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Synthetic Studies on the Natural Multidrug Resistance Modulator, Irciniasulfonic Acid B

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Synthetic studies on the natural multidrug resistance (MDR) modulator irciniasulfonic acid (ISA)-B utilizing cross metathesis and the Horner–Wadsworth–Emmons olefination is described. The key intermediate, 7-hydroxy-2-nonanone was optically resolved using a cyclopenta[*b*]furan derivative (ALBO-V).

In our continuing research for bioactive compounds from marine invertebrates, we isolated novel fatty acid analogs, ISA[1] and ISA-B (**1**)[2] from the Japanese marine sponge *Ircinia* sp. (Figure 1). These compounds reversed multidrug resistance (MDR) against a membrane glycoprotein (termed P-glycoprotein or P-gp) overexpressing cancer cells. In this letter, we report on the synthesis of deacyl ISA-B (**2**), which is a deacyl derivative of ISA-B. First, the total synthesis of ISA, via a nucleophilic ring-opening reaction with racemic epoxide and hex-1-yne, and a cuprate addition to α,β-unsaturated alkynyl ester was reported by Dobbs's group.[3] Because deacyl ISA-B (**2**) consists of a regioisomeric hydroxy fatty acid, (2*Z*,8*R*)-8-hydroxy-3-methyl-2-decenoic acid (**18**), we opted to synthesize **2** utilizing cross metathesis (CM) reactions[4] and the Horner–Wadsworth–Emmons (HWE) olefination.[5]

Treatment of commercially available 1-penten-3-ol (**3**) with 1 equiv of 5-hexen-2-one (**4**) and 0.6 mol % of the Hoveyda–Grubbs catalyst 2nd generation **5**[6] in refluxing CH_2Cl_2 provided the desired CM product **6** in a yield of 48%. However, the reaction was not carried out efficiently because a self-metathesis of **3** and **4** occurred. It was reported that a two-step CM procedure provided CM products selectively.[4] According to this method, 1-penten-3-ol (**3**) was first self-metathesized with catalyst **5** to provide the homodimer **7**. Then treatment of compound **7** with 0.5 equiv of **4** and 0.1 mol % of **5** provided the 7-hydroxy-5-nonen-2-one (**6**)[7] in a 72% yield (Scheme 1).

The racemic alcohol **8**, which was prepared by the catalytic reduction of **6** was optically resolved using (*R*)-3a-allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan (ALBO-V).[8] Treatment of **8** with ALBO-V gave diastereomeric acetal, and this was easily separated into **9** and **10** by silica gel column chromatography [ΔR_f value of **9**/**10** on TLC 0.05 (*n*-hexane/EtOAc = 2/1)]. Part of the acetals **9** and **10** were treated with PPTS in MeOH to obtain optically active alcohols **11** and **12**, and their specific rotations were $[\alpha]_D = -11.4°$ for **11**, and $+11.4°$ for **12**, respectively. The absolute configuration at C-7 of **12** was determined to be an *S*-configuration by the application of a modified Mosher's method,[9] so that **9** and **11** have *R*-configuration at C-7 in the same way as the natural product. Optically pure acetal **9** reacted with *t*-butyl diethoxyphosphorylacetate (**14**) and KO*t*-Bu to give unsaturated ester **15**, which was a mixture of an *E*/*Z* (5.5/1) isomer. Because the natural ISA-B has trisubstituted *Z*-olefin, we attempted *Z*-selective HE olefination using trifluoroethoxyphosphoryl ester and $KN(TMS)_2$/18-crown-6,[10] however, the reactivity to ketone was poor, so that 2*Z*,8*R* (**15a**) and 2*E*,8*R* (**15b**) olefin was separated by silica gel column chromatography. The structures of **15a** and **15b** were confirmed by the characteristic allylic methyl and methylene proton signals in ^{1}H NMR [**15a**: δ_H 1.81 (3H, d, $J = 1.3$ Hz), 2.57 (2H, m)]. Before the deprotection of the *t*-butyl group of **15a**, cyclopenta[*b*]furanoacetal was replaced with the acetyl group to avoid hydroxy elimination. Compound **15a** was treated with PPTS to give hydroxy derivative **16**. Next, the hydroxy group was protected with Ac_2O/pyridine to give acetyl derivative **17**. The *t*-butyl group in **17** was removed using TFA, and then the acetyl group was removed using NaOMe to afford (2*Z*,8*R*)-8-hydroxy-3-methyl-2-decenoic acid (**18**),[11] successively.

Finally, direct condensation of hydroxy fatty acid **18** and taurine using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM)[12] gave deacyl ISA-B (**2**) (Scheme 2). The spectroscopic data of **2** was in full agreement with those of the deacyl derivative of natural ISA-B.[13]

In conclusion, we have developed a synthesis of optically pure deacyl ISA-B using a CM reaction followed by HWE olefination via chiral resolution with ALBO-V. This method is applicable for obtaining stereoisomer of deacyl ISA-B. The reversing MDR activities of the ISA-B analogs will be reported elsewhere.

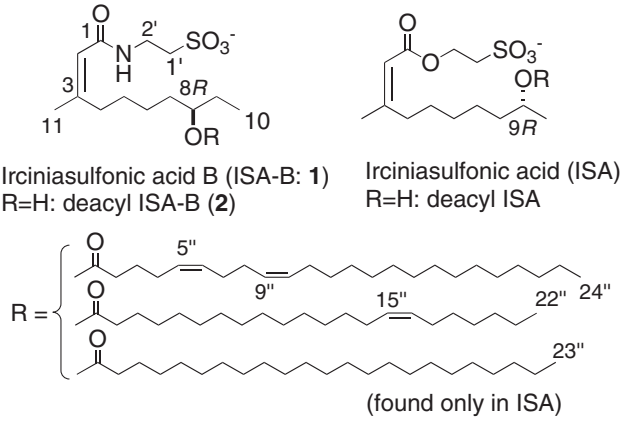
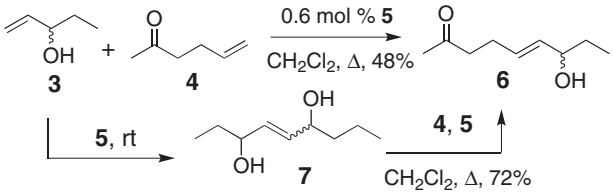
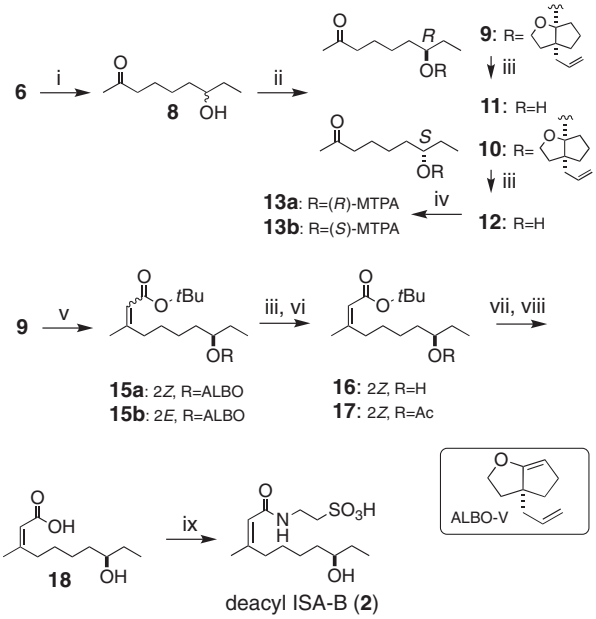


Figure 1. Structures of ISAs.



Scheme 1. Cross metathesis reactions using Hoveyda–Grubbs catalyst 2nd generation.



Scheme 2. Reagents and conditions: (i) H_2, Rh–Al_2O_3, EtOH, 0 °C, 3 h, 72%; (ii) ALBO-V, PPTS, CH_2Cl_2, rt, 1.5 h, **9**: 45%, **10**: 50%; (iii) PPTS, MeOH, rt, **11**: 68%, **12**: 85%, **16**: 45%; (iv) (*R*)- or (*S*)-MTPACl, pyridine, rt, 3.5 h; (v) $(EtO)_2P(O)CH_2COO$*t*-Bu (**14**), KO*t*-Bu, THF, 0 °C–rt, 12 h, **15a**: 11%, **15b**: 60%; (vi) Ac_2O, pyridine, rt; (vii) TFA, CH_2Cl_2, rt; (viii) 0.1 M NaOMe, MeOH, rt, 84% (yield of vi–viii); (ix) taurine, DMT-MM, *N*-methylmorpholine, acetone/H_2O, rt, 12 h, 46%.

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9 I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092; (*R*)-MTPA ester (**13a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.895 (3H, t, $J = 7.3$ Hz, H-9), 1.151 (2H, m, H-5), 2.087 (3H, s, H-1), 2.309 (2H, t, $J = 7.3$ Hz, H-3), 5.002 (1H, m, H-7); (*S*)-MTPA ester (**13b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.789 (3H, t, $J = 7.3$ Hz, H-9), 1.286 (2H, m, H-5), 2.101 (3H, s, H-1), 2.380 (2H, t, $J = 7.3$ Hz, H-3), 5.005 (1H, m, H-7).
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11 Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, $J = 7.5$ Hz, H-10), 1.33–1.53 (8H, methylenes), 1.89 (3H, d, $J = 1.3$ Hz, H-11), 2.62 (2H, t, $J = 6.4$ Hz, H-4), 3.51 (1H, m, H-8), 5.66 (1H, s, H-2).
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13 Synthetic deacyl ISA-B (**2**): $[\alpha]_D$ +8.0° (*c* 0.24, MeOH), deacyl derivative of natural ISA-B: $[\alpha]_D$ +9.0° (*c* 1.0, MeOH), negative HRFABMS *m/z*: 306.1308 $[M - H]^-$ calcd for $C_{13}H_{24}O_5NS$ Δmmu = −6.7, ^{1}H NMR (600 MHz, CD_3OD): δ 0.92 (3H, t, $J = 7.3$ Hz, H-10), 1.28–1.48 (8H, methylenes), 1.83 (3H, d, $J = 1.0$ Hz, H-11), 2.60 (2H, t, $J = 6.8$ Hz, H-4), 2.96 (2H, t, $J = 6.8$ Hz, H-2′), 3.43 (1H, m, H-8), 3.60 (2H, t, $J = 6.8$ Hz, H-1′), 5.64 (1H, s, H-2).

