereogenic center. It is evident that this structural feature introduces, from a synthetic viewpoint, a complexity that is not present in cyathanes that lack this oxygen function. We report herein the total synthesis of racemic sarcodonin G (**3**), a cyathane isolated from the fungus *Sarcodon scabrosus*.[4a]

(*E*)-5-Iodo-3-trimethylgermylpent-2-ene (**7**), the key electrophile employed in our synthesis, was prepared as summarized in Scheme 1. Reaction of ethyl pent-2-ynoate (**4**)

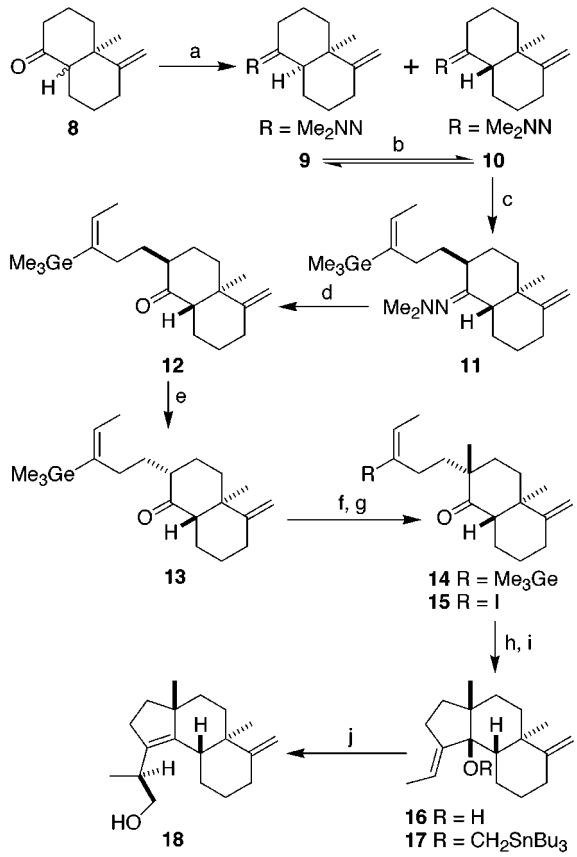
Scheme 1



with dilithium (trimethylgermyl)(methyl)(cyano)cuprate,[9] followed by addition of acetic acid, gave a high yield of a mixture of **5** and the corresponding geometric isomer in a ratio of ~3.5:1, respectively. Chromatographic separation (silica gel) of these materials afforded **5** (71%)[10] which, upon subjection to stereoselective deconjugation[11] via the corresponding enolate anion, produced **6**. Reduction of ester **6** with DIBALH, followed by treatment of the resultant alcohol with $Ph_3P{\cdot}I_2$,[12] gave the required iodide **7** in very good overall yield from **4**.

Treatment (Scheme 2) of the known[13] mixture of bicyclic ketones **8** (*trans*:*cis* ~3.5:1) with Me_2NNH_2 in the presence of 10-camphorsulfonic acid (CSA), followed by chromatography (silica gel) of the resultant mixture of the dimethylhyrazones (ratio ~1:1), provided **9** and **10** in yields of 39 and 43%, respectively. Acid-catalyzed equilibration (CSA, refluxing benzene) of **9** and subsequent separation of the resultant isomers was repeated twice to afford additional quantities of pure **10**. The overall yield of **10** from **8** was 71%. Treatment of **10** with KDA[14] in THF containing DMPU

Scheme 2[a]



[a] Reagents and conditions: (a) Me_2NNH_2, CSA, PhH, reflux, 72 h (82%); (b) CSA, PhH, reflux, 48 h; (c) KDA, THF, DMPU, −78 °C, 2 h; **7**, −78 °C, 2 h; (d) HOAc, NaOAc, THF, H_2O, 65 °C, 18 h (69% from **10**); (e) NaOMe, MeOH, 65 °C, 3 h (82%); (f) $LiNEt_2$, THF, −78 °C, 10 min; to 0 °C, 30 min; MeI, rt, 1.5 h (85%); (g) NIS, CH_2Cl_2, 0 °C, 15 min (90%); (h) BuLi, THF, −78 °C, 40 min; H_2O (86%); (i) KH, 18-crown-6, THF, rt, 30 min; Bu_3SnCH_2I, rt, 40 min; (j) BuLi, THF, −78 °C, 10 min; 0 °C, 10 min; rt, 10 min; H_2O (88% from **16**).

and alkylation[15] of resultant anion with iodide **7** furnished **11**, which, upon subjection to hydrolysis with aqueous HOAc in the presence of NaOAc,[16] gave the corresponding ketone **12** in 69% yield from **10**. Upon treatment with sodium methoxide in warm methanol, **12** was converted into a mixture consisting primarily of **13** (66% yield after chromatography), accompanied by a minor amount (22%) of a mixture of other isomers. Resubjection of the latter material to methoxide-induced equilibration and subsequent chromatographic separation increased the overall yield of pure **13** to 82%. Sequential treatment of ketone **13** with lithium diethylamide and iodomethane in THF provided the single methylated product **14** (85% yield). The expected stereochemical outcome of this reaction (axial alkylation) was confirmed by ^{1}H NMR nuclear Overhauser enhancement difference (NOED) experiments (see Figure 1). In the ^{1}H

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(10) All new compounds reported herein that were isolated and purified exhibited spectra in accord with assigned structures and gave satisfactory elemental (C, H) combustion analyses and/or molecular mass determinations (high-resolution mass spectrometry).
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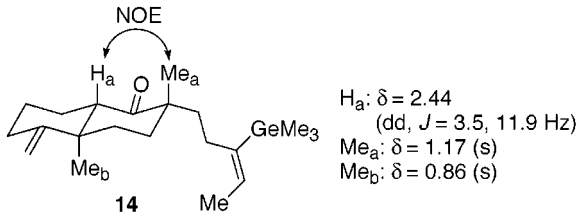


Figure 1.

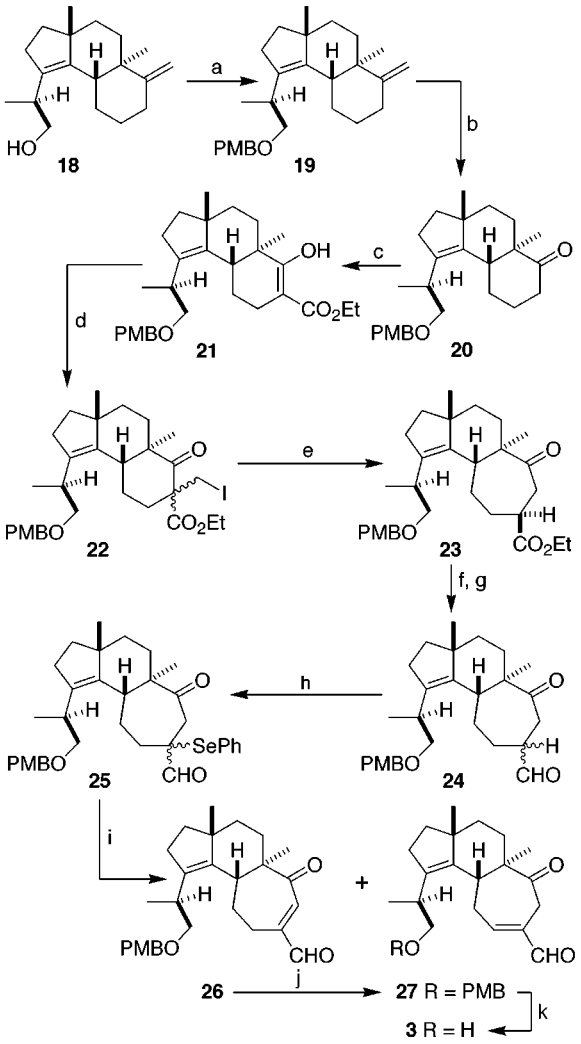
NMR spectrum of **14** the newly introduced methyl group (Me_a, Figure 1) gives rise to a singlet at δ 1.17, while suitable correlation experiments established that the angular proton H_a produces a doublet of doublets at δ 2.44 with coupling constants (J) of 3.5 and 11.9 Hz (axial−equatorial and axial-axial coupling, respectively). Irradiations at δ 1.17 and 2.44 resulted in mutual enhancement of these two resonances, thus establishing the cis relationship between H_a and Me_a.

Treatment of alkenyltrimethylgermane **14** with *N*-iodosuccinimide in CH_2Cl_2[17] effected clean iododegermylation to afford iodo alkene **15**. Rapid lithium−iodine exchange, effected by treatment of latter substance with butyllithium in THF at −78 °C, followed by intramolecular attack of the resultant alkenyllithium function on the carbonyl carbon,[18] provided, in excellent yield, the single tricyclic alcohol **16**. On the basis of previously reported studies[18b] and molecular modeling, the relative configuration of the carbinol carbon in **16** could be assigned with confidence. It is apparent that the molecular conformation necessary for cyclization of the alkenyllithium intermediate leading to the corresponding trans-fused alcohol would be considerably more strained (angle strain in the forming five-membered ring; steric strain involving the methyl group α to carbonyl function) than that giving rise to the cis-fused epimer **16**.

Sequential treatment of the tertiary allylic alcohol **16** with KH and tributylstannylmethyl iodide in THF containing 18-crown-6 gave ether **17**. Subjection of the latter material to the Still−Mitra [2,3]-sigmatropic rearrangement protocol[19] produced, in excellent overall yield from **16**, tricycle **18**. Thus, this transformation, the stereospecific nature of which has been well-established,[19,20] produced a key intermediate that contained the required C-3−C-4 double bond and possessed the correct relative configuration at C-18 (cyathane numbering).

Conversion of intermediate **18** into (±)-sarcodonin G (**3**) is summarized in Scheme 3. Sequential treatment of alcohol **18** with KH and *p*-methoxybenzyl chloride (PMBCl) in THF gave ether **19**. Chemoselective oxidative cleavage of the exocyclic double bond of **19** was achieved by use of potassium periodate in the presence of a catalytic amount of osmium tetroxide.[7b] Ethoxycarbonylation[21] of the resultant

Scheme 3[a]



[a] Reagents and conditions: (a) KH, THF, rt; PMBCl, Bu_4NI, rt, 20 h (96%); (b) OsO_4, KIO_4, *t*-BuOH, $NaHCO_3$, H_2O, rt, 72 h (65%); (c) KH (catalytic amount), NaH, $(EtO)_2CO$, THF, 65 °C, 20 h; dilute aqueous HCl (74%); (d) TBAF, THF, rt; CH_2I_2, rt, 30 min (78%); (e) SmI_2, THF, rt, 20 min; H_2O (71%); (f) DIBALH, Et_2O, 0 °C, 30 min; rt, 1 h; NH_4Cl, NH_3, H_2O (pH 9); (g) Dess−Martin periodinane, CH_2Cl_2, rt; $NaHCO_3$, $Na_2S_2O_3$, H_2O (86% from **23**); (h) piperidine, 4 Å molecular sieves, PhH, 80 °C, 1 h; PhSeCl, THF, −78 °C, 30 min; H_2O; (i) KIO_4, THF, MeOH, H_2O (2:2:1), rt, 20 min (78% from **24**); (j) DBN, PhH, 80 °C, 20 h (95%); (k) DDQ, CH_2Cl_2, H_2O (91%).

ketone **20** provided enol ester **21**, which, upon sequential treatment with TBAF[22] and diiodomethane, was transformed into a diastereomeric mixture of ketones **22** (78%, ratio ~2.5:1, configurations undetermined). Samarium diiodide mediated ring expansion[23] of **22** furnished, in 71% yield, the single keto ester **23**. Evidence for the orientation of the ethoxycarbonyl function in **23** was provided by ^{1}H NMR NOED experiments, as indicated in Figure 2. Irradiation at δ 1.07

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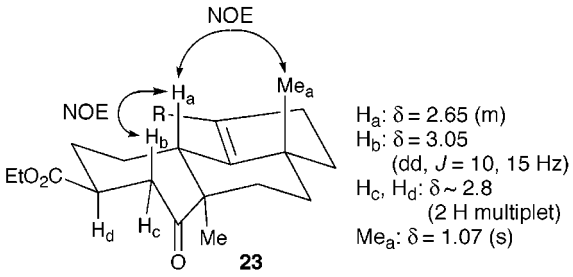

Figure 2.

(Me_a singlet) caused enhancement of the signal due to the angular proton H_a (δ 2.65). On the other hand, irradiation at δ 2.65 (H_a) increased the intensity of the Me_a singlet and of the resonance due to H_b, a pair of doublets with coupling constants (J) of 10 and 15 Hz. The larger of these two coupling constants is presumably related to the geminal coupling between H_b and H_c. The magnitude of the second coupling constant, associated with the coupling between H_b and H_d, shows that these two hydrogens have a trans diaxial-type relationship. Consequently, the ethoxycarbonyl group must be equatorially oriented as shown in **23** (Figure 2).

Subjection of keto ester **23** to reduction with excess DIBALH in diethyl ether and subsequent oxidation of the resultant diol with the Dess−Martin reagent[24] afforded keto aldehyde **24** (86% from **23**) as a mixture of epimers. Treatment of **24** with piperidine in benzene in the presence of molecular sieves, followed by reaction of the resultant geometrically isomeric mixture of enamines (chemoselectively derived from the aldehyde function) with phenylselenenyl chloride,[25] provided selenide **25** (mixture of epimers). Oxidation−elimination of the selenide function of **25** produced a mixture of positional isomers **26** and **27** (~30:1, respectively, 78% overall yield from **24**). Treatment of this mixture with DBN in refluxing benzene effected clean isomerization of **26** into **27** and allowed the isolation of the latter substance in 95% yield. Removal of the PMB protecting group by reaction of **27** with DDQ in aqueous dichloromethane[26] afforded (±)-sarcodonin G (**3**)[27] (91% yield).

The work described herein represents, to our knowledge, the first reported total synthesis of a cyathane diterpenoid (i.e., sarcodonin G (**3**)) that possesses an oxygen function at C-19 and, consequently, a C-18 stereogenic center. The key steps of the synthetic pathway involve the stereoselective BuLi-mediated cyclization of iodo ketone **15** to afford allylic alcohol **16**, the transformation of tributylstannylmethyl ether **17** into tricyclic alcohol **18** via a Still−Mitra [2,3]-sigmatropic rearrangement process, and the SmI_2-induced ring expansion of α-iodomethyl ketone **22** to provide **23**, which possesses the cyathane carbon skeleton.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support and for a Postgraduate Scholarship (to K.L.C).

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(27) This racemic material, an amorphous solid (mp ~132 °C), displayed the following: IR (KBr) 3445, 1703, 1640, 1450, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 6.70−6.73 (m, 1 H), 3.71−3.75 (m, 1 H), 3.41−3.51 (m, 3 H), 3.36 (br d, 1H, J = 12.6 Hz), 3.10−3.20 (m, 1 H), 2.98−3.08 (m, 1 H), 2.69−2.80 (m, 1 H), 2.21−2.40 (m, 3 H), 1.95 (dt, 1 H, J = 13.4, 5.0 Hz), 1.58−1.70 (m, 2 H), 1.49−1.55 (m, 1 H), 1.46 (br s, 1 H), 1.24−1.30 (m, 1 H), 1.14 (s, 3 H), 1.03 (s, 3 H), 0.97 (d, 3 H, J = 6.9 Hz); ^{13}C (100.6 MHz, $CDCl_3$) 210.3, 192.2, 153.2, 141.3, 135.9 (2 C), 65.8, 55.3, 49.8, 39.7, 37.7, 35.5, 35.2, 34.1, 32.7, 32.1, 28.6, 24.8, 15.6, 12.7. Exact mass calcd for $C_{20}H_{28}O_3$: 316.2039. Found (HRMS): 316.2038. These data agree well with those reported for the natural product (ref 4a).