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The first total synthesis of a 12-membered macrolide balticolid

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ABSTRACT

Herein the first total synthesis of balticolid, a 12-membered macrolide is described.

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Many novel pharmacologically active secondary metabolites have been isolated from marine microorganisms.[1] Several 12-membered macrolides have been isolated from fungal metabolites (for e.g. cladospolides,[2] pandangolides[3]). Balticolid **1**, a new 12-membered macrolide was isolated by Shushni et al,[4] from the marine fungus belonging to the *Ascomycetous* species. The structure was determined as (4*R*,5*E*,9*E*,12*R*)-4-hydroxy-12-methyloxacyclododeca-5,9-diene-2,8-dione possessing an antiviral activity (*anti*-HSV) with an IC_{50} value of 0.45 μM. Structurally, balticolid attracted our attention due to its differently positioned functional groups than related macrolides. For instance, the presence of a sensitive methylene at C7 flanked by the vinyl ketone (C8–C10) and allylic alcohol (C4–C6) moieties along with the two *E*-olefinic bonds at C5–C6 and C9–C10 makes this molecule synthetically interesting (Fig. 1). As a part of our interest in the synthesis of such biologically active macrolides,[5] herein we describe the total synthesis of balticolid **1**.

Ever since the discovery of Grubbs catalyst, metathesis[6] based synthetic strategies of natural products not only influenced the way synthetic chemists think but also shortened the sequences en route. Our synthetic plan (Scheme 1) involved RCM of the ester **5** that could be accessed from intermediates **6** and **7**, to furnish macrocycle **4a**. Alcohol **6** and acid **7** were synthesized independently. Subsequent transformations of macrocycle **4a** resulted in target compound **1**.

Thus, the synthesis of balticolid **1** primarily involved the synthesis of two key fragments **6** and **7** followed by their transformations into the target. Firstly, synthesis of alcohol intermediate **6** was undertaken (Scheme 2). Accordingly, base induced ring-opening reaction of (*R*)-propylene oxide with protected propargyl alcohol resulted in the corresponding alkylated propargylic alcohol which on reported[5a] transformations gave the allylic alcohol **8**. Compound **8** on oxidation (IBX/DMSO/EtOAc/rt/3 h) afforded the aldehyde (85%), which was further converted to **9** on Barbier allylation (Zn/allylbromide/satd. NH_4Cl/THF/0 °C to rt/12 h) followed by the protection of the ensuing alcohol as its silyl-ether (TBS-Cl/imidazole/DMAP/CH_2Cl_2/0 °C to rt/1 h). Furthermore compound **9** on PMB-deprotection (DDQ conditions[7]) furnished the requisite alcohol **6** (80%).

Next, the synthesis of the acid component **7** (Scheme 3) was taken up. Accordingly, allylic alcohol **10** was identified as an important precursor and hence synthesis of **10** was accomplished by adopting a literature inspired procedure.[5c] Further, compound **10** was converted into its MOM-ether (MOM-Cl/DIPEA/CH_2Cl_2/0 °C to rt/12 h) to afford compound **11** (90%). The silyl group in compound **11** was deprotected under conventional conditions (TBAF/THF/0 °C to rt/2 h) to afford the corresponding primary alcohol that was oxidized[8a] {TEMPO/BIAB/CH_2Cl_2:H_2O (1:1)/0 °C to rt/2 h} to the desired acid **7** (91% over two steps).[8b]

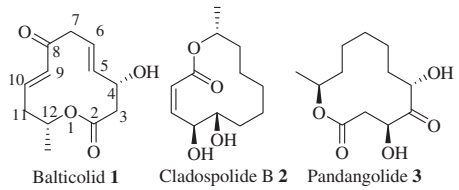

Figure 1.

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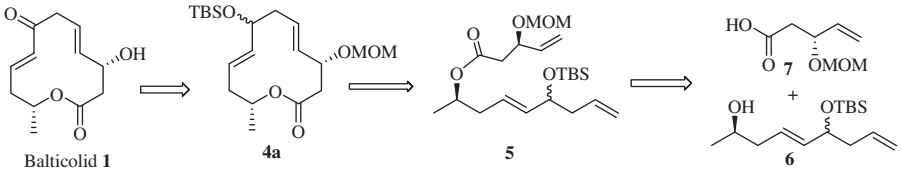
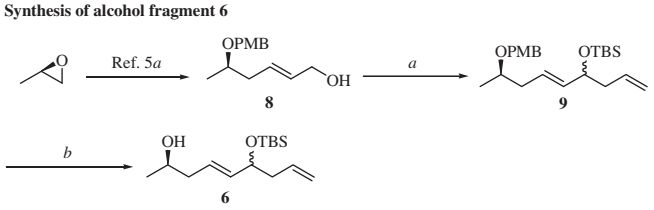
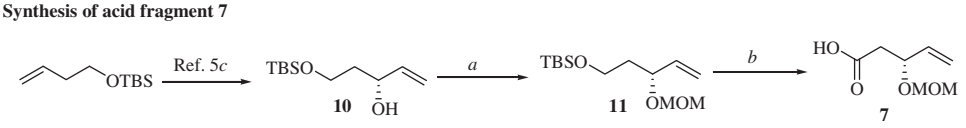


Scheme 1. Retrosynthesis.

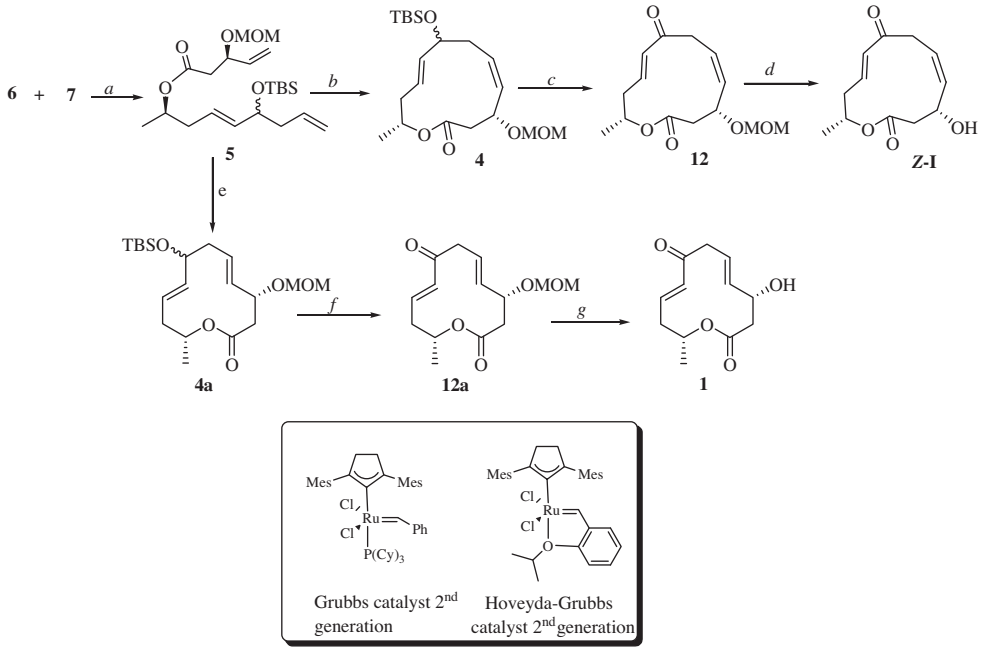


Scheme 2. Reagents and conditions: (a) (i) IBX, DMSO, EtOAc, rt, 3 h, 85%; (ii) Zn, allylbromide, THF, satd. NH_4Cl, 0 °C to rt, 12 h, 85%; (iii) TBS-Cl, imidazole, cat. DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 95%, (b) DDQ, CH_2Cl_2:H_2O (18:1), 0 °C to rt, 1 h, 80%.

Having the requisite fragments **6** and **7** in hand, esterification (DCC/DMAP/CH_2Cl_2/0 °C to rt, Scheme 4) between them furnished ester **5** (79%). Next, the crucial RCM of ester **5** (G-II/CH_2Cl_2/reflux/12 h) resulted in chromatographically inseparable diastereomeric macrolides **4** (1:1 ratio in 75% combined yield), epimeric at C8 center as a single geometric isomer. However, no efforts were made to separate the isomers because the epimeric carbon eventually transforms into a ketone functionality in further steps. Thus, the epimeric mixture of macrolides **4** on desilylation (TBAF/THF/0 °C to rt/2 h) followed by oxidation (Dess–Martin periodinane/CH_2Cl_2/0 °C to rt/2 h) gave macrocylic vinyl ketone **12** (82%), which on further deprotection (PMB-silica/neat/rt/0.5 h) of MOM-group gave the presumable target macrolide in 95% yield as an exclusive geometric isomer. This compound was characterized from its spectral data.[9] The spectral data of the synthetic sample did not match with the reported one. For instance, its ^1H NMR spectrum revealed the characteristic allylic olefinic proton (H4) appearing at δ 4.35–4.27 ppm as a multiplet and H5 proton and H6 appearing at δ 5.53–5.47 as a multiplet, while the same proton (H4) reportedly resonated at δ 4.54 ppm as a multiplet and H5 proton at δ 5.73 as a dd (J = 15.9, 2.8 Hz) and H6 at δ 5.75 as a multiplet. The ^{13}C NMR spectrum too revealed certain discrepancies: for instance C4 appeared at



Scheme 3. Reagents and conditions: (a) MOM-Cl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h, 90%, (b) (i) TBAF, THF, 0 °C to rt, 2 h, 91%; (ii) TEMPO, BAIB, CH_2Cl_2: H_2O (1:1), 0 °C to rt, 2 h, 91%.



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h, 79%, (b) G-II (10 mol %), CH_2Cl_2, reflux, 12 h; 75%, (c) (i) TBAF, THF, 0 °C to rt, 2 h, 80%; (ii) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h, 82%, (d) PMB-silica, neat, 0.5 h, 95%, (e) HG-II (10 mol %), toluene, reflux, 12 h, 70%, (f) (i) TBAF, THF, 0 °C to rt, 2 h, 82%; (ii) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h, 83%, (g) PMB-silica, neat, 0.5 h, 93%.

δ 71.5 ppm in contrast to the reported value at δ 69.1 ppm while C6 appeared at δ 128.6 ppm instead of at δ 125.2 ppm. Also, the specific rotation value did not match with the reported value {$[\alpha]_D^{25}$ +195.2 (*c* 0.25, MeOH); Lit.[4] $[\alpha]_D^{25}$ +135.2 (*c* 0.35, MeOH)}. Based on the above data, the geometry of the newly formed double bond was tentatively assigned as *Z* and the compound was christened as *Z*-**1**.[9]

Hence, ester **5** on RCM under Hoveyda-Grubbs II conditions (Scheme 4, conditions e[10]) gave a mixture of separable macrolides **4** and **4a** (1:3 ratio, 70% combined yield) as respective epimers. Each macrolide set was separated and characterized independently.[9] The less polar minor macrolide set was found to have comparable data with the macrolide-**4** that was obtained earlier under G-II conditions and matched when a co-tlc was run. Since macrolide **4** was already shown to afford isomeric target molecule (*Z*-**1**), it was decided that the rest of the synthetic sequence be carried out on macrolide **4a**. Thus, compound **4a,** which was thought to be different due to its *E*-geometry around the newly formed double bond, was taken up next. Accordingly, epimeric mixture of macrolide **4a** on desilylation (TBAF/THF/0 °C to rt/2 h) followed by oxidation (Dess–Martin periodinane/CH_2Cl_2/0 °C to rt/2 h) furnished macrocylic vinyl ketone **12a** (83%), which on further deprotection of MOM-group, under similar conditions as mentioned above, gave balticolid **1** (93%). Compound **1** was characterized by its spectral data. The spectral data of the synthetic sample matched with the reported data and hence assigned as **1**.[4,9] For instance, the ^{1}H NMR spectrum of **1** revealed the characteristic the allylic olefinic proton (C4) at δ 4.50 ppm as a broad singlet and C5 proton and C6 appearing at δ 5.74–5.65 as a multiplet. The ^{13}C NMR spectrum of **1** displayed C4 at δ 69.0 ppm while C6 appeared at δ 125.1 ppm. The specific rotation was found to be $[\alpha]_D^{25}$ +141.2 (*c* 0.38, MeOH) {Lit.[4] $[\alpha]_D^{25}$ +135.2 (*c* 0.35, MeOH)}. HRMS spectrum of **1** displayed the $[M+Na]^+$ at 247.0934 while calculated gave 247.0940 for the molecular formula $C_{21}H_{26}O_3Na$ as an additional support.

In summary, synthesis of balticolid **1** was accomplished via Hoveyda-Grubbs II catalyst assisted RCM of ester **5** in good yields and selectivity. The key intermediates **6** and **7** were accessed from common and inexpensive starting materials. Alongside, isomeric balticolid *Z*-**1** was also synthesized.

Acknowledgments

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9. *Spectral data of some selected compounds*. *Compound* ***11***: Pale yellow liquid. $[\alpha]_D^{25}$ +141.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71–5.64 (m, 1H), 5.22–5.10 (m, 2H), 4.66 (d, 1H, *J* = 7.0 Hz), 4.50 (d, 1H, *J* = 6.5 Hz), 4.14 (q, 1H, *J* = 7.0 Hz), 3.73–3.63 (m, 2H), 3.34 (br s, 3H), 1.84–1.76 (m, 1H), 1.70–1.64 (m, 1H), 0.89 (br s, 9H), 0.04 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 117.0, 93.8, 74.2, 59.2, 55.3, 38.2, 25.8, −5.3; HRMS: *m*/*z* calcd for $C_{13}H_{28}O_3NaSi$ $[M+Na]^+$: 283.1699; found: 283.1704. *Compound* ***7***: Pale yellow liquid. $[\alpha]_D^{25}$ +193.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77–5.63 (m, 1H), 5.34–5.22 (m, 2H), 4.65 (d, 1H, *J* = 6.7 Hz), 4.54–4.44 (m, 2H), 3.33 (br s, 3H), 2.70–2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 136.3, 118.3, 93.9, 73.5, 55.5, 40.7; HRMS: *m*/*z* calcd for $C_7H_{12}O_4Na$ $[M+Na]^+$: 183.0627; found: 183.0631. *Compound* ***9***: Colorless liquid. $[\alpha]_D^{25}$ −11.76 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2H, *J* = 8.3 Hz), 6.79 (d, 2H, *J* = 8.3 Hz), 5.80–5.60 (m, 1H), 5.59–5.40 (m, 2H), 5.02–4.96 (m, 2H), 4.40 (dd, 2H, *J* = 18.8, 11.3 Hz), 4.06 (q, 1H, *J* = 12.0, 6.0 Hz), 3.78 (br s, 3H), 3.54–3.46 (m, 1H), 2.38–2.09 (m, 4H), 1.13 (d, 3H, *J* = 6.0 Hz), 0.87 (br s, 9H), 0.02 (d, 6H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 135.3, 135.1, 130.9, 129.0, 126.3, 116.5, 113.6, 74.3, 73.2, 69.9, 55.1, 43.0, 39.1, 39.0, 25.8, 19.4, 18.2, −4.7, −4.2; HRMS: *m*/*z* calcd for $C_{23}H_{38}O_3NaSi$ $[M+Na]^+$: 413.2482; found: 413.2491. *Compound* ***6***: Yellow oil. $[\alpha]_D^{25}$ −3.07 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82–5.68 (m, 1H), 5.59–5.46 (m, 2H), 5.01 (br d, *J* = 15.5 Hz), 4.16–4.09 (m, 1H), 3.80–3.73 (m, 1H), 2.29–2.16 (m, 3H), 2.16–2.05 (m, 1H), 1.17 (d, 3H, *J* = 6.0 Hz), 0.89 (s, 9H), 0.03 (d, 6H, *J* = 11.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 134.9, 125.9, 116.8, 72.7, 66.9, 43.0, 41.9, 25.7, 22.5, 18.1, −4.8; HRMS: *m*/*z* calcd for $C_{15}H_{30}O_2NaSi$ $[M+Na]^+$: 293.1907; found: 293.1910. *Compound* ***5***: Yellow oil. $[\alpha]_D^{25}$ +138.2 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76–5.64 (m, 2H), 5.48–5.45 (m, 2H), 5.30 (d, 1H, *J* = 17.1 Hz), 5.19 (d, 1H, *J* = 9.9 Hz), 5.01–4.98 (m, 2H), 4.92–4.86 (m, 1H), 4.63 (d, 1H, *J* = 6.6 Hz), 4.50 (d, 1H, *J* = 6.6 Hz), 4.43 (m, 1H), 4.08–4.07 (m, 1H), 3.80 (br s, 3H), 2.60–2.54 (m, 1H), 2.42–2.38 (m, 1H), 2.31–2.16 (m, 3H), 1.19 (d, 3H, *J* = 6.0 Hz), 0.87 (br s, 9H), 0.01 (d, 6H, *J* = 12.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 136.8, 134.9, 124.7, 117.9, 116.7, 94.1, 73.9, 72.9, 70.6, 60.3, 55.5, 43.0, 41.1, 38.4, 29.6, 25.8, 20.9, 19.3, 18.2, 14.1, −4.7; HRMS: *m*/*z* calcd for $C_{22}H_{40}O_5NaSi$ $[M+Na]^+$: 435.2548; found: 435.2675. *Compound* ***4***: Pale yellow liquid. $[\alpha]_D^{25}$ +202.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.44–5.36 (m, 1H), 5.21–5.12 (m, 4H), 4.69 (d, 1H, *J* = 6.4 Hz), 4.52 (d, 1H, *J* = 6.4 Hz), 4.36–4.29 (m, 1H), 4.01–3.94 (m, 1H), 3.35 (s, 3H), 2.72 (dd, 1H, *J* = 12.8, 3.9 Hz), 2.48–2.38 (m, 2H), 1.23 (d, 3H, *J* = 6.4 Hz), 0.86 (s, 9H), 0.02 (d, 6H, *J* = 10.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.8, 135.8, 132.0, 128.1, 93.4, 74.6, 73.9, 68.6, 55.4, 42.0, 40.7, 25.8, 20.7, −4.3; HRMS: *m*/*z* calcd for $C_{20}H_{36}O_5NaSi$ $[M+Na]^+$: 407.2224; found: 407.2231. Compound **4a**: Yellow oil. $[\alpha]_D^{25}$ + 171.9 (*c* 0.17, $CHCl_3$); ^{1}H NMR (75 MHz, $CDCl_3$): δ 5.67–5.53 (m, 1H), 5.39–5.12 (m, 3H), 5.09–5.00 (m, 1H), 4.69 (br s, 2H), 4.44–4.36(m, 1H), 4.19–4.10 (m, 1H), 3.41 (s, 3H), 2.75–2.63 (m, 1H), 2.56 (dd, 1H, *J* = 13.7, 3.5 Hz), 2.48–2.30 (m, 2H), 2.24–2.05 (m, 2H), 1.24 (d, 3H *J* = 7.9 Hz), 0.89 (s, 9H), 0.04 (d, 6H, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 143.0, 136.0, 131.1, 128.3, 126.4, 94.3, 72.8, 71.9, 69.4, 55.4, 41.1, 40.4, 39.1, 25.8, 20.2, 18.2, −4.5; HRMS: *m*/*z* calcd for $C_{20}H_{36}O_5NaSi$ $[M+Na]^+$: 407.2224; found: 407.2221. *Compound* ***12***: Yellow oil. $[\alpha]_D^{25}$ +130.6 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59–6.53 (m, 1H), 5.94 (d, 1H, *J* = 16.1 Hz), 5.72–5.66 (m, 1H), 5.45–5.34 (m, 1H), 5.24–5.17 (m, 1H), 4.66 (d, 1H, *J* = 6.4 Hz), 4.52 (d, 1H, *J* = 6.8 Hz), 4.41–4.36 (m, 1H), 3.38–3.30 (m, 4H), 3.18 (dd, 1H, *J* = 13.7, 4.0 Hz), 2.82 (dd, 1H, *J* = 12.5, 4.0 Hz), 2.47 (br t, 1H, *J* = 12.1 Hz), 2.39–2.28 (m, 2H), 1.30 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 169.3, 144.6, 134.0, 131.9, 129.9, 93.7, 74.4, 69.6, 55.3, 45.1, 41.9, 38.7, 20.8; HRMS: *m*/*z* calcd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1208; found: 291.1202. *Compound* ***12a***: Pale yellow oil. $[\alpha]_D^{25}$ +110.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67–6.56 (m, 1H), 5.91 (d, 1H, *J* = 16.2 Hz), 5.87–5.77 (m, 1H), 5.48 (dd, 1H, *J* = 15.8, 4.9 Hz), 5.14–5.03 (m, 1H), 4.68 (dd, 2H, *J* = 14.5, 6.9 Hz), 4.47–4.45 (m, 1H), 3.40 (br s, 3H), 3.26 (d, 2H, *J* = 6.6 Hz), 2.76 (dd, 1H, *J* = 13.4, 4.5 Hz), 2.52 (dd, 1H, *J* = 13.4, 3.9 Hz), 2.49–2.28 (m, 1H), 1.30 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 169.1, 144.9, 134.0, 131.9, 126.0, 122.1, 94.5, 71.8, 55.5, 51.9, 50.8, 50.6, 40.8, 38.4, 20.5; HRMS: *m*/*z* calcd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1208; found: 291.1199. *Balticolid Z-***1**: Yellow oil. $[\alpha]_D^{25}$ +195.0 (*c* 0.25, MeOH); ^{1}H NMR (75 MHz, CD_3OD): δ 6.60 (m, 1H), 5.87 (d, 1H, *J* = 16.2 Hz), 5.53–5.47 (m, 2H), 5.09 (m, 1H), 4.28 (m, 1H), 3.36–3.29 (m, 1H), 3.0 (dd, 1H, *J* = 14.3, 3.3 Hz), 2.63 (dd, 1H, *J* = 12.4, 4.7 Hz), 2.40–2.17 (m, 3H), 1.21 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 202.0, 171.8, 147.5, 138.1, 132.8, 128.6, 72.1, 71.5, 45.9, 44.8, 39.7, 21.1; HRMS: *m*/*z* calcd for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0940; found: 247.0948. *Balticolid* ***1***: Pale yellow oil. $[\alpha]_D^{25}$ +142.5 (*c* 0.38, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 6.76–6.68 (m, 1H), 5.95 (d, 1H, *J* = 16.3 Hz), 5.74–5.64 (m, 2H), 5.11–5.03 (m, 1H), 4.50–4.49 (m, 1H), 3.37 (dd,1H, *J* = 13.2, 6.6 Hz), 3.19–3.15 (m, 1H), 2.63 (dd, 1H, *J* = 13.5, 4.6 Hz), 2.58 (dd, 1H, *J* = 13.2, 3.4 Hz), 2.50–2.45 (m, 1H), 2.36–2.28 (m, 1H), 1.28 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 202.5, 171.8, 148.0, 138.2, 132.6, 125.0, 72.0, 69.0, 45.6, 43.2, 39.5, 21.0; HRMS: *m*/*z* calcd for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0940; found: 247.0934.
10. The authors are thankful to the referees for asking us to describe all the RCM reactions performed. The set of RCM reactions used are as follows: firstly the RCM of compound **5** was conducted in reflux methylene chloride under G-II catalyst which resulted in macrocyle as an exclusive *Z*-isomer with complete consumption of starting material. Next, in order to check if temperature plays a role in altering the double bond geometry, the same reaction was conducted in reflux toluene. Yet, the macrocycle obtained was again *Z*-isomer. Hence, when the RCM was performed with Hoveyda-Grubbs II catalyst in reflux methylene chloride, two macrocyclic products (*Z*:*E* = 1:1 based on tlc) were formed though no complete conversion of the started material **5** was observed. However, for the same reaction when conducted at elevated temperature in toluene, complete conversion was observed to result in macrocylic products with altered geometric ratio in favor of *E*-isomer (*Z*:*E* = 1:3 based on tlc). It maybe deduced that while the conversion (RCM under HG-II conditions) was dependent on temperature, the double bond geometry was dependent both on the catalyst and the temperature.