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Formal total synthesis of borrelidin: synthesis of C1–C11 fragment via desymmetrization strategy

J. S. Yadav *, Padmavani Bezawada, Venugopal Chenna

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A stereoselective formal total synthesis of borrelidin is described. The synthetic strategy for synthesis of C1–C11 fragment features desymmetrization of Diels–Alder adduct, Sharpless asymmetric epoxidation, regioselective opening of chiral epoxide, and alkylation using Evans chiral auxiliary.

Borrelidin **(1)**, a structurally unique 18-membered macrolide antibiotic possessing *anti-Borrelia* activity was first isolated from *Streptomyces rochei* in 1949 by Berger et al.[1] First planar structure was proposed by Keller-Schierlein in 1967,[2] and X-ray crystallographic studies by Anderson et al. revealed its absolute structure.[3] It has reduced polypropionate moiety with four methyl groups possessing a distinctive *syn/syn/anti* relationship, a *Z/E* cyanodiene unit at C12–C15, and a cyclopentane carboxylic acid subunit at C17. Borrelidin possesses antiviral,[4] antibacterial activity,[1,5] in addition to anti-angiogenesis effects[6] and is found to display inhibitory activity toward cyclin-dependent kinase Cdc28/Cln2 of *Saccharomyces cerevisiae*.[7] Interesting biological activity and complex structural feature of borrelidin attracted many synthetic chemists which resulted in first total synthesis by Morken and co-workers,[8] followed by efforts from various other groups for the total synthesis through synthetic[9–11] and biosynthetic pathways.[12]

Our ongoing research on the synthesis of biologically active molecules by desymmetrization strategy, and the fascinating biological activity of borrelidin encouraged us to select this molecule as a target for total synthesis. We herein report the synthesis of C1–C11 fragment of borrelidin **1**.

The retrosynthetic plan for the borrelidin **1** was similar to the Satoshi Omura's approach[10] in which borrelidin **1** could be easily obtained from the carboxylic acid compound **3** and the alcohol **4**. Compound **3** would be synthesized from compound **5** by simple reduction and oxidation reactions, which in turn could be obtained from compound **6** by extending two carbons using Wittig reaction and stereoselective Evans alkylation. Compound **6** is obtained by stereoselective opening of epoxide **7**, which in turn could be obtained from compound **8**. Compound **8** is accessible from the known precursor **9** (Scheme 1).

Our synthesis started with the precursor **9**, which was prepared earlier in our group and utilized to make several natural products.[15] Compound **9** was hydroformylated, further protected as methanesulfonate, and treated with DBU to get olefin **10**.[16] The olefin **10** was stereoselectively reduced to obtain compound **11**, which on further reductive ring opening with DIBAL-H yielded compound **12**. Protection of 1,3-diol as acetonide and deprotection of benzyl group provided compound **13**, which was selectively protected as monobenzyl ether and the secondary hydroxyl group was converted into the xanthate ester and reduced to obtain compound **14**. Deprotection of acetonide and selective primary hydroxyl protection with TBDPS–Cl yielded compound **8** (Scheme 2).

Compound **8** was converted to xanthate ester, further reduced to provide compound **15**, which was subjected to debenzylation followed by oxidation and further extension of two carbon units by a C2 Wittig reaction yielded compound **16**. The ester was reduced to alcohol and subjected to Sharpless asymmetric epoxidation[13] to obtain compound **7**. Protection of hydroxyl group followed by reductive opening of epoxide afforded compound **17**. The resulting hydroxyl group was protected with TBDMS–Cl and TBDPS group was selectively deprotected using NH_4F and MeOH[17] to afford compound **6** (Scheme 3).

Compound **6** was oxidized to aldehyde, and subjected to Wittig reaction to obtain compound **18**. The resulting olefin was selectively hydrogenated using $NiCl_4$ and $NaBH_4$[18] and then the ester was hydrolyzed in basic conditions to yield compound **19**. The acid

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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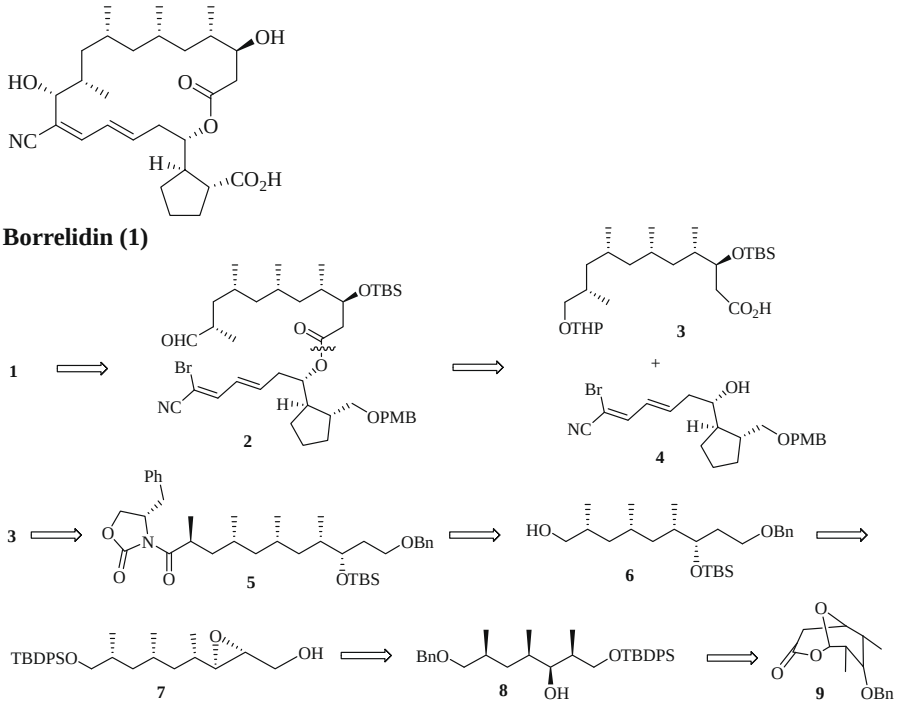
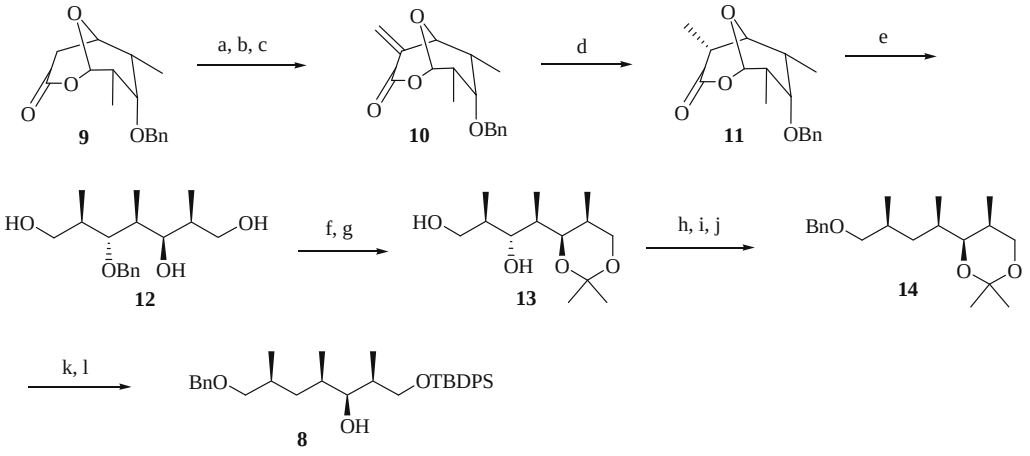
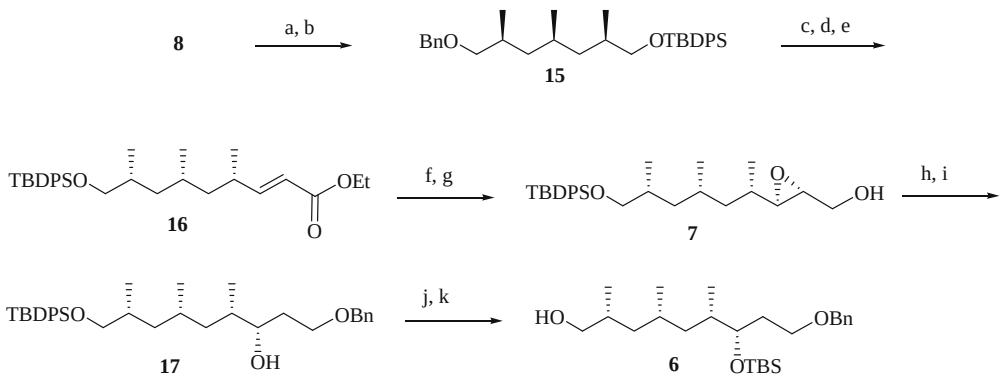


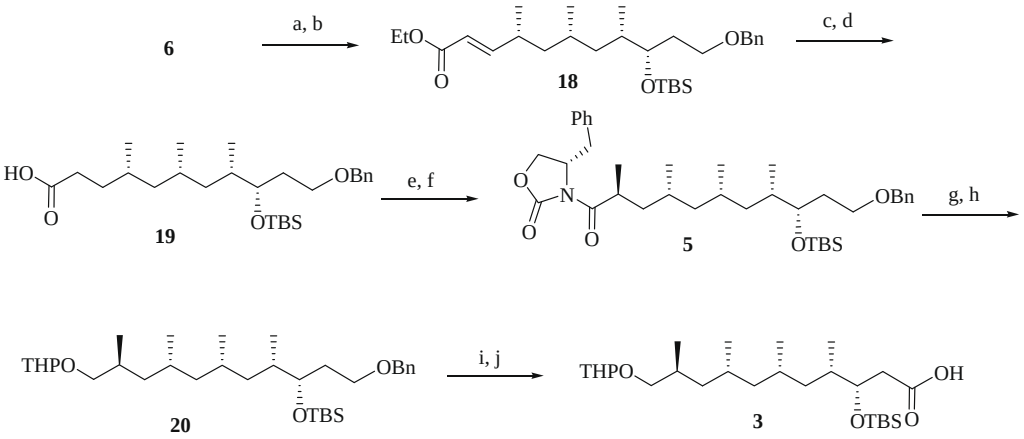
Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) LDA, paraformaldehyde, THF, −78 °C; (b) MsCl, Et_3N, DCM, 0 °C–rt; (c) DBU, DCM, rt, 60% (three steps); (d) H_2, 10%, Pd–C, Na_2CO_3, EtOAc, rt, 95%; (e) DIBAL-H, DCM, rt, 85%; (f) 2,2-DMP, acetone, PTSA, rt; (g) Li, Naphthalene, −23 °C, 65% (two steps); (h) NaH, BnBr, THF, 0 °C; (i) NaH, CS_2, MeI, THF; (j) Bu_3SnH, cat. AIBN, toluene, reflux, 77% (three steps); (k) cat. PTSA, MeOH; (l) TBDPS–Cl, imidazole, DCM, rt, 79% (two steps).



Scheme 3. Reagents and conditions: (a) NaH, CS_2, MeI, THF; (b) Bu_3SnH, cat. AIBN, toluene, reflux, 83% (two steps); (c) Li, Naphthalene, −23 °C; (d) IBX, DMSO, THF, rt; (e) $Ph_3P{=}CHCOOEt$, benzene, rt, 80% (three steps); (f) DIBAL-H, DCM, rt; (g) (−)-DIPT, TBHP, titanium isopropoxide, DCM, 80% (two steps); (h) Red-Al, THF, 0 °C; (i) NaH, BnBr, THF, 0 °C, 73% (two steps); (j) TBSOTf, 2,6-lutidine, DCM, 0 °C; (k) NH_4F, MeOH, rt, 78% (two steps).



Scheme 4. Reagents and conditions: (a) IBX, DMSO, THF, rt; (b) $Ph_3P{=}CHCOOEt$, benzene, rt, 95% (two steps); (c) $NaBH_4$, $NiCl_4$, MeOH; (d) LiOH, MeOH, H_2O, THF (1:1:1), 0 °C 78% (two steps); (e) Et_3N, Piv-Cl, THF, then (*S*)-4-benzyl-2-oxazolidinone, LiCl; (f) NaHMDS, MeI, THF, −78 °C, 59% (two steps); (g) $NaBH_4$, MeOH; (h) 3,4-dihydropyran, cat. PTSA, DCM, 72% (two steps); (i) Li, naphthalene, THF, −23 °C; (j) BAIB, TEMPO, acetone, water (8:2), 55% (two steps).

group was activated by forming mixed anhydride, coupled to Evans chiral oxazolidinone and stereoselectively methylated to obtain compound **5**.[14] Compound **5** was reduced to alcohol and was protected as THP ether to provide compound **20**. Li-Naphthalene mediated deprotection of benzyl group yielded free alcohol, which was smoothly oxidized by using TEMPO, BAIB[19] to obtain the final compound **3**. Analytical data were compared and found to be identical with those of the reported compound[10] (Scheme 4). All the important compounds were characterized by their spectral data. [20–26]

In conclusion we have completed the synthesis of C1–C11 fragment of borrelidin, all the stereogenic centers were obtained through desymmetrization strategy, Sharpless asymmetric epoxidation, regioselective opening of chiral epoxide and stereoselective alkylation using Evan's chiral auxiliary.

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20. *Analytical data for compound* ***11***: Colorless oil; $[\alpha]_D^{25}$ −78.44 (*c* 0.5, $CHCl_3$). IR (KBr): 2926, 1742, 1452, 1387, 1200, 1069, 970 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.21 (m, 5H), 5.37 (d, *J* = 2.3 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.03 (dd, *J* = 4.4, 6.5 Hz, 1H), 3.62-3.58 (m, 1H), 3.04 (q, *J* = 7.2, 14.5 Hz, 1H), 2.40-2.29 (m, 1H), 2.07-1.96 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 137.9, 128.6, 128.5, 128.0, 100.9, 80.0, 77.8, 74.8, 41.6, 41.0, 40.3, 15.3, 13.6, 12.6. MS (ESI): *m/z* 313.1 $(M+Na)^+$. HRMS (ESI): calcd for $C_{17}H_{22}O_4Na$: 313.1415. Found: 313.1411.
21. *Analytical data for compound* ***8***: Viscous liquid; $[\alpha]_D^{25}$ +10.8 (*c* 1.9, $CHCl_3$). IR (KBr): 3452, 2957, 2926, 2856, 1639, 1458, 1427, 1368, 1107, 1022, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.71–7.59 (m, 4H), 7.48–7.21 (m, 11H), 4.47 (s, 2H), 3.76–3.56 (m, 2H), 3.54–3.43 (m, 1H), 3.39–3.28 (m, 1H), 3.26–3.14 (m, 1H), 2.15 (br s, 1H), 1.96–1.53 (m, 3H), 1.49–1.33 (m, 1H), 1.05 (s, 9H), 1.0–0.77 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 135.9, 135.8, 133.5, 133.3, 130.0, 129.9, 128.5, 127.9, 127.7, 127.6, 96.3, 75.4, 73.3, 68.8, 37.9, 37.1, 33.7, 31.1, 27.1, 19.4, 19.1, 15.9, 11.1. MS (ESI): *m/z* 541.0 $(M+Na)^+$. HRMS (ESI): calcd for $C_{33}H_{46}O_3$ Na Si: 541.3113. Found : 541.3100.
22. *Analytical data for compound* **7**: Colorless oil; $[\alpha]_D^{25}$ +17.7 (*c* 0.6, $CHCl_3$). IR (KBr): 3441, 2958, 2928, 2859, 1724, 1466, 1428, 1382, 1108, 823, 740, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.59 (m, 4H), 7.43–7.30 (m, 6H), 3.81–3.71 (m, 1H), 3.55–3.43 (m, 2H), 3.33–3.42 (m, 1H), 2.89–2.83 (m, 1H), 2.62–2.53 (m, 1H), 1.78–1.62 (m, 1H), 1.58–1.39 (m, 4H), 1.38–1.22 (m, 3H), 1.05 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 134.0, 129.5, 127.5, 68.8, 61.8, 60.6, 58.4, 41.3, 41.3, 33.1, 32.7, 27.6, 26.8, 20.7, 19.2, 18.0, 17.7. MS (ESI): *m/z* 477.0 $(M+Na)^+$. HRMS (ESI): calcd for $C_{28}H_{42}O_3NaSi$: 477.2800. Found: 477.2819.
23. *Analytical data for compound* ***6***: Colorless liquid; $[\alpha]_D^{25}$ −21.0 (*c* 2.4, $CHCl_3$). IR (KBr): 3417, 2954, 2927, 2856, 1720, 1460, 1373, 1252, 1080, 1042, 835, 773, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.25 (m, 5H), 4.49 (ABq, *J* = 11.8, 17.7 Hz, 2H), 3.73–3.65 (m, 1H), 3.60–3.43 (m, 3H), 3.33 (dd, *J* = 6.9, 10.5 Hz, 1H), 1.82–1.48 (m, 5H), 1.47–1.21 (m, 2H), 0.98–0.77 (m, 20H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 134.8, 129.6, 128.3, 127.6, 127.4, 72.9, 67.8, 67.6, 40.9, 40.2, 35.6, 33.3, 33.1, 29.7, 28.0, 26.5, 25.9, 21.3, 18.1, 15.5, -4.25, -4.44. MS (ESI): *m/z* 445.0 $(M+Na)^+$. HRMS (ESI) : calcd for $C_{25}H_{46}O_3NaSi$: 445.3113. Found: 445.3103.
24. *Analytical data for compound* **18**: Viscous liquid; $[\alpha]_D^{25}$ −21.1 (*c* 1.0, $CHCl_3$). IR (KBr): 3447, 2956, 2923, 2853, 1720, 1649, 1461, 1368, 1254, 1217, 1091, 1042, 835, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.24 (m, 5H), 6.76 (dd, *J* = 8.6, 15.6 Hz, 1H), 5.78 (d, *J* = 15.4 Hz, 1H), 4.48 (ABq, *J* = 11.8, 17.7 Hz, 2H), 4.18 (q, *J* = 7.1, 14.3 Hz, 2H), 3.73–3.63 (m, 1H), 3.55–3.44 (m, 2H), 2.51–2.33

(m, 1H), 1.80–1.53 (m, 4H), 1.50–1.32 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 0.97–0.82 (m, 14H), 0.78 (d, J = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 154.3, 138.5, 128.3, 127.6, 127.4, 119.9, 72.9, 72.6, 67.5, 60.1, 43.3, 40.1, 35.3, 34.3, 32.2, 29.6, 27.9, 25.9, 20.9, 20.3, 18.0, 15.2, 14.2, −4.30, −4.49. MS (ESI): m/z 491.1 $(M+H)^+$. HRMS (ESI): calcd for $C_{29}H_{50}O_4NaSi$: 513.3376. Found: 513.3397.

25. *Analytical data for compound* **5**: Colorless liquid; $[\alpha]_D^{25}$ +9.3 (c 1.7, $CHCl_3$). IR (KBr): 3448, 2956, 2925, 2854, 1782, 1636, 1457, 1383, 1212, 1099, 835, 770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.17 (m, 10H), 4.74–4.60 (m, 1H), 4.48 (ABq, J = 11.8, 17.3 Hz, 2H), 4.23–4.10 (m, 2H), 3.87–3.73 (m, 1H), 3.71–3.62 (m, 1H), 3.54–3.43 (m, 2H), 3.30–3.18 (m, 1H), 2.76 (dd, J = 9.6, 13.2 Hz, 1H), 1.80–1.43 (m, 6H), 1.38–1.14 (m, 8H), 0.96–0.76 (m, 18H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 152.9, 138.5, 135.3, 129.4, 128.8, 128.2, 127.6, 127.4, 127.2, 72.9, 67.6, 65.9, 55.4, 45.1, 40.2, 39.4, 37.8, 35.4, 33.3, 29.6, 27.6, 26.3, 25.9, 20.9, 20.4, 18.1, 16.5, 15.4, −4.25, −4.45. MS (ESI): m/z 660.0 $(M+Na)^+$. HRMS (ESI): calcd for $C_{38}H_{59}NNaO_5Si$: 660.4055. Found: 660.4066.

26. *Analytical data for compound* **3**: Colorless oil; $[\alpha]_D^{25}$ −29.1 (c 0.6, $CHCl_3$). IR (KBr): 2954, 2926, 2855, 1738, 1711, 1462, 1379, 1254, 1077, 1032, 835, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (m, 1H), 4.04 (m, 1H), 3.86 (m, 1H), 3.51 (m, 2H), 3.16 (m, 1H), 2.46 (d, J = 6.04 Hz, 2H), 1.89–1.33 (m, 11H), 0.95–0.78 (m, 26H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 99.1, 98.6, 74.0, 73.7, 72.8, 62.2, 62.0, 45.6, 40.7, 40.2, 39.0, 35.9, 30.9, 30.8, 30.7, 27.5, 27.3, 27.2, 25.8, 25.5, 21.0, 20.9, 20.7, 19.6, 19.4, 18.0, 16.7, 16.6, 15.2, −4.5, −4.6. MS (ESI, nagative mode): m/z 471.1 $(M-H)^+$; MS (ESI): m/z 495.0 $(M+Na)^+$. HRMS (ESI): calcd for $C_{26}H_{52}NaO_5Si$: 495.3476. Found: 495.3486.