JOC The Journal of Organic Chemistry

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Total Synthesis of (−)-Tirandamycin C Utilizing a Desymmetrization Protocol

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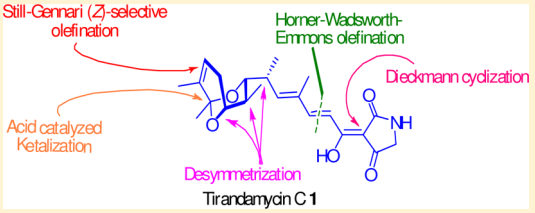
Supporting Information

ABSTRACT: A highly stereoselective total synthesis of (−)-tirandamycin C has been achieved following a desymmetrization protocol developed in our group, Horner−Wadsworth−Emmons olefination, acid-catalyzed ketalization, Still−Gennari (*Z*)-selective olefination, and Dieckmann cyclization as key reactions.



INTRODUCTION

Marine organisms have been found to be a rich source of bioactive secondary metabolites, which are often used as lead structures in the development of novel pharmaceuticals.[1] Among them, some members of the tetramic acid family, belonging to an emerging class of potent antibiotics, have unique chemical structures composed of a 2,6-dioxabicyclononane skeleton and the characteristic dienoyl tetramic acid moiety formed from the condensation of an amino acid to a polyketide derived acyl chain.[2] They exhibit a wide breadth of biological activities such as HIV-1 integrase inhibition, bacterial DNA-directed RNA polymerase inhibition, and potent antimicrobial activity.[3] These compounds continue to attract significant interest due to their broad structural diversity and potent biological activities. Recently, during a screen to discover new natural products from marine derived actinomycetes with activity against vancomycin-resistant *Enterococcus faecalis* (VRE), tirandamycin C and tirandamycin D were isolated from the marine environmental isolate *Streptomyces* sp. 307−9,[4] which also produced previously identified products tirandamycins A[5] and B.[6] Spectral analysis of tirandamycins C and D indicated structural similarity to A and B, with differences only in the pattern of pendant oxygenation on the bicyclic ketal system. They exhibited antibacterial activity against Gram-positive bacteria and in vitro activity against bacterial RNA polymerase.

The distinct structural features and potent pharmacological properties render this family of antibiotics worthy targets for synthetic exploration.[7] The only synthesis of tirandamycin C (**1**) has been recently reported by Roush et al.[8] The most significant synthetically challenging feature of the tirandamycins is the *anti,anti*-dipropionate stereotriad unit. We recently disclosed the synthesis of saliniketals A and B employing our desymmetrization technique to create contiguous chiral centers from a single bicyclic precursor **12**.[9] To demonstrate the potential of this protocol in the synthesis of stereochemically complex natural products and, equally to gain further insight into the structure−activity relationship of tirandamycins, we report herein a new flexible synthetic protocol for tirandamycin C (**1**). We designed the synthetic strategy as shown in Figure 2. This strategy involves a late stage tetramic acid unit formation via Dieckmann cyclization. The key precursor **5** could be obtained via Horner−Wadsworth−Emmons olefination of aldehyde **7** with phosphonate **8**. Aldehyde **7** in turn could be accessible from intermediate **9** via acid catalyzed ketalization. The α,β-unsaturated ketone intermediate **9** could be obtained via Still−Gennari (*Z*)-selective coupling of phosphonate **10** and aldehyde **11** which in turn could be achieved from a known bicyclic intermediate **12**.

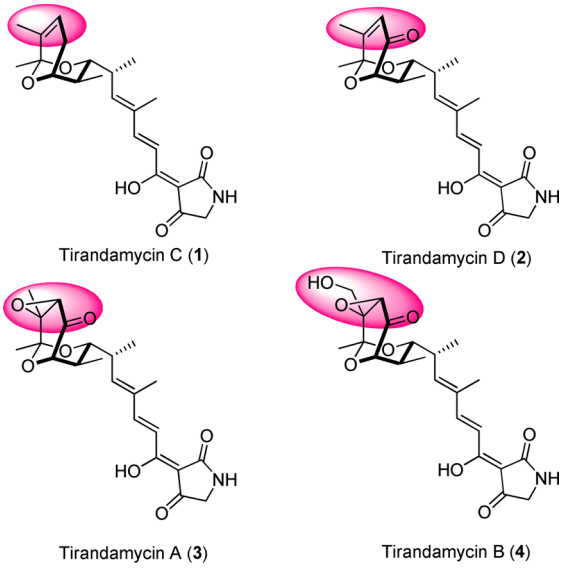


Figure 1. Structures of tirandamycins A, B, C, and D.

Received: August 9, 2012

   dx.doi.org/10.1021/jo3016709 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

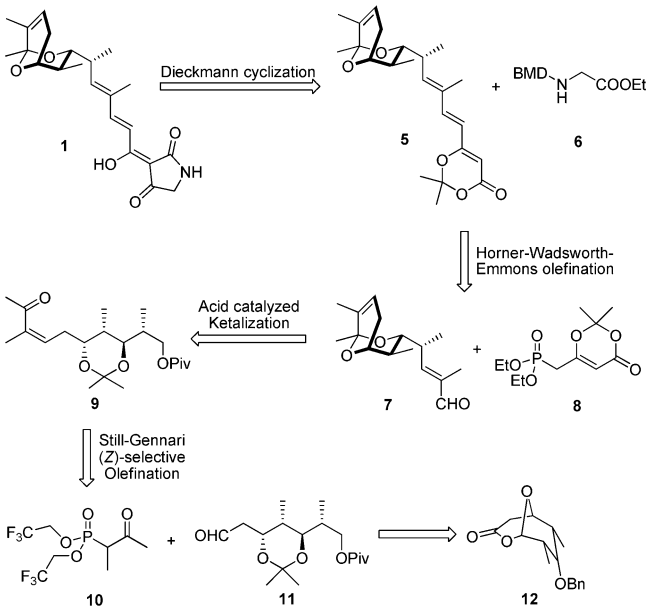


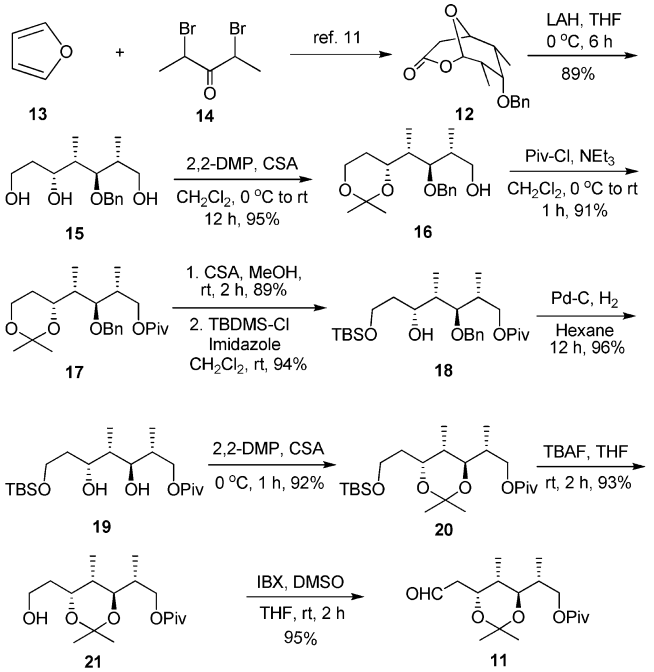
Figure 2. Retrosynthetic analysis.

RESULTS AND DISCUSSION

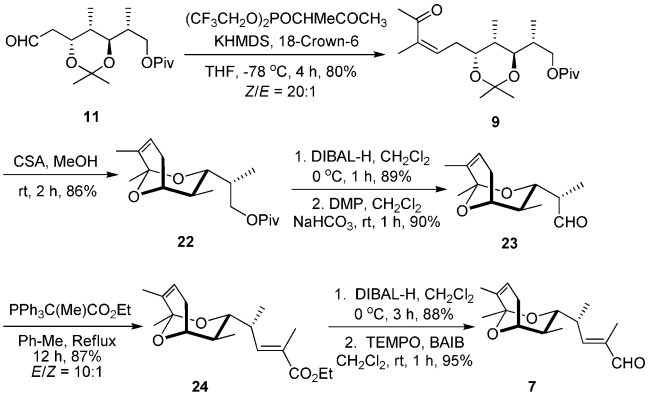
Our first objective focused on the stereoselective synthesis of the 2,6-dioxabicyclic skeleton **7**. As outlined in Scheme 1, the key fragment **11**, which contains all of the required stereocenters of target molecule **1** was prepared starting from a known precursor **12**.[9−11] The diastereomeric purity of compound **12** was ≥98% as per the HPLC analysis. Lithium aluminum hydride mediated reduction of **12** followed by acetonide protection afforded **16** in 95% yield. The primary hydroxyl group was protected with PivCl and subsequent deprotection of the acetonide group followed by chemoselective primary hydroxyl group protection with TBDMSCl yielded **18** (76% over three steps). The benzyl protecting group was removed by hydrogenation to obtain diol **19** followed by acetonide protection of the two secondary hydroxyl groups, which produced compound **20** in 92% yield. The silyl ether was removed by using TBAF to obtain **21** in 93% yield, which on treatment with IBX,[12] furnished aldehyde **11** in 95% yield.

Aldehyde **11** on subsequent Still−Gennari (*Z*)-selective olefination[13] with **10** resulted in formation of alkene **9** in 80% yield (20:1 ratio). Acid catalyzed intramolecular cyclization of the *α,β*-unsaturated ketone **9** yielded a dioxabicyclo intermediate **22** in 86% yield. The pivaloyl protecting group of **22** was reduced with DIBAL-H to afford a primary alcohol which on subsequent oxidation with the Dess-Martin periodinane,[14] followed by Wittig olefination, afforded alkene **24** in 73% over three steps. The ester group was reduced with DIBAL-H to provide an allylic alcohol which, on subsequent oxidation with TEMPO and BAIB, afforded aldehyde **7** in 95% yield (Scheme 2).[15]

Scheme 1. Synthesis of Aldehyde 11



Scheme 2. Synthesis of Aldehyde 7



Our next objective was to introduce the tetramic acid unit conjugated with two olefinic double bonds. Treatment of phosphonate **8**[16] with NaH in anhydrous THF followed by addition of aldehyde **7** furnished the triene **5** in 93% yield.[17] The intermediate **5** and *N*-dimethoxybenzyl protected glycine ester (**6**)[18] were heated under reflux in toluene to produce coupling product **25** in 99% yield.[19]

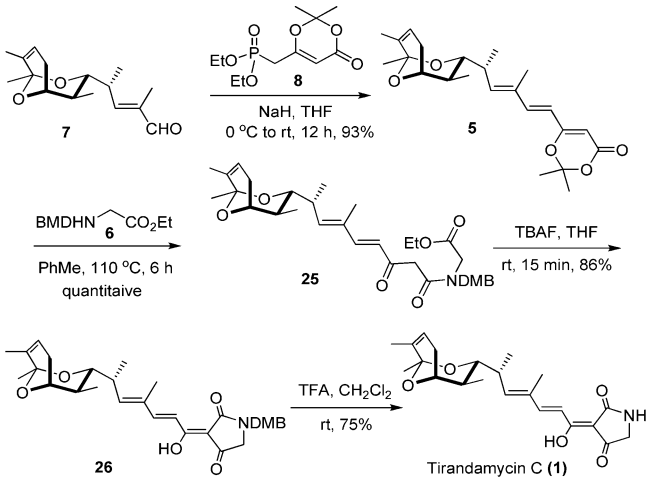
Dieckmann cyclization of the diketo ester **25** by using TBAF as a mild base in THF afforded *N*-dimethoxybenzyl protected tirandamycin C (**26**) in 86% yield.[20] To get the desired final product, deprotection of the DMB group was needed and, thus, intermediate **26** upon treatment with TFA in CH_2Cl_2 yielded **1** in 75% yield (Scheme 3).[21] The spectral (^1H and ^{13}C NMR) and analytical data {$[\alpha]_D^{29}$ −56.7 (*c* = 0.55, EtOH; 96.1%ee); lit.[8] $[\alpha]_D^{25}$ −59 (*c* = 0.11, EtOH)) were in good agreement with the values reported for natural product.

CONCLUSIONS

We have achieved a highly stereoselective total synthesis of tirandamycin C in 20 steps with 12% overall yield starting from a known bicyclic intermediate **12** followed by Horner−Wadsworth−Emmons olefination, acid catalyzed ketalization, Still-Gennari (*Z*)-selective olefination, and Dieckmann cyclization as key reactions. Following the same protocol, synthesis of related natural products is in progress and will be reported in due course.

dx.doi.org/10.1021/jo3016709 | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Accomplishment of the Total Synthesis of (−)-Tirandamycin C



EXPERIMENTAL SECTION

General Method. Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, diethyl ether from Na and benzophenone; CH_2Cl_2, DMSO, DMF, hexane from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60−120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} $degcm^2g^{-1}$. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wavenumber (cm^{-1}). TOF analyzer type was used for the HRMS measurement. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

(3*R*,4*S*,5*R*,6*R*)-5-(Benzyloxy)-4,6-dimethylheptane-1,3,7-triol (15). To an ice-cooled suspension of LAH (3.43 g, 90.5 mmol) in THF (150 mL) was added a solution of lactone **12** (10.0 g, 36.2 mmol) in THF (50 mL) under nitrogen atmosphere. The reaction mixture was stirred for 6 h at room temperature. After complete consumption of starting material (monitored by TLC), it was quenched with saturated ammonium chloride solution (100 mL) and the formed precipitate was filtered off on a pad of diatomaceous earth using ethyl acetate. The filtrate was concentrated under reduced pressure to get crude triol which was purified by column chromatography over silica gel (ethyl acetate: hexane = 3:2) to afforded triol **15** (9.08 g, 89%) as a viscous liquid. $[\alpha]_D^{29}$ +9.7 (c = 1.5, $CHCl_3$); IR (neat): ν 3412, 2964, 2881, 1716, 1648, 1457, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35−7.27 (m, 5H), 4.66 (s, 2H), 4.22 (dd, J = 12.1, 2.2 Hz, 1H), 3.82−3.70 (m, 3H), 3.63 (m, 1H), 3.48 (dd, J = 7.5, 3.7 Hz, 1H), 3.39 (br s, 1H), 2.73 (brs, 1H), 2.01 (m, 1H), 1.85 (m, 1H) 1.69 (m, 1H), 1.39 (m, 1H), 1.09 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 128.5, 128.0, 127.8, 87.9, 76.0 70.3, 64.8, 61.5, 39.1, 37.7, 36.5, 14.9, 11.7 ppm; HRMS (ESI) m/z calcd. for $C_{16}H_{26}O_4Na$ $[M + Na]^+$: 305.1728, found: 305.1735.

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpentan-1-ol (16). To a stirred solution of triol **15** (8.0 g, 28.3 mmol) in anhydrous dichloromethane (75 mL) was added 2,2-dimethoxypropane (20.85 mL, 170.2 mmol) followed by a catalytic amount of CSA (750 mg) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After completion of reaction (monitored by TLC), it was quenched with H_2O (20 mL). Organic layer was separated and aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrate to dryness under reduced pressure and purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as the mobile phase to afford compound **16** (8.7 g, 95%) as a white solid. Mp 116.5 °C; $[\alpha]_D^{29}$ −29.6 (c = 1.0, $CHCl_3$); IR (neat): ν 3471, 2983, 2959, 2898, 2833, 2071, 1602, 1456, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.24 (m, 5H), 4.63 (dd, J = 12.8, 11.3 Hz, 2H), 4.26 (dt, J = 12.1, 2.2 Hz, 1H), 3.93 (td, J = 12.1, 3.0 Hz, 1H), 3.87−3.77 (m, 2H), 3.54 (m, 1H), 3.44 (dd, J = 9.1, 3.0 Hz, 1H), 2.60 (br s, 1H), 1.96−1.71 (m, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.24 (m, 1H), 1.18 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.5, 127.7, 127.2, 98.1, 85.6, 77.0, 75.2, 67.4, 64.5, 60.0, 41.4, 36.2, 30.0, 28.6, 19.5, 16.2, 10.5 ppm; HRMS (ESI) m/z calcd. for $C_{19}H_{30}O_4Na$ $[M + Na]^+$: 345.2041, found: 345.2027.

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpentyl Pivalate (17). To a stirred solution of alcohol **16** (5.0 g, 15.5 mmol) in CH_2Cl_2 (70 mL), was added triethyl amine (6.5 mL, 46.5 mmol), pivaloyl chloride (2.88 mL, 23.3 mmol) and DMAP (0.19 g, 1.55 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was allowed to come to room temperature and continued for additional 1 h. The reaction was quenched by addition of H_2O (50 mL) and the organic layer was separated. The aqueous layer wes extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using ethyl acetate and hexane (1:19) as the mobile phase to afford pivalate ester **17** (5.7 g, 91%) as a colorless liquid. $[\alpha]_D^{29}$ −7.8 (c = 1.55, $CHCl_3$); IR (neat): ν 3441, 2972, 1727, 1462, 1377, 1282, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33−7.22 (m, 5H), 4.60 (s, 2H), 4.32−4.21 (m, 2H), 3.96−3.85 (m, 2H), 3.79 (dd, J = 10.9, 5.5 Hz, 1H), 3.36 (dd, J = 9.4, 2.2 Hz, 1H), 2.16 (m, 1H), 1.85 (qd, J = 12.2, 5.5 Hz, 1H), 1.70 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.25 (m, 1H), 1.19 (s, 9H), 1.09 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 138.8, 128.3, 127.3, 126.9, 98.0, 82.8, 74.8, 67.2, 65.7, 60.0, 40.9, 38.7, 35.0, 30.0, 28.4, 27.1, 19.5, 16.0, 10.4 ppm; HRMS (ESI) m/z calcd. for $C_{24}H_{38}O_5Na$ $[M + Na]^+$: 429.2616, found: 429.2597.

(2*R*,3*R*,4*S*,5*R*)-3-(Benzyloxy)-5,7-dihydroxy-2,4-dimethylheptyl Pivalate. To a solution of compound **17** (5.0 g, 12.3 mmol) in MeOH (50 mL), camphoresulphonic acid (0.43 g, 1.84 mmol) was added at room temperature and stirred for 2 h. After completion of the reaction (monitored by TLC), it was quenched with Et_3N (10 mL). The reaction mass was concentrate under reduced pressure to afford the crude product, which on purification by silica gel column chromatography using ethyl acetate and hexane (2:3) as the mobile phase afforded the diol (4.01 g, 89%) as a white solid. Mp 89.0 °C; $[\alpha]_D^{29}$ +24.3 (c = 0.9, $CHCl_3$); IR (neat): ν 3305, 2958, 2925, 2855, 1726, 1459, 1400, 1290, 1055 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$): δ 7.36−7.26 (m, 5H), 4.58 (dd, J = 15.1, 10.5 Hz, 2H), 4.25 (dd, J = 10.5, 3.7 Hz, 1H), 4.20 (m, 1H), 4.10 (dd, J = 11.3, 6.0 Hz, 1H), 3.81−3.74 (m, 2H), 3.40 (dd, J = 8.3, 3.0 Hz, 1H), 3.35 (s, 1H), 2.54 (brs, 1H), 2.24 (m, 1H), 1.86 (m, 1H), 1.73 (m, 1H), 1.37 (m, 1H), 1.22 (s, 9H), 1.13 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 137.4, 128.6, 128.1, 127.8, 86.8, 76.0, 70.5, 66.0, 61.9, 38.9, 38.5, 36.4, 35.7, 27.2, 14.7, 12.0 ppm; HRMS (ESI) m/z calcd. for $C_{21}H_{34}O_5Na$ $[M + Na]^+$: 389.2303, found: 389.2308.

(2*R*,3*R*,4*S*,5*R*)-3-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethylheptyl Pivalate (18). To an ice cooled solution of diol (4.0 g, 10.92 mmol) and imidazole (1.86 g, 27.32 mmol) was added TBDMSCl (2.47 g, 16.39 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0 °C for 1 h and quenched with aqueous NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography utilizing ethyl acetate and hexane (1:20) as mobile phase to afford silyl ether **18** (4.93 g, 94%) as a colorless liquid. $[\alpha]_D^{29}$ +11.8 (c = 1.55, $CHCl_3$); IR (neat): ν 3521, 3031, 2957, 2930, 2883, 2858, 1729, 1462, 1397, 1248, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32- 7.26 (m, 5H), 4.62 (ABq, δ_A 4.68, δ_B 4.57 J = 10.9 Hz, 2H), 4.26 (dd, J = 10.9, 4.3 Hz, 1H), 4.16 (m,

dx.doi.org/10.1021/jo3016709 | J. Org. Chem. XXXX, XXX, XXX−XXX

1H), 4.02 (dd, J = 10.9, 6.8 Hz, 1H), 3.82−3.69 (m, 2H), 3.41 (t, J = 6.0 Hz, 1H), 3.19 (s, 1H), 2.19 (m, 1H), 1.84−1.66 (m, 2H), 1.40 (m, 1H), 1.29 (s, 9H), 1.04 (d, J = 2.4 Hz, 3H), 1.02 (d, J = 2.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 138.0, 128.4, 127.8, 127.7, 85.8, 75.9, 68.5, 65.9, 61.6, 39.2, 38.8, 37.4, 35.5, 27.2, 25.8, 18.1, 15.1, 11.1, −5.5 ppm; HRMS (ESI) m/z calcd. for $C_{27}H_{49}O_5Si$ $[M + H]^+$: 481.3349, found: 481.3352.

(2*R*,3*R*,4*S*,5*R*)-7-(*tert*-Butyldimethylsilyloxy)-3,5-dihydroxy-2,4-dimethylheptyl Pivalate (19). To a solution of compound **18** (2.0 g, 4.16 mmol) in anhydrous hexane (15 mL) was added catalytic amount of Pd−C (150 mg, 10%) under hydrogen ballon pressure and stirred at room temperature for 12 h. After complete consumption of starting material (monitored by TLC), it was filtered through a small pad of diatomaceous earth and concentrated to dryness under reduced pressure. The residue was purified by silica gel column schromatography utilizing ethyl acetate and hexane (1:9) as mobile phase to obtain alcohol **19** (1.56 g, 96%) as a colorless oil. $[\alpha]_D^{29}$ +4.7 (c = 1.08, $CHCl_3$); IR (neat): ν 3445, 2959, 1726, 1468, 1286, 1163, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (dd, J = 10.8, 4.3 Hz, 1H), 4.15 (d, J = 9.8, 1H), 4.11 (dd, J = 10.8, 6.5 Hz, 1H), 3.89 (m, 1H), 3.83−3.77 (m, 2H), 3.38 (br s, 1H), 2.03 (m, 1H), 1.89−1.76 (m, 2H), 1.45 (m, 1H), 1.20 (s, 9H), 0.99 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 7.6 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 77.4, 73.6, 66.3, 63.1, 38.8, 38.1, 36.0, 34.8, 27.2, 25.7, 18.0, 14.7, 12.0, −5.6 ppm; HRMS (ESI) m/z calcd. for $C_{20}H_{42}O_5Si$ $[M + H]^+$: 391.2879, found: 391.2879.

(*R*)-2-((4*R*,5*S*,6*R*)-6-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl Pivalate (20). To a stirred solution of diol **19** (2.0 g, 5.12 mmol) in anhydrous dichloromethane (40 mL) was added 2,2-dimethoxypropane (6.1 mL, 51.28 mmol) followed by a catalytic amount of CSA (150 mg) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combine organic layer was dried over anhydrous Na_2SO_4, concentrated to dryness under reduced pressure and purified by silica gel column chromatography using ethyl acetate and hexane (1:19) as mobile phase to afford compound **20** (2.03 g, 92%) as light yellow oil. $[\alpha]_D^{29}$ +8.5 (c = 1.0, $CHCl_3$); IR (neat): ν 2958, 2933, 2882, 2859, 1732, 1463, 1255, 1221, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (dd, J = 10.9, 4.5 Hz, 1H), 4.0−3.93 (m, 2H), 3.66−3.60 (m, 2H), 3.17 (dd, J = 7.2, 6.9 Hz, 1H), 1.92 (m, 1H), 1.79 (m, 1H), 1.63−1.45 (m, 2H), 1.27 (s, 6H), 1.20 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 100.3, 76.1, 66.0, 65.5, 59.6, 38.8, 37.2, 37.1, 33.8, 27.2, 25.9, 25.3, 23.4, 18.2, 13.9, 12.8, −5.4 ppm; HRMS (ESI) m/z calcd. for $C_{23}H_{46}O_5SiNa$ $[M + Na]^+$: 453.3019, found: 453.3002.

(*R*)-2-((4*R*,5*S*,6*R*)-6-(2-Hydroxyethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propyl Pivalate (21). To an ice cooled solution of silyl ether **20** (2.0 g, 4.65 mmol) in anhydrous THF (15 mL) was added TBAF (9.3 mL, 1 M solution in THF, 9.3 mmol). The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with aqueous ammonium chloride solution (20 mL). The reaction mixture was extracted with ethyl acetate (3 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography utilizing ethyl acetate and hexane (1:6) as mobile phase to afford alcohol **21** (1.36 g, 93%) as a colorless liquid. $[\alpha]_D^{29}$ −3.54 (c = 1.0, $CHCl_3$); IR (neat): ν 3446, 2972, 1727, 1462, 1379, 1226, 1164, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.16 (dd, J = 10.7, 3.4 Hz, 1H), 4.03 (m, 1H), 3.96 (dd, J = 10.9, 6.9 Hz, 1H), 3.76−3.71 (m, 2H), 3.21 (dd, J = 7.1, 5.6 Hz, 1H), 1.98−1.70 (m, 3H), 1.48 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.19 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.7, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 100.4, 76.1, 69.2, 65.8, 61.6, 38.7, 37.2, 37.0, 32.6, 27.1, 25.4, 23.3, 14.0, 12.8 ppm; HRMS (ESI) m/z calcd. for $C_{17}H_{32}O_5Na$ $[M + Na]^+$: 339.2147, found: 339.2148.

(*R*)-2-((4*R*,5*S*,6*R*)-2,2,5-Trimethyl-6-((*Z*)-3-methyl-4-oxopent-2-enyl)-1,3-dioxan-4-yl)propyl Pivalate (9). Iodoxybenzoic acid (1.4 g, 4.75 mmol) was taken in anhydrous DMSO (4.5 mL) and stirred for 30 min. Alcohol **21** (1.0 g, 3.16 mmol) in anhydrous THF (10 mL) was added to the reaction mixture at room temperature and allowed to stir for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with Et_2O (20 mL), stirred for 15 min. The solid precipitate was filtered off and washed with Et_2O (2 × 10 mL). The organic layer was washed with H_2O (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and filtered through a small pad of silica gel to give aldehyde **11** (944 mg, 95%) as a colorless liquid which was used for the next step without further purification.

To a solution of bis(2,2,2-trifluoroethyl)3-oxobutan-2-ylphosphonate **10** (2.4 g, 80% purity, 6.01 mmol) and 18-crown-6 (1.41 g, 6.01 mmol) in 30 mL anhydrous THF at −78 °C was added KHMDS (10.2 mL, 0.5 M in toluene, 5.11 mmol) dropwise under argon. After stirring for 30 min at −78 °C, a solution of aldehyde **11** (944 mg, 3.0 mmol) in anhydrous THF (20 mL) was added at −78 °C dropwise and the resulting mixture stirred for another 1 h at −78 °C. The reaction mixture was gradually warmed to room temperature in 4 h. Saturated NH_4Cl solution (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) as mobile phase to obtain enone **9** (885 mg, 80%) as a 20:1 ratio of Z/E isomers. $[\alpha]_D^{29}$ +9.27 (c = 1.0, $CHCl_3$); IR (neat): ν 3639, 2973, 2937, 1728, 1462, 1380, 1284, 1225, 1161, 1021 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (t, J = 5.9 Hz, 1H), 4.16 (dd, J = 10.9, 4.9 Hz, 1H), 3.99 (dd, J = 9.9, 6.9 Hz, 1H), 3.81 (m, 1H), 3.22 (dd, J = 6.9, 5.9 Hz, 1H), 2.47−2.36 (m, 2H), 2.25 (s, 3H), 1.96 (s, 3H), 1.95 (m, 1H), 1.84 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 178.5, 136.1, 136.0, 100.4, 76.1, 69.4, 65.9, 38.8, 37.0, 30.9, 29.9, 27.2, 25.3, 23.3, 21.1, 13.9, 12.7 ppm; HRMS (ESI) m/z calcd. for $C_{21}H_{36}O_5$ Na $[M + Na]^+$: 391.2455, found: 391.2478.

(*R*)-2-((1*R*,3*R*,4*S*,5*R*)-1,4,8-Trimethyl-2,9-dioxabicyclo[3.3.1]-non-7-en-3-yl)propyl Pivalate (22). To a stirred solution of enone **9** (0.8 g, 2.17 mmol) in MeOH (10 mL), was added catalytic amount CSA (50 mg) at 0 °C and stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), MeOH was removed under reduced pressure and the residue was dissolve in ethyl acetate (20 mL) and washed with sodium bicarbonate solution (10 mL). The extract was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using ethyl acetate and hexane (1:24) as mobile phase to afford bicyclic compound **22** (580 mg, 86%) as a light yellow oil. $[\alpha]_D^{29}$ −26.75 (c = 1.0, $CHCl_3$); IR (neat): ν 3451, 2926, 1727, 1638, 1458, 1374, 1286, 1158 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (br s, 1H), 4.33 (dd, J = 10.8, 5.8 Hz, 1H), 3.96 (dd, J = 6.8, 5.8 Hz, 1H), 3.88 (dd, J = 10.8, 7.8 Hz, 1H), 3.46 (dd, J = 10.8, 1.9 Hz, 1H), 2.38 (m, 1H), 2.23 (m, 1H), 2.04 (m, 1H), 1.95 (dd, J = 18.6, 3.9 Hz, 1H), 1.59 (s, 3H), 1.36 (s, 3H), 1.20 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 132.4, 123.3, 95.4, 75.8, 71.2, 65.438.7, 34.2, 33.2, 27.2, 24.2, 24.0, 18.3, 15.3, 13.4 ppm; HRMS (ESI) m/z calcd. for $C_{18}H_{30}O_4Na$ $[M + Na]^+$: 333.2041, found: 333.2028.

(*R*)-2-((1*R*,3*R*,4*S*,5*R*)-1,4,8-Trimethyl-2,9-dioxabicyclo[3.3.1]-non-7-en-3-yl)propan-1-ol. A stirred solution of Piv-protected bicyclic compound **22** (550 mg, 1.77 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with DIBAL-H (2.8 mL, 3.89 mmol, 20% solution in toluene) at 0 °C and stirred for 1 h. The reaction was quenched with MeOH (1 mL) and saturated aqueous sodium potassium tartrate solution (10 mL). The mixture was warmed to room temperature and stirred for 2 h. Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). Combined organic layer was dried over Na_2SO_4, concentrated under reduced pressures. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as mobile phase to afford alcohol (357 mg, 89%) as a colorless liquid. $[\alpha]_D^{29}$ −51.1 (c = 1.0, $CHCl_3$); IR (neat): ν

dx.doi.org/10.1021/jo3016709 | J. Org. Chem. XXXX, XXX, XXX−XXX

3451, 2963, 2926, 1455, 1375, 1222, 1178, 1116, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.70 (br s, 1H), 4.02−3.91 (m, 2H), 3.56 (dd, J = 11.3, 2.3 Hz, 1H), 3.47 (dd, J = 11.3, 3.7 Hz, 1H), 2.40 (m, 1H), 2.29 (m, 1H), 1.95 (m, 1H), 1.76 (m, 1H), 1.62−1.59 (m, 3H), 1.39 (s, 3H), 1.07 (d, J = 7.5 Hz, 3H), 0.74 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.6, 123.8, 95.8, 78.5, 71.0, 63.3, 34.6, 34.2, 24.4, 24.0, 18.2, 15.1, 13.3 ppm; HRMS (ESI) m/z calcd. for $C_{13}H_{22}O_3Na$ $[M + Na]^+$: 249.1466, found: 249.1472.

(*R,E*)-Ethyl-2-methyl-4-((1*R*,3*R*,4*S*,5*R*)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)pent-2 (24). To a stirred solution of primary alcohol (320 mg, 1.41 mmol) and solid anhydrous $NaHCO_3$ (356 mg) in CH_2Cl_2 (30 mL) at 0 °C was added Dess−Martin periodinane (900 mg, 2.11 mmol). The resulting reaction mixture was stirred at 0 °C to room temperature for 1 h. After completion of the reaction (monitored by TLC), the mixture was filtered through filter paper. The filtrate was washed with saturated $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and filtered through a small pad of silica gel to give aldehyde **23** (286 mg, 90%) as a colorless oil which was used for the next step without further purification.

The resulting aldehyde **23** (286 mg, 1.27 mmol) and (carbethoxyethylidene)triphenyl phosphorane (2.3 g, 6.39 mmol) were dissolved in toluene (30 mL), heated at 110 °C for 12 h. Toluene was removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as mobile phase to afford ester **24** (342 mg, 87%) as a10:1 *E/Z* isomers. $[\alpha]_D^{29}$ −23.1 (c = 0.7, $CHCl_3$); IR (neat): ν 3635, 2963, 2929, 2876, 1710, 1650, 1447, 1375, 1243 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (dd, J = 10.5, 0.9 Hz, 1H), 5.66 (br s, 1H), 4.22−4.16 (m, 2H), 3.90 (m, 1H), 3.43 (dd, J = 10.5, 1.9 Hz, 1H), 2.68 (m, 1H), 2.37 (m, 1H), 1.95−1.84 (m, 2H), 1.83 (d, J = 0.95 Hz, 3H), 1.62−1.60 (m, 3H), 1.40 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.67 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 142.6, 132.5, 127.8, 123.2, 95.4, 76.2, 71.0, 60.4, 34.9, 34.3, 24.2, 24.1, 18.3, 16.5, 14.3, 13.2, 12.4 ppm; HRMS (ESI) m/z calcd. for $C_{18}H_{28}O_4Na$ $[M + Na]^+$: 331.1880, found: 331.1885.

(*R,E*)-2-Methyl-4-((1*R*,3*R*,4*S*,5*R*)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)pent-2-en-1-ol. A stirred solution of ester **24** (350 mg, 1.13 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated with DIBAL-H (2.55 mL of 1 M solution in toluene, 2.55 mmol) at 0 °C and stirred for 3 h. The reaction was quenched with MeOH (1 mL) and saturated aqueous sodium potassium tartrate solution (10 mL). The reaction mixture was warmed to room temperature and stirred for 5 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:4) as mobile phase to afford alcohol (266 mg, 88%) as a colorless liquid. $[\alpha]_D^{29}$ −44.36 (c = 1.0, $CHCl_3$); IR (neat): ν 3455, 2960, 2925, 1456, 1370, 1222, 1175, 1114, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.65 (br s, 1H), 5.57 (d, J = 9.8 Hz, 1H), 4.02 (s, 2H), 3.90 (t, J = 6.8 Hz, 1H), 3.38 (dd, J = 10.5, 2.2 Hz, 1H), 2.56 (m, 1H), 2.36 (m, 1H), 1.68 (s, 3H), 1.62−1.58 (m, 3H), 1.37 (s, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.2, 132.8, 127.3, 123.3, 95.6, 77.6, 71.3, 69.4, 34.7, 33.1, 24.5, 24.4, 18.5, 17.8, 13.9, 13.6 ppm; HRMS (ESI) m/z calcd. for $C_{16}H_{26}O_3Na$ $[M + Na]^+$: 289.1779, found: 289.1766.

(*R,E*)-2-Methyl-4-((1*R*,3*R*,4*S*,5*R*)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)pent-2-ena (7). To a stirred solution of alcohol (200 mg, 0.75 mmol) and iodobenzene diacetate (362 mg, 1.12 mmol) in anhydrous CH_2Cl_2 (10 mL) was added TEMPO (11.7 mg, 0.075 mmol) at room temperature and stirred for 1 h. After completion of reaction (monitored by TLC), it was quenched with saturated aqueous solution of $NaHCO_3$ (5 mL) followed by saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) as mobile phase to afford aldehyde **7** (189 mg, 95%) as a pale yellow viscous liquid. $[\alpha]_D^{29}$ −40.2 (c = 0.7, $CHCl_3$); IR (neat): ν 3332, 2962, 2927, 1679, 1459, 1379, 1338, 1265, 1193, 1159, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.46 (s, 1H), 6.75 (m, 1H), 5.71 (br s, 1H), 3.95 (t, J = 6.3 Hz, 1H), 3.53 (dd, J = 10.5, 2.2 Hz, 1H), 2.91 (m, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.64−1.62 (m, 3H), 1.43 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.8, Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 155.1, 139.1, 132.3, 123.2, 95.4, 76.1, 70.8, 35.1, 34.3, 24.1, 24.0, 18.2, 16.4, 13.1, 9.1 ppm; HRMS (ESI) m/z calcd. for $C_{16}H_{25}O_3$ $[M + H]^+$: 265.1804, found: 265.1801.

2,2-Dimethyl-6-((*R*,1*E*,3*E*)-3-methyl-5-((1*R*,3*R*,4*S*,5*R*)-1,4,8-trimethyl-2,9-dioxabicyclo [3.3.1]non-7-en-3-yl)hexa-1,3-dienyl)-4*H*-1,3-dioxin-4-one (5). In a flame-dried, two-necked RB flask, charged with NaH (39 mg, 60% suspension in mineral oil, 0.99 mmol) under argon atmosphere, anhydrous THF (5 mL) was added and cool to 0 °C. To this stirred solution phosphonate **8** (316 mg, 1.1 mmol) in anhydrous THF (20 mL) was added dropwise at 0 °C and was allowed to stir for 30 min. Then aldehyde **7** (150 mg, 0.568 mmol) in THF (10 mL) was added at 0 °C. The resulting mixture was allowed to stir for 12 h at room temperature. The reaction was quenched with saturated aqueous solution of NH_4Cl (5 mL), extracted with ethyl acetate (3 × 10 mL). Combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford compound **5** (216 mg, 93%) as a colorless liquid. $[\alpha]_D^{29}$ +4.32 (c = 1.08, $CHCl_3$); IR (neat): ν 3448, 2925, 1724, 1624, 1380, 1269, 1203, 1118, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J = 15.8 Hz, 1H), 6.11 (d, J = 9.8 Hz, 1H), 5.87 (d, J = 15.8 Hz, 1H), 5.69 (br s, 1H), 5.28 (s, 1H), 3.93 (m, 1H), 3.46 (dd, J = 10.5, 2.2 Hz, 1H), 2.75 (m, 1H), 2.39 (m, 1H), 1.99−1.87 (m, 2H), 1.81 (d, J = 1.5 Hz, 3H), 1.75 (s, 3H), 1.74 (s, 3H), 1.63−1.60 (m, 3H), 1.42 (s, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.1,143.4, 142.4, 132.8, 132.4, 123.2, 117.0, 106.1, 95.4, 93.7, 76.5, 71.0, 34.9, 34.1, 25.1, 24.8, 24.3, 24.1, 18.3, 17.1, 13.1, 12.0 ppm; HRMS (ESI) m/z calcd. for $C_{23}H_{32}O_5Na$ $[M + Na]^+$: 411.2147, found: 411.2145.

Ethyl-2-((*R*,4*E*,6*E*)-*N*-(2,4-dimethoxybenzyl)-6-methyl-3-oxo-8-((1*R*,3*R*,4*S*,5*R*)-1,4,8-tri-methyl-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)nona-4,6-dienamido)acetate (25). Compound **5** (80 mg, 0.21 mmol) and DMB-glycine ester **6** (62.5 mg, 0.25 mmol) were dissolved in anhydrous toluene (5 mL) in a flame dry RB flask equipped with a condenser under argon atmosphere. The solution was heated to reflux at 110 °C for 6 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and hexane (2:3) as mobile phase to afford compound **25** (119 mg, 99%) as pale yellow oil. $[\alpha]_D^{29}$ −5.2 (c = 1.35, $CHCl_3$); IR (neat): ν 3449, 2925, 2854, 1744, 1615, 1585, 1507, 1462, 1206, 1120 cm^{-1}; ^1H NMR (ketone and enol forms, 300 MHz, $CDCl_3$): δ 14.0 (s, 0.5H), 7.32 (d, J = 15.8 Hz, 0.5H), 7.13 (d, J = 15.8 Hz, 1H), 7.02 (m, 1H), 6.44−6.39 (m, 2H), 6.22 (m, 1H), 6.01 (d, J = 9.8 Hz, 1H), 5.75 (d, J = 15.8 Hz 1H), 5.66 (br s, 1H), 5.26 (s, 0.5H), 4.50 (s, 2H), 4.21−4.09 (m, 2H), 4.07−4.04 (m, 2H), 3.97 (s, 1H), 3.90 (m, 1H), 3.83−3.78 (m, 6H), 3.43 (m, 1H), 2.71 (m, 1H), 2.35 (m, 1H), 1.91 (m, 2H), 1.79 (m, 3H), 1.60 (s, 3H), 1.30−1.23 (m, 3H), 1.04−0.97 (m, 3H), 0.69−0.63 (m, 3H) ppm; ^{13}C NMR (ketone and enol forms, 75 MHz, $CDCl_3$): δ 193.9, 172.9, 170.2, 169.5, 169.3, 169.0, 168.1, 160.9, 160.5, 158.6, 158.1, 149.8, 145.5, 145.0, 141.2, 140.0, 133.1, 132.7, 132.6, 132.5, 131.4, 130.0, 128.5, 123.5, 123.1, 123.0, 120.4, 116.4, 115.8, 104.2, 103.9, 98.6, 98.5, 98.2, 95.4, 95.3, 88.6, 76.6, 71.0, 61.1. 60.0, 55.3, 55.2, 48.3, 47.2, 47.0, 46.8, 46.6, 34.9, 34.8, 34.3, 34.0, 24.2, 24.1, 18.3, 17.2, 17.0, 14.1, 13.2, 12.1 ppm; HRMS (ESI) m/z calcd. for $C_{33}H_{45}NO_8Na$ $[M + Na]^+$: 606.3042, found: 606.3049.

Dimethoxybenzyl (DMB) Protected Tirandamycin C (26). A stirred solution of diketo compound **25** (50 mg, 0.09 mmol) in anhydrous THF (2 mL) under argon atmosphere was treated with TBAF (0.214 mL, 1 M solution in THF, 0.22 mmol) and the resulting yellow solution stirred for 15 min at room temperature. After

dx.doi.org/10.1021/jo3016709 | J. Org. Chem. XXXX, XXX, XXX−XXX

completion of the reaction (monitored by TLC), it was quenched with 10% HCl solution (2 mL) and extracted with ethyl acetate (3 × 10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:1) as mobile phase to afford DMB protected tirandmycin C **26** (39.7 mg, 86%) as a pale yellow oil. $[\alpha]_D^{29}$ −49.7 (c = 0.7, $CHCl_3$); IR (neat): ν 3414, 2959, 2870, 1710, 1616, 1470, 1380, 1291, 1206, 1159, 1118, 1033, 882, 787 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 15.6 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 15.6 Hz, 1H), 6.48−6.44 (m, 2H), 6.29 (d, J = 10.4 Hz, 1H), 5.69 (br s, 1H), 4.57 (s, 2H), 3.94 (t, J = 6.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.64 (s, 2H), 3.48 (dd, J = 10.4, 2.0 Hz, 1H), 2.80 (m, 1H), 2.38 (m, 1H), 1.98−1.84 (m, 2H), 1.89 (s, 3H), 1.62−1.59 (m, 3H), 1.42 (s, 3H), 1.04 (d, J = 6.3 Hz, 3H), 0.68 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 174.0, 173.5, 160.9, 158.6, 149.6, 146.2, 134.0, 132.5, 131.2, 123.2, 116.1, 116.0, 104.3, 100.7, 98.5, 95.4, 76.6, 71.0, 55.6, 55.4, 40.0, 35.0, 34.5, 24.3, 24.1, 18.3, 17.0, 13.2, 12.2 ppm; HRMS (ESI) m/z calcd. for $C_{31}H_{40}NO_7$ $[M + H]^+$: 538.2782, found: 538.2789.

Tirandamycin C (1). To a stirred solution of dimethoxybenzyl (DMB) protected tirandamycin C **26** (25 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (2 mL), was added CF_3CO_2H (1 mL). The resulting wine red solution was stirred at room temperature for 30 min and then quenched with ice pieces. The light yellow solution was extracted with CH_2Cl_2 (3 × 10 mL), combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by reversed-phase HPLC to give tirandamycin C **1** (13.5 mg, 75%) as yellow oil. $[\alpha]_D^{29}$ −56.7 (c = 0.55, EtOH); IR (neat): ν 3422, 2950, 2924, 2853, 1617, 1570, 1460, 1378, 1292, 1237, 1119, 1041 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2): δ 7.62 (d, J = 15.6 Hz, 1H), 7.12 (d, J = 15.6 Hz, 1H), 6.32 (d, J = 10.3 Hz, 1H), 5.70 (br s, 1H), 3.90 (t, J = 6.2 Hz, 1H), 3.78 (s, 2H), 3.49 (dd, J = 10.7, 1.5 Hz, 1H), 2.83 (m, 1H), 2.33 (m, 1H), 1.93 (m, 1H), 1.91 (d, J = 0.7 Hz, 3H), 1.84 (m, 1H), 1.61 (m, 3H), 1.38 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.68 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2): δ 192.9, 177.0, 174.8, 150.5, 147.5, 134.5, 132.9, 123.6, 116.0, 100.2, 95.8, 77.0, 71.3, 52.0, 35.5, 35.0, 24.5, 24.5, 18.4, 17.2, 13.3, 12.3 ppm; HRMS (ESI) m/z calc. for $C_{22}H_{30}NO_5$ $[M + H]^+$: 388.2123, found: 388.2129.

Ethyl 2-(2,4-dimethoxybenzylamino)acetate (6). Ethyl bromoacetate (0.8 mL, 7.18 mmol) was added dropwise to a solution of (2,4-dimethoxybenzyl)amine (1.0 g, 5.98 mmol) and triethyl amine (2.5 mL, 17.94 mmol) in anhydrous THF (10 mL) at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred overnight. Brine (20 mL) was added, and the reaction mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and hexane (1:1) as mobile phase to afford compound **6** (1.19 g, 79%). IR (neat): ν 3342, 2939, 2837, 1738, 1613, 1507, 1461, 1290, 1263, 1207, 1157, 1130, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 7.9 Hz, 1H), 6.46−6.44 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (s, 2H), 3.37 (s, 2H), 1.95 (br s, 1H), 1.26 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 160.0, 158.5, 130.4, 119.7, 103.5, 98.2, 60.3, 55.0, 49.8, 47.8,13.9 ppm; HRMS (ESI) m/z calcd. for $C_{13}H_{19}NO_4Na$ $[M + Na]^+$: 276.1211, found: 276.1211.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.D. and S.S.H. thank the CSIR for financial assistance in the form of a research fellowship.

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