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SYNTHESIS OF (±)-IRCINIANIN, A MARINE SPONGE SESTERTERPENE

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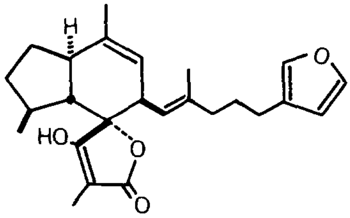
Abstract: A biogenetic-type synthesis of (±)-ircinianin (**1**) via intramolecular Diels-Alder reaction of **2** is described.

Ircinianin (**1**), a sesterterpene isolated from marine sponge *Ircinia wistarii*[1], is structurally unique among those isolated from the same species such as fasciculatin (**3**)[2] and strobilinin (**4**)[3] in that it contains a tricyclic spirotetronic acid system. It has been suggested that **1** would be biosynthesized from the triene **2** via intramolecular Diels-Alder reaction.[1a] In this communication we describe the first synthesis of (±)-ircinianin (**1**) along the suggested biogenetic pathway.



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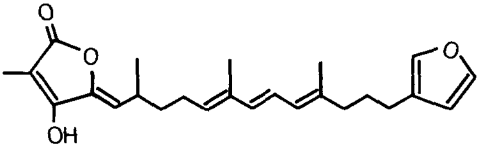

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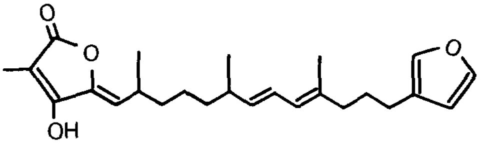

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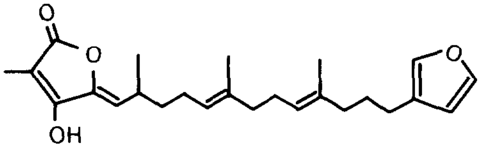

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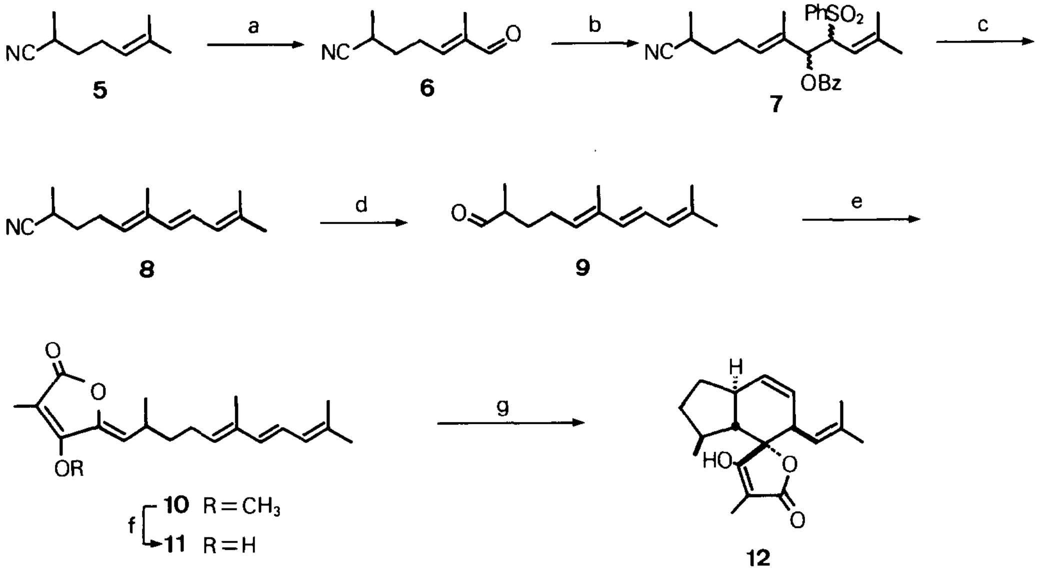
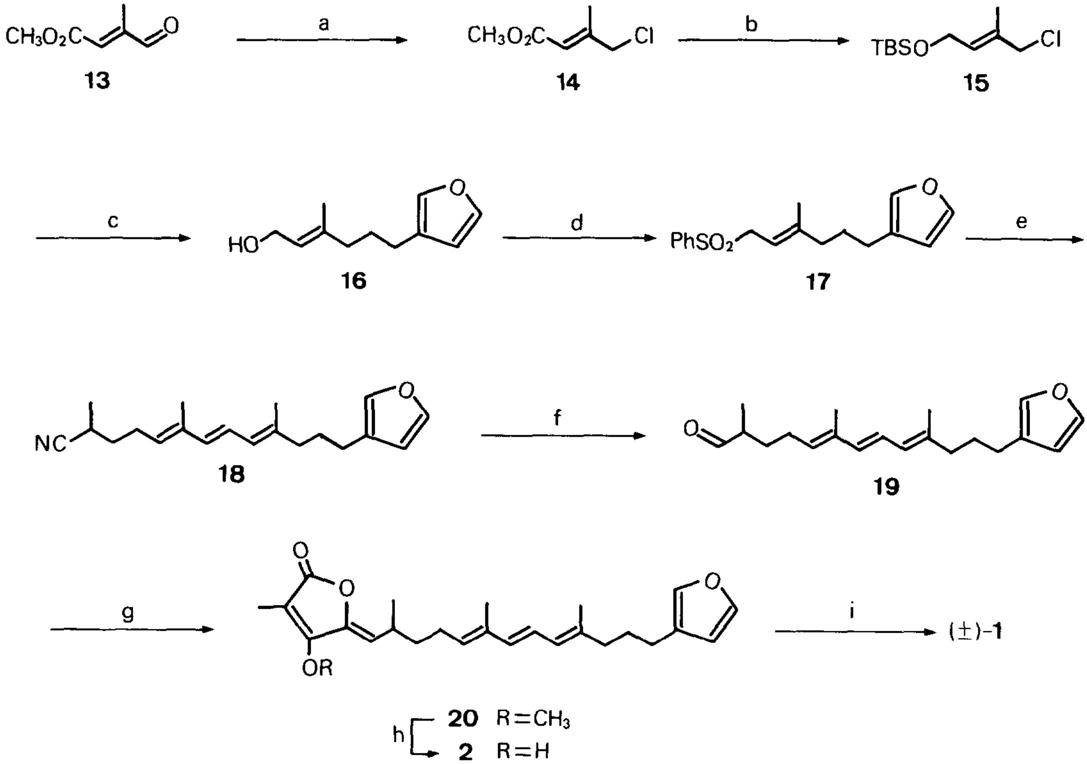
In order to test the feasibility of the proposed cycloaddition, we had preliminarily prepared a model triene **11**. Allylic oxidation[4] of **5**,[5] obtained by α-alkylation of propiononitrile with 5-bromo-2-methyl-2-pentene, gave the aldehyde **6** in 36% yield. Sodium amalgam mediated reductive elimination[6] of the α-benzoyloxysulfone **7**, obtained by addition of lithiated phenyl prenyl sulfone to **6** followed by benzoylation, produced the trans triene **8** in

47% yield. Treatment of **8** with diisobutylaluminum hydride (DIBAL) and subsequent hydrolysis of the resulting aldimine by passing through a column of silica gel produced the sensitive aldehyde **9**. It was immediately allowed to react with 4-lithiated methyl 2-methyltetronate[7], and then converted to the condensation product **10** in 40% overall yield by sequencial treatment with tifluoroacetic anhydride and DBU in situ . Although it was not possible at this stage to establish the geometry of the newly formed exo double bond, the Z configuration was assigned from the result of the subsequent cycloaddition reaction. O-Demethylation of **10** was carried out with n-PrSLi to give the corresponding tetronic acid **11** in 67% yield. The intramolecular Diels-Alder reaction of **11** was effected by heating in refluxing benzene for 75 min to afford the spirotetronic acid **12**[8] in 71% yield as a single diastereomer, which in the ^{1}H NMR spectrum showed a triplet for the angular proton (H-3a) at 1.46 ppm (J = 10.7 Hz) indicative of the trans ring-fusion. Further structural confirmation was made on the basis of a close similarity of the spectral data of irciniania (1).



a) SeO$_2$, t-BuOOH, 36%. b) n-BuLi, PhSO$_2$CH$_2$CH=C(CH$_3$)$_2$, THF, -78°C; BzCl. c) Na-Hg, THF-MeOH; 47%. d) DIBAL, THF; silica gel. e) LDA, methyl 2-methyltetronate, HMPA, THF, -78°C; (CF$_3$CO)$_2$O, rt; DBU, rt; 40%. f) n-PrSLi, HMPA; 67%. g) benzene, reflux, 75 min, 71%.

With the biogenetic-type cycloaddition under mild conditions achieved, we were encouraged to apply our strategy to the synthesis of **1**. Treatment of methyl γ-oxosenecioate (**13**)[9] with NaBH$_4$ and subsequent chlorination with NCS/Me$_2$S[10] afforded the chloride **14** in 80% yield. Reduction of **14** to the corresponding alcohol with DIBAL followed by O-t-butyldimethylsiliylation provided the allylic chloride **15** in 58% yield. Coupling of **15** with 2-(3-furyl)ethylmagnesium bromide[11] in the presence of Li_2CuCl_4[12] and subsequent desilylation with HF in CH_3CN[13] produced the furylalcohol **16** in 41% yield. Chlorination of **16** with NCS/Me_2S followed by exposure to $PhSO_2Na$ provided the sulfone **17** in 71% yield. Transformation of **17** into the Diels-Alder precursor **2** was accomplished in 11% overall yield according to the same procedure described for the triene **11**. Finally, when **2** was heated in refluxing benzene for 60 min, the intramolecular Diels-Alder reaction proceeded smoothly to yield (±)-ircinianin (**1**) in 72% yield as a sole product. Its structure was confirmed by comparison of its spectral data with those in the literature.



a) $NaBH_4$, MeOH; NCS, Me_2S, CH_2Cl_2; 80%. b) DIBAL, THF; TBSCl, imidazole, DMF; 58%. c) 2-(3-furyl)ethylmagnesium bromide, Li_2CuCl_4; aq HF, CH_3CN, 41%. d) NCS, Me_2S, CH_2Cl_2; $PhSO_2Na$, DMF; 71%. e) n-BuLi, THF, -78°C; **6**; BzCl; Na-Hg, THF-MeOH; 32%. f) DIBAL, THF; silica gel. g) LDA, methyl 2-methyltetronate, HMPA,THF, -78°C; $(CF_3CO)_2O$, rt; DBU, rt; 40%. h) n-PrSLi, HMPA; 63%. i) benzene, reflux, 60 min; 72%.

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8) **12**: mp 202-204 ^{o}C, ^{1}H NMR (270 MHz) δ 0.88 (d, *J* = 6.6 Hz, 3H), 1.46 (t, *J* = 10.7 Hz), 1.66 (d, *J* = 1.2 Hz, 3H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.71 (s, 3H), 1.83 (d, *J* = 1.2 Hz, 3H), 2.37-2.52 (m, 1H), 3.15 (dm, *J* = 10.0 Hz, 1H), 5.07 (br s, 1H), 5.08 (dm, *J* = 10.0 Hz, 1H), 6.00 (br s, 1H).

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14) (±)-**1**: mp 123-125 ^{o}C, ^{1}H NMR (270 MHz) δ 0.88 (d, *J* = 6.4 Hz, 3H), 1.46 (t, *J* = 11.2 Hz, 1H), 1.64 (d, *J* = 1.2 Hz, 3H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.71 (s, 3H), 2.15 (t, *J* = 5.1 Hz, 3H), 2.15 (t, *J* = 5.1 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.55 (br m, 1H), 3.15 (dm, *J* = 9.4 Hz, 1H), 5.03 (m, 1H), 5.10 (dm, *J* = 9.4 Hz), 6.15 (br s, 1H), 6.28 (br s, 1H), 7.23 (br s, 1H), 7.36 (m, 1H).

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