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The first total synthesis of (*S*)-clavulazine from D-mannitol☆

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Abstract—The first total synthesis of the marine natural product (*S*)-clavulazine has been accomplished. D-Mannitol was used as a chiral starting material; enantioselective zinc-mediated allylation, and ring-closing metathesis are the key steps in the synthesis. Subsequent condensation followed by dehydrogenation yielded the natural product, (*S*)-clavulazine.

Several families of natural alkaloids that display important biological properties have been reported from marine sponges. Yoshimasa and co-workers reported the isolation of palythazine, isopalythazine, and similar alkaloids from *Palythoa tuberculosa*,[1a] all of which incorporate a pyrazine skeleton. The absolute stereochemistry of palythazine was conclusively established after the first total synthesis.[1b] Clavulazine (**1**) (Fig. 1) isolated from the Okinawan soft coral *Clavularia viridis*,[2] possesses a unique pyrano fused pyrazine ring system with a single asymmetric center. Recently Ya-Ching Shen and co-workers isolated clavulazole A, clavulazole B, and clavulazine (**1**).[3] These compounds, structurally related to furazano[3,4-*b*]pyrazine derivatives show a biological activity in the field of antimicrobials,[4a] herbicides, plant growth regulators[4b] and Gram-positive bacteria.[4c] Tetrahydropyrido[3,4-*b*]pyrazine derivatives are effective medicines for skin disease caused by the proliferation of keratinocytes[4d] leading to much current interest in fused pyrazine compounds for medicine and agriculture. We herein report the synthesis of dihydropyrano[3,4-*b*]pyrazine (clavulazine **1**).

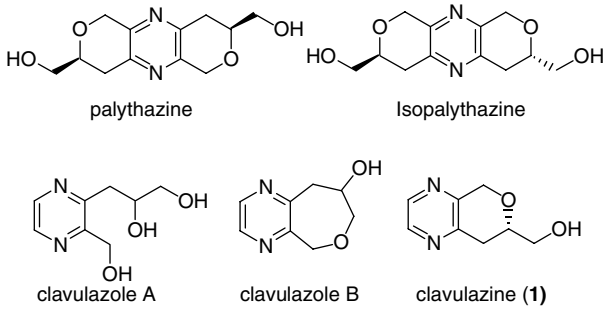
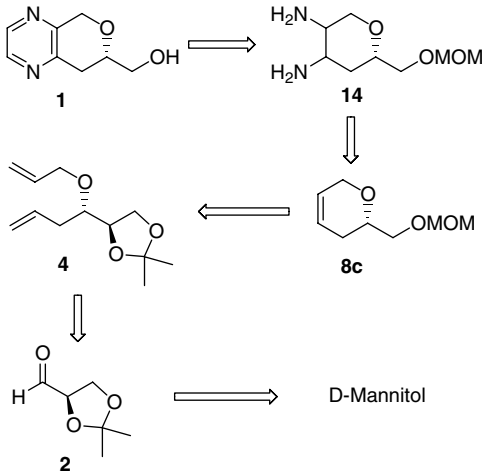


Figure 1.

Our synthetic plan for the total synthesis of clavulazine utilized commercial D-mannitol. Enantioselective zinc-mediated allylation to control the stereogenic center, a ring-closing metathesis (RCM) to the pyran ring and diamine condensation with glyoxal followed by aromatization with DDQ are the key steps. The retrosynthesis is summarized in Scheme 1.



Scheme 1. Retrosynthetic analysis of clavulazine.

Keywords: Clavulazine; Glyoxal; Grubbs' catalyst; Zinc allylation.
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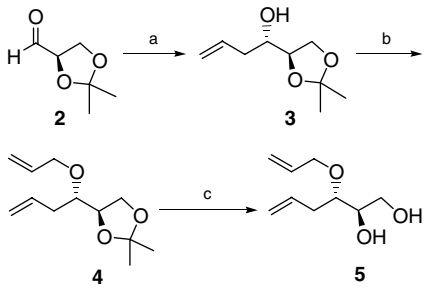
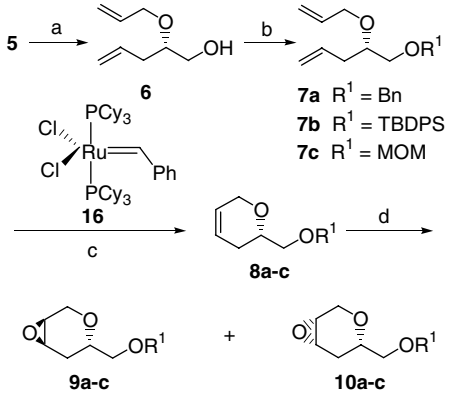


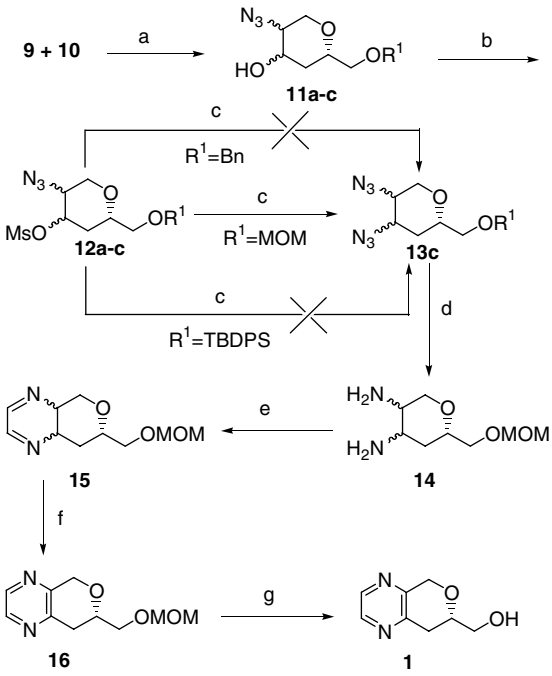
Scheme 2. Reagents and conditions: (a) Zn, THF, allyl bromide, satd NH_4Cl, 0 °C, 2 h, 74%; (b) NaH, dry THF, allyl bromide, 0 °C, 3 h, 86%; (c) 2 N HCl, THF, rt, 3 h, 90%.

As depicted in Scheme 2, Zn mediated[5a–d] addition of allyl bromide at 0 °C to the chiral synthon (*R*)-2,3-*O*-isopropylideneglyceraldehyde[5e–g] **2** proceeded with a good enantioselectivity (95% ee) to give homoallylic alcohol **3**. Allylation of the hydroxyl group using allyl bromide and NaH at 0 °C afforded **4**.[6] Diol **5** was prepared from **4** by treatment with THF and 2 N HCl at 0 °C to rt[7a] (Scheme 2).

Alcohol **6** was produced from **5** by oxidation with $NaIO_4$ and satd $NaHCO_3$ in DCM at 0 °C,[7b] followed by $NaBH_4$ reduction in methanol. The primary hydroxyl group in **6** was protected using benzyl bromide, TBDPSCl, and MOM-Cl. For the preparation of **13**, when the primary alcohol was protected with Bn or with TBDPSCl the azide formation was sluggish. We found that the MOM group was the most effective for the conversion of **12** to azide **13**. Alcohol **6** was treated with methoxymethyl chloride and DIPEA in THF to furnish protected alcohol **7c**.[8] Exposure of **7c** to Grubbs' first generation catalyst **16** in DCM at room temperature proceeded efficiently to give pyran **8c**[9] in a modest yield. This was next epoxidized with *m*-CPBA to afford regioisomers **9c** and **10c** (60:40)[10] (Scheme 3).



Scheme 3. Reagents and conditions: (a) $NaIO_4$, $NaHCO_3$, DCM, 0 °C–rt, 8 h, then $NaBH_4$, MeOH, 15 min, 93%; (b) (i) for **7a**, BnBr, NaH, dry THF, 0 °C, 4 h, 82%; (ii) for **7b**, TBDPSCl, imidazole, dry THF, 0 °C, 2 h, 85%; (iii) for **7c**, DIPEA, MOMCl, dry DCM, 0 °C, 2 h, 78%; (c) (i) for **8a**, Grubbs' catalyst, dry DCM, rt, 4 h, 77%; (ii) for **8b**, Grubbs' catalyst, dry DCM, rt, 6 h, 80%; (iii) for **8c**, Grubbs' catalyst, dry DCM, rt, 3 h, 73%; (d) (i) *m*-CPBA, $NaHCO_3$, dry DCM, 5 h, 65%, 33:32 (**9a**, **10a**); (ii) *m*-CPBA, $NaHCO_3$, dry DCM, 6 h, 62%, 32:30 (**9b**, **10b**); (iii) *m*-CPBA, $NaHCO_3$, dry DCM, 4 h, 60%, 35:25 (**9c**, **10c**).



Scheme 4. Reagents and conditions: (a) (i) for **11a**, NaN_3, EtOH:H_2O (3:1), NH_4Cl, 80 °C, 8 h, 57%; (ii) for **11b**, NaN_3, EtOH:H_2O (3:1), NH_4Cl, 80 °C, 9 h, 58%; (iii) for **11c**, NaN_3, EtOH:H_2O (3:1), NH_4Cl, 80 °C, 6 h, 62%; (b) (i) for **12a**, CH_3SO_3Cl, dry TEA, dry DCM, 0 °C, 3 h, 82%; (ii) for **12b**, CH_3SO_3Cl, dry TEA, dry DCM, 0 °C, 4 h, 85%; (iii) for **12c**, CH_3SO_3Cl, dry TEA, dry DCM, 0 °C, 2 h, 88%; (c) NaN_3, dry DMF, 100 °C, overnight, 59%; (d) Pd–C, H_2, EtOH, 4 h, rt, 78%; (e) 40% glyoxal, 4 Å molecular sieves, EtOH, 80 °C, 36 h; (f) DDQ, dry toluene, 80 °C, 24 h; (g) 2 N HCl, THF, 0 °C–rt, 1 h (for 3 steps, the overall yield was 15%).

Epoxides **9c** and **10c** were opened with NaN_3, ethanol:water (3:1) and NH_4Cl under reflux to furnish azido alcohol **11c** as a mixture of diastereoisomers. The free hydroxyl group in **11c** was converted to the methansulfonyl derivative **12c** with MsCl and TEA at 0 °C. Subsequent treatment with sodium azide in dry DMF at 100 °C afforded diazide **13c** in a 59% yield.[11]

Hydrogenation of **13** in the presence of Pd–C in absolute ethanol was uneventful and led to diamine **14**.[12] Cyclization of diamine **13** with 40% glyoxal and 4 Å molecular sieves in ethanol at reflux for 36 h afforded **15**.[13] Crude **14** was aromatized by dehydrogenation with DDQ in toluene for 24 h at 80 °C to afford **16**.[14] Final deprotection of the MOM group with 2 N HCl in THF furnished (*S*)-clavulazine (**1**) (Scheme 4).

In summary, the first total synthesis of (*S*)-clavulazine was accomplished via 15 steps from D-mannitol. Spectral data are provided in Ref. 15.

Acknowledgements

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15. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. Spectral data of selected compounds: (**3**) $[\alpha]_D^{25}$ +11.0 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 172 (M^+, 15), 157 (5), 101 (40), 83 (5), 69 (10), 59 (35), 43 (100); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.09–5.75 (m, 1H), 5.16–5.06 (m, 2H), 3.99–3.83 (m, 3H), 3.73–3.66 (m, 1H), 2.35–2.31 (m, 2H), 1.93 (1H, –OH), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 134.5, 118.6, 109.5, 78.6, 70.5, 65.7, 38.1, 27.0, 25.7; (**7c**) $[\alpha]_D^{25}$ −0.71 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 186 (M^+, 25), 141 (20), 123 (25), 111 (15), 82 (20), 70 (12), 55 (95), 45 (100); IR (KBr, neat) 3450, 3078, 2928, 1642, 1438, 1149, 1113, 1045; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.96–5.76 (m, 2H), 5.31–5.03 (m, 4H), 4.61 (s, 2H), 4.15–4.02 (m, 2H), 3.53 (m, 3H), 3.35 (s, 3H), 2.32 (q, 2H, $J = 7.55$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 135.6, 134.8, 117.4, 116.8, 97.1, 77.9, 71.1, 69.6, 55.5, 36.5; IR (KBr, neat) 3431, 2924, 1641, 1244, 1153, 1111, 1038; (**8c**) $[\alpha]_D^{25}$ −1.52 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 158 (M^+, 18), 112 (7), 97 (20); 81 (12), 69 (10), 45 (100); IR (KBr, neat): 3431, 2924, 2852, 1641, 1244, 1153, 1111, 1038; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.83–5.77 (m, 1H), 5.74–5.68 (m, 1H), 4.62 (s, 2H), 4.21–4.18 (m, 2H), 3.75–3.67 (m, 1H), 3.54–3.52 (m, 2H), 3.35 (s, 3H), 2.14–2.03 (m, 1H), 1.98–1.88 (m, 1H);^{13}C NMR ($CDCl_3$, 75 MHz): 126.23, 123.44, 96.56, 72.44, 70.23, 65.66, 55.04, 27.03; (**9c**) $[\alpha]_D^{25}$ −18.5 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 174 (M^+, 30), 131 (35), 115 (15), 101 (25), 85 (30), 45 (100); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.58 (s, 2H), 4.20 (d, 1H, $J = 13.5$ Hz), 3.86 (d, 1H, $J = 12.8$ Hz), 3.49–3.28 (m, 4H), 3.32 (s, 3H), 3.01 (d, 1H, $J = 3.7$ Hz), 1.92–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 96.5, 71.7, 69.7, 64.3, 55.0, 49.0, 48.7, 25.8; (**12c**): $[\alpha]_D^{25}$ −16.8 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 295 (M^+, 20), 195 (25), 150 (40), 108 (16), 81 (7), 45 (100); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.86 (d, 1H, $J = 3.7$ Hz), 4.63 (s, 2H), 4.02 (d, 1H, $J = 2.26$ Hz), 3.98–3.86 (m, 2H), 3.61–3.52 (m, 3H), 3.37 (s, 3H), 3.10 (s,3H), 2.13–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 96.9, 74.8, 71.3, 70.0, 65.3, 57.2, 55.5, 39.1, 29.5; (**13c**): $[\alpha]_D^{25}$ −16.0 (*c* 0.01, $CHCl_3$); EIMS (relative intensity) *m/z*: 242 (M^+, 18), 198 (23), 153 (20), 108 (13), 92 (25), 45 (100); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.60 (s, 2H), 4.13 (dd, 1H, $J = 1.60$, 12.82 Hz), 3.63–3.48 (m, 6H), 3.33 (s, 3H), 1.90–1.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 96.6, 70.6, 69.5, 64.2, 58.6, 58.4, 55.2, 32.1; (**1**): colorless solid, mp 98–99 °C; $[\alpha]_D^{25}$ −96.2 (*c* 0.17, $CHCl_3$), [lit.[1] −99.4 (*c* 0.17, $CHCl_3$)]; EIMS (relative intensity) *m/z*: 166 (M^+, 60), 148 (15), 135 (100), 107 (90), 80 (26), 52 (13); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38 (d, 1H, $J = 2.5$ Hz), 8.35 (d, 1H, $J = 2.5$ Hz), 4.99 (d, 1H, $J = 16.4$ Hz), 4.85 (d, 1H, $J = 16.4$), 4.01 (m, 1H), 3.85 (dd, 1H, $J = 6.9$, 12.6 Hz), 3.82 (dd, 1H, $J = 6.7$, 12.0 Hz), 3.01 (m, 2H), 2.05 (d, –OH, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 150.2, 149.9, 145, 145.2, 75.8, 68.3, 61.0, 31.8.