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Stereoselective total synthesis of 10-*epi*-tirandamycin E

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ABSTRACT

A stereoselective total synthesis of 10-*epi*-tirandamycin E is described, employing desymmetrization protocol, ring-closing metathesis (RCM), acid-catalyzed ketalization, substrate controlled dihydroxylation and Horner-Wadsworth-Emmons olefination as key reactions.

1. Introduction

The tirandamycins belong to a small group of naturally occurring dienoyl tetramic acids with diverse molecular architecture, are an important class of compounds in medicinal chemistry. Compounds containing a tetramic acid structural unit exhibit broad biological activities such as antibacterial, antiviral, anti-HIV-1, cytotoxicity, mycotoxicity, antitumor, and antimicrobial activities.[1] In 1970s tirandamycin A (**1**) and tirandamycin B (**2**), two of the more well-known members of this family, were isolated from *Streptomyces species* (Fig. 1).[2] In 2011, tirandamycin G (**6**), a novel dienoyl tetramic acid with inhibitory activity against the *B. Malayi* AsnRS was isolated by Shen and co-workers[3] from *Streptomyces* sp.; 17944 along with two known tirandamycin A (**1**) and tirandamycin B (**2**). Tirandamycins also exhibited antibacterial activity against Gram-positive bacteria and in vitro activity against bacterial DNA-directed RNA polymerase.[4] Previously, tirandamycins have not been identified for the use in the prevention and treatment of lymphatic filariasis (LF). Consequently, tirandamycins represent a new lead structure for the discovery and development of antifilarial drugs. In addition to the dienoyl tetramic acid moiety, tirandamycins possess another fascinating structural element, the 2,6-dioxabicyclononane skeleton. In the tirandamycin family, two types of 2,6-dioxabicyclononane structures are known. One is the oxabicyclononane structure with an epoxy ketone moiety (tirandamycin A and B) and the other incorporates a double bond (tirandamycin C, D and E),[5] but tirandamycin G contains vicinal dihydroxy in 2,6-dioxabicyclononane skeleton (Fig. 1).

The complex molecular architecture and potent pharmacological properties render this family of antibiotics worthy targets for their biosynthetic[6] and synthetic exploration.[7] The most significant challenging feature of the tirandamycins synthesis is the *anti, anti*-dipropionate stereotriad unit which is used for the construction of 2,6-dioxabicyclononane skeleton. Recently, we have successfully employed our own developed desymmetrization protocol for the synthesis of 2,6-dioxabicyclononane skeleton of tirandamycin C (**3**).[8] To further demonstrate the utility of desymmetrization protocol, we tried to synthesize tirandamycin G that led to the synthesis of 10-*epi*-tirandamycin E, which is described in this manuscript.

Our retrosynthetic analysis for the synthesis of tirandamycin G (**6**) is illustrated in Scheme 1. We envisioned that tirandamycin G (**6**) could be assembled from the bicyclic aldehyde **7** and Schlessinger's phosphonate **8**[7a,7c] *via* Horner-Wadsworth-Emmons olefination. Aldehyde **7** in turn could be accessible from an advanced 2,6-dioxabicyclononane intermediate **9** *via* substrate controlled dihydroxylation. The bicyclic framework of **9** could be prepared by elaboration of lactone **10**, which in turn would arise from esterification of acid **12** with diol **11**, followed by ring-closing metathesis

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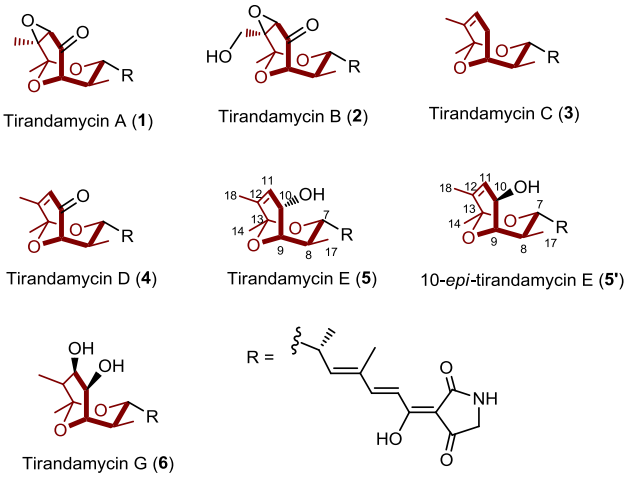
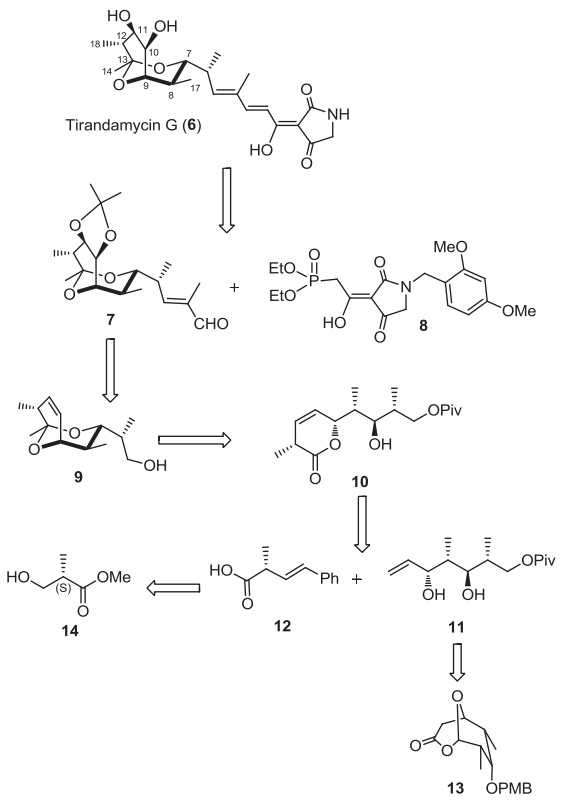


Fig. 1. Structures of tirandamycins (**1**–**6**).

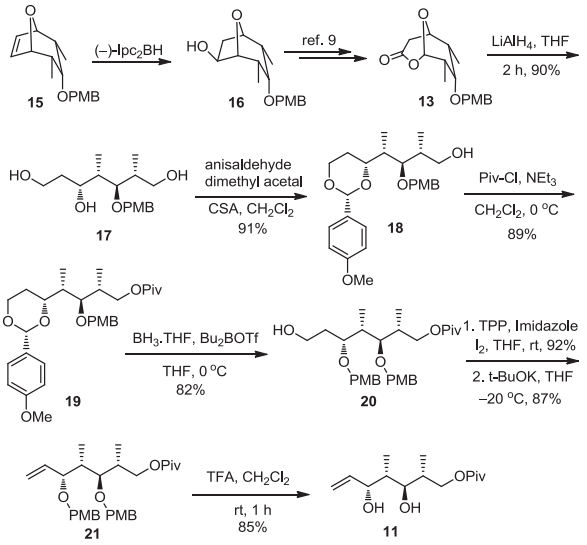
(RCM) reaction. Diol **11** in turn could be achieved from a known bicyclic lactone **13**.[9]

2. Result and discussion

Our first objective focused on the stereoselective synthesis of the 2,6-dioxabicyclic skeleton **9**. As outlined in Scheme 2, the fragment **11** was prepared following a desymmetrization of bicylic olefin **15** using Brown's chiral hydroboration followed by oxidation *via* known lactone **13**, which was widely used as a building block for the synthesis of polypropionated natural products in our group.[10] Lithium aluminum hydride reduction of **13** afforded triol **17** in



Scheme 1. Retrosynthetic analysis.

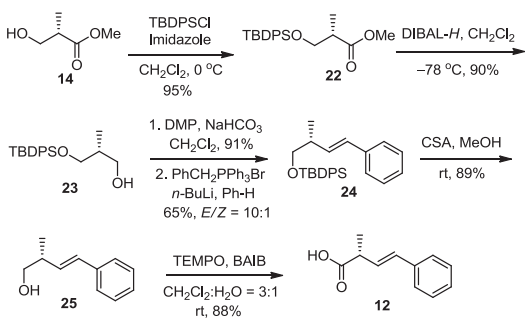


Scheme 2. Synthesis of the fragment **11**.

Our first objective focused on the stereoselective synthesis of the 2,6-dioxabicyclic skeleton **9**. As outlined in Scheme 2, the fragment **11** was prepared following a desymmetrization of bicylic olefin **15** using Brown's chiral hydroboration followed by oxidation *via* known lactone **13**, which was widely used as a building block for the synthesis of polypropionated natural products in our group.[10] Lithium aluminum hydride reduction of **13** afforded triol **17** in 90% yield. The conversion of triol **17** to PMB acetal **18** was carried out using anisaldehyde dimethyl acetal[11] and substoichiometric amount of camphorsulfonic acid (CSA). The primary hydroxyl group of compound **18** was protected as pivaloyl ester with PivCl and Et_3N in anhydrous CH_2Cl_2 to obtain compound **19** in good yield. Regioselectively reductive opening of PMB acetal with BH_3.THF and Bu_2BOTf led to the primary alcohol **20**.[12] The hydroxy was converted to its iodo, followed by elimination with *t*-BuOK in THF smoothly afforded olefin **21** (80% yield over two steps). The di-PMB protecting group in the resulted olefin **21** were removed using TFA in CH_2Cl_2 at room temperature to furnish the diol **11** in good yield (Scheme 2).

Preparation of the acid **12** began with protection of the Roche's ester as its TBDPS ether with TBDPS-Cl and imidazole in CH_2Cl_2 at 0 °C. DIBAL-*H* reduction of **22** afforded corresponding alcohol which on treatment with the Dess-Martin periodinane[13] reagent gave aldehyde. The aldehyde was immediately subjected to Wittig olefination with benzyltriphenylphosphonium bromide and *n*-BuLi in benzene at 0 °C to furnish olefin **24** as a 10:1 ratio of *E/Z* isomers (53% yield over three steps). The TBDPS group present in compound **24** was deprotected with CSA in MeOH to obtain alcohol **25**. TEMPO-BAIB[14] mediated oxidation of the resulting alcohol in CH_2Cl_2-water (3:1) afforded the acid **12** in 88% yield (Scheme 3).

Having diol **11** and acid fragment **12** in hand, our next objective was to couple both the fragments. Initially, esterification of acid **12** with alcohol **11** was performed activatin with dicyclohexyl carbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine



Scheme 3. Synthesis of the fragment **12**.

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(DMAP) in CH_2Cl_2 to afford ester as an inseparable mixture of regioisomers (1:1) in good yield. To improve the selectivity for the required regioisomer **26**, the esterification was examined at low temperature and at high dilution conditions using dicyclohexyl carbodiimide (DCC) and catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 at −40 °C which resulted better selectivity towards allylic hydroxy to afford required ester **26** along with unrequired regioisomer **27** as an inseparable mixture (**26**/**27** = 4:1) (Scheme 4). The ester **26** along with its regioisomer **27**, were subjected to ring-closing metathesis reaction using Grubbs II generation[15] catalyst in refluxing toluene to furnish lactone **10** (59% for two steps). The regioisomer **27** did not participate in the ring-closing metathesis reaction and thus got separated during the purification by silica gel column chromatography. Lactone **10** was converted to Weinreb amide[16] **28** by using methoxymethylamine hydrochloride and trimethylaluminum in anhydrous CH_2Cl_2 at 0 °C with good yield. The resulting Weinreb amide **28** was treated with excess methyllithium[17] (4 equiv.) in THF to convert it to the corresponding methyl ketone followed by deprotection of pivaloyl group to afford triol. The crude triol was subjected to acid-catalyzed intramolecular ketalization using CSA in CH_2Cl_2 to form the crucial 2,6-dioxabicyclononane skeleton **9** in 80% yield over two steps. Having successfully constructed the advanced 2,6-dioxabicyclononane skeleton, diastereoselective dihydroxylation of **9** from the *exo* face of the 2,6-dioxabic-ycloоctane skeleton under Upjohn conditions[18] afforded vicinal diols **29** in moderate yield (dr ≥ 99 by HPLC). The assignment of vicinal diol stereochemistry was confirmed by NOE experiment in the next step. The vicinal dihydroxy of **29** was protected as its acetonide **30** by using 2,2-dimethoxypropane (2,2-DMP) in CH_2Cl_2 in presence of catalytic amount of CSA (Scheme 4). In the NOESY spectrum of compound **30**, the NOE interactions between H-10 and H-7 and C-18 methyl (Fig. 2) supported the assigned relative stereochemistry of the acetonide protected vicinal diol **30**.

Hydroxy compound **30** was then oxidized with Dess-Martin periodinane[13] followed by Wittig olefination with $PPh_3C(Me)CHO$ (**32**)[19] to obtain α,β-unsaturated aldehyde **7** as E/Z isomers (20:1) in good yield. Coupling of the potassium dianion of Schlessinger's phosphonate (**8**)[7a,7c] with bicyclic aldehyde **7** under Horner-Wadsworth-Emmons olefination conditions furnished acetonide and *N*-dimethoxybenzyl-protected tirandamycin G **33** in 80% yield (Scheme 5).

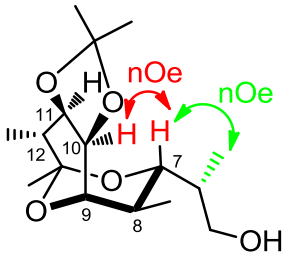
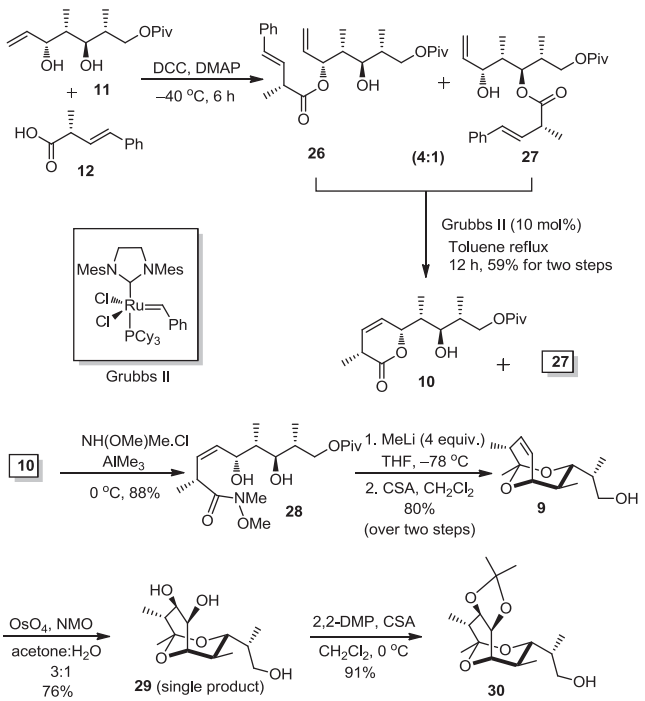


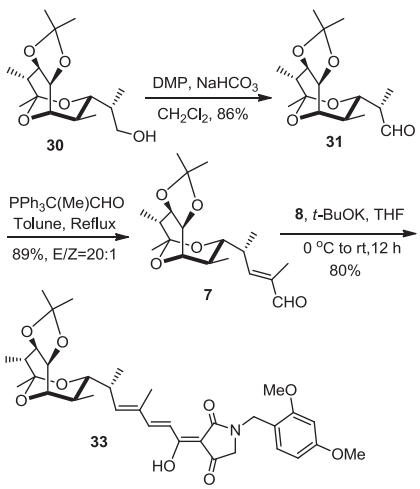
Fig. 2. NOE correlations of compound **30**.

To achieve the total synthesis of tirandamycin G (**6**), deprotection of the acetonide on the hydroxy at C_{10} and C_{11} and *N*-dimethoxybenzyl (DMB) protecting group was planned. For the same, compound **33** was treated with TfOH and thioanisole in CH_2Cl_2 which resulted in complete decomposition of starting material. Again, compound **33** was treated with TFA in CH_2Cl_2 (1:1) to get the desired tirandamycin G (**6**) instead 10-*epi*-tirandamycin E (**5′**) was obtained (Table 1).[6] The formation of 10-*epi*-tirandamycin E (**5′**) was confirmed by comparing thoroughly with the ^1H and ^{13}C NMR data of the tirandamycin E (**5**). The plausible pathways for the formation of the 10-*epi*-tirandamycin E (**5′**) was explained in Fig. 3. In the presence of TFA in CH_2Cl_2 (1:1), the 2,6-dioxabicyclononane skeleton opens up to afford keto diol intermediate **34**, followed by deprotonation and deprotection of the acetonide group forms the stable α,β-unsaturated keto intermediate **35**. The acid-catalyzed intramolecular ketalization of **35** with TFA in CH_2Cl_2 reoccurs to form the crucial 2,6-dioxabicyclononane skeleton present in **5′** followed by deprotection of the DMB group furnishes 10-*epi*-tirandamycin E.

Next, it was attempted initially to remove the acetonide protecting group only under mild conditions to avoid the elimination. Accordingly, when compound **33** was treated with 2 N HCl, it ended up with intractable mixture of compounds. Moreover, treatment of compound **33** in CSA-MeOH and $CuCl_2$–CH_3CN conditions also led to decomposition of the starting material (Table 1).



Scheme 4. Synthesis of 2,6-dioxabicyclononane skeleton **30**.



Scheme 5. Synthesis of bicylic acetonide and DMB protected tirandamycin G (**33**).

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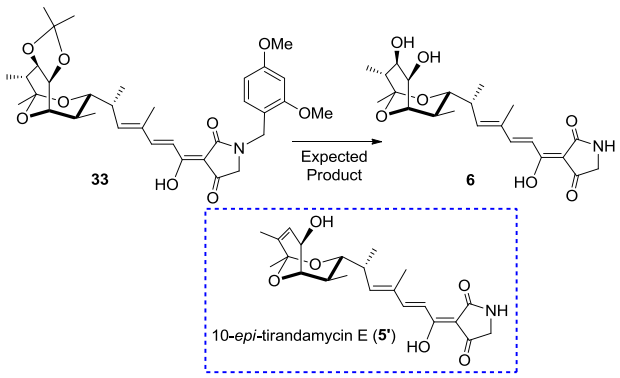

Moreover, deprotection of *N*-dimethoxybenzyl (DMB) protecting group under DDQ conditions also led to an intractable mixture of compounds.

3. Conclusion

In summary, we have made an effort towards the total synthesis of tirandamycin G, which resulted in the total synthesis of 10-*epi*-tirandamycn E (**5′**). We have developed a stereoselective route for the total synthesis of 10-*epi*-tirandamycin E employing desymmetrization protocol, ring-closing metathesis, acid-catalyzed ketalization, substrate controlled dihydroxylation and Horner-Wadsworth-Emmons olefination as key reactions. The total synthesis of tirandamycin G is in progress by changing the protecting groups and will be reported in due course of time.

4. Experimental section

4.1. General remarks

Experiments which required an inert atmosphere were carried out under argon in flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled over KOH. Commercially available reagents were used as received. Unless detailed otherwise, “work-up” means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with 5% aqueous $NaHCO_3$ (aqueous NH_4Cl) was performed. Washing with brine, drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure followed by chromatography on a silica gel column (60–120 mesh) with the indicated eluent furnished the corresponding products. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). High resolution mass spectra were run by the electron impact mode (ESIMS, 70 eV) or by the FAB mode (*m*-nitrobenzyl alcohol matrix), using an orbitrap mass analyzer. IR data were measured with oily films on NaCl plates (oils) or KBr pellets (solids) and are given only for molecules with relevant functional groups (OH, C=O). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2g^{-1} and were measured at 25 °C. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad.

Table 1
Different deprotection conditions.

Entry	Reaction conditions	Duration (h)	Results
1	TfOH, thioanisole CH_2Cl_2, rt	12 h	Decomposed
2	TFA, CH_2Cl_2 (1:1), rt	1 h	10-*epi*-Tirandamycin E (60% yield)
3	2 N HCl, MeOH, rt	4 h	Intractable mixture
4	CSA, MeOH, rt	6 h	Decomposed
5	$CuCl_2$, CH_3CN, rt	3 h	Decomposed
6	DDQ, CH_2Cl_2, H_2O, rt	2 h	Intractable mixture

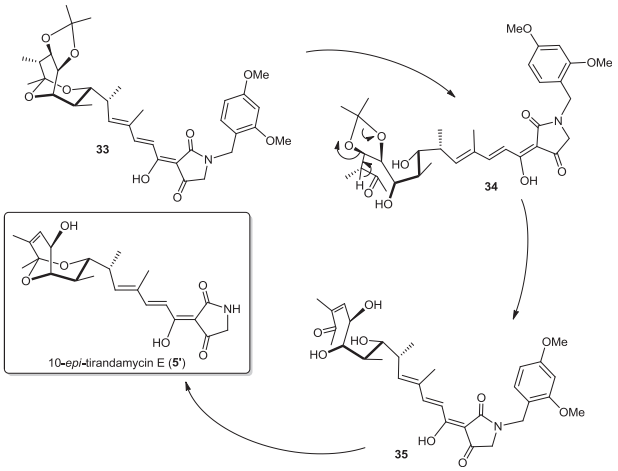

Fig. 3. Plausible pathways for the formation of 10-*epi*-tirandamycin E (**5′**).

4.2. (S)-Methyl 3-(tert-butyldiphenylsilyloxy)-2-methylpropanoate (**22**)

To an ice cooled solution of Roche's ester (**14**) (5.0 g, 42.37 mmol) and imidazole (5.76 g, 84.74 mmol), was added TBDPSCl (14.5 ml, 55.09 mmol) in CH_2Cl_2 (80 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 (1:25) as mobile phase to afford silyl ether **22** (14.3 g, 95%) as a colorless liquid. Rf (5% ethyl acetate/hexane) 0.5; $[\alpha]_D^{29}$ +13.6 (c = 1.16, $CHCl_3$); IR (neat): ν 3070, 2935, 2859, 1741, 1466, 1429, 1255, 1199, 1109, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4H), 7.45–7.35 (m, 6H), 3.38 (dd, J = 9.8, 6.8 Hz, 1H), 3.73 (dd, J = 9.8, 5.2 Hz, 1H), 3.68 (s, 3H), 2.72 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 135.5, 133.4, 129.6, 127.6, 65.9, 51.4, 42.3, 26.7, 19.2, 13.4 ppm; HRMS (ESI) *m/z* calc. for $C_{21}H_{28}O_3NaSi$ $[M + Na]^+$: 379.1699, found: 379.1700.

4.3. (R)-3-(tert-Butyldiphenylsilyloxy)-2-methylpropan-1-ol (**23**)

A stirred solution of ester **22** (10.0 g, 28.08 mmol) in anhydrous CH_2Cl_2 (100 mL), was treated with DIBAL-*H* (44.15 mL of 1.4 M solution in toluene, 61.8 mmol) at −78 °C and stirred for 2 h. The reaction was quenched with MeOH (5 mL) and saturated aqueous sodium potassium tartrate solution (50 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 × 50 mL). Combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude product was

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purified by silica gel column chromatography using ethyl acetate and hexane (1:10) as mobile phase to afford alcohol **23** (8.29 g, 90%) as a colorless liquid. R_f (15% ethyl acetate/hexane) 0.45; $[\alpha]_D^{29}$ +5.1 (c = 1.0, $CHCl_3$); IR (neat): ν 3435, 3056, 2956, 2861, 1466, 1426, 1389, 1107, 1037, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.63 (m, 4H), 7.49–7.34 (m, 6H), 3.73 (dd, J = 10.5, 4.5 Hz, 1H), 3.70–3.65 (m, 2H), 3.59 (dd, J = 9.8, 7.5 Hz, 1H), 2.00 (m, 1H), 1.06 (s, 9H), 0.83 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.2, 129.7, 127.7, 68.5, 67.4, 37.3, 26.8, 19.1, 13.1 ppm; HRMS (ESI) m/z calc. for $C_{20}H_{28}O_2NaSi$ $[M + Na]^+$: 351.1750, found: 351.1755.

4.4. (R,E)-tert-butyl(2-methyl-4-phenylbut-3-enyloxy)diphenylsilane (**24**)

To a stirred solution of primary alcohol **23** (7.5 g, 22.86 mmol) and solid anhydrous $NaHCO_3$ (5.76 g, 68.58 mmol) in CH_2Cl_2 (75 mL) at 0 °C, was added Dess-Martin periodinane (14.6 g, 34.3 mmol). The resulting reaction mixture was stirred at 0 °C to room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and saturated aqueous solution of $NaHCO_3$ (30 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 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 (6.78 g, 91%) as colorless oil which was used for the next step without further purification.

To a solution of benzyltriphenylphosphonium bromide (10.8 g, 24.95 mmol) in anhydrous benzene (75 mL) at 0 °C, was added n-BuLi (15.6 mL, 24.59 mmol, 1.6 M in hexane) dropwise and the resulting solution was warmed to room temperature then stirred for 1 h. The solution was cooled to 0 °C and treated with a solution of aldehyde (6.78 g, 20.79 mmol) in anhydrous benzene (15 mL). The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (100 mL) and extracted with diethyl ether (3 × 75 mL). Combined extracts were washed with brine (100 mL), 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 (1:49) as mobile phase to afford E-olefin **24** (5.4 g, 65%) as a colorless oil. R_f (5% ethyl acetate/hexane) 0.7; $[\alpha]_D^{29}$ +12.1 (c = 1.0, $CHCl_3$); IR (neat): ν 3020, 2960, 2940, 2860, 1430, 1200, 1120, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.63 (m, 4H), 7.44–7.26 (m, 11H), 6.40 (d, J = 15.8 Hz, 1H), 6.15 (dd, J = 15.8, 7.5 Hz, 1H), 3.66–3.56 (m, 2H), 2.56 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 135.6, 134.8, 133.3, 129.5, 128.4, 127.6, 126.9, 126.0, 68.6, 39.7, 26.9, 19.3, 16.6 ppm; HRMS (ESI) m/z calc. for $C_{27}H_{32}ONaSi$ $[M + Na]^+$: 423.2115, found: 423.2108.

4.5. (R,E)-2-Methyl-4-phenylbut-3-en-1-ol (**25**)

To a solution of compound **24** (5.0 g, 12.5 mmol) in MeOH (50 mL), camphoresulphonic acid (0.58 g, 2.50 mmol) was added at room temperature and stirred for 6 h. After completion of the reaction (monitored by TLC), it was quenched with Et_3N (10 mL). The reaction mass was concentrated under reduced pressure to afford the crude product, which on purification by silica gel column chromatography using ethyl acetate and hexane (1:5) as the mobile phase afforded the alcohol **25** (1.92 g, 95%) as a colorless oil. R_f (20% ethyl acetate/hexane) 0.65; $[\alpha]_D^{29}$ +26.1 (c = 1.1, $CHCl_3$); IR (neat): ν 3383, 3060, 3027, 2960, 2930, 2874, 1492, 1453,1378, 1274, 1032, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 6.50 (d, J = 16.0 Hz, 1H), 6.10 (dd, J = 16.0, 8.0 Hz, 1H), 3.60 (dd, J = 10.3, 6.8 Hz, 1H), 3.53 (dd, J = 10.2, 6.7 Hz, 1H), 2.55 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1, 132.4, 130.9, 128.5, 127.2, 126.1, 67.3, 40.1, 16.4 ppm; HRMS (EI) m/z calc. for $C_{11}H_{14}O$ $[M]^+$: 162.1043, found: 162.1045.

4.6. (R,E)-2-Methyl-4-phenylbut-3-enoic acid (**12**)

To a stirred solution of alcohol **25** (1.75 g, 10.8 mmol) in dichloromethane-water (30 mL, 2:1 ratio), was added bis(acetoxy) iodobenzene (BAIB) (8.7 g, 27.0 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (810 mg, 5.4 mmol) sequentially and stirred for 6 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous solution of $Na_2S_2O_7$ and stirred for 10 min. 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 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (3:7) as mobile phase to afford acid **12** (1.67 g, 88%) as a yellow oil. R_f (40% ethyl acetate/hexane) 0.60; $[\alpha]_D^{29}$ −30.0 (c = 1.05, $CHCl_3$); IR (neat): ν 2974, 2931, 1710, 1627, 1450, 1398, 1230, 1137, 1031, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.18 (m, 5H), 6.51 (d, J = 15.8 Hz, 1H), 6.28 (dd, J = 15.8, 8.3 Hz, 1H), 3.34 (m, 1H), 1.40 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9, 136.7, 131.6, 128.5, 127.9, 127.6, 126.3, 43.0, 17.1 ppm; HRMS (EI) m/z calc. for $C_{11}H_{12}O_2$ $[M]^+$: 176.0832, found: 176.0838.

4.7. (3R,4S,5R,6R)-5-(4-methoxybenzyloxy)-4,6-dimethyl heptane-1,3,7-triol (**17**)

To an ice cooled suspension of LAH (3.72 g, 98.0 mmol) in THF (150 mL), was added a solution of lactone **13** (10.0 g, 32.6 mmol) in THF (50 mL) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. After complete consumption of starting material (monitored by TLC), it was quenched with saturated aqueous solution of NH_4Cl (100 mL) and the formed precipitate was filtered off on a pad of Celite using ethyl acetate. The filtrate was concentrated under reduced pressure to get the crude triol which was purified by column chromatography over silica gel ethyl acetate and hexane (3:2) as mobile phase to afford triol **17** (9.17 g, 90%) as a viscous liquid. Rf (pure ethyl acetate) 0.55; $[\alpha]_D^{29}$ +6.7 (c = 1.1, $CHCl_3$); IR (neat): ν 3412, 2935, 1612, 1513, 1461, 1248, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.62 (s, 2H), 4.25 (m, 1H), 3.85–3.67 (m, 4H), 3.80 (s, 3H), 3.48 (dd, J = 8.3, 3.7 Hz, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.44 (m, 1H), 1.12 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 129.6, 114.0, 88.1, 75.6, 70.5, 65.1, 61.7, 55.2, 39.2, 37.8, 36.5, 15.0, 11.9 ppm; HRMS (ESI) m/z calc. for $C_{17}H_{28}O_5Na$ $[M + Na]^+$: 335.1829, found: 335.1831.

4.8. (2R,3R,4S)-3-(4-methoxybenzyloxy)-4-((4R)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2-methyl pentan-1-ol (**18**)

To a stirred solution of triol **17** (8.0 g, 25.6 mmol) in anhydrous CH_2Cl_2 (75 mL), anisaldehye dimethyl acetal (5.23 mL, 30.7 mmol) was added followed by catalytic amount of camphorsulfonic acid (580 mg) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous solution of $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified on silica gel column chromatography using ethyl acetate and hexane (1:4) as mobile phase to afford compound **18** (10.0 g, 91%) as pale yellow liquid. R_f (50% ethyl acetate/hexane)

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0.5; $[\alpha]_D^{29}$ −52.4 (c = 1.3, $CHCl_3$); IR (neat): ν 3453, 2961, 2929, 1613, 1514, 1461, 1248, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 6.94–6.85 (m, 4H), 5.41 (s, 1H), 4.54 (q, J = 11.3 Hz, 2H), 4.32–4.19 (m, 2H), 4.00–3.85 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59–3.51 (m, 2H), 2.17–2.01 (m, 2H), 1.97–1.81 (m, 2H), 1.20 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 159.2, 131.4, 130.2, 129.3, 127.2, 113.8, 113.4, 100.8, 85.4, 75.7, 75.3, 67.2, 64.2, 55.1, 41.0, 35.9, 28.5, 16.1, 10.9 ppm; HRMS (ESI) m/z calc. for $C_{25}H_{34}O_6Na$ $[M + Na]^+$: 453.2247, found: 453.2244.

4.9. (2R,3R,4S)-3-(4-methoxybenzyloxy)-4-((4R)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2-methylpentyl pivalate (**19**)

To a stirred solution of alcohol **18** (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 was 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 **19** (5.31 g, 89%) as a colorless liquid. R_f (15% ethyl acetate/hexane) 0.45; $[\alpha]_D^{29}$ −22 (c = 1.0, $CHCl_3$); IR (neat): ν 3424, 2964, 2928, 1725, 1613, 1514, 1248, 1163, 1034, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 8.6 Hz, 2H), 7.28–7.24 (m, 2H), 6.93–6.84 (m, 4H), 5.40 (s, 1H), 4.52 (ABq, δ_A 4.55, δ_B 4.49, J = 10.7 Hz, 2H), 4.32–4.18 (m, 3H), 3.98–3.87 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.47 (dd, J = 9.6, 2.4 Hz, 1H), 2.25–2.00 (m, 3H), 1.82 (m, 1H), 1.19 (s, 9H), 1.10 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 159.8, 159.1, 131.6, 130.9, 129.1, 127.3, 113.8, 113.5, 100.9, 82.8, 75.8, 75.0, 67.3, 65.7, 55.3, 40.8, 38.7, 34.9, 27.2, 27.0, 16.1, 10.9 ppm; HRMS (ESI) m/z calc. for $C_{30}H_{42}O_7Na$ $[M + Na]^+$: 537.2822, found: 537.2825.

4.10. (2R,3R,4S,5R)-7-Hydroxy-3,5-bis(4-methoxybenzyloxy)-2,4-dimethylheptyl pivalate (**20**)

Compound **19** (5.0 g, 9.72 mmol) was dissolved in a solution of BH_3.THF complex (1 M in THF, 48.5 mL). After the mixture was stirred at 0 °C for 5 min, dibutylboron triflate (1 M in CH_2Cl_2, 9.72 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for another 1 h. Subsequently, triethylamine (1.5 mL) and methanol (1.5 mL) were added until the evolution of H_2 gas had ceased. The solvents were concentrated under reduced pressure, and the residue was co-evaporated with methanol (3 × 50 mL). The residue was purified by silica gel column chromatography using ethyl acetate and hexane (1:4) as the mobile phase to afford the primary alcohol **20** (4.10 g, 82%) as a colorless oil. R_f (50% ethyl acetate/hexane) 0.5; $[\alpha]_D^{29}$ −9.5 (c = 1.0, $CHCl_3$); IR (neat): ν 3446, 2964, 2932, 1725, 1612, 1585, 1513, 1461, 1398, 1286, 1248, 1167, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.24–7.20 (m, 4H), 6.87–6.84 (m, 4H), 4.52–4.48 (m, 2H), 4.45–4.38 (m, 2H), 4.27 (dd, J = 10.8, 4.9 Hz, 1H), 4.0 (dd, J = 10.8, 7.6 Hz, 1H), 3.87 (td, J = 6.4, 2.6 Hz, 1H), 3.79 (s, 6H), 3.76–3.66 (m, 2H), 3.39 (dd, J = 7.8, 3.9 Hz, 1H), 2.20 (m, 1H), 1.99–1.88 (m, 2H), 1.73 (m, 1H), 1.20 (s, 9H), 1.07 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 159.0, 130.9, 130.8, 129.1, 129.0, 113.7, 83.7, 76.7, 74.4, 71.2, 66.0, 60.4, 55.2, 39.8, 38.8, 35.2, 35.0, 27.2, 15.8, 11.5 ppm; HRMS (ESI) m/z calc. for $C_{30}H_{44}O_7Na$ $[M + Na]^+$: 539.2974, found: 539.2976.

4.11. (2R,3R,4S,5R)-3,5-bis(4-methoxybenzyloxy)-2,4-dimethylhept-6-enyl pivalate (**21**)

To a stirred solution of alcohol **20** (5.0 g, 9.69 mmol) in anhydrous THF (75 mL) were added imidazole (1.3 g, 19.40 mmol), triphenyl phosphine (TPP) (4.9 g, 19.37 mmol) and iodine (4.92 g, 19.40 mmol) separately at 0 °C under nitrogen. After 30 min the reaction was quenched by an aqueous saturated hypo solution (30 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and filtered through a small pad of silica gel to give iodo compound (5.58 g, 92%) as a yellow oil which was used for the next step without further purification.

To a stirred solution of iodo compound (5.58 g, 8.91 mmol) in anhydrous THF (100 mL) was added ^{t}BuOK (1.24 g, 11.14 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at −20 °C for 15 min. After complete consumption of the starting material (monitored by TLC), it was quenched with saturated aqueous ammonium chloride solution (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (100 mL), 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 (1:20) as mobile phase to afford olefin **21** (3.86 g, 87%) as a colorless oil. R_f (10% ethyl acetate/hexane) 0.55; $[\alpha]_D^{29}$ −21.1 (c = 1.0, $CHCl_3$); IR (neat): ν 3427, 2971, 2837, 1725, 1611, 1513, 1462, 1397, 1285, 1248, 1167, 1085, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H), 7.19 (d, J = 8.7 Hz, 2H), 6.88–6.84 (m, 4H), 5.84 (m, 1H), 5.28–5.23 (m, 2H), 4.53 (d, J = 11.3 Hz, 1H), 4.38 (ABq, δ_A 4.43, δ_B 4.33 J = 10.8 Hz, 2H), 4.27–4.13 (m, 3H), 3.94 (dd, J = 10.8, 7.8 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.45 (dd, J = 8.8, 3.0 Hz, 1H), 2.17 (m, 1H), 1.87 (m, 1H), 1.18 (s, 9H), 1.06 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 158.9, 138.1, 131.0, 129.0, 128.8, 117.0, 113.6, 82.8, 79.3, 74.2, 69.5, 65.9, 55.1, 41.7, 38.7, 34.8, 27.1, 15.9, 10.3 ppm; HRMS (ESI) m/z calc. for $C_{30}H_{42}O_6Na$ $[M + Na]^+$: 521.2859, found: 521.2860.

4.12. (2R,3R,4S,5R)-3,5-dihydroxy-2,4-dimethylhept-6-enyl pivalate (**11**)

To a stirred solution of di-PMB protected olefin **21** (3.75 g, 7.53 mmol) in anhydrous CH_2Cl_2 (20 mL), was added CF_3CO_2H (10 mL). The resulting wine red solution was stirred at room temperature for 3 h and then quenched with ice pieces. The light yellow solution was extracted with CH_2Cl_2 (3 × 30 mL), combined extracts were washed with saturated aqueous solution of sodium bicarbonate and 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 (1:4) as mobile phase to afford diol **11** (1.65 g, 85%) as colorless oil. R_f (50% ethyl acetate/hexane) 0.65; $[\alpha]_D^{29}$ +6.7 (c = 1.2, $CHCl_3$); IR (neat): ν 3444, 2972, 2933, 1724, 1645, 1460, 1399, 1287, 1164, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.90 (m, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 4.49 (m, 1H), 4.27 (dd, J = 11.1, 5.6 Hz, 1H), 4.19 (dd, J = 11.1, 4.6 Hz, 1H), 3.44 (m, 1H), 2.09 (m, 1H), 1.89 (m, 1H), 1.22 (s, 9H), 1.00 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 138.7, 115.1, 77.5, 73.6, 66.3, 38.9, 38.6, 36.0, 27.2, 14.6, 11.8 ppm; HRMS (ESI) m/z calc. for $C_{14}H_{26}O_4Na$ $[M + Na]^+$: 281.1723, found: 281.1725.

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*4.13. (2R,3R,4R)-3-Hydroxy-2-methyl-4-((2R,5R)-5-methyl-6-oxo-5,6-dihydro-2H-pyran-2-yl)pentyl pivalate (**10**)*

To a stirred solution of carboxylic acid **12** (681 mg, 3.87 mmol) and diol **11** (1.0 g, 3.87 mmol) in anhydrous CH_2Cl_2 (20 mL) at −40 °C, were added a solution of 1,3-dicyclohexylcarbodiimide (DCC) (985 mg, 4.65 mmol) in anhydrous dichloromethane (10 mL) and 4-dimethylaminopyridine (DMAP) (47 mg, 0.38 mmol) in anhydrous dichloromethane (5 mL). The reaction mixture was gradually warmed to room temperature in 4 h. After completion of the reaction (monitored by TLC), the precipitate of dicyclohexyl urea was filtered off and the filtrate washed with saturated aqueous ammonium chloride solution (20 mL) and then water (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and filtered through a small pad of silica gel to give mixture of ester **26** and **27** (1.41 g, 88%) as (4:1) inseparable regio isomer of ester which was used for the next step without further purification.

To a solution of mixture of ester **26** and **27** (1.41 g, 3.38 mmol) was added Grubbs II catalyst (286 mg, 0.338 mmol) in toluene (338 mL, 0.01 M) and heated at 110 °C for 12 h. After completion of the reaction, toluene was removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate and hexane (2:3) as mobile phase to afford lactone **10** (720 mg, 59% for two steps) as yellow oil. R_f (50% ethyl acetate/hexane) 0.3; $[\alpha]_D^{29}$ −19 (c = 1.0, $CHCl_3$); IR (neat): ν 3444, 2960, 2931, 1719, 1464, 1386, 1109, 1078, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (m, 1H), 5.68 (m, 1H), 5.52 (m, 1H), 4.28 (dd, J = 11.3, 5.3 Hz, 1H), 3.97 (dd, J = 11.3, 6.8 Hz, 1H), 3.70 (m, 1H), 3.06 (m, 1H), 2.12 (m, 1H), 1.93 (m, 1H), 1.40 (d, J = 7.5 Hz, 3H), 1.21 (s, 9H), 1.08 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 172.8, 128.9, 125.9, 78.9, 74.2, 64.9, 40.6, 38.7, 34.4, 34.3, 27.1, 17.5, 15.6, 9.7 ppm; HRMS (ESI) m/z calc. for $C_{17}H_{28}O_5Na$ $[M + Na]^+$: 335.1829, found: 335.1831.

*4.14. (2R,3R,4S,5R,8R,Z)-3,5-dihydroxy-9-(methoxy (methyl) amino)-2,4,8-trimethyl-9-oxonon-6-enyl pivalate (**28**)*

To a suspension of methoxymethylamine hydrochloride (419 mg, 4.32 mmol) in anhydrous dichloromethane (10 mL) at 0 °C, was added dropwise trimethylaluminum (2.0 M in hexane, 2.16 mL, 4.32 mmol). When complete dissolution was observed, the solution was transferred *via* cannula to a solution of lactone **10** (450 mg, 1.44 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being quenched with saturated Rochelle's salts (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were 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 (1:1) as mobile phase to afford hydroxy amide **28** (473 mg, 88%) as colorless liquid. R_f (pure ethyl acetate) 0.3; $[\alpha]_D^{29}$ −16.2 (c = 1.3, $CHCl_3$); IR (neat): ν 3440, 2969, 2932, 1725, 1639, 1459, 1392, 1285, 1163, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.65 (dd, J = 11.0, 8.4 Hz, 1H), 5.56 (m, 1H), 4.80 (dd, J = 8.2, 1.3 Hz, 1H), 4.27–4.20 (m, 2H), 3.93 (m, 1H), 3.74 (s, 3H), 3.47 (m, 1H), 3.19 (s, 3H), 2.09 (m, 1H), 1.88 (m, 1H), 1.22 (s, 9H), 1.21 (d, J = 6.0 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 170.9, 131.1, 130.7, 76.9, 68.8, 65.8, 60.1, 39.1, 38.5, 35.6, 34.4, 26.9, 17.8, 14.5, 11.9 ppm; HRMS (ESI) m/z calc. for $C_{19}H_{35}NO_6Na$ $[M + Na]^+$: 396.2358, found: 396.2363.

*4.15. (R)-2-((1R,3R,4S,5R,8S)-1,4,8-Trimethyl-2,9-dioxabicy- clo [3.3.1]non-6-en-3-yl)propan-1-ol (**9**)*

To a stirred solution of hydroxy amide **28** (350 mg, 0.94 mmol) in anhydrous THF (10 mL), MeLi (2.51 mL, 1.5 M in diethyl ether, 3.76 mmol) was added dropwise at −78 °C under argon. After 10 min, the reaction mixture was warmed to 0 °C, stirred for 15 min, and then quenched with saturated aqueous solution of NH_4Cl (5 mL). Organic layer was separated, and the aqueous phase extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude hemiketal was dissolved in dichloromethane (25 mL) and treated with CSA (22 mg, 0.094 mmol) at room temperature. After 2 h, the reaction was quenched with triethylamine (0.5 mL) and 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 obtain bicyclic compound **9** (170 mg, 80%) as colorless oil; R_f (30% ethyl acetate/hexane) 0.4; $[\alpha]_D^{29}$ +41.2 (c = 1.0, $CHCl_3$); IR (neat): ν 3451, 2963, 2926, 1636, 1455, 1375, 1223, 1176, 1118, 1072, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (dd, J = 10.5, 3.0 Hz, 1H), 5.75 (m, 1H), 4.30 (m, 1H), 4.00 (dd, J = 11.3, 3.0 Hz, 1H), 3.83 (dd, J = 10.5, 2.2 Hz, 1H), 3.35 (m, 1H), 2.85 (m, 1H), 2.52 (m, 1H), 2.24 (m, 1H), 1.75 (m, 1H), 1.35 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.07 (d, J = 7.5 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 123.2, 98.0, 78.5, 71.6, 64.0, 38.4, 34.1, 33.7, 27.4, 15.0, 14.1, 12.7 ppm; HRMS (ESI) m/z calc. for $C_{13}H_{22}O_3Na$ $[M + Na]^+$: 249.1466, found: 249.1472.

*4.16. (1S,3R,4R,5S,6R,7R,8S)-3-((R)-1-Hydroxypropan-2-yl)-1,4,8-trimethyl-2,9-dioxabicyclo-[3.3.1]- nonane-6,7-diol (**29**)*

To a solution of olefin **9** (150 mg, 0.664 mmol) in acetone-H_2O (3:1, 10 mL) at 0 °C, was added a solution of OsO_4 (1.32 mL, 0.025 M in toluene, 0.033 mmol) followed by the addition of NMO (225 mg, 1.66 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 2 days. The reaction mixture was diluted with EtOAc (10 mL), quenched with $Na_2S_2O_3$ (2.0 M, 5.0 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), 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 (1:1) as mobile phase to obtain triol **29** (132 mg, 76%) as colorless oil. R_f (pure ethyl acetate) 0.3; $[\alpha]_D^{29}$ −16.1 (c = 1.1, $CHCl_3$); IR (neat): ν 3429, 2916, 2927, 2876, 1726, 1612, 1513, 1459, 1249, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.11 (dd, J = 6.4, 2.1 Hz, 1H), 3.93 (dd, J = 11.3, 3.2 Hz, 1H), 3.88 (m, 1H), 3.76 (dd, J = 10.3, 3.8 Hz, 1H), 3.59–3.52 (m, 2H), 2.41 (m, 1H), 1.82–1.75 (m, 2H), 1.36 (s, 3H), 1.17 (d, J = 7.1 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 99.2, 80.8, 76.0, 70.7, 67.1, 63.2, 44.2, 35.7, 31.2, 27.1, 15.3, 12.6, 12.4 ppm; HRMS (ESI) m/z calc. for $C_{13}H_{24}O_5Na$ $[M + Na]^+$: 283.1516, found: 283.1514.

*4.17. (R)-2-((3aR,4S,5S,7R,8R,9S,9aS)-2,2,4,5,8-Pentamethyl hexahydro-3aH-5,9-epoxy[1,3]dioxolo[4,5-d]oxocin-7-yl)pro-pan-1-ol (**30**)*

To a stirred solution of diol **29** (120 mg, 0.461 mmol) in anhydrous dichloromethane (5 mL), was added 2,2-dimethoxy- propane (0.6 mL, 4.61 mmol) followed by a catalytic amount of CSA (20 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 NEt_3 (2.0 mL). The reaction mixture was concentrated to dryness under reduced pressure and purified by silica gel

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column chromatography using ethyl acetate and hexane (1:5) as mobile phase to afford compound **30** (126 mg, 91%) as colorless oil. R_f (50% ethyl acetate/hexane) 0.55; $[\alpha]_D^{29}$ +43.5 (c = 1.2, $CHCl_3$); IR (neat): ν 3435, 2961, 1739, 1663, 1456, 1413, 1374, 1165, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.26 (d, J = 5.0 Hz, 1H), 4.10 (d, J = 5.8 Hz, 1H), 4.02 (m, 1H), 3.93 (dd, J = 10.8, 3.3 Hz, 1H), 3.54 (dd, J = 10.8, 3.3 Hz, 1H), 3.22 (dd, J = 10.8, 1.7 Hz, 1H), 2.37 (m, 1H), 1.88–1.76 (m, 2H), 1.51 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 7.5 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.2, 99.1, 81.0, 77.3, 73.2, 70.3, 63.1, 44.1, 35.0, 32.7, 28.2, 27.2, 26.3, 15.1, 14.5, 13.1 ppm; HRMS (ESI) m/z calc. for $C_{16}H_{29}O_5$ $[M + H]^+$: 301.2009, found: 301.2011.

4.18. (R,E)-2-Methyl-4-((3aR,4S,5S,7R,8R,9S,9aS)-2,2,4,5,8-pentamethylhexahydro-3aH-5,9-epoxy[1,3] dioxolo[4,5-d]oxo-cin-7-yl)pent-2-enal (7)

To a stirred solution of primary alcohol **30** (100 mg, 0.33 mmol) and solid anhydrous $NaHCO_3$ (125 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added Dess-Martin periodinane (284 mg, 0.66 mmol). The resulting reaction mixture was stirred at 0 °C to room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 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 **31** (85 mg, 86%) as a colorless oil which was used for the next step without further purification.

The resulting aldehyde **31** (85 mg, 0.285 mmol) and ylide **32** (110 mg, 0.342 mmol) were dissolved in toluene (15 mL) and 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 α,β-unsaturated aldehyde **7** (86 mg, 89%) as a 20:1 E/Z isomers. R_f (30% ethyl acetate/hexane) 0.4; $[\alpha]_D^{29}$ +30.1 (c = 1.0, $CHCl_3$); IR (neat): ν 3450, 2929, 2860, 1686, 1538, 1457, 1376, 1217, 1186, 1138, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.45 (s, 1H), 6.68 (dd, J = 10.7, 1.2 Hz, 1H), 4.21 (d, J = 5.3 Hz, 1H), 4.10 (d, J = 6.0 Hz, 1H), 4.04 (dd, J = 7.6, 6.1 Hz, 1H), 3.20 (dd, J = 11.3. 1.7 Hz, 1H), 2.91 (m, 1H), 1.94 (m, 1H), 1.89 (m, 1H), 1.78–1.77 (m, 3H), 1.53 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.16 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 153.7, 139.4, 108.2, 98.8, 78.3, 77.4, 72.9, 70.3, 44.2, 35.0, 33.3, 28.2, 26.9, 26.3, 16.5, 14.5, 12.9, 9.3 ppm; HRMS (ESI) m/z calc. for $C_{19}H_{31}O_5$ $[M + H]^+$: 339.2166, found: 339.2173.

4.19. Acetonide and N-DMB protected tirandamycin G (33)

To a flame-dried, 25-mL two-nacked round bottom flask equipped with a rubber septum and argon inlet needle was charged with KO-t-Bu (69 mg, 0.616 mmol) and anhydrous THF (10 mL). A solution of phosphonate **8** (114 mg, 0.264 mmol) in anhydrous THF (5.0 mL) was added and the mixture was stirred at 0 °C for 30 min. A solution of aldehyde **7** (30 mg, 0.0 88 mmol) in anhydrous THF (5.0 mL) was added dropwise and the mixture was stirred at room temperature for 12 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (2:3) as mobile phase to give acetonide and dimethoxybenzyl (DMB) protected tirandamycin G (**33**) (42 mg, 80%) as a pale yellow oil: R_f (50% ethyl acetate/hexane) 0.25; $[\alpha]_D^{29}$ +3.5 (c = 0.7, $CHCl_3$); IR (neat): ν 3451, 2924, 2853, 1704, 1617, 1572, 1466, 1375, 1294, 1237, 1211, 1160, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 15.8 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 15.8 Hz, 1H), 6.46 (s, 2H), 6.21 (d, J = 10.1 Hz, 1H), 4.58 (s, 2H), 4.19 (d, J = 5.0 Hz, 1H), 4.04 (m, 1H), 4.03 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 2H), 3.14 (d, J = 10.8 Hz, 1H), 2.78 (m, 1H), 1.96 (m, 1H), 1.90 (s, 3H), 1.87 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H),0.80 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 173.8, 173.4, 160.9, 158.6, 149.2, 144.5, 134.2, 131.2, 116.4, 116.0, 108.1, 104.3, 100.8, 98.7, 98.5, 78.6, 72.9, 70.4, 55.6, 55.3, 44.2, 40.0, 35.1, 33.1, 28.2, 26.9, 26.3, 17.0, 14.5, 12.9, 12.2 ppm; HRMS (ESI) m/z calc. for $C_{34}H_{45}NO_9Na$ $[M + Na]^+$: 634.2986, found: 634.2989.

4.20. 10-epi-tirandamycin E (5′)

To a stirred solution of acetonide and dimethoxybenzyl (DMB) protected tirandamycin G **33** (20 mg, 0.032 mmol) in anhydrous CH_2Cl_2 (1.0 mL), was added CF_3CO_2H (1.0 mL). The resulting wine red solution was stirred at room temperature for 1 h and then quenched with ice pieces. The light yellow solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give 10-*epi*-tirandamycin E (**5′**) (7.8 mg, 60%) as yellow oil. R_f (10% MeOH/CH_2Cl_2) 0.6; $[\alpha]_D^{29}$ +8.1 (c = 0.1, $CHCl_3$); IR (neat): ν 3445, 3425, 2948, 2914, 2851, 1619, 1578, 1464, 1379, 1291, 1247, 1115, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 15.6 Hz, 1H), 7.15 (d, J = 15.6 Hz, 1H), 6.30 (d, J = 9.8 Hz, 1H), 5.93 (br s, 1H), 3.94 (m, 1H), 3.82 (s, 2H), 3.77 (d, J = 5.0 Hz, 1H), 3.37 (d, J = 10.8 Hz, 1H), 3.13 (m, 1H), 2.80 (m, 1H), 1.91 (s, 3H), 1.88 (m, 1H), 1.68 (s, 3H), 1.45 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5, 176.5, 175.3, 150.4, 146.3, 136.5, 134.3, 125.1, 116.0, 99.8, 95.4, 78.4, 77.6, 76.4, 51.6, 34.5, 33.3, 24.1, 18.2, 17.0, 12.7, 12.2 ppm; HRMS (ESI) m/z calc. for $C_{22}H_{29}NO_6Na$ $[M + Na]^+$: 426.1918, found: 426.1922.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.01.057.

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