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Total synthesis of motualevic acids A–E

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ABSTRACT

The first total synthesis of motualevic acids A–E, isolated from *Siliquariaspongia* sp., starting from commercially available 1,10-decanediol, is described. The key steps in the synthetic sequence involve stereoselective olefination, Corey–Fuchs reaction, and amide coupling.

Motualevic acids A–F (**1**–**6**), a new class of brominated long chain acids, along with a new enantiomer of (4*E*)-*S*-antazirine[1,2] **7** (Fig. 1) were recently isolated from *Siliquariaspongia* sp. by Bewley and co-workers.[3] The crude extracts from *Siliquariaspongia* sp. are found to inhibit the growth of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) in a disk diffusion assay. Antimicrobial disk diffusion assays performed with pure motualevic acids A–F (**1**–**6**) and (4*E*)-*R*-antazirine **7** traced the MRSA-inhibitory activity to acids **1** and **6**, which inhibited the growth of MRSA at loadings of 10 and 5 μg/disk, respectively. The same assay performed with SA showed compounds **1**, **2**, **5,** and **6** to be active at respective loadings of 10, 10, 50, and 2 μg/disk. Based on their observation,[3] antimicrobial activity toward MRSA is dependent on the presence of a carboxylic acid group. This is supported by the fact that ester bearing antazirines and azirinomycine[1,2] lack antimicrobial activity while azirinomycine showed antimicrobial activity in its naturally occurring acid form. The new residues of natural products with simple and interesting structure along with significant biological profile attracted us for the total synthesis of motualevic acids A–E.

The synthetic strategy, we planned, will not only give motualevic acids but also their analogs, which may have interesting biological properties. Our synthesis started from a key intermediate[4] **8**, which in turn can be synthesized from a commercially available 1,10-decanediol. Treatment of **8** with KCN in the presence of catalytic amount of 18-crown-6 in acetonitrile at room temperature gave cyanide moiety[5] that was treated with DIBAL-H at −78 °C to provide aldehyde[6] **9** in 75% yield over two steps. Two carbon Wittig olefination was carried out in CH_2Cl_2 at room temperature to get α,β-unsaturated ester[7] **10** exclusively as the (*E*)-isomer in 80% yield. Deprotection of the THP ether moiety in **10** with catalytic amount of PTSA in MeOH resulted in a primary hydroxyl functional group that was oxidized using Swern oxidation reaction conditions to get aldehyde **11** in 88% overall yield. The aldehyde **11** was converted to *gem*-dibromoalkene **12** by Corey–Fuchs reaction[8] in 86% yield. The ester hydrolysis using LiOH in THF/MeOH/H_2O system resulted in the desired motualevic acid E[9] (**5**) with 72% yield (Scheme 1).

The motualevic acid E (**5**) was coupled with glycine methyl ester hydrochloride using EDCI, HOBt as coupling reagents in the presence of Et_3N in CH_2Cl_2 to give methyl ester of motualevic acid A.

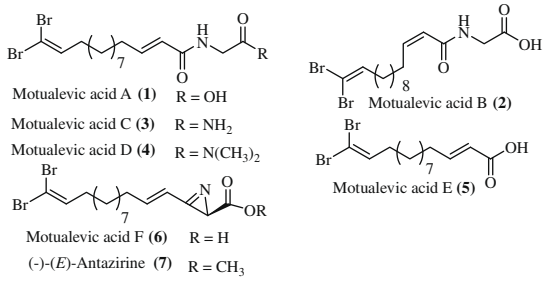
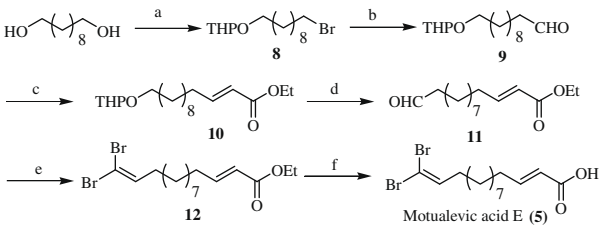


Figure 1. Structures of motualevic acids A–F and (4*E*)-*R*-antazirine.



Scheme 1. Reagents and conditions: (a) (i) HBr, toluene, reflux, 16 h; (ii) DHP, PPTS, CH_2Cl_2, 16 h, 73% over two steps; (b) (i) KCN, 18-crown-6, CH_3CN, 50 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 75% over two steps; (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, overnight, 80%; (d) (i) PTSA, MeOH, 0 °C to rt, 4 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h, 88% over two steps; (e) CBr_4, Ph_3P, CH_2Cl_2, 1 h, 86%; (f) LiOH, THF/MeOH/H_2O (3:1:1), overnight, 72%.

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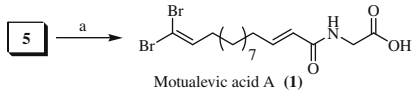
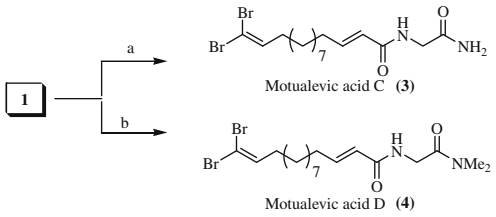
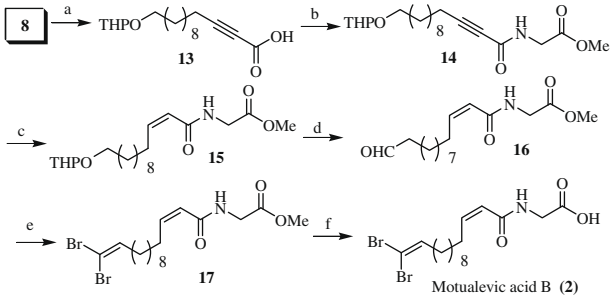


Scheme 2. Reagents and conditions: (a) (i) EDCI, HOBt, $CH_3O_2CCH_2NH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (ii) LiOH, THF/MeOH/H_2O (3:1:1), 2 h, 76% over two steps.



Scheme 3. Reagents and conditions: (a) $ClCO_2C_2H_5$, NH_4OH, Et_3N, THF, −20 °C, 1.5 h, 83%; (b) EDCI, HOBt, $(CH_3)_2NH{\cdot}HCl$, Et_3N, CH_2Cl_2 0 °C to rt, 2 h, 65%.



Scheme 4. Reagents and conditions: (a) LDA (4 equiv), HC≡CCO_2H (2 equiv), THF–HMPA (3:1), 16 h, 50%; (b) EDCI, HOBt, glycine methyl ester hydrochloride, Et_3N, CH_2Cl_2, 2 h, 69%; (c) Pd/$CaCO_3$/Pb, MeOH, 0.25 h, 72%; (d) (i) PTSA, MeOH, 0 °C to rt, 5 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h 85%; (e) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 1 h, 70%; (f) LiOH, THF/MeOH/H_2O (3:1:1), 1 h, 82%.

Subsequent hydrolysis with LiOH in THF/MeOH/H_2O system afforded motualevic acid A[10] (**1**) in 76% yield over two steps (Scheme 2).

Motualevic acids C (**3**) and D (**4**) can be derived from motualevic acid A (**1**) as shown in Scheme 3. To motualevic acid A **(1)** and ethyl chloroformate in the presence of Et_3N in THF at −20 °C, was added NH_4OH to give motualevic acid C[11] **(3)** in 83% yield. Motualevic acid A **(1)** was reacted with *N,N′*-dimethylamine hydrochloride using EDCI, HOBt in the presence of Et_3N in CH_2Cl_2 to give motualevic acid D[12] **(4)** in 65% yield.

For the synthesis of motualevic acid B **(2)**, the *Z* isomer of motualevic acid A **(1)**, we adopted a different synthetic strategy. Treatment of **8** at −15 °C at room temperature for 16 h with dianion of propiolic acid,[13] prepared in situ by reacting propiolic acid in HMPA with LDA in THF at −40 °C and at −15 °C for 2 h, gave the acetylenic acid **13** in moderate yield. The acid **13** was reacted with glycine methyl ester hydrochloride using EDCI, HOBt in the presence of Et_3N in CH_2Cl_2 to give the expected product **14** in 69% yield. Partial hydrogenation of the acetylenic moiety in **14** using Lindlar's catalyst in MeOH furnished the *Z* geometry olefin **15** in 72% yield. The *Z* geometry of the double bond was apparent from the small ^3J coupling of 11.3 Hz between 2H and 3H. Deprotection of the THP group of **15** using a catalytic amount of PTSA in MeOH resulted in a primary hydroxyl group that was oxidized to aldehyde with Swern oxidation reaction conditions to give compound **16** in 85% yield over two steps. The aldehyde **16** was converted to terminal dibromide **17** in 70% yield under Corey–Fuchs[6] reaction conditions. Subsequent hydrolysis using LiOH in a mixture of THF/H_2O/MeOH system gave the desired motualevic acid B[14] **(2)** in 72% yield (Scheme 4). The spectral data of the newly synthesized compounds **1**–**5**[9–12,14] coincided with those of the natural material.[3]

In conclusion, we have achieved the first total synthesis of motualevic acids A–E in a practically applicable way starting from commercially available 1,10-decanediol employing well established methods, stereoselective olefination, Corey–Fuchs reactions, amide coupling as the key steps. Application of this strategy to obtain analogs of the motualevic acids A–F as well as antazirine and its analogs for evaluation of their biological activity is under progress and will be reported in due course.

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9. *Spectral data of motualevic acid E* (**5**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (dt, J = 15.9, 6.7 Hz, 1H), 6.36 (t, J = 7.5 Hz, 1H), 5.87 (d, J = 15.9 Hz, 1H), 2.24 (q, J = 6.7 Hz, 2H), 2.10 (dt, J = 7.5, 6.7 Hz, 2H), 1.53–1.40 (m, 4H), 1.37–1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 152.1, 138.6, 120.5, 88.4, 32.8, 32.1, 29.2, 29.1, 29.0, 28.9, 28.8, 27.7, 27.6; IR (film): ν_{max} 2927, 2854, 1696, 1649, 1222 cm^{-1}; ESI-MS: m/z 403 [M+Na]$^+$.
10. *Spectral data of motualevic acid A* (**1**): ^{1}H NMR (300 MHz, CD_3OD): δ 6.82 (dt, J = 15.8, 6.8 Hz, 1H), 6.50 (t, J = 7.5 Hz, 1H), 6.02 (d, J = 15.8 Hz, 1H), 3.92 (s, 2H), 2.24 (q, J = 6.8 Hz, 2H), 2.14 (dt, J = 7.5, 6.7 Hz, 2H), 1.56–1.30 (m, 14H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.7, 168.6, 145.9, 140.3, 124.5, 89.1, 43.2, 33.9, 33.0, 30.7, 30.5, 30.4, 30.2, 30.0, 29.4, 28.8; IR (film): ν_{max} 2919, 2849, 1733, 1661, 1557, 1262 cm^{-1}; ESI-MS: m/z 438 [M+H]$^+$.
11. *Spectral data of motualevic acid C* (**3**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (dt, J = 15.1, 6.8 Hz, 1H), 6.42–6.32 (m, 3H), 5.84 (d, J = 15.1 Hz, 1H), 5.57 (bs, 1H), 4.05 (d, J = 5.2 Hz, 2H), 2.18 (dt, J = 7.5, 6.8 Hz, 2H), 2.08 (dt, J = 7.5, 6.8 Hz, 2H), 1.50–1.37 (m, 4H), 1.35–1.24 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 168.0, 146.6, 139.2, 123.0, 88.2, 42.9, 32.9, 32.0, 29.6, 29.3, 29.2, 29.1, 28.9, 28.1, 27.7; IR (film): ν_{max} 2917, 2848, 1660, 1625, 1551, 1461, 1274, 1132 cm^{-1}; ESI-MS: m/z 437 [M+H]$^+$.
12. *Spectral data of motualevic acid D* (**4**): ^{1}H NMR (300 MHz, CD_3OD): δ 6.81 (dt, J = 15.3, 6.8 Hz, 1H), 6.47 (t, J = 7.1 Hz, 1H), 6.0 (d, J = 15.3 Hz, 1H), 4.11 (s, 2H), 3.05 (s, 3H), 2.95 (s, 3H), 2.21 (q, J = 6.8 Hz, 2H), 2.11 (q, J = 7.1 Hz, 2H), 1.53–1.38 (m, 4H), 1.35–1.25 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD): δ 172.0, 168.0, 146.6, 140.6, 124.6, 89.4, 41.9, 36.6, 35.2, 34.0, 33.0, 30.6, 30.5, 30.4, 30.2, 30.1, 29.4, 28.8; IR (film): ν_{max} 2919, 2850, 1672, 1617, 1507, 1461, 1407, 1216; ESI-MS: m/z 467 [M+H], 489 [M+Na]$^+$.
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14. *Spectral data of motualevic acid B* (**2**): ^{1}H NMR (300 MHz, CD_3OD): δ 6.49 (t, J = 7.5 Hz, 1H), 6.07 (dt, J = 11.3, 7.5 Hz, 1H), 5.87 (d, J = 11.3 Hz, 1H), 3.82 (s, 2H), 2.63 (q, J = 7.5 Hz, 2H), 2.12 (q, J = 7.5 Hz, 2H), 1.54–1.26 (m, 14H); IR (film): ν_{max} 2925, 2855, 1705, 1670, 1607, 1460, 1218 cm^{-1}; ESI-MS: m/z 438 [M+H]$^+$.