Communication

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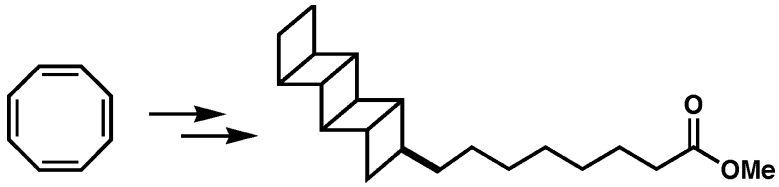

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Total Synthesis of (±)-Pentacycloanammoxic Acid

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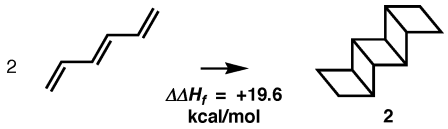
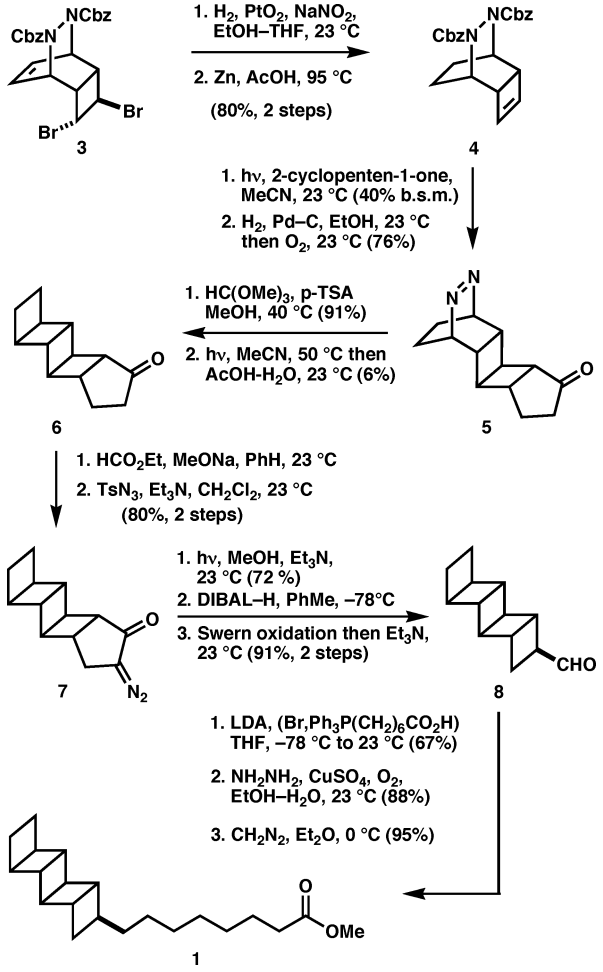
The recent report of the isolation of the remarkable pentacyclic C_{20}-fatty acid methyl ester **1** (see Scheme 1) from the anammoxic microbe *Candidatus Brocadia anammoxidans* opens a fascinating new chapter in the field of natural products.[1] We now describe the first synthesis of **1**, referred to herein as pentacycloanammoxic acid methyl ester, as the racemate. The absolute configuration of natural **1** is unknown at present. Glycerol derivatives of pentacycloanammoxic acid are major membrane constituents in the special organelles of anammoxic microbes that contain the toxic intermediates (H_2NNH_2 and NH_2OH) involved in energy production from nitrite and ammonia.[1,2] These lipids impart unusual density and impermeability to the membranes because of their structural rigidity and size. Although the mode of biosynthesis of **1** is totally unknown, it is certain to be unprecedented because of its structural novelty and high ring strain. From the known heat of formation (ΔH_f) of 1,3*E*,5-hexatriene (+40.1 kcal/mol[3a]) and the calculated ΔH_f (99.8 kcal/mol[3b]) of the core ring system of **1** (**2**, pentacyclo-[6.4.0.02,7.03,6.09,12]dodecane), we can conclude that the formation of **1** from two hexatriene units is thermodynamically very unfavorable. Clearly, the high angle strain of ladderanes such as **2** severely limits the possible synthetic approaches. Previous syntheses of unnatural ladderanes have employed[4] nonspecific oligomerization of cyclobutadienes[5] or photochemical [2 + 2]-cycloaddition[6] processes.



The point of departure for our synthesis (Scheme 1) was the known[7] tricyclic dibromide **3** that was prepared from cyclooctatetraene by reaction with 1 equiv of Br_2 in CH_2Cl_2 at −15 °C and subsequent [4 + 2]-cycloaddition of the resulting bicyclic dibromide to dibenzyl azodicarboxylate in C_6H_6 at 80 °C (64% yield overall). The structure and stereochemistry of **3**, mp 108−109 °C, were demonstrated by single-crystal X-ray diffraction analysis (Figure 1).[8] Selective, halogen-sparing reduction of the olefinic linkage in **3** was effected using H_2 (1 atm), platinum oxide catalyst, and sodium nitrite (3 mol %) in EtOH−THF at 23 °C to give dihydro **3**, which upon treatment with activated zinc powder in HOAc at 95 °C afforded the cyclobutene derivative **4** (70−80% yield from **3**).

Cyclobutene **4** was transformed into the pentacyclic azo ketone **5** by the sequence: (1) ultraviolet irradiation under N_2 at 23 °C of a concentrated CH_3CN solution of **4** and 2-cyclopentenone (added in several portions over a 36 h period) using a medium-pressure Hanovia Hg source and apparatus until ca. 50% consumption of **4** was estimated, followed by purification of the resulting 1:1 cycloadduct by silica gel flash column chromatography (40% yield of 1:1 adduct based on recovered **4**),[9] (2) Cbz cleavage using H_2 (1 atm) and Pd−C catalyst in EtOH at 23 °C for 2 h, and (3) O_2 oxidation of the resulting hydrazine (without isolation) to the bridged azo ketone **5** (56−76%). The structure and stereochemistry of **5** were verified by single-crystal X-ray diffraction analysis (Figure 2).[8] Ketone **5** was converted into the pentacyclic ladderane

Scheme 1



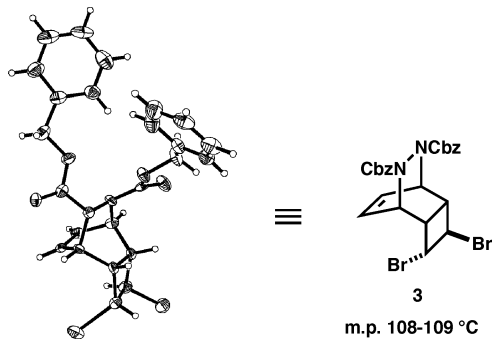


Figure 1. ORTEP representation of compound **3**.

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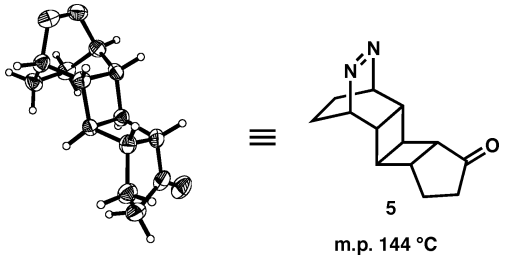

Figure 2. ORTEP representation of compound **5**.

ketone **6** by protection as the dimethoxy ketal in 91% yield, ultraviolet irradiation in CH_3CN solution at 50 °C under N_2, to effect loss of nitrogen, and deketalization by exposure to HOAc−H_2O at 23 °C to give, after chromatographic purification, the required pentacycle in 6% yield. The anti relationship of the fused cyclobutanes in **6** was unambiguously established by nOe (NOESY1D experiments on a 600 MHz NMR spectrometer). The problem of improving the yield in the photochemical N_2 extrusion step has not yet been solved, and it remains an unmet challenge to minimize the formation of unsaturated products from fragmentation and various unidentified and apparently oligomeric (polar) materials. This has been a recurring issue with the N_2 extrusion reaction of other bridged azo compounds.[10] α-Hydroxymethylenation of ketone **6** (HCOOEt, NaOMe, C_6H_6 at 23 °C) followed by treatment with tosyl azide−Et_3N in CH_2Cl_2 at 23 °C provided the α-diazo ketone **7** (80% yield from **6**).[11] Photo−Wolff rearrangement of **7** by ultraviolet irradiation at 23 °C in methanol solution in the presence of triethylamine gave a 3:1 mixture of *endo*- and *exo*-methyl esters (72%), which was transformed into the aldehyde **8** without purification of intermediates by the sequence: (1) reduction COOMe → CH_2OH using *i*-Bu_2AlH in C_7H_8 at −78 °C (>95% yield), (2) Swern oxidation CH_2OH → CHO (95% yield), and (3) epimerization of the *endo*/*exo* diastereomers (at C_α of formyl) in Et_3N solution under N_2 at 23 °C for 6 days to give **8** and the *endo* diastereomer in a ratio of 7:1 (>95%). The methyl ester of (±)-pentacycloanammoxic acid (**1**) was synthesized from **8** by the sequence: (1) Wittig coupling with the ylide from 7-triphenylphosphonioheptanoate[12] in THF to form selectively the *Z* olefinic product, (2) double bond reduction by diimide[13] (generated from H_2NNH_2, O_2, and $CuSO_4$ as catalyst) in EtOH−H_2O at 23 °C, and (3) esterification with CH_2N_2 in ether (95% yield). The ^1H NMR (600 MHz) and ^{13}C NMR (125 MHz) spectra of synthetic **1** as well as nOe observed were in complete agreement with the data reported[1] for naturally derived **1**, as was the mass spectrum; HRMS calcd. for $C_{21}H_{33}O_2$ ($M + H^+$), 317.2480; found, 317.2475. Our synthesis validates the proposed structure of anammoxic acid. An authentic sample of **1** was not available from the original investigators.[1]

In the synthesis of (±)-pentacycloanammoxic acid that is summarized in Scheme 1, the 20-carbon target structure was established from three building blocks: cyclooctatetraene, 2-cyclopentenone, and 7-bromoheptanoic acid via a relatively concise pathway. The stereochemical selectivity was very good, as expected from literature precedents. The [2 + 2]-photocycloaddition of 2-cyclopentenone to **4** was highly *exo*-selective.[9b] The photochemical extrusion of the ketal of **5** selectively produced the all-anti pentacycle **6** in a process that must involve a ring flip prior to transannular bond formation. The stereochemistry of this reaction may be rationalized by the sequence: (1) homolytic dissociation of one C−N bond in the photoexcited state of the azo compound to give an N/C diradical, (2) cyclohexyl ring flip of this intermediate, and (3) transannular bond formation by a radical displacement of molecular nitrogen with inversion. This point must remain a speculation even though there have been several theoretical and mechanistic studies on the photochemical decomposition of such cyclic azo compounds (especially bicyclo[2.2.2]-diazooctane).[10] Unfortunately, this large body of work afforded no useful guidance as to the improvement of the yield of **6** in the N_2 extrusion step. It is likely that transannular bond formation in this photochemical reaction is disfavored by the high angle strain in the product **6**.[14] The ring contraction of the α-diazoketone **7** proceeded cleanly, despite the greater ring strain in the product to form, after trapping of the intermediate ketene with methanol, the *endo*-methyl ester, as expected for steric reasons.

The above discussion underscores the extraordinary nature of the biosynthesis of **1** by anammoxic microbes(s), especially if it occurs from a C_{20}-fatty acid derivative via a thermally activated (i.e., nonphotochemical) process.

Supporting Information Available: Experimental procedures and characterization data for the process shown in Scheme 1 (PDF). X-ray crystallographic data for **3** and **5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) It should be mentioned that experiments on the thermolysis of **5** yielded no detectible amounts of **6**.

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