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(+)-Zwittermicin A. Rapid Assembly of C9-C15 and a Formal Total Synthesis

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Abstract

A short, enantioselective synthesis of the C9-C15 portion of (+)-zwittermicin A is reported that exploits directional functionalization of the known hepta-2,5-diyne-1,7-diol by partial reduction of the two triple bonds followed by Sharpless asymmetric epoxidation and boron-directed double ring opening with sodium azide under Miyashita conditions. Subsequent desymmetrization of the C_2 -symmetric diazidotetraol product converges upon (–)-**3** – the enantiomer of the key intermediate of our earlier structural proof and synthesis of (–)-zwittermicin A – and constitutes a formal synthesis of (+)- zwittermicin A.

Introduction

(+)-Zwittermicin A (**1**) is a highly polar, water-soluble aminopolyol antibiotic isolated from the soil-born bacterium *Bacillus cereus*¹ with significant activity against phytopathogenic fungi.^{1,2} More importantly, **1** enhances the activity of the endotoxin from *Bacillus thuringiensis*, the active ingredient in biocontrol agents used against crop pests³ and gypsy moth *Lymantria dispar*⁴ which annually defoliates millions of hectares of forests in the North Eastern United States of America. Handelsman and coworkers have shown that *B. cereus* and other bacteria that produce **1** are ubiquitous in soil⁵ suggesting **1** may constitute a benign

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Supporting Information Available: Description of general and experimental features. ¹H and ¹³C NMR spectra for compounds (–)-**3**, **6**, **7**, **9**, and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

biocontrol alternative to pest management strategies currently based on synthetic pesticides. The rising interest in **1** as a “green” biopesticide, particularly in China, has stimulated studies of its unique biosynthesis and mechanism of action.⁶ Despite appearances, the biosynthesis of (+)-**1** does not originate in carbohydrate metabolism, but from a non-ribosomal peptide synthetase/polyketide synthase pathway (NRPS/PKS) involving two newly described type 1 PKS extender units: hydroxymalonyl-acyl carrier protein (ACP) and aminomalonyl-ACP.⁶ Zwittermicin A has proved difficult to isolate in substantial quantities due to its highly-polar, charged nature at physiological pH and sensitivity to alkaline conditions.¹ For example, until recently the purification of (+)-**1** required application of the arcane technique of preparative paper electrophoresis,¹ although purifications have been achieved more recently by reversed phase HPLC.^{6c} Zwittermicin A [(+)-**1**] has not yet been synthesized. Contemporary interest in (+)-**1** and the difficulty in obtaining the compound from natural sources underscore an outstanding need for practical syntheses of (+)-**1**.

We recently determined the absolute stereostructure of (+)-**1** based on amino acid configurational analysis of the corresponding acid-hydrolysate (6 M HCl, 110 °C),⁷ deductive reasoning from systematic ¹³C NMR spectroscopic comparisons of (+)-**1** with diastereomeric models (e.g. L-**2**) constituting C9-C15 of **1**,⁷ and the total synthesis of the unnatural enantiomer, (–)-**1**.⁸ The differentially protected key intermediate, (+)-**3**, was synthesized in 17 steps from L-serine.⁸ At the time, the lengthy route from the arbitrarily chosen L-enantiomer of serine was dictated by the need for all six stereoisomeric 2,6-diaminoheptane-1,3,5,7-tetraols (e.g. **2**) for structure elucidation of (+)-**1**. As it turned out, natural (+)-**1** is correlated with D-serine. Here, we outline an improved asymmetric route to the *pseudo*-C₂ symmetric C9-C15 segment successfully converging upon key intermediate (–)-**3** which may be employed for synthesis of (+)-**1** using chemistry parallel to that we previously described for (–)-**1**.⁸

Results and Discussion

Conceptually, synthesis of **1** takes advantage of the nominal C₂ axial symmetry embodied within **3** and bidirectional assembly from known diyne **4** that constitutes the intact C9-C15 carbon skeleton (Scheme 1).⁹

The route exploits asymmetric reagent control over the achiral starting material, **4**, with an intact C9–C15 carbon skeleton and capitalizes upon highly enantioselective double Sharpless epoxidation¹⁰ and a double regioselective Miyashita-type opening of epoxide rings in **5** by two equivalents of NaN₃ which directs the nitrogen groups to C2 and C6.¹¹ One disadvantage of this route, which only became apparent during the course of investigations, was unexpectedly high water-solubility of a key intermediate which precluded standard extractive workup by solvent-partitioning, and necessitated a different isolation-purification strategy (vide infra).

The known diepoxide **5** was prepared in two steps from **4** according to Hoffmann and coworkers¹² using a double Sharpless asymmetric epoxidation,¹⁰ that sets the absolute configuration depicted using (+)-diethyl tartrate as the auxiliary (lit. 98% *ee*¹²). Although not previously reported as such, compound **5** was found to be crystalline and conveniently purified by recrystallization. Treatment of the diepoxide **5** with NaN₃ in the presence of trimethylborate under Miyashita conditions (B(OMe)₃, DMF, 50 °C, Scheme 2)¹¹ gave the C₂ symmetric diazidotetraol **6** in 80% yield as a mixture of diastereomers (*dr* 10:1:1:1).

At first, the unexpectedly high water-solubility of **6** proved troublesome for purification. After some experimentation it was found most efficient to concentrate the crude product until almost dry, followed by trituration (x2)– first with MeOH, then with a mixture of MeOH and CH₂Cl₂ – and finally recrystallization from MeOH to give **6** as a diastereomerically pure crystalline solid.

It was desirable to desymmetrize **6** by mono-*O*-protection at the primary OH group with a reductively labile protecting group that could be later cleaved, simultaneously, with hydrogenolysis of the azide groups to reveal the NH₂ groups. Selective *O*-benzylation of the primary OH groups would satisfy these criteria. Successful desymmetrization of diols using Ag₂O/BnBr has been reported,¹³ but in our hands these conditions were unsatisfactory with **6** and led to inseparable mixtures of products. It was found that more efficient mono-*O*-protection of the C1 hydroxyl (Scheme 2) could be achieved with a trityl group.

A survey (Table 1) of reaction conditions found that optimized yields of monoprotected diazidotetraol **7** (69% yield) were obtained with 0.8 equiv of chlorotriphenylmethane in pyridine (entry 3).¹⁴ The undesired doubly-tritylated side product **8** was recycled to **7** upon treatment with acid (CF₃COOH, MeOH, 48% yield).

Protection of the 1,3-diol OH groups in triol **7** was achieved by conversion to an external acetonide **9** (Scheme 3). Optimization of the ratio of terminal and internal acetonides required a fine balance of reaction temperature, limited reagent equivalencies, acid catalyst and time (Table 2). Reaction of **7** with excess 1,1-dimethoxypropane and acetone at 50 °C (entry 1) led to complete loss of starting material, but gave an unacceptable mixture of **9**, the internal acetonide **10** and the mono-methyl mixed acetal **11**. Treatment of **7** with 2.5 equivalents of 2-methoxypropene at 0 °C to room temperature returned only starting material, however, a higher temperature (50 °C) and use of 2.0 equivalents of reagent gave good conversion and a high ratio of the desired compound (**9**:**10**:**11** = 64:8:14, entry 7). Optimal conditions were found with slightly more 2-methoxypropene (2.5 equiv) that gave slightly better conversion of **7**, and the highest yield of **9** (73%, entry 6) while minimizing equilibration to the internal acetonide **10**.¹⁵

After protection of the secondary hydroxyl group in **9** as the MOM ether **12** (90% yield),¹⁶ simultaneous removal of the *O*-trityl protecting group and reduction of the two N₃ groups was effected by hydrogenation (Pd-C, H₂, 7 atm, TFA/CF₃CH₂OH) to give the TFA double salt of diamine **13**,¹⁷ that was converted without purification to the *bis-N,N*-dibenzylamine (–)-**3** (BnBr, K₂CO₃, CH₃CN, 47%, over two steps).¹⁸ The product (–)-**3** was identical in all respects to (+)-**3** except for optical rotation which was opposite in sign ((–)-**3**, [α] –25.2, *c* 2.8 CHCl₃; lit.⁸ (+)-**3**, [α]_D²¹ +28.8, *c* 2.01, CHCl₃). Since we had previously demonstrated transformation of (+)-**3** to (–)-*ent*-zwittermicin A [(–)-**1**],⁸ the foregoing constitutes a formal synthesis of the natural product, (+)-**1**.

Some comments on the synthesis of (–)-**3** are in order. The target is rapidly assembled from the achiral di-yne **4** with introduction of asymmetry in form of known diepoxide **5** obtained through a conventional Sharpless epoxidation. Critical for the success of this rapid target assembly is the regioselective introduction of the two nitrogens by strategic use of a double epoxide opening of **5** with NaN₃ under Miyashita conditions. The regioselectivity of the Miyashita conditions generally favors a rare *endo* mode ring opening at C2 through a metal-chelated intermediate.^{11c,19} The isomer ratio obtained by azide attack at C2 or C3 of the epoxyalcohol is substrate dependent; C2 attack gives 2-azido-1,3-diols with regioselectivity that increases with substitution at C4 by bulky groups, but particularly oxy substituents (e.g. BnO, silyloxy). In our earlier synthesis of stereoisomers of **2** by a linear approach involving opening of differentially protected *mono*-epoxyalcohols,⁷ we found stereoisomers behaved differently toward NaN₃-B(OMe)₃. The highest ratio of C-2 to C-3 azide attack was found for an unwanted *syn*-3,5 isomer (9:1), but the *anti*-3,5 isomer required for the natural relative configuration of **1** gave a lower ratio (7:3).⁷ In the case of diepoxide **5**, with an *anti*-3,5 configuration, the regioselectivity of highly directed double-epoxide ring opening (~10:1, azide attack at C2 and C6) appears to be amplified by two factors: the presence of the second epoxide ring in **5** and enhanced preference of azide attack at C2 in the intermediate alkoxy azide formed

from the first ring opening. In the latter case, with an unencumbered C5 substituent (1,2-oxirane), the directing effect is less likely to be simply steric in nature, but may be dependent on secondary dipole interactions. Since this reaction is useful for installation of vicinal N,O-functional groups in asymmetric synthesis of other biologically important aminoalkanols (e.g. phytosphingosines²⁰), the substitution patterns that determine regioselectivity of epoxyalcohol ring opening under Miyashita conditions are deserving of further study.

In conclusion, (–)-**3** was synthesized in 10 steps from commercially available materials. This represents a substantially shorter route (seven fewer steps) than our previous synthesis of (+)-**3** from L-serine. The rapid assembly of the C9-C15 portion of (+)-**1** was made possible through three efficient bidirectional functionalizations, starting with a symmetrical di-yne, with stereo- and regiocontrol of N and O addition reactions. This formal synthesis of zwittermicin A [(+)-**1**] validates a route for procurement of quantities of the natural product for ongoing investigations of its biological properties.

Experimental Section

General experimental

Details of general procedures can be found in the Supporting Information.

(2R,3S,5S,6R)-2,6-diazidoheptane-1,3,5,7-tetraol (**6**)

Under an atmosphere of nitrogen, trimethylborate (1.56 mL, 1.43 g, 13.7 mmol) was added to a solution of **5** (550 mg, 3.43 mmol) in anhydrous DMF (17.2 mL). The solution was stirred for 30 min at room temperature then NaN₃ (893 mg, 13.7 mmol) was added and the reaction was heated to 40 °C and stirred for 4 h then heated to 50 °C. for a further 4 h. The reaction was cooled to room temperature and quenched by addition of a saturated solution of NaHCO₃ (50 mL) and the solution stirred a further 1h. The mixture was concentrated to dryness under reduced pressure then treated with methanol (200 mL) and the solids removed by filtration. The solution was again concentrated, followed by addition of a mixed solvent (3:2 MeOH/CH₂Cl₂, 200 mL) before concentration of the filtrate under reduced pressure. Purification of the crude product by flash chromatography (silica, gradient 1:19 to 3:2 MeOH-CH₂Cl₂) followed by reversed phase chromatography (20 g of C₁₈-silica, 1:19 MeOH-H₂O) provided **6** (672 mg, 80%, *dr* 10:1.1:1 by NMR analysis) as white solid. Recrystallization of the solid from methanol gave pure **6** (393 mg): mp 132 °C; IR (neat) ν 3201, 2950, 2919, 2871, 2137, 2097, 1445, 1405, 1320, 1267, 1137, 1078, 1064, 1029, 1006, 910, 862 cm⁻¹; [α]_D²¹ +5.3 (c 2.13, CH₃OH); ¹H NMR (500 MHz, CD₃OD) δ 3.87 (m, 2H), 3.81 (dd, *J* = 11.6, 3.7 Hz, 2H), 3.60 (dd, *J* = 11.6, 8.1 Hz, 2H), 3.45 (m, 2H), 1.59 (dd, *J* = 7.8, 5.2 Hz, 2H); ¹³C NMR (125 MHz, CD₃OD) δ 70.4 (CH), 68.5 (CH), 63.0 (CH₂), 37.0 (CH₂); HRMS *m/z* 245.1004 [M – H][–], calcd. for C₇H₁₃N₆O₄ 245.1004.

(2R,3S,5S,6R)-2,6-diazido-7-(trityloxy)heptane-1,3,5-triol (**7**)

Method 1—Under an atmosphere of nitrogen chlorotriphenylmethane (104 mg, 374 μ mol) was added to a stirred solution of tetraol **6** (115 mg, 467 μ mol) in pyridine (2.3 mL) at room temperature. The mixture was heated to 60 °C and stirred for 5 h. The mixture was then concentrated under reduced pressure and separated by flash chromatography (silica, 25 to 50% ethyl acetate in hexane then 20% methanol in dichloromethane) to provided **7** (125 mg, 69%) and **8** (39 mg, 14%) as viscous oils along with recovered **6**.

Method 2—Under an atmosphere of nitrogen, a solution of diol **8** (38 mg, 52 μ mol) in MeOH was adjusted to pH 2 with TFA and stirred at room temperature for 10 h. The mixture was quenched with triethylamine (0.5 mL) and concentrated under reduced pressure. Separation of the mixture by flash chromatography (silica, 1:1 EtOAc-hexane, then 1:4 MeOH-CH₂Cl₂)

provided **7** (12.2 mg, 48%) and recovered **8** (7.6 mg, 20%) as viscous oils along with some **6**.

7—IR (neat) ν 3349, 3086, 3058, 3032, 2928, 2883, 2094, 1658, 1595, 1489, 1448, 1317, 1264, 1218, 1072, 1031, 900, 855, 747 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -21.6 (*c* 6.25, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.47–7.44 (m, 6H), 7.34–7.30 (m, 6H), 7.25 (tt, *J* = 7.2, 1.2 Hz, 3H), 4.00–3.93 (m, 2H), 3.81 (m, 2H), 3.49–3.44 (m, 2H), 3.40–3.35 (m, 2H), 1.59 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.4 (C), 128.7 (CH), 128.2 (CH), 127.5 (CH), 87.8 (C), 69.0 (CH), 68.9 (CH), 66.4 (CH), 65.5 (CH), 63.7 (CH_2), 62.5 (CH_2), 35.4 (CH_2); HRESIMS *m/z* 511.2067 [*M* + *Na*] $^+$, calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_6\text{O}_4\text{Na}_1$ 511.2064.

(2*S*,3*R*)-3-azido-1-((4*S*,5*R*)-5-azido-2,2-dimethyl-1,3-dioxan-4-yl)-4-(trityloxy)butan-2-ol (9)

Under an atmosphere of nitrogen 2-methoxypropene (3.6 μL , 19 μmol) was added to a stirred solution of triol **7** (9.2 mg, 19 μmol) and PPTS (0.4 mg, 2 μmol) in DMF (100 μL) at room temperature. The mixture was heated to 50 $^\circ\text{C}$ and stirred for 4 h, cooled to room temperature and quenched with saturated aqueous NaHCO_3 (3 mL). The mixture was extracted with ethyl acetate (3 $\times$ 4 mL) and combined organic extracts washed with brine (3 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Separation of the mixture by flash chromatography (silica, 1:9 EtOAc-hexane) provided **9** (7.3 mg, 73%) and **10** (1.7 mg, 17%) as viscous oils. **9**: $[\alpha]_{\text{D}}^{22}$ -29.0 (*c* 6.56, CHCl_3); IR (neat) ν 3465, 3058, 2993, 2923, 2877, 2101, 1596, 1489, 1448, 1380, 1264, 1200, 1159, 1070, 980, 898, 821, 747, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49–7.44 (m, 6H), 7.35–7.30 (m, 6H), 7.26 (tt, *J* = 7.4, 1.2 Hz, 3H), 3.96 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.94–3.84 (m, 2H), 3.69 (dd, *J* = 11.5, 10.0 Hz, 1H), 3.49 (m, 1H), 3.45 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.35 (dd, *J* = 10.0, 6.9 Hz, 1H), 3.24 (ddd, *J* = 10.0, 10.0, 5.8 Hz, 1H), 2.60 (d, *J* = 7.5 Hz, OH), 1.78 (ddd, *J* = 14.3, 9.5, 2.6 Hz, 1H), 1.58 (ddd, *J* = 14.3, 8.6, 2.3 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.6 (C), 128.7 (CH), 128.1 (CH), 127.4 (CH), 99.3 (C), 87.6 (C), 69.7 (CH), 68.0 (CH), 65.9 (CH), 63.6 (CH_2), 62.4 (CH_2), 58.0 (CH), 35.4 (CH_2), 28.8 (CH_3), 19.2 (CH_3); HRESIMS *m/z* 551.2372 [*M* + *Na*] $^+$, calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_6\text{O}_4\text{Na}_1$ 551.2377.

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^1H NMR (500 MHz, CDCl_3) δ 7.47–7.44 (m, 6H), 7.34–7.29 (m, 6H), 7.25 (tt, *J* = 7.2, 1.2 Hz, 3H), 3.98 (dt, *J* = 8.9, 6.3 Hz, 1H), 3.91 (dt, *J* = 9.5, 6.0 Hz, 1H), 3.74 (bm, 1H), 3.67 (bm, 1H), 3.55 (m, 1H), 3.47 (m, 1H), 3.27 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.22 (dd, *J* = 10.0, 4.8 Hz, 1H), 1.99 (bs, OH), 1.79 (m, 1H), 1.70 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H); LRESIMS *m/z* 551.20 [*M* + *Na*] $^+$, calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_6\text{O}_4\text{Na}_1$ 551.2377.

(4*S*,5*R*)-5-azido-4-((2*S*,3*R*)-3-azido-2-(methoxymethoxy)-4-(trityloxy)butyl)-2,2-dimethyl-1,3-dioxane (12)

Chloromethyl methyl ether (115 μL , 1.51 mmol) was added to a stirred solution of alcohol **9** (80.0 mg, 151 μmol) and Hünig's base (500 μL , 3.03 mmol) in dichloromethane (200 μL) at 0 $^\circ\text{C}$. The mixture was warmed to room temperature and stirred for 38 h then quenched by addition of water (5 mL). The mixture was extracted with ethyl ether (4 $\times$ 5 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the mixture by flash chromatography (silica, 1:9 EtOAc-hexane) provided **12** (75.2 mg, 90%) as a viscous oil: IR (neat) ν 3058, 2992, 2935, 2886, 2100, 1596, 1490, 1448, 1371, 1264, 1221, 1197, 1154, 1076, 1030, 981, 918, 808, 763, 747, 702 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -33.6 (*c* 4.55, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.47–7.44 (m, 6H), 7.34–7.30 (m, 6H), 7.25 (tt, *J* = 7.3, 1.2 Hz, 3H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 3.96 (dd, *J* = 11.5, 5.4 Hz, 1H), 3.87 (m, 1H), 3.81 (m, 1H), 3.75–3.65 (m, 2H), 3.36 (s, 3H), 3.26 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.15 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.12 (dd, *J* = 9.7, 5.4 Hz, 1H), 1.92

(ddd, $J = 14.0, 10.0, 2.0$ Hz, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.28 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.7 (C), 128.8 (CH), 128.0 (CH), 127.3 (CH), 99.0 (C), 97.6 (CH_2), 87.4 (C), 75.0 (CH), 68.5 (CH), 65.8 (CH), 63.3 (CH_2), 62.5 (CH_2), 58.8 (CH), 56.1 (CH_3), 34.4 (CH_2), 28.8 (CH_3), 19.3 (CH_3); HRESIMS m/z 595.2629 $[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_5\text{Na}_1$ 595.2639.

(2R,3S)-2-amino-4-((4S,5R)-5-amino-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol (13)

10% Pd/C (6.3 mg, 5.9 μmol , 25 mol % Pd) was added to a solution of **12** (13.1 mg, 23.5 μmol) in dry trifluoroethanol (1.5 mL) and the mixture agitated under H_2 (7 atm) for 17 h in a Parr shaker. The mixture was adjusted to pH 4 with TFA, placed under H_2 (7 atm) and agitated for a further 4.5 h on a Parr shaker. Filtration of the mixture through a 0.45 μm syringe filter and concentration under reduced pressure provided crude **13** which was used without further purification.

(2R,3S)-2-(dibenzylamino)-4-((4S,5R)-5-(dibenzylamino)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(methoxymethoxy)butan-1-ol ((-)-3)

Benzylbromide (56.3 μL , 471 μmol) was added dropwise to a stirred solution of amine **13** (<6.6 mg, 23.5 μmol) and K_2CO_3 (195 mg, 1.41 mmol) in anhydrous acetonitrile (550 μL) at room temperature. The mixture was stirred for 4.5 d then quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (4 $\times$ 4 mL) and combined extracts washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the mixture by flash chromatography (silica, step gradient of 1:9 to 1:3 EtOAc-hexane) provided (-)-**3** (7.0 mg, 47%) as an amorphous solid: IR (neat) ν 3476, 3065, 3030, 2995, 2943, 2882, 2812, 1597, 1492, 1457, 1379, 1265, 1221, 1151, 1108, 1029, 977, 916, 758, 706 cm^{-1} ; $[\alpha]_{\text{D}}^{21}$ -25.2 (c 2.80, CHCl_3 ; lit.⁸ for (+)-**3** $[\alpha]_{\text{D}}^{21}$ +28.8° (CHCl_3 , c 2.01)); ^1H NMR (500 MHz, CDCl_3) δ 7.40-7.23 (m, 20H), 4.77 (d, $J = 6.4$ Hz, 1H), 4.68 (d, $J = 6.4$ Hz, 1H), 4.15 (m, 1H), 4.02 (t, $J = 9.6$ Hz, 1H), 4.00-3.88 (m, 6H), 3.84 (d, $J = 13.6$ Hz, 2H), 3.70 (d, $J = 13.6$ Hz, 2H), 3.59 (d, $J = 14.0$ Hz, 2H), 3.40 (s, 3H), 3.31 (bs, 1H), 2.78-2.70 (m, 2H), 2.14 (dd, $J = 13.6, 9.6$ Hz, 1H), 1.90 (ddd, $J = 14.8, 10.8, 2.4$ Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.0 (C), 139.7 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 127.1 (CH), 98.9 (CH), 98.7 (C), 76.2 (CH), 67.0 (CH), 62.6 (CH), 58.5 (CH_2), 58.0 (CH), 57.9 (CH_2), 56.5 (CH_3), 54.9 (CH_2), 54.8 (CH_2), 38.7 (CH_2), 27.9 (CH_3), 20.9 (CH_3); HRMS m/z 639.3791 $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{40}\text{H}_{51}\text{N}_2\text{O}_5$ 639.3793.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Retrosynthetic analysis of zwittermicin A (+)-1

Scheme 2.
Synthesis of protected diazidotetrol **7**.

Scheme 3.
Synthesis of (-)-3.

Table 1Optimization of desymmetrization of **6** by mono-tritylation.

Entry #	TrCl, equiv	temp (°C)	time (h)	yields 7:8 ^a (%)
1	1.0	50	4	54:19
2	0.8	23	17	54:17
3	0.8	60	69	69:14

^a, isolated yields

Table 2
Conversion of diol **7** to external acetonides **9**, **11** and internal acetonide **10** in DMF.

Entry #	reagent	equiv	catalyst	temp (°C)	time (h)	yields 9 , 10 , 11 (%) ^b	rec'd 7 (%)
1	Me ₂ C(OMe) ₂ -acetone ^a	Xs	PPTS	50	4	24	0
2	CH ₂ =C(OMe)CH ₃	2.5	PPTS	0 to 23	36	0	100
3	CH ₂ =C(OMe)CH ₃ ^c	2.5	TsOH ^c	0 to 23	28	0	100
4	CH ₂ =C(OMe)CH ₃	2.0	TsOH	0 to 23	2	0	<i>f</i>
5	CH ₂ =C(OMe)CH ₃	2.0	CSA	0 to 23	20	47:18:0	<i>df</i>
6	CH ₂ =C(OMe)CH ₃	2.5	PPTS	50	4	73:17:0	<i>ef</i>
7	CH ₂ =C(OMe)CH ₃	2.0	PPTS	50	4	64:8:14	<i>f</i>

^a, 1:1, no DMF.

^b, isolated yields.

^c, mol. sieves 4 Å.

^d, partial loss of Tr group.

^e, some remaining **7**.

^f, not determined