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Total Synthesis of (-)-Axamide-4 and (-)-Axisonitrile-4

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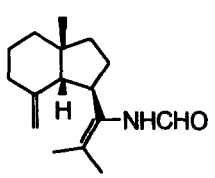
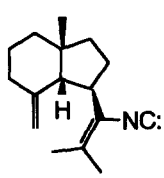
Abstract: The first asymmetric total synthesis of the title compounds, unnatural enantiomers, has been achieved.

Axanes such as (+)-axamide-4 and (+)-axisonitrile-4 were isolated from the marine sponge *Axinella cannabia*, and possess a series of nitrogen-containing functional groups rarely found in natural products.[1] The structure assignments were based on the crystal structure analysis of a derivative of axisothiocyanate-1.[2] We were interested in (ent)-axane-4 group and envisioned the synthesis of the unnatural enantiomers, (-)-axamide-4 and (-)-axisonitrile-4, since natural products with an isonitrile group show various biological activities and the antipodes often show different activities. There is only one racemic synthesis of the axane-4 group.[3] We report herein the first enantioselective synthesis of axamide-4 [(-)-**1**] and axisonitrile-4 [(-)-**2**].



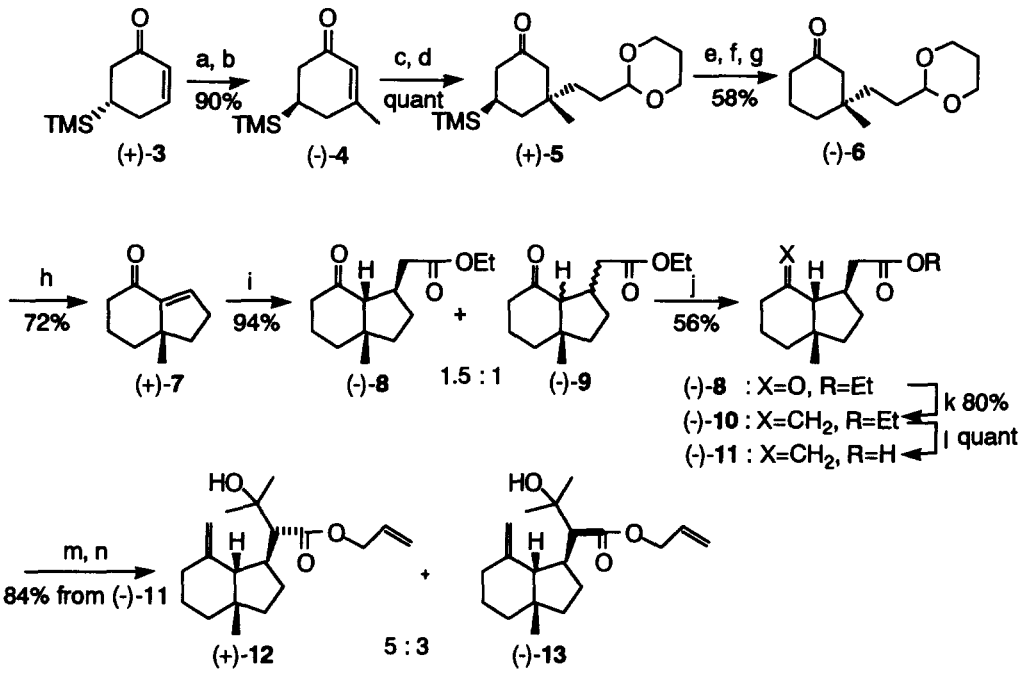
(+)-axamide-4 [(+)-**1**]



(+)-axisonitrile-4 [(+)-**2**]

Enone (-)-**4** was prepared from (+)-**3** according to our reported method[4] in 90% yield (Scheme 1). 1,4-Addition of the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane gave quantitatively the trans adduct (+)-**5** as an exclusive diastereomer. Treatment of (+)-**5** with excess $CuCl_2$ in DMF at 60 °C and then with TBAF in THF gave the corresponding desilylated enone whose hydrogenation in the presence of 10% Pd-C in ethanol gave (-)-**6**. Treatment of (-)-**6** with 6M HCl in THF gave the bicyclic enone (+)-**7** in 72% yield. $SnCl_4$ catalyzed 1,4-addition of a ketene silyl acetal to the enone (+)-**7** afforded a 1.5:1 mixture of (-)-**8** and a chromatographically inseparable diastereomer in high yield. Isomerization of (-)-**9** to (-)-**8** under thermodynamically controlled conditions was examined, i.e., the mixture was treated

Scheme 1



a) MeLi, THF; b) PCC, CH_2Cl_2; c) BrMg-(dioxolane), CuBr/Me_2S, HMPA, TMSCl, THF;

d) KF, MeOH; e) $CuCl_2$, DMF; f) TBAF, THF; g) Pd-C, H_2, EtOH; h) 6 M HCl, THF;

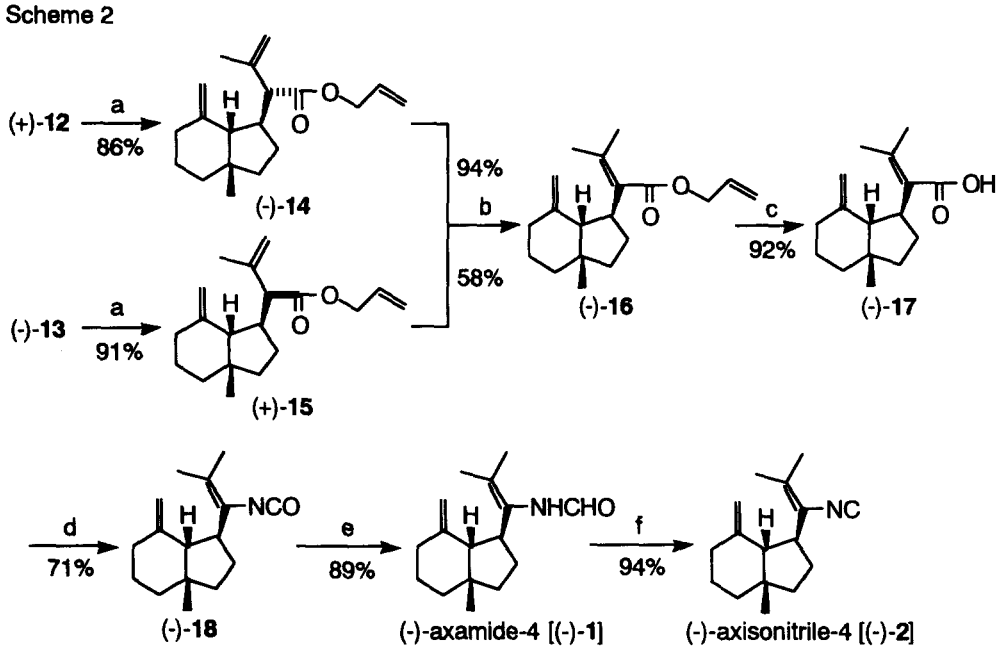
i) CH_2=C(OTBDMS)OEt, $SnCl_4$, CH_2Cl_2; j) *t*-BuOK, *t*-BuOH; k) Ph_3P=CH_2, *t*-BuOH; l) NaOH, MeOH;

m) LDA, THF, 50 °C, then acetone; n) allyl bromide, $NaHCO_3$, DMF.

with *t*-BuOK in *t*-BuOH to give (-)-**8** as a sole product in 56% yield.[5] The structure of the keto ester (-)-**8** was confirmed by the spectral data reported by Hart.[3a] The Wittig olefination of (-)-**8** followed by hydrolysis of the ester moiety afforded acid (-)-**11**. Reaction of (-)-**11** *via* the dianion with acetone proceeded in good yield and the produced hydroxy acid was treated with allyl bromide in the presence of $NaHCO_3$ in DMF to afford (+)-**12** (52%) and (-)-**13** (32%), whose structures were tentatively assigned with analogy of the corresponding methyl ester.[3a] Dehydration of (+)-**12** and (-)-**13** was achieved with $POCl_3$ in pyridine to afford esters, (-)-**14** and (-)-**15**, in high yields (Scheme 2). Treatment of (-)-**14** and (-)-**15** with *t*-BuOK in *t*-BuOH gave a mixture of (-)-**16**, (-)-**14**, and (-)-**15** with the same ratio (20:2:3), respectively.[6] The mixture could not be separated by column chromatography. Deprotection of the allyl

ester (-)-16[7] was accomplished in the presence of 15 mol% tetrakis(triphenylphosphine) palladium(0) and an excess amount of $BuNH_2$ to provide acid (-)-17 which still contained a small amount of isomers. The synthesis of (-)-axamide-4 (1) and (-)-axisonitrile-4 (2) from the acid (-)-17 was carried out according to Hart's method.[3a] The Curtius rearrangement with diphenyl phosphorazidate (DPPA) provided isocyanate (-)-18 which was separable from the minor isomers. Reduction of the isocyanate (-)-18 with Super Hydride ($LiEt_3BH$) gave (-)-axamide-4 [(-)-1][8] in 89% yield. Treatment of (-)-axamide [(-)-1] with *p*-TsCl in pyridine afforded (-)-axisonitrile-4 [(-)-2][8] in 94% yield. The spectral data of synthesized (-)-1 and (-)-2 were identical with Hart's data[3a] and those of the natural products.[1e] In summary, the first asymmetric synthesis of two members of axane-4 group was accomplished starting with (+)-3. Since (-)-3 is also readily available,[9] this procedure promises the synthesis of (+)-axamide-4 and (+)-axisonitrile-4.

Scheme 2



a) $POCl_3$, pyridine; b) *t*-BuOK, *t*-BuOH; c) 15 mol% $Pd^0(PPh_3)_4$, $BuNH_2$, THF;

d) NaH, THF then DPPA, THF; e) $LiEt_3BH$, THF; f) *p*-TsCl, pyridine.

Acknowledgement

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5) The starting mixture of (-)-**8** and (-)-**9** already contained about 60% of (-)-**8**, therefore, this result may be attributed to selective decomposition of (-)-**9**. Many attempts to improve the yield were unsuccessful.

6) (-)-**16**: oil; $[\alpha]_D^{23}$ -60.1° (*c* 1.2, $CHCl_3$); IR (neat) 1710 (C=O), 1640, 990, 890 (C=C); ^1H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.18-1.86 (m, 7H), 1.68 (s, 3H), 1.79 (s, 3H), 1.95-2.20 (m, 3H), 2.29 (d, J=10.9 Hz, 1H), 3.28 (ddd, J=10.9, 10.9, 6.9 Hz, 1H), 4.53-4.74 (m, 4H), 5.26 (dd, J=10.6, 1.5 Hz, 1H), 5.37 (dd, J=17.2, 1.5 Hz, 1H), 5.99 (ddt, J=17.2, 10.6, 5.9 Hz, 1H); ^{13}C NMR δ 20.6, 23.1, 23.8, 25.0, 27.8, 30.7, 33.2, 40.5, 42.2, 43.4, 58.9, 64.8, 110.9, 118.8, 131.4, 132.3, 136.4, 147.1, 170.2; Found: m/z 288.2099. Calcd for $C_{19}H_{28}O_2$: M, 288.2090.

7) Hydrolysis of the corresponding methyl ester was unsuccessful.

8) (-)-Axamide-4 [(-)-**1**]: mp 99-100.5 °C; $[\alpha]_D^{21}$ -66.4° (*c* 0.3, $CHCl_3$); [(+)-**1**]: lit.[1e] mp 81-84°C; $[\alpha]_D$ +63° ($CHCl_3$); (-)-axisonitrile-4 [(-)-**20**]: mp 65.5-66.5 °C; $[\alpha]_D^{18}$ -57.6° (*c* 0.5, $CHCl_3$); [(+)-**2**]: lit.[1e] mp 56-58 °C; $[\alpha]_D$ +51.4° (*c* 1.0, $CHCl_3$).

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