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Studies towards the total synthesis of (−)-borrelidin: a strategy for the construction of the C11–C15 cyanodiene fragment and the utility of RCM for macrocyclization using model systems☆

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Abstract—We report here a methodology for the construction of a conjugated cyanodiene synthon and the propensity of such synthons to participate in the olefin metathesis reaction. To this end, we have developed a strategy for the construction of the C11–C15 fragment of borrelidin and demonstrated the utility of the RCM reaction in the preparation of the final macrolide. To our knowledge, this is the first example of a RCM with a nitrile functionality on a diene.

Borrelidin[1] was shown 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 and has attracted the attention of several synthetic groups around the world[2] (Fig. 1).

The conjugated cyanodiene unit is unprecedented in natural product structures, and is an essential feature for the anti-microbial action of borrelidin. In our endeavors to synthesize this complex macrolide, we envisioned a strategy employing the versatile RCM or cross-metathesis reaction involving a conjugated cyanodiene synthon to construct the final macrolide.

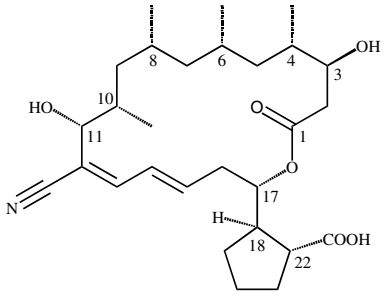

Figure 1.

Even though RCM reactions on conjugated dienes and their utility in macrolide construction are known,[3] ring closing metathesis/cross-metathesis of a conjugated cyanodiene is unprecedented. A literature search revealed a rather interesting pattern, indeed the striking power of RCM methodology is reflected in the synthesis of heterocycles,[4] lactones,[5] sulfones[6] and sulfonamides.[7] The involvement of α,β-unsaturated esters in RCM and cross-metathesis are numerous,[8] in contrast, no examples of α,β-unsaturated nitriles in RCM have been reported, even when the cyano functionality is situated at the terminus of the diene,[9] the only exception being a cross-metathesis involving acrylonitrile.[10] We initially wanted to test the feasibility of our hypothesis in appropriate model systems due to these limited results.

The ylide **1** generated from triphenylphosphine and chloroacetonitrile was treated with bromine in the presence of sodium hexamethyldisilylamide to give the corresponding bromo-ylide **2**.[11] Ylide **2** was reacted with *E*-crotonaldehyde in dichloromethane to afford the cyanodiene **3** in 58% yield[12] as a mixture of isomers. Reaction of **3** with isopropylmagnesium bromide and addition of undecylenic aldehyde to the resulting

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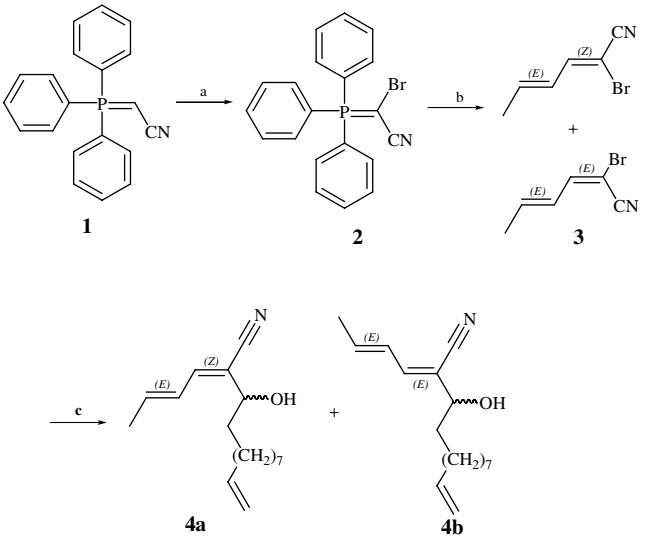
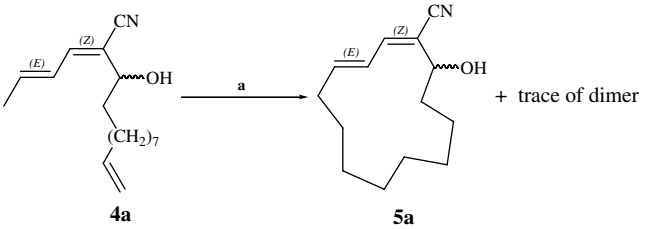
Grignard product gave a mixture of *E*,*Z* (**4a**) and *E*,*E* (**4b**) isomers[13] in 65% yield (Scheme 1) favouring the *E*,*E* isomer (**4b**). Compound **4** was subjected to column chromatography to give the individual isomers **4a** and **4b** which were characterized by NOE studies.[14]

Compound **4a**, when subjected to ring closing metathesis[15] with 5 mol % of Grubbs' II catalyst in refluxing dichloromethane (0.6 mM with respect to substrate) for 18 h, gave the macrocycle **5a** and unreacted starting material as observed on TLC. Addition of another 5 mol % of the catalyst and refluxing for 28 h afforded, exclusively, **5a**[16] in a yield of 54% along with a trace amount of dimer (Scheme 2). The geometry of the newly formed double bond was deduced to be *E* from the coupling constant value of 15.6 Hz. No chromatographic or spectroscopic evidence of the *Z* isomer was observed. From this study, it was evident that the geometry of the conjugated cyanodiene in **5a** is *Z*,*E* which is in accordance with the geometry in borrelidin.[17]

In contrast, when isomer **4b** was subjected to ring closing metathesis with 5 mol % of Grubbs' II catalyst in refluxing dichloromethane (0.6 mM with respect to substrate) for 18 h, formation of both macrocycle **5b**[18] and dimer **6** was observed along with unreacted starting diene. Addition of another 5 mol % of the catalyst with reflux for 28 h increased the amount of dimer. Column purification gave **5b** and **6** with yields of 24% and 22%, respectively, along with 26% of the unreacted diene (Scheme 3). To our surprise the geometry of the newly formed double bond was found to be *Z* from the coupling constant value of 11.0 Hz. No chromatographic or spectroscopic evidence for the formation of the *E* isomer was observed.



Scheme 1. Reagents and conditions: (a) $NaN(SiMe_3)_2$, Br_2, toluene, −78 °C to rt, (72%); (b) *E*-crotonaldehyde, CH_2Cl_2, rt, (58%); (c) (i) *i*-PrMgBr, THF, −40 °C, (ii) undecylenic aldehyde, rt, (65% over two steps).



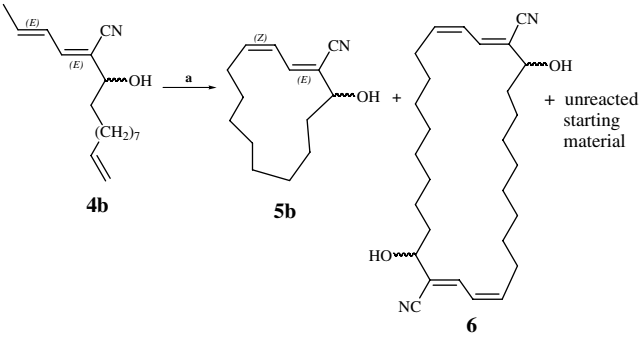
Scheme 2. Reagents and conditions: (a) Grubbs' II, catalyst (10 mol %), CH_2Cl_2 (0.6 mM), reflux, 28 h (54%).

Intrigued by the anomalous behaviour of the isomers **4a** and **4b** during RCM, we sought to substantiate our findings by studying the NOE interactions in compounds **5a** and **5b**. The NOE studies also confirmed the *E* and *Z* geometries. To assess the role of the OH group in these reactions, the hydroxyl functionality in **4b** was oxidized to a ketone with Dess–Martin reagent. The ring closing metathesis of this ketone with 15 mol % of Grubbs' II catalyst in refluxing dichloromethane (0.5 mM with respect to substrate) for 52 h proved to be very sluggish.

We propose the following models for the contrasting geometries of the newly formed double bonds during RCM. In **4a**, the *Z* geometry of the double bond adjacent to the cyano group forces the ruthenium complex on the terminal diene to attack the conjugated double bond from the top thereby forming the cyclized compound **5a** with an *E* double bond (Fig. 2a). On the other hand, when the geometry is *E* (**4b**), the molecule adopts a conformation where the ruthenium complex attacks the conjugated diene from the bottom affording **5b** with a *Z* double bond (Fig. 2b). Further experiments are required in order to prove this hypothesis.

The formation of the dimer as a major product in the RCM of **4b**, even at high dilution, shows the propensity of this isomer to participate in cross-metathesis more readily than **4a**. Further studies are ongoing in this direction. The higher catalyst/substrate ratio required in these reactions may be due to catalyst decomposition mediated by the nitrile group.[10]

In conclusion, we have undertaken a study on the ring closing metathesis of a conjugated cyanodiene. To this end, we have demonstrated a strategy for building the *Z*,*E* C11–C15 conjugated cyanodiene synthon in borrelidin. To our knowledge, this is the first example of a



Scheme 3. Reagents and conditions: (a) Grubbs' II catalyst (10 mol %), CH_2Cl_2 (0.6 mM), reflux, 28 h (**5b**, 24% and **6**, 22%).

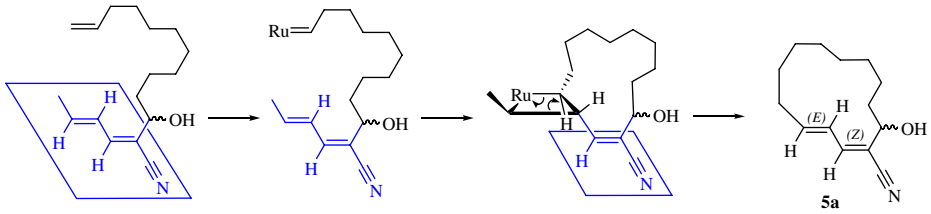


Figure 2a.

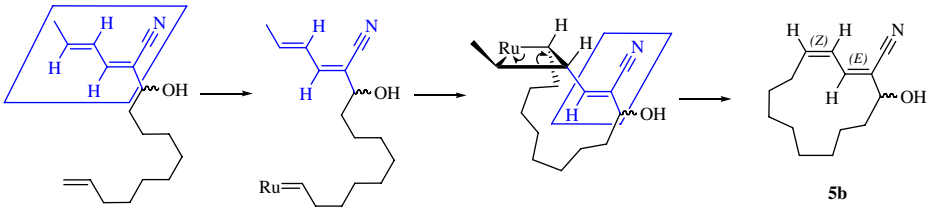


Figure 2b.

RCM with a nitrile functionality on a diene. Further studies are ongoing towards the total synthesis of the macrolide.

Acknowledgements

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12. Compound **3**: *E*,*Z* mixture: $[\alpha]_D^{25}$ −1.3 (*c* 1.00, $CHCl_3$); IR (KBr): 3420, 2923, 2853, 1718, 1502, 1362, 1174, 1118; Mass (*m*/*z*): CI: 173 (M^++1, for ^{81}Br); ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (dd, 3H, $J = 1.61$ Hz, 6.71 Hz), 1.92 (d, 3H, $J = 5.4$ Hz), 6.17–6.26 (m, 2H), 6.31–6.42 (m, 2H), 7.10–7.13 (d, 1H, $J = 11$ Hz), 7.16–7.18 (d, 1H, $J = 9.4$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 18.7, 19.1, 83.8, 85.5, 127.3, 127.5, 141.6, 143.8, 145.7, 149.8.
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14. Compound **4a**: $[\alpha]_D^{25}$ −0.9 (*c* 1.00, $CHCl_3$); IR (KBr): 3443, 2927, 2855, 2212, 1640, 1442, 1035; ESMS: 262 (M^++1), 279 (M^++NH_4), 284 (M^++Na); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.80 (m, 15H), 1.90 (dd, 3H, $J = 1.57$ Hz, 6.7 Hz), 2.01–2.06 (m, 2H), 4.59–4.61 (m, 1H), 4.90–5.00 (m, 2H), 5.75–5.86 (m, 1H), 6.11–6.19 (m, 1H), 6.30–6.40 (qdd, 1H, $J = 1.6$ Hz, 11.2 Hz, 14.7 Hz), 6.70 (d, 1H, $J = 11.5$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 18.8, 25.2, 28.8, 29.0, 29.2, 29.3, 29.4, 33.7, 36.0, 67.3, 114.1, 114.7, 118.6, 125.2, 139.1, 141.2, 144.3. Compound **4b**: $[\alpha]_D^{25}$ 0.6 (*c* 1.00, $CHCl_3$); IR (KBr): 3423, 2927, 2855, 2213, 1642, 1443, 1043; ESMS: 262 (M^++1), 279 (M^++NH_4), 284 (M^++Na); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.80 (m, 15H), 1.90 (dd, 3H, $J = 1.6$ Hz, 6.9 Hz), 2.01–2.06 (m, 2H), 4.59–4.61 (m, 1H), 4.90–5.0 (m, 2H), 5.70–5.80 (m, 1H), 6.10– 6.19 (m, 1H), 6.40–6.50 (qdd, 1H, $J = 1.6$ Hz, 11.2 Hz, 15.0 Hz), 6.70 (d, 1H, $J = 11.0$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 18.5, 25.2, 28.8, 29.0, 29.2, 29.3, 29.4, 33.7, 36.1, 72.5, 114.0, 114.5, 116.3, 127.8, 139.1, 139.9, 143.8.
15. *Typical procedure for the RCM reaction*: To the starting diene (**4a** or **4b**) in dry dichloromethane (0.6 mM with respect to substrate) was added 5 mol % of Grubbs' II catalyst (Aldrich) as a solution in dichloromethane. The contents were refluxed under argon for 18 h and subsequently another 5 mol % of the catalyst was added and refluxing continued for 28 h. Dichloromethane was removed under reduced pressure and the residue was purified by column chromatography over 230–400 silica gel. Elution of the column with 15% ethyl acetate in hexanes afforded the pure compound as a gummy mass.
16. Compound **5a**: IR (KBr): 3421, 2928, 2857, 2214, 1639, 1383, 1190, 1053; ESMS: 220 (M^++1), 237 (M^++NH_4), 456 ($2M^+$+NH_4); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–2.10 (m, 15H), 2.30–2.40 (m, 2H), 4.80 (dd, 1H, $J = 4.1$ Hz, 10.9 Hz), 6.01–6.09 (m, 1H), 6.32–6.39 (dd, 1H, $J = 15.3$ Hz, 11.0 Hz), 6.85–6.88 (d, 1H, $J = 10.7$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 24.0, 25.5, 26.5, 26.7, 27.3, 27.8, 33.5, 35.6, 66.6, 115.7, 118.1, 125.6, 143.6, 143.7.
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18. Compound **5b**: IR (KBr): 3408, 2928, 2857, 2217, 1631, 1460, 1051; ESMS: 220 (M^++1), 237 (M^++NH_4), 456 ($2M^+$+NH_4); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.80 (m, 15H), 2.20–2.30 (m, 2H), 4.35–4.37 (m, 1H), 5.81–5.88 (m, 1H), 6.53–6.58 (t, 1H, $J = 11.0$ Hz), 7.10 (d, 1H, $J = 11.0$ Hz); ^{13}C (50 MHz, $CDCl_3$) δ 22.8, 24.5, 25.0, 25.8, 26.5, 26.6, 27.8, 33.5, 73.4, 116.0, 116.6, 125.6, 139.0, 141.3.