Total Synthesis of (±)-Antheridium-Inducing Factor (A_{An}, 2) of the Fern *Anemia phyllitidis*. Clarification of Stereochemistry

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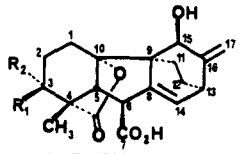
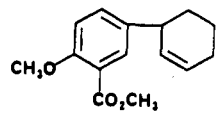
Antheridiogen-An (A_{An}) is a recently discovered plant hormone which stimulates sex-organ development and spore germination in certain species of ferns.[1] The scarcity of naturally derived A_{An} has unfortunately limited the study of its role in plant biology. A collaborative effort involving three groups culminated in the proposal of a novel gibberellin-related structure (**1**) for A_{An}.[2] In this paper we report a total synthesis of (±)-A_{An} that dictates revision of the formula to **2**.



1 R_1=OH, R_2=H
2 R_1=H, R_2=OH



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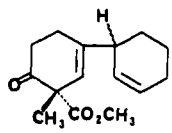

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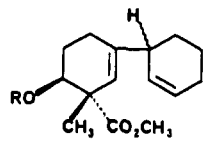
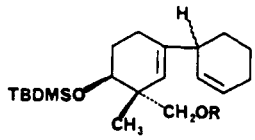
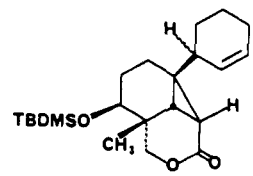


5 R=H
6 R=TBDMS



7 R=H
8 R=COCHN$_2$



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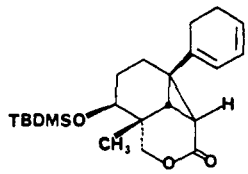

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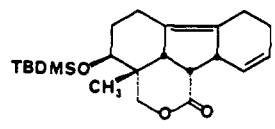

11

Rings A and C were joined at the start of the synthesis by reaction of methyl 2-methoxy-5-iodobenzoate[3] and bis (π-cyclohexenyl)nickel bromide[4] (1.4 equiv) in dimethylformamide at 33–37 °C for 40 h to afford after flash chromatography on silica gel the oily air-sensitive coupling product **3** (80%).[5] A solution of **3** in tetrahydrofuran (THF) containing 1 equiv of *tert*-butyl alcohol was added to a solution of 2.6 equiv of sodium and 2 equiv of *tert*-butyl alcohol in liquid ammonia at −78 °C over 6 min, excess sodium was quenched by addition of isoprene, excess methyl iodide was added, and the mixture was brought to 23 °C with evaporation of ammonia to give after acidification, extractive isolation, and chromatography keto ester **4** (85%).[6] Reduction of the ketonic function of **4** using zinc borohydride (3.3 equiv 0.15 M) in ether containing cyclohexene (to trap any borane) at −57 °C produced, after quenching at −57 °C with acetic acid in methanol and isolation, the alcohol **5**[6] and the carbinol epimer[6] in a ratio of 8:1. Silylation of the mixture using 1.8 equiv of *tert*-butyldimethylsilyl triflate and 2 equiv of 2,6-lutidine[7] in methylene chloride at −78 °C for 13 min followed by isolation and chromatography gave silyl ether **6** (69% from **4**).[6] Relative stereochemistry at the adjacent stereocenters in **5** and **6** is unambiguously indicated by much evidence;[8,9] it corresponds to the product expected by hydride attack at the less-screened face of the keto group in a zinc-chelated β-keto ester.[10] Treatment of ester **6** with 2.4 equiv of diisobutylaluminum hydride in methylene chloride at −78 °C for 10 min afforded >97% of the corresponding primary alcohol **7**, which was esterified[11] with the tosylhydrazone of glyoxylic acid chloride (1.8 equiv of dimethylaniline 15 min, 0 °C in methylene chloride) and then transformed into the diazo ester **8**[11] by addition of triethylamine (90.5% overall from 6). Internal carbenoid addition was effected by heating **8** with copper(II) bis(salicylaldehyde)*tert*-butylimine[11] in toluene at reflux for 14.5 h which generated stereospecifically the cyclopropyl lactone **9** in 84% yield. The cyclohexene **9** was then transformed to the cyclohexadiene **10** by the sequence: (1) reaction with a small excess of bromine in carbon tetrachloride–ether at 0 °C to form four isomeric *trans*-dibromides of **9** and (2) reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (excess) in dimethylformamide for 2 h at 50 °C which converted two of the dibromides to diene **10** and left the others unchanged; recovered dibromides were converted to **9** by treatment with zinc–acetic acid–ether (the yield of **10** from **9** was 63% corrected for recovery, 48% uncorrected).

The B ring of A_{An} was next put in place by a novel version of the vinylcyclopropane–cyclopentene rearrangement. Addition of a solution of cyclopropyl diene lactone **10** to a 0.1 M solution of diethylaluminum chloride (excess) in methylene chloride at 0 °C (over 3 min) and reaction at 0 °C for an additional 9 min afforded after quenching with methanol and isolation the tetracyclic lactone **11** in 80% yield. Attempts to effect the conversion **10** → **11**

(1) Näf, U.; Nakanishi, K.; Endo, M. *Bot. Rev.* **1975**, *41*, 315.
(2) Nakanishi, K.; Endo, M.; Näf, U.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 5579.
(3) Prepared in >97% yield from 5-iodosalicyclic acid (Aldrich Co.) by reaction with dimethyl sulfate (5 equiv) and potassium carbonate (3 equiv) in acetone at reflux for 5.3 h.
(4) Bis(π-cyclohexenyl)nickel bromide was prepared from 1-bromo-2-cyclohexene and 2.8 equiv of nickel carbonyl in benzene, initially mixed at 23 °C and then heated at 62 °C for 1 h, freed of solvent by concentration in vacuum, and dissolved in dimethylformamide, all under argon. See: (a) Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755. (b) Semmelhack, M. F. *Org. React.* **1972**, *19*, 115.
(5) All processes involving air-sensitive reactants or products were conducted under an inert atmosphere. Satisfactory infrared, proton magnetic resonance (^{1}H NMR), and mass spectral data were obtained for synthetic intermediates using chromatographically purified and homogeneous samples. Reaction products were generally purified by flash chromatography on silica gel.
(6) Obtained as a 1:1 mixture of epimers at the doubly allylic carbon, of no consequence in the synthesis since this center becomes trigonal at a later stage.
(7) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(8) (a) Reduction of pure hydroxy ester **5** with diisobutylaluminum hydride afforded a 1,3-diol which was converted to the acetonide by reaction with acetone–tosic acid. The ^{1}H NMR spectrum of the acetonide indicates a trans fusion since the proton at the fusion appears as a doublet of doublets (J = 11, 4 Hz) and must be axial (that proton would be equatorial to the carbocyclic ring for the cis-fused acetonide). (b) The intramolecularly H bonded hydroxyl proton in **5** is coupled to the vic-carbinol proton with J of 2.8 Hz whereas the corresponding coupling constant for the carbinol diastereomer of **5** (also intramolecularly H bonded) is 9.0 Hz.
(9) The coupling constants of the carbinyl proton at C(3) to the vic protons at C(2) in all subsequent intermediates in the synthesis are consistent only with a trans arrangement of the C(3) proton and the C(4) methyl group. ^{1}H NMR data for the C(3) proton are as follows for the indicated intermediates: **9** ($CDCl_3$) δ 3.50 (br s, W_H = 5 Hz), **11** (C_6D_6) δ 3.12 (m, W_H = 6 Hz), **12** (C_6D_6) δ 3.07 (d, J = 2 Hz), **13** (C_6D_6) δ 3.74 (dd, J = 4, 11 Hz), **14** (C_6D_6) δ 3.82 (dd, J = 4, 12 Hz), **15** (C_6D_6) δ 4.40 (dd, J = 4.0, 11.3 Hz), **18** (C_6D_6) δ 3.72 (br s, W_H = 7 Hz). Ring A has the flipped-chair arrangement in compounds **13–17** as compared to **9–12**, **18–20**, **1**, and **2**.
(10) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.
(11) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

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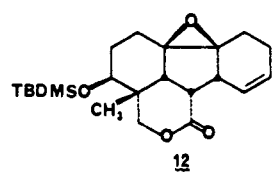
thermally were unsuccessful. Epoxidation of **11** using 2.9 equiv of peroxyacetic acid in ethyl acetate at 25 °C for 10.5 h afforded stereoselectively the β-epoxide **12** (by attack at the less screened face of the double bond),[12] in 72% yield after chromatography. Exposure of **12** to excess lithium diethylamide in THF at 0 °C provided the corresponding conjugated dienol **13** (79%) by syn elimination.[13]



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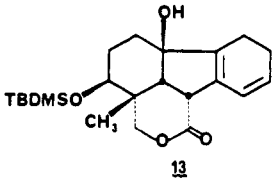

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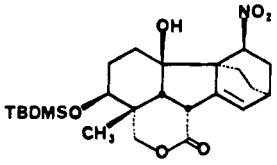

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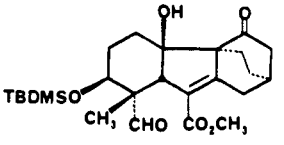

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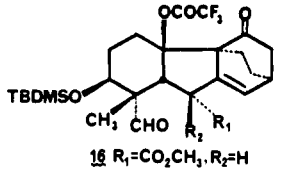
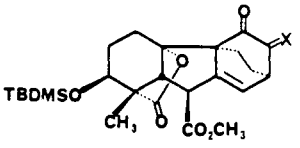


16 R_1=CO_2CH_3, R_2=H
17 R_1=H, R_2=CO_2CH_3



18 X=H_2
19 X=CH_2

TBDMS= $SiMe_2tBu$

Reaction of diene **13** with excess nitroethylene[14] in benzene in the presence of *N,N*-dibornylamine (0.14 equiv) at 26 °C for 4.5 h proceeded with orientational specificity and stereospecificity to provide the Diels–Alder adduct **14** in 76% yield.[15] The nitro lactone **14** was saponified (17 equiv of potassium hydroxide–aqueous ethanol, 23 °C, 12 h), solvent was removed in vacuo, and the basic residue was subjected to potassium ruthenate oxidation (10 equiv of potassium persulfate, 0.2 equiv of ruthenium trichloride, *tert*-butyl alcohol–water (1:3.7)[16] at 23 °C for 3–9 h) to provide after acidification, extraction, esterification with diazomethane, and chromatography the hydroxy keto aldehyde **15** (68% overall).[17,18] Trifluoroacetylation of **15** (excess trifluoroacetic anhydride in 1:1 pyridine–methylene chloride at −23 °C for 1.25 h) occurred with concomitant $\alpha,\beta \rightarrow \beta,\gamma$ migration of the double bond to produce **16** (90%) which was isomerized to the more stable β-(methoxycarbonyl) epimer **17** by treatment with 0.16 M DBU in dry THF at −22 °C for 20 min (90% yield). The aldehyde function in **17** was oxidized using 11 equiv of sodium chlorite[19] in water–*tert*-butyl alcohol in the presence of sodium dihydrogen phosphate and trimethylethylene at 23 °C for 25 min and the resulting carboxylic acid was lactonized (after extractive isolation and azeotropic drying with toluene at 20 mm) by stirring in trifluoroethanol containing 2,6-lutidine (ca. 10 equiv) at 24 °C for 7 h to afford **18** (>95% overall yield). α-Methylenation of **18** to give **19** was effected in 60% overall yield by the following sequence:[20] (1) treatment of ketone **18** in THF at −78 °C with excess (>10 equiv) of triethylamine and trimethylchlorosilane followed by 1.1 equiv of lithium diisopropylamide to form the corresponding enol silyl ether which was separated by extractive isolation and dried azeotropically with toluene at 20 mm; (2) reaction with a mixture of diisopropylethylamine, propylene oxide (silyl iodide scavenger), methyl iodide, and dimethylmethyleneammonium iodide at 25 °C for 3.5 h, followed by aqueous K_2CO_3 at 25 °C.

Reduction of the carbonyl function of **19** proceeded with >20:1 stereoselectivity using excess sodium borohydride in methanol at −30 °C for 2.4 h to afford alcohol **20** in 91% yield.[21] Desilylation of **20** (pyridine–HF complex in acetonitrile at 24 °C for 5 h) afforded (99%) the methyl ester of (±)-**1**, the 270-MHz ^{1}H NMR spectrum of which was very different from that reported for A_{An} methyl ester with respect to the protons at C(3) and C(5).[22]

The 3α-alcohol **2** was therefore synthesized. Desilylation of **19** using pyridine–HF in acetonitrile at 24 °C for 5 h proceeded cleanly to give the 3β-alcohol (99% yield) which was oxidized to the corresponding 3-ketone (96% yield) with 3.3 equiv of pyridinium dichromate in methylene chloride in the presence of 4A molecular sieves. Reduction of this diketone using excess sodium borohydride in methanol at −30 °C for 2.5 h afforded the methyl ester of (±)-**2** (>75% yield). Saponification of (±)-**2** methyl ester with 1:1 1 M aqueous lithium hydroxide–dimethoxyethane at 0 °C for 30 min provided (±)-**2** in >90% yield. ^{1}H NMR and infrared spectral data of (±)-**2**, (±)-**2** methyl ester, and (±)-**2** methyl ester 3-benzoate were identical with those of A_{An} and the corresponding derivatives.[22] Mass spectra of the methyl esters of (±)-2 and A_{An} were identical. Chromatographic mobility of (±)-**2** relative to gibberellic acid (GA_3) (as standard) was identical with that reported for A_{An}.[22]

As a consequence of our results it is clear that antheridium-inducing factor, A_{An}, must be regarded as possessing stereostructure **2** rather than **1** as originally supposed.[2] The fault in the previous assignment[2] stems from the reliance on a dubious chemical shift argument and also the incorrect assumption that ring A in A_{An} adopts a boat conformation.[23,24]

(12) Small amounts of the isomeric α-epoxide could be obtained in addition to **12** when the epoxidation was carried out in methylene chloride as solvent. The ^{1}H NMR spectra of **12** and the stereoisomeric α-epoxide allowed independent assignment of stereochemistry.

(13) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064.

(14) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyenger, R. *J. Org. Chem.* **1980**, *45*, 1185.

(15) The hindered, weakly basic (pK_a 4.7 in 9:1 ethanol–water) secondary amine was used in order to stabilize the acid-sensitive dienol **13** during this reaction. Dibornylamine was prepared by Dr. A. W. Gross in this laboratory. The location of the nitro group in adduct **14** is indicated clearly by ^{1}H NMR peaks due to the proton α to nitro (δ 4.51 (dd, J = 4,9 Hz)). The β-orientation of the nitroethylene bridge and the endo stereochemistry of the nitro group follow from the observation of (1) strong deshielding by nitro of protons at C(5) and C(6) in **14** relative to **13** and (2) hydrogen bonding between ketone and tertiary hydroxyl groups in **15**.

(16) (a) Griffith, W. P.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1979**, 58. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

(17) The bridged keto function in **15** is strongly hydrogen bonded to the tertiary hydroxyl function (^{1}H NMR peaks due to OH at δ 5.62 (d, J = 2.6 Hz); infrared OH stretch at 3460 cm^{-1} either in dilute solution in $CHCl_3$ or as neat film). Ultraviolet absorption (max at 238 nm, ε 6800), infrared data (ester C=O stretch at 1710 cm^{-1}), and ^{1}H NMR data (no vinyl protons) all indicate conjugation between C=C and ester functions in **15**.

(18) The transformation of **14** to **15** is unusual in terms of the number of structural changes involved. These include (1) olefinic bond transposition, (2) δ-lactone hydrolysis, (3) RuO_4 oxidation of CH_2OH to CHO, and (4) oxidative Nef conversion of nitronate to ketonic carbonyl (a novel and potentially generally useful Ru(VI) oxidation). It is likely that the initial event is base-catalyzed isomerization of **14** to the more stable α,β-unsaturated lactone which then is saponified to the α,β-unsaturated carboxylate ion.

(19) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

(20) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.

(21) The β-stereochemistry of the hydroxyl group follows from the observation of hydrogen bonding to the ester carbonyl function (infrared), a coupling of 11 Hz between the OH proton and the vicinal carbinol proton, and a >0.25 ppm downfield shift of the 1 β-proton of **20** as compared to the C(15)-epimeric alcohol (also isolated and characterized).

(22) Since authentic samples of the antheridiogen A_{An} and its various derivatives were unavailable, comparisons were based on spectral data. We are grateful to Prof. Koji Nakanishi and Dr. Mamoru Endo for supplying spectra of all known A_{An} derivatives (Endo, M. Ph.D. Dissertation, Tohoku University, 1972).

(23) ^{1}H NMR found for the C(3) proton in (±)-**1** (CD_3COCD_3) δ 3.77 (d, J = 2.6 Hz), in (±)-**2** (CD_3COCD_3) δ 3.73 (dd, J = 5.6, 10.9 Hz). These data are consistent with the expected chair form for the A ring. Found for the C(5) proton: in (±)-**1** δ 3.57 (d, J = 9.6 Hz), in (±)-**2** δ 2.85 (d, J = 9.2 Hz).

Supplementary Material Available: Spectroscopic data (proton magnetic resonance, infrared, and mass spectral) for compounds **1-20**, methyl esters of **1** and **2**, and methyl ester of the benzoate of **2** (5 pages). Ordering information is on any current masthead page.

(24) This investigation was assisted financially by a grant from the National Science Foundation.

Actinobolin via the Anomeric Effect[1]

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Actinobolin (**1a**), isolated by Haskell and Bartz[2] in 1959 from cultures of *Streptomyces griseoviridies* var. *atrofacienes*, found little favor as an antibiotic, one reason being the fact that it was not readily absorbed through the stomach walls. This demerit, coupled with the subsequent discovery that the antibiotic hardens enamel,[3] has caused a reawakening of interest in actinobolin as a cariostatic agent. The discovery, 20 years later, of the antitumor agent bactobolin,[4] structurally related although not a congenor, has enhanced interest in these isocoumarins.[5] An elegant synthesis of (+)-**1**, based on an intramolecular Diels-Alder strategy, was recently reported by Ohno and co-workers.[6] In this paper, we report an alternative route to *N*-acetyldesalanylactinobolin [(+)-**1b**] (Scheme I).

The structural elucidation of **1a** was a tour de force for Munk and Haskell.[7,8] X-ray[9] and ^{1}H NMR[7,8] data indicated that the molecule exists in conformation **1d**, a fact that manifests itself in the ease with which the C-9 and C-10 hydroxyls can be acetonated.[8,10] For purposes of synthetic strategy, this glycol residue would have been easier to deal with if it were trans diaxial, as in the unpopulated conformer **1e**, since an epoxide, for example, Ia, would then be a logical synthon. Our recent studies on *annulated pyranosides*[12] have shown that systems such as Ia conform to the dictates of the anomeric effect,[13] even in the face of multiple nonbonded interactions. This propensity would be severely taxed by the formidable task of favoring conformation Ia (poised for nucleophilic attack at C-9) over Ib (which would lead to the "wrong" diaxial diol because of preferential cleavage at C-10) and secondly by the need to immobilize the olefinic precursor in conformation IIa so that the erected C-4 substituent would, by steric hindrance, augment the preference for epoxidation from the convex face of this oxa-*cis*-decalin surface.

A crucial element of our synthetic strategy grew out of the discovery that the masked α-enone moiety in Danishefsky diene Diels-Alder adducts[14] can be unveiled by treatment with lithium aluminum hydride.[15] With this in mind, enone **2**[16] was converted into the adduct **3a**[17] and thence to oxime **3b** in virtually quantitative yields. Reduction of the latter with lithium aluminum hydride followed by acetic anhydride quench led to a 4:1 mixture of enone **4a**[17] and alcohol **4b**, the latter being convertible into the former by manganese dioxide oxidation.[15] The configuration at C-4 of **4** follows from our earlier studies on analogous systems[12,15] (Scheme II).

Enone **4a** presented on opportune stage at which to introduce the C-7 oxygen of actinobolin. Lead tetraacetate proved to be the reagent of choice for this α-oxygenation,[18] even though the product **5**[17] was contaminated with approximately 10% of the regioisomeric α-acetoxy ketone. Having served its purpose, the C-8 carbonyl now had to be removed, but because conventional direct methods failed,[19] a circuitous path had to be followed. Sodium borohydride reduction led to an acetoxy alcohol which was not **6a** since it failed to regenerate **5** upon treatment with manganese dioxide. Acyl migration[20] had evidently occurred leading to the regioisomer **6b**.[21]

Palladium-catalyzed deoxygenation[22] of the allylic acetate **6b** failed; however, the carbonate **7**,[17] which incidentally served to establish the C-7,C-8 stereochemistry, led to **8**[17] smoothly under the recently prescribed conditions of Sutherland.[23] Reaction of **8** with MCPBA afforded compound **9a**, and the fact that the molecule did indeed have the conformation shown was evident from the fact that $J_{1,2}$ remained $\sim$1 Hz. The prospect for the desired trans-diaxial opening of the epoxide therefore seemed bright.

It was necessary to protect the alcohol of **9a**[17] so that it could be readily released for the future oxidation. However, cleavage of the epoxide proved to be strangely dependent upon the protecting group used. Thus, acetolysis left the benzyl ether **9b** unaffected. Fortunately the α-ethoxyethyl derivative **9c** yielded a single product.

That the oxirane had indeed been opened at C-9 of **9c** to give the desired product **10a**[17] (rather than at C-10 of **9d** which would have given the wrong diaxial isomer) was evident from two pieces

(1) This work is supported by NIH (AI 20117) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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