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# A cross metathesis strategy for the synthesis of highly functionalized conjugated cyanodienes: synthesis of the C3–C17 framework of (−)-borrelidin ☆

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**Abstract**

A cross metathesis strategy for the synthesis of highly functionalized conjugated cyanodienes was developed and was successfully applied in the synthesis of the C3–C17 framework of (−)-borrelidin.


*Keywords:* Borrelidin; Cross metathesis; Grubbs' catalyst

Borrelidin (**1**) is a naturally occurring nitrile produced by several *Streptomycete* species and was first isolated by Jampolsky and Goldberg.[1] Structure elucidation showed it to be an 18-membered macrolide distinguished by a 1,3,5,7-'skipped' methylene chain (C4–C10), a cyclopentane carboxylic acid fragment and a conjugated cyanodiene unit.[2,3] Borrelidin has anti-malarial,[4] antiviral, and antibacterial activity,[5] and anti-angiogenesis effects.[6] The efforts toward the total synthesis[7] of this unique macrolide resulted in the first total synthesis by Morken and co-workers.[8] Subsequently, various other groups attempted the total synthesis through synthetic[9–11] and biosynthetic pathways.[12] Wilkinson et al. prepared a set of novel borrelidin analogs by precursor-directed biosynthesis and showed the importance of the nitrile group at C12 for the anticancer activity of borrelidin.[13] In our endeavors[14] toward the total synthesis of borrelidin, we were interested in exploiting a unique conjugated cyanodiene synthon to prepare simpler and diverse analogs of borrelidin and envisioned a cross metathesis strategy for the construction of the final macrolide (Fig. 1).

Although cross metathesis of conjugated diene esters and amides has been reported,[15] the cyano group, in contrast, has chemistry of its own and behaves differently in metathesis reactions perhaps because of its small size and high electronegativity.[16] Hence, we chose to validate our strategy in appropriate models and here we report the cross metathesis of 2-bromohexa-2,4-dienenitrile with a set of

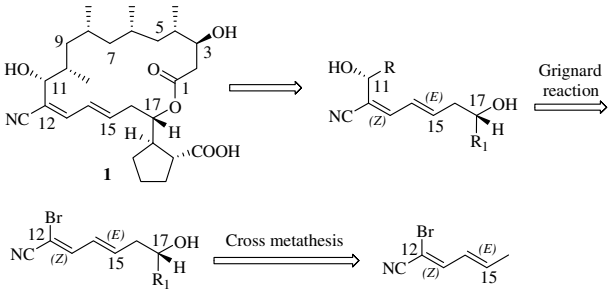


Fig. 1.

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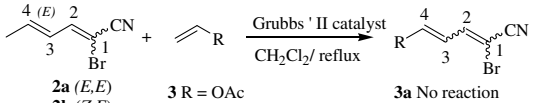
diverse alkenes and further apply this strategy for the construction of the C3–C17 framework of borrelidin.

Our journey started with cyanodiene **2** synthesized as a mixture of isomers **2a** and **2b**.[14] Studies began with the cyanodiene **2a** (*E*,*E*) and vinyl acetate **3** (Scheme 1). A reaction mixture containing **2a**, vinyl acetate, and Grubbs' catalyst I was refluxed in dichloromethane, but no reaction occurred and the starting partners were recovered. The more active Grubbs' II catalyst also did not yield the required products. Next we carried out the reaction with methyl acrylate **4** under similar conditions. The reaction was sluggish and the required product **4a** was formed in a low yield. Nevertheless, excellent *E* selectivity at the newly formed alkene along with strict retention of the adjacent *E* alkene encouraged us to pursue this route further (Scheme 1; **4a**). The cyano and the bromo groups were sufficiently deactivating and in combination with Grubbs' catalyst II, the α,β-double bond was more deactivated relative to the γ,δ-double bond to give the single product **4a**. This finding encouraged us to perform a series of reactions to define the scope of the cross metathesis reaction (Scheme 1; products **5a**–**12a**). All the reactions proceeded chemoselectively with a series of olefins under standard reaction conditions. With this impetus we next performed the metathesis reactions with the same set of alkene partners on the *Z*,*E* isomer **2b**, since the double bond geometry of the conjugated cyanodiene fragment in borrelidin is *Z*,*E*. The required products (entries **4b**–**12b**) were obtained again with a high degree of *E* selectivity along with retention of the spectator *Z* alkene. The reactions were generally clean and the yields were moderately good with 40–60% of the unreacted starting material recovered from the reactions and it is noteworthy that all the reactions proceeded with high *E* selectivity in view of the small size of the nitrile group, which is responsible for the *Z* selectivity observed during the cross metathesis of acrylonitrile.[16b]




**2a** (*E*,*E*)
**2b** (*Z*,*E*)

| | |
|---|---|
| **3** R = OAc | **3a** No reaction<br>**3b** No reaction |
| **4** R = $COOCH_3$ | **4a** 4%, >99% *E*<br>**4b** 18%, >99% *E* |
| **5** R = Ph | **5a** 39%, >99% *E*<br>**5b** 66%, >99% *E* |
| **6** R = $(CH_2)_9Br$ | **6a** 38%, >99% *E*<br>**6b** 61%, 12:1 *E*,*Z* |
| **7** R = $(CH_2)_8CHO$ | **7a** 41%, 8.8:1 *E*,*Z*<br>**7b** 46%, 5.2:1 *E*,*Z* |
| **8** R = $C(CH_3)_3$ | **8a** 16%, 4.5:1 *E*,*Z*<br>**8b** 19%, 4:1 *E*,*Z* |
| **9** R = $CH_2CH(OH)CH_3$ | **9a** 58%, 6.5:1 *E*,*Z*<br>**9b** 56%, 4:1 *E*,*Z* |
| **10** R = CHO | **10a** No reaction<br>**10b** No reaction |
| **11** R = CN | **11a** No reaction<br>**11b** No reaction |
| **12** R =  | **12a** 29%, >99% *E*<br>**12b** 29%, >99% *E* |

Scheme 1.

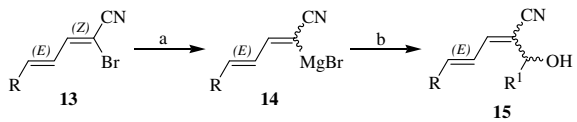
The cross metathesis products from both **2a** and **2b** were single compounds resulting from reaction at C4 and showed tolerance to sensitive functional groups like halogen, aldehyde, and ester as evidenced by the synthesis of compounds **4**, **6**, and **7**, respectively. No reaction occurred with acrylonitrile and acrolein (Scheme 1). Both compounds **2a** and **2b** reacted with the unprotected secondary alcohol **9** to give products **9a** and **9b** in 58% and 56% yield with 6.5:1 and 4:1 selectivity allowing for recovery of the unreacted starting material (Scheme 1; product 9). In general the *E* selectivity with the *E*,*E* isomer **2a** was greater than with the *Z*,*E* isomer **2b**, but the yields for the *Z*,*E* isomer **2b** were higher.

We were interested in further functionalization of these cross metathesis products to arrive at the C11–C17 fragment of borrelidin. Knochel and co-workers showed[17] that the bromo moiety in cyanodiene **13** can participate in the reaction with isopropyl magnesium bromide and the so formed organomagnesium species **14** can react with aldehydes to generate compounds of type **15** (Scheme 2).

We chose to study compound **9b**[18] as it contains features very similar to those of the C11–C17 fragment of borrelidin.

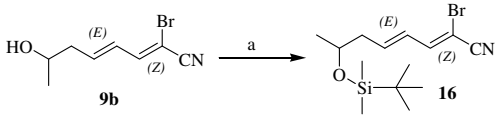
As outlined in Scheme 3, compound **9b** after separation by column chromatography from the minor unwanted *Z*,*Z* isomer was reacted with TBS triflate to give the TBS ether **16** in 88% yield (Scheme 3). This was reacted with **26**, which was an advanced intermediate in our endeavors toward the top C1–C10 part of borrelidin, as the aldehyde component for the model Grignard reaction. The synthesis of **26** is outlined in Scheme 4.

Ketone **19** obtained from the known lactone **17**[19] was subjected to a Wittig reaction with methyltriphenyl phosphonium bromide to afford alkene **20** (Scheme 4). The ester group in compound **20** was reduced with lithium aluminum



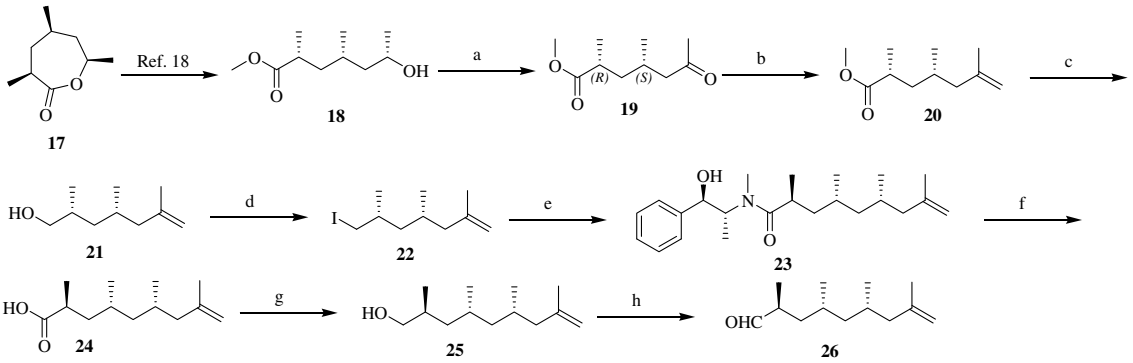

**13** **14** **15**

Scheme 2. Reagents and conditions: (a) *i*-PrMgBr, THF, −40 °C; (b) $R_1$–CHO, rt.



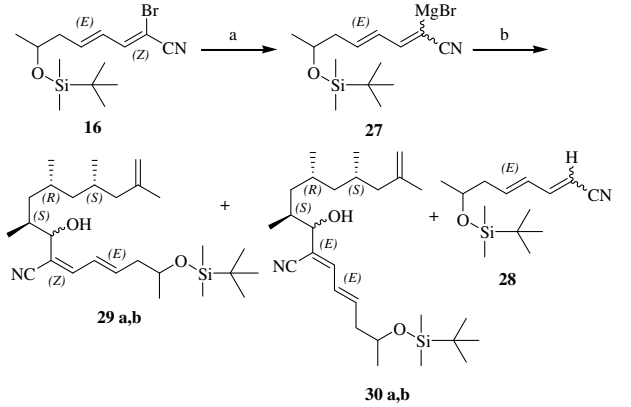

**9b** **16**

Scheme 3. Reagents and conditions: (a) TBS triflate, Hunig's base, $CH_2Cl_2$, 0 °C, 88%.




Scheme 4. Reagents and conditions: (a) $CrO_3$, acetone, rt, 90%; (b) $PPh_3Br$, *n*-BuLi, THF, 0 °C, 66%; (c) $LiAlH_4$, THF, rt, 1 h, 94%; (d) $PPh_3$, $I_2$, imidazole ACN/ether, rt, 2 h, 96%; (e) LDA, LiCl, (1*R*,2*R*)-pseudoephedrine propionamide, rt, 18 h, 88%; (f) 2 N aq NaOH/*t*-BuOH/MeOH, reflux, 28 h, 91%; (g) $LiAlH_4$, THF, rt, 1 h, 94%; (h) Dess–Martin periodanane, $CH_2Cl_2$, rt, 76%.

hydride in THF to give alcohol **21**, which was converted into the corresponding iodo compound **22** using Garreg–Samuelson's method.[20] The iodo product **22** was subjected to a Myer's alkylation with 1*R*,2*R*-(−)-pseudoephedrine propionamide in the presence of LDA and LiCl to give the alkylated product **23** in 88% yield. Compound **23** on base hydrolysis furnished acid **24**, which on reduction with lithium aluminum hydride gave alcohol **25**.[21] Oxidation of the alcohol with Dess–Martin periodanane afforded aldehyde **26** in 76% yield (Scheme 4). With both components **16** and **26** now available, the stage was set for the Grignard reaction. This reaction would give the C3–C17 framework of borrelidin and would serve as an advanced model study and validate this strategy in our quest for the total synthesis of borrelidin. Compound **16** afforded the organomagnesium species **27** upon treatment with *i*-PrMgBr in THF (Scheme 5). In situ addition of a THF solution of aldehyde **26** to the organomagnesium species **27** afforded the de-brominated cyanodiene **28** and four major compounds along with other minor components. A careful chromatography separation gave the two sets of diastereomers, namely *Z*,*E*-**29ab** (9%, 4%) corresponding to the C3–C17 framework of borrelidin and *E*,*E*-**30ab** (6%, 4%), respectively, as colorless oils.[22] Compound **28** accounted for 70% of




Scheme 5. Reagents and conditions: (a) *i*-PrMgBr, THF, −40 °C; (b) **26**, THF, −40 °C, **28** (70%), **29ab** (9%, 4%), **30ab** (6%, 4%).

the total yield and the other minor components were not isolated or characterized due to very low yields and may account for the other four diastereomers possible from the distal stereocenter in **16**.

We initially attributed the formation of the de-halogenated product **28** to moisture in the reaction mixture, but a recent report by Nagamitsu et al. also reported similar observations during a samarium iodide-mediated Reformatsky reaction on the cyanodiene.[23] Lowering the temperature to −40 °C and subsequently to −78 °C did not provide any effective control on the formation of the de-halogenated compound **28** (Scheme 5). No studies to ascertain the stereochemistry at the C-11 hydroxyl center were carried out as we envisioned a strategy wherein the C-11 hydroxyl group would be oxidized to the ketone, and subsequently, reduced stereoselectively back to the hydroxyl after the final macrocyclization.

In summary we have described the first cross metathesis study on both the isomers of a conjugated cyanodiene and demonstrated that this reaction can be employed as a strategy in the synthesis of borrelidin. Apart from excellent chemoselectivity and diastereoselectivity, tolerance to several functional groups such as halogen, aldehyde, and ester was observed. We also demonstrated that the cross metathesis proceeds with a high degree of *E* selectivity in contrast to the *Z* selectivity observed during the cross metathesis of acrylonitrile. Further, we converted the halogen into a Grignard reagent and reacted it with an aldehyde. In this way we have successfully installed the C3–C17 framework of borrelidin. The future efforts of our group will focus on completing the total synthesis of borrelidin and synthesis of simplified analogs and to testing them for anticancer and anti-malarial activities.

## Acknowledgments

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18. *Compound* **9b**: *(2Z,4E)-2-bromo-7-hydroxy-octa-2,4-dienenitrile*: To a solution of 24.6 mg (0.000028 mol, 5 mol %) of Grubbs' catalyst II in 1 mL of $CH_2Cl_2$ were added 100 mg (0.00058 mol) of (2*Z*,4*E*)-2-bromo-hexa-dienenitrile (**2b**) and 99.9 mg (0.0011 mol) of pent-4-en-2-ol, and the solution was stirred at 40 °C for 12 h. After 12 h another 24.6 mg (0.000028 mol, 5 mol %) of Grubbs' catalyst II was added and the reaction was continued for a total of 24 h. The volatiles were removed by rotary evaporation, and the residue was purified by flash chromatography to give 70 mg (56%, 4:1 *E*,*Z*) of compound **9b** as a colorless oil. $[\alpha]_D^{25}$ −6.8 (*c* 0.5, MeOH); IR (neat) 3444, 3408, 2964, 2926, 2854, 2220, 1770, 1712, 1633, 1581, 1454, 1379, 1261, 1103, 1045, 975, 939, 802, 648, 536 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ *Z*,*E* isomer distinct signals: 7.76 (d, $J = 10.2$ Hz, 1H), 6.58 (dt, $J = 7.5$ Hz, 15.0 Hz, 1H), 6.34 (dd, $J = 10.2$ Hz, 15.0 Hz, 1H), 4.64 (br s, 1H), 3.76–3.73 (m, 1H), 2.30–2.26 (m, 2H), 1.06 (d, $J = 6.1$ Hz, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 145.5, 144.5, 128.3, 114.0, 86.0, 66.8, 42.8, 23.2; ESMS *m*/*z* 214 (M−1); HRMS: ($M^+$+H) calcd for $C_8H_{11}BrNO$, 216.0024; found, 216.0020.
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21. *Compound* **25**: *(2S,4R,6S)-2,4,6,8-Tetramethyl-8-nonenol*: To a suspension of 0.080 g (0.00206 mol) of lithium aluminum hydride in 5 mL of dry THF and at 0 °C was added 0.175 g (0.000825 mol) of acid **24** as a solution in THF. The contents were stirred at room temperature for 1 h and quenched with saturated $Na_2SO_4$ and extracted with ethyl acetate. The residue obtained on concentration was purified by column chromatography over 100–200 mesh silica gel. Elution of the column with 40% ether in hexanes gave on concentration and drying 0.155 g (95%) of alcohol **25** as a pale yellow oil. $[\alpha]_D^{25}$ −26.4 (*c* 0.5 $CHCl_3$); IR (neat) 3340, 3073, 2957, 2916, 2871, 1650, 1581, 1461, 1378, 1333, 1080, 1038, 987 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.72 (br s, 1H), 4.64 (br s, 1H), 3.47–3.45 (m, 1H), 3.43–3.39 (m, 1H), 2.04–1.99 (m, 1H), 1.78–1.69 (m, 2H), 1.68 (s, 3H), 1.66–1.60 (m, 1H), 1.29–1.21 (m, 2H), 1.10–1.04 (m, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 6.4$ Hz, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 144.8, 111.3, 69.2, 46.0, 45.8, 40.1, 33.2, 27.7, 27.1, 22.2, 20.0, 19.7, 16.1; ESMS *m*/*z* 216 ($M^+ + NH_4$); HRMS: $(M-H)^+$ calcd for $C_{13}H_{25}O$, 197.1905; found, 197.1888.
22. *Compounds* **29a**,**b** *and* **30a**,**b**: *2-[5-(tert-Butyl-dimethyl-silanyloxy)-hex-2Z,4E-diene]-3-hydroxy-4(S),6(R),8(S),10-tetramethyl-undec-10ene nitrile*: To a solution of 0.127 g (0.000369 mol) of 2-bromo-7-(*tert*-butyl-dimethyl-silanyloxy)-octa-2*Z*,4*E*-diene nitrile 16 in dry tetrahydrofuran was added 0.203 mL (0.000403 mol) of a 2 M solution of isopropyl magnesium bromide in THF at −40 °C. The resulting pale red solution was stirred at −40 °C for 30 min after which 80 mg (0.000406 mol) of aldehyde **26** in 2 mL of THF was added at −40 °C and the contents were stirred for 1 h. Saturated brine solution was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by chromatography using a chromatotron. Elution of the plate with 5% ether in hexanes afforded 49 mg (51%) of the debromination product **28** and further elution with 8% ether in hexanes gave **29a**,**b** (26 mg (9%, *Z*,*E*), 12 mg (4%, *Z*,*E*)) and **30a**,**b** (18 mg (6%, *E*,*E*), 12 mg (4%, *E*,*E*)), as colorless oils. *Compound* **29a**: $[\alpha]_D^{25}$ −4.4 (*c* 0.45, $CHCl_3$); IR (neat) 3454, 3072, 2956, 2927, 2856, 2212, 1726, 1641, 1587, 1462, 1377, 1363, 1255, 1126, 1082, 1037, 1004, 975 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.79 (dd, $J = 11.2$ Hz, 3.2 Hz, 1H), 6.37 (dd, $J = 11.2$ Hz, 15.4 Hz, 1H), 6.14 (dt, $J = 7.5$ Hz, 15.0 Hz, 1H), 4.72 (br s, 1H), 4.63 (br s, 1H), 4.25–4.21 (m, 1H), 3.92–3.88 (m, 1H), 2.30 (t, $J = 6.58$ Hz, 2H), 2.03–1.98 (m, 1H), 1.88–1.85 (m, 1H), 1.78–1.61 (m, 2H), 1.66 (s, 3H), 1.31–0.90 (m, 5H), 1.13 (d, $J = 6.1$ Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.88 (s, 9H), 0.83 (d, $J = 6.7$ Hz, 3H), 0.82 (d, $J = 6.1$ Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 144.7, 143.0, 125.8, 125.7, 114.7, 111.4, 72.4, 67.8, 45.9, 45.8, 43.4, 43.3, 39.5, 39.1, 36.1, 29.6, 27.7, 27.1, 25.7, 23.7, 22.2, 19.8, 19.6, 15.3, 14.8, −4.4, −4.7; ESMS *m*/*z* 912 ($2M^+$+$NH_4$), 896 ($2M^+$+1), 470 ($M^+$+Na), 465 ($M^+$+$NH_4$), 448 ($M^+$+1); HRMS: calcd for $C_{27}H_{49}NO_2SiCl$, 482.3221; found, 482.3210. *Compound* **29b**: $[\alpha]_D^{25}$ −10.4 (*c* 0.25, $CHCl_3$); IR (neat) 3435, 2958, 2927, 2856, 2212, 1726, 1641, 1587, 1462, 1379, 1257, 1126, 1083, 1037, 1029, 1004, 975 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.79 (d, $J = 11.2$ Hz, 1H), 6.38 (dd, $J = 11.5$ Hz, 15.0 Hz, 1H), 6.13 (dt, $J = 7.5$ Hz, 14.7 Hz, 1H), 4.72 (br s, 1H), 4.63 (br s, 1H), 4.25–4.24 (m, 1H),3.93–3.88 (m, 1H), 2.30 (t, $J = 6.4$ Hz, 2H), 2.03–1.99 (m, 1H), 1.89–1.84 (m, 1H), 1.77–1.60 (m, 2H), 1.66 (s, 3H), 1.34–0.94 (m, 5H), 1.13 (d, $J = 6.0$ Hz, 3H), 1.03 (d, $J = 6.4$ Hz, 3H), 0.87 (s, 9H),

0.82 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.4$ Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 144.8, 144.6, 143.2, 125.7, 118.9, 114.7, 111.4, 72.3, 67.8, 45.9, 43.3, 39.6, 36.1, 29.6, 29.4, 27.7, 27.1, 25.8, 23.7, 22.2, 19.8, 19.6, 14.8, −4.4, −4.7; ESMS *m*/*z* 917 ($2M^+$+Na), 912 ($2M^+$+$NH_4$), 895 ($2M^+$+1), 470 ($M^+$+Na), 465 ($M^+$+$NH_4$), 448 ($M^+$+1); HRMS: ($2M^+$+$HCOO^-$) calcd for $C_{55}H_{99}N_2O_6Si_2$, 939.7042; found, 939.7065. *Compound* **30a**: $[\alpha]_D^{25}$ −7.0 (*c* 0.6, $CHCl_3$); IR (neat) 3469, 3074, 2958, 2927, 2856, 2214, 1726, 1641, 1598, 1462, 1377, 1255, 1128, 1082, 1039, 1002, 971, 887 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.80–6.75 (m, 1H), 6.52 (dd, $J = 11.0$ Hz, 14.9 Hz, 1H), 6.15 (dt, $J = 7.5$ Hz, 15.0 Hz, 1H), 4.72 (br s, 1H), 4.64 (br s, 1H), 4.03–3.99 (m, 1H), 3.94–3.89 (m, 1H), 2.32 (t, $J = 6.7$ Hz, 2H), 2.03–1.98 (m, 1H), 1.94–1.90 (m, 1H), 1.77–1.58 (m, 2H), 1.68 (s, 3H), 1.34–0.96 (m, 5H), 1.14 (d, $J = 5.9$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 6.4$ Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 144.6, 144.3, 141.5, 128.2, 114.7, 111.3, 67.9, 46.0, 45.9, 45.8, 43.0, 35.5, 35.3, 29.6, 27.7, 27.2, 27.1, 25.8, 23.7, 22.2, 19.8, 19.7, 18.0, 15.6, 13.5, −4.4, −4.7; ESMS *m*/*z* 917 ($2M^+$+Na), 912 ($2M^+$+$NH_4$), 470 ($M^+$+Na), 465 ($M^+$+$NH_4$), 448 ($M^+$+1); HRMS: ($2M^+$+$HCOO^-$) calcd for $C_{55}H_{99}N_2O_6Si_2$, 939.7042; found, 939.7045. *Compound* **30b**: $[\alpha]_D^{25}$ −6.80 (*c* 0.25, $CHCl_3$); IR (neat) 3431, 2958, 2927, 2856, 1641, 1587, 1460, 1379, 1255, 1128, 1083, 1024, 887 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.77 (d, $J = 11.2$ Hz, 1H), 6.53 (dd, $J = 11.0$ Hz, 15.0 Hz, 1H), 6.14 (dt, $J = 7.2$ Hz, 14.7 Hz, 1H), 4.72 (br s, 1H), 4.64 (br s, 1H), 4.01 (t, $J = 4.4$ Hz, 1H), 3.93–3.89 (m, 1H), 2.32 (t, $J = 6.4$ Hz, 2H), 2.03–2.00 (m, 1H), 1.99–1.90 (m, 1H), 1.77–1.58 (m, 2H), 1.58 (s, 3H), 1.34–0.96 (m, 5H), 1.15 (d, $J = 6.4$ Hz, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.88 (m, 12H), 0.82 (d, $J = 6.4$ Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 144.7, 144.4, 141.6, 128.3, 118.9, 114.1, 111.4, 67.9, 45.9, 45.8, 43.0, 40.1, 35.3, 29.6, 29.4, 27.7, 27.2, 25.8, 23.7, 22.2, 19.8, 19.7, 13.6, −4.4, −4.7; ESMS *m*/*z* 912 ($2M^+$+$NH_4$), 470 ($M^+$+Na), 465 ($M^+$+$NH_4$), 448 ($M^+$+1); HRMS: ($2M^+$+$HCOO^-$) calcd for $C_{55}H_{99}N_2O_6Si_2$, 939.7042; found, 939.7056.

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