Total Synthesis of (±)-Nakafuran-8, a Marine Metabolite with Antifeedant Properties, based on Formal Bridgehead Substitution of a Bicyclo[2.2.2]oct-5-en-2-one System

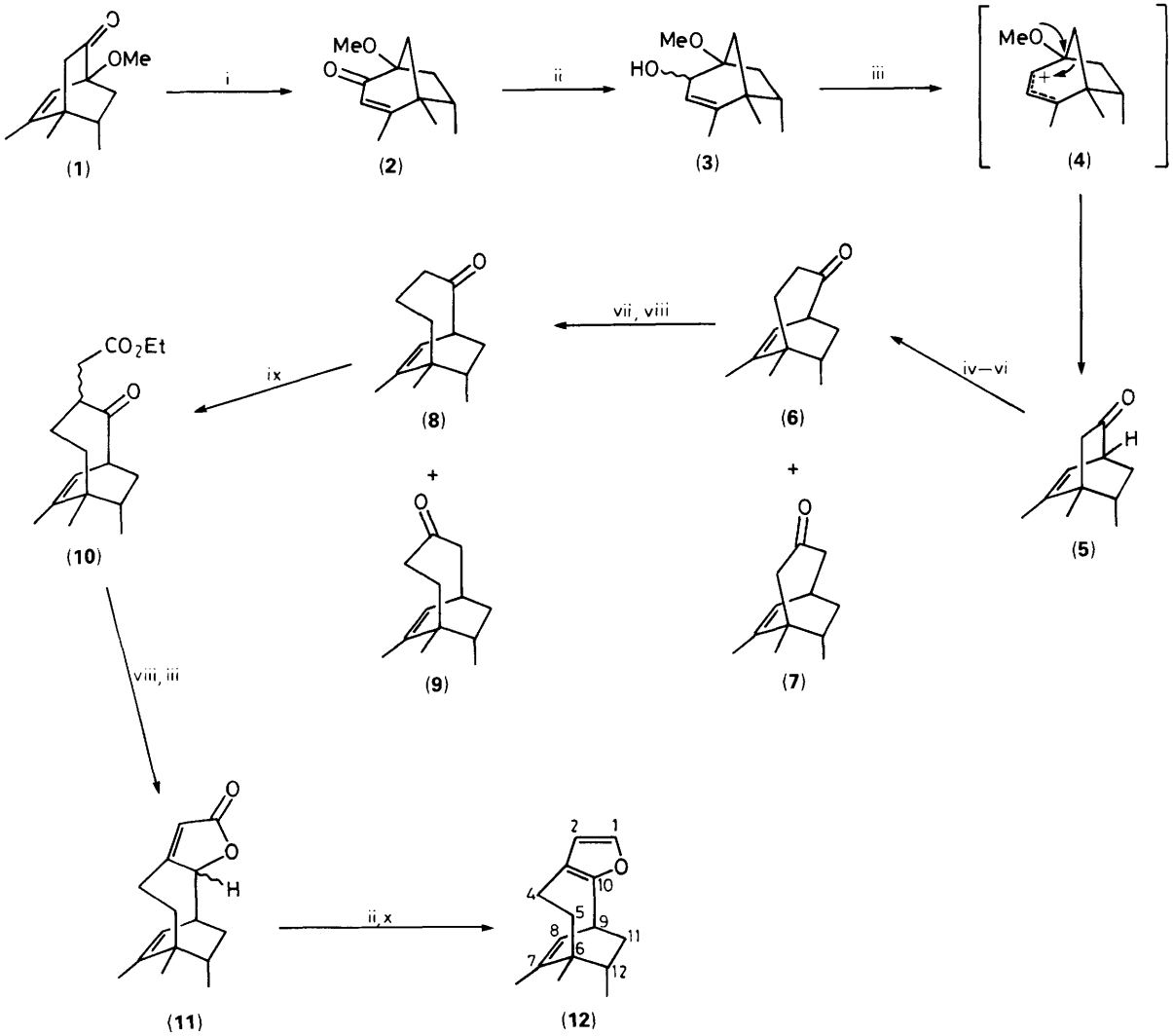
Tadao Uyehara,* Mika Sugimoto, Ichiro Suzuki, and Yoshinori Yamamoto*

Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

The first total synthesis of (±)-nakafuran-8, a furanosesquiterpene containing a bicyclo[4.2.2]decane skeleton, has been accomplished starting from 1-methoxy-4,5,8-*endo*-trimethylbicyclo[2.2.2]oct-5-en-2-one by a rearrangement strategy including the formal bridgehead substitution of this methoxy group by hydrogen on the basis of a pinacol-type rearrangement and the double ring-enlargement of this product to give 6,7,10-*exo*-trimethylbicyclo[4.2.2]dec-7-en-2-one *via* the bicyclo[3.2.2]non-6-en-2-one.

Nakafuran-8 (**12**), antifeedant against common reef fishes,[1] is the metabolite of the marine sponges *Dysidea fragilis*[1] and *D. etheria*[3] and some nudibranches[1,2] which feed the former sponge. The total synthesis of this compound is of particular interest because of the unique bicyclo[4.2.2]decadiene skeleton, which has a furan ring and three adjacent methyl groups, including the 12-*exo*-methyl, in addition to the biological properties. We report the first total synthesis of (±)-(**12**) (Scheme 1).

The bicyclo[4.2.2.]dec-7-en-2-one (**8**) seemed to be a reasonable synthetic intermediate to be derived from (**5**) by two ring enlargements. However, the substitution pattern of (**5**) is different from that of the major Diels–Alder adduct derived from 1,2,6-trimethylcyclohexa-1,3-diene and a dienophile which is synthetically equal to a ketene, such as α-chloroacrylonitrile. Recently, we have developed a method to replace the C-1 bridgehead methoxy group of a bicyclo[2.2.2]oct-5-en-2-one by an alkyl or an aryl group or even



Scheme 1. *Reagents*: i, BF_3–2MeOH, CH_2Cl_2; ii, DIBAH, hexane; iii, *p*-TsOH, PhH, reflux; iv, Me_3SiCN, ZnI_2; v, $LiAlH_4$; vi, $NaNO_2$, AcOH, H_2O; vii, Me_3SiCHN_2, BF_3–OEt_2; viii, K_2CO_3, MeOH, H_2O; ix, lithium di-isopropylamide, tetrahydrofuran, HMPA, ICH_2CO_2Et; x, H_3O^+.

hydrogen.[4] Therefore, a reasonable precursor of (**5**) is the ketone (**1**) which has already been prepared stereoselectively starting from 3,4,5-trimethylanisole *via* Birch reduction followed by Diels–Alder reaction with α-chloroacrylonitrile.[5]

The ketone (**1**) was transformed into the α,β-unsaturated ketone (**2**)† by treatment with BF_3–2MeOH in dry CH_2Cl_2 at room temperature for 30 min. Di-isobutylaluminium hydride (DIBAH) reduction of (**2**) in hexane followed by treatment of the resulting alcohols (**3**) with toluene-*p*-sulphonic acid (*p*-TsOH), (0.1 equiv.) in boiling benzene for 1 h gave the desired ketone (**5**) in 74% overall yield from (**1**). This outcome reflects preferential migration of the two-carbon bridge of (**4**).

Tieffeneau–Demjanov ring expansion of (**5**),[6] by sequential treatment with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide,[7] lithium aluminium hydride, and then sodium nitrite in aqueous acetic acid, gave a mixture of (**6**)[8] and (**7**), 12 : 1, in 61% yield. Ring enlargement of (**6**) was carried out using a combination of trimethylsilyldiazomethane and BF_3–ether[9] at −78 °C. After desilylation with K_2CO_3 in aqueous methanol, the higher homologues (**8**) and (**9**) were obtained in 67% yield in a ratio of 2 : 1.

Treatment of the lithium enolate of (**8**) with ethyl iodoacetate in the presence of hexamethylphosphoric triamide (HMPA), (−78 to 20 °C) gave a stereoisomeric mixture of keto esters (**10**) in quantitative yield. Hydrolysis of (**10**) with K_2CO_3 in aqueous methanol followed by treatment with *p*-TsOH[10] in boiling benzene for 4.5 h gave a mixture of the conjugated lactones (**11**). DIBAH reduction of (**11**) followed by acidic work-up gave the furan, (±)-(**12**), in 37% yield from (**8**), whose spectral characteristics are identical with those of natural nakafuran-8.‡

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† All new compounds gave satisfactory spectral, microanalytical, and/or high high-resolution mass spectral data.

‡ ^{13}C NMR spectrum (67.5 MHz, $CDCl_3$) of (±)-(**12**): δ 150.95 (s), 141.04 (s), 138.27 (d), 124.43 (d), 118.40 (s), 113.64 (d), 47.94 (t), 40.80 (s), 38.98 (t), 36.50 (d), 34.67 (d), 24.25 (q), 23.09 (t), 20.23 (q), and 18.67 (q).