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Truncated borrelidin analogues: synthesis by sequential cross metathesis/olefination for the southern fragment and biological evaluation†

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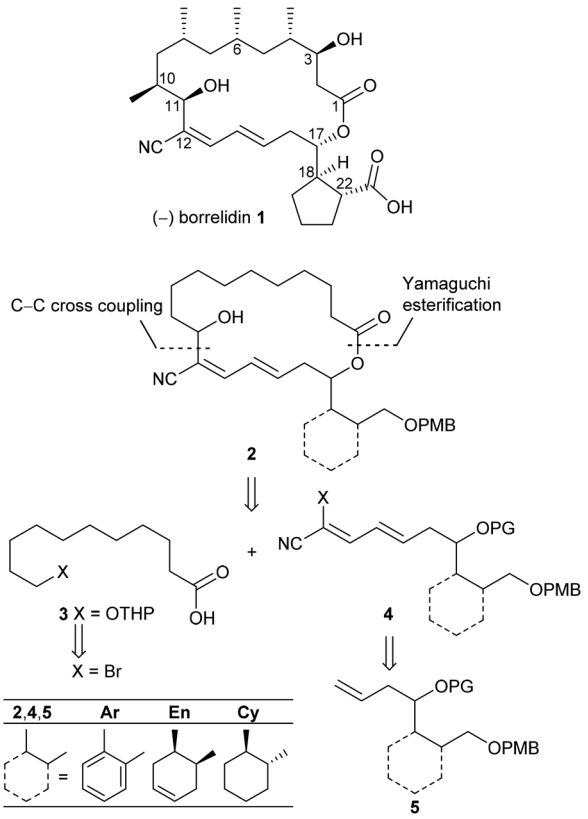
The construction of novel borrelidin analogues is reported in which the northern fragment is truncated to a simple hydroxyundecanecarboxylate and the original cyclopentanecarboxylic acid in the southern fragment is replaced with different six-membered rings. The required precursors were prepared by cross metathesis of the appropriate carbocycle-based homoallylic alcohol with crotonaldehyde followed by HWE olefination of the resulting enal with bromocyanophosphonate. The key aldehyde for intramolecular cross coupling was accessible by oxidation of the hydroxy group of the linked undecanecarboxylate unit. Grignard mediated macrocyclization finally yielded the borrelidin related products. The investigation is complemented by SAR studies and quantum-chemical calculations.

Introduction

Polyketide natural products consist of a huge variety of structurally diverse compounds originating from a modified fatty acid biosynthesis. They display a broad spectrum of biological activities relevant for medicinal chemistry and drug development.[1] A prominent member of this family is (−)-borrelidin (**1**) (Scheme 1), which was isolated by Berger *et al.* in 1949 from *Streptomyces rochei*.[2] Apart from its activity against borrelia, the major cause of lyme disease,[2–4] a broad biological profile has been discovered. Borrelidin (**1**) exhibits antiviral activity,[5] inhibits angiogenesis[6] as well as several enzymes such as cyclin-dependent kinase Cdc28/Cln2 of *Saccharomyces cerevisiae*[7] and threonyl tRNA synthetase.[8] In addition, anti-malarial activity against chloroquine-resistant strains of *Plasmodia falsiparum* has been reported.[9] The promising biological activities have stimulated several synthetic endeavours[3] and up to now five total syntheses have been reported by the groups of Morken,[10] Hanessian,[11] Theodorakis,[12] Omura[13]



Scheme 1 Retrosynthetic approach to borrelidin analogues **2** with different rings at C-17 and truncated northern fragment.

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† Electronic supplementary information (ESI) available: General procedures and syntheses of the described derivatives, preliminary studies on olefination reactions, NMR studies on the stereochemistry of the terminal double bond in bromocyanodiene (**4En)dBr**, quantum-chemical calculation of (**27Ar**) as well as ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c6ob01358a

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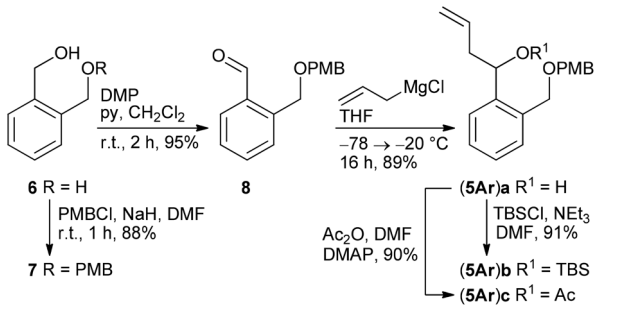
and Minnaard[14] complemented by synthetic studies.[15] Hahn *et al.* synthesized complex intermediates in order to probe the dehydratase from borrelidin biosynthesis.[16] By employing precursor-directed biosynthesis Wilkinson *et al.* prepared several borrelidin analogues with modified C-17 side chains and were able to separate anti-angiogenetic from cytotoxic activities.[17,18] Omura's group reported that esterification of the free carboxylic acid with various triazolyl-containing alcohols led to improved anti-malarial activity and reduced cytotoxicity.[9] With borrelidin B containing an aminomethyl group in place of the nitrile function the need for the CN group for threonyl tRNA synthetase inhibition was demonstrated.[19] In a comparative cytological study loss of biological activity for borrelidin congeners with amide functions at C-12 and C-22 was observed.[20] In all cases, however, the macrocycle of **1** was retained. These results motivated us to study borrelidin analogues with modified macrocyclic skeletons regarding their potential cytotoxic properties. Taking the concept of truncated natural products discussed by Gademann *et al.*[21] and Maier[22] and successfully demonstrated by Nakata[23] for kendomycin analogues into account, we aimed to prepare the borrelidin related compounds **2** with different rings in the side chain at C-17 and the complex polyketide region truncated to a simple 11-hydroxyundecane chain (Scheme 1). The retrosynthesis is based on disconnection of **2** into the northern fragment **3** and the southern fragment **4**, which can be traced back to known 11-bromoundecanoic acid and precursors **5**. The latter requires different routes starting from known compounds.

As key steps for the connection of northern and southern fragments **3** and **4** an esterification and C–C coupling following Omura's strategy[13] or, alternatively, Grignard coupling according to Iqbal's method[24a] were performed. To access cyanodienes **4** from precursors **5**, the suitability of cross metathesis *versus* olefination or Knoevenagel-type condensation was studied based on seminal contributions by Iqbal.[24b] The results of the synthesis and biological investigation of southern fragments **4** and borrelidin analogues **2** are reported below.

Results and discussion

Synthesis of cyanodienes 4a–c

According to a procedure by Jay-Smith *et al.*[25] 1,2-benzenedimethanol **6** prepared from diethyl phthalate by $LiAlH_4$ reduction[26] was mono-protected with PMBCl to yield **7** in 88%. Subsequent Dess–Martin oxidation afforded the known aldehyde **8** in 95% yield (Scheme 2). While the Sakurai reaction of **8** with allyltrimethylsilane in the presence of various Lewis acids[27] either resulted in no conversion at all or led to complete decomposition of the starting material, treatment of **8** with the corresponding Grignard reagent provided the desired alcohol **(5Ar)a** in 89% yield. TBS protection of **(5Ar)a** gave derivative **(5Ar)b** in 91% yield. As we aimed at a maximum flexibility with respect to the coupling of fragments **3** and **4** (Scheme 1), we also introduced the acetyl protecting group in **(5Ar)a** under standard acetylation conditions, which would



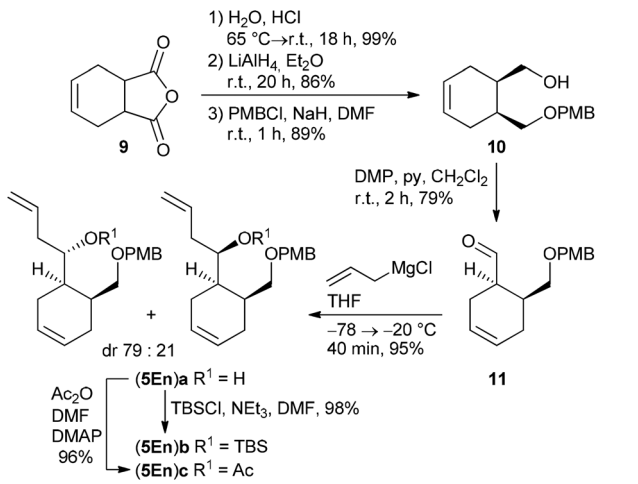
Scheme 2 Synthesis of benzene-based homoallylic alcohols **(5Ar)a–c**.

allow a Yamaguchi macrolactonization as the intramolecular step. Precursor **(5Ar)c** served as a model acyl-protected substrate for the synthesis of the southern fragment.

Cyclohexene-derived homoallylic alcohols **(5En)a–c** were prepared following a similar strategy (Scheme 3). Acidic hydrolysis of 4-cyclohexene-1,2-dicarboxylic anhydride **9**[28] followed by $LiAlH_4$ reduction and monoselective PMB-protection gave alcohol **10** in 76% overall yield (over three steps). After Dess–Martin oxidation, the resulting aldehyde **11** was subjected to a Grignard reaction to yield the homoallylic alcohol **(5En)a** in 95% as a diastereomeric mixture (dr 79 : 21), which was separated by HPLC for characterization. TBS-protection or acetylation of the diastereomeric alcohol **(5En)a** provided the target compounds **(5En)b** and **(5En)c** in 98% and 96% yield, respectively.

The cyclohexane-derived homoallylic alcohol **(5Cy)a** was prepared from diol **13**, which was obtained from the known D-dimenthyl succinate **12** by a Yamamoto asymmetric carbocyclization[16,29,30] followed by $LiAlH_4$ reduction (Scheme 4).

Mono-PMB protection of **13** and subsequent Swern oxidation afforded aldehyde **14** in 91% overall yield (over both steps). The Grignard reaction of **14** with allylmagnesium chloride led to an inseparable diastereomeric mixture of



Scheme 3 Synthesis of cyclohexene-based homoallylic alcohols **(5En)a–c** which were further used as diastereomeric mixtures.

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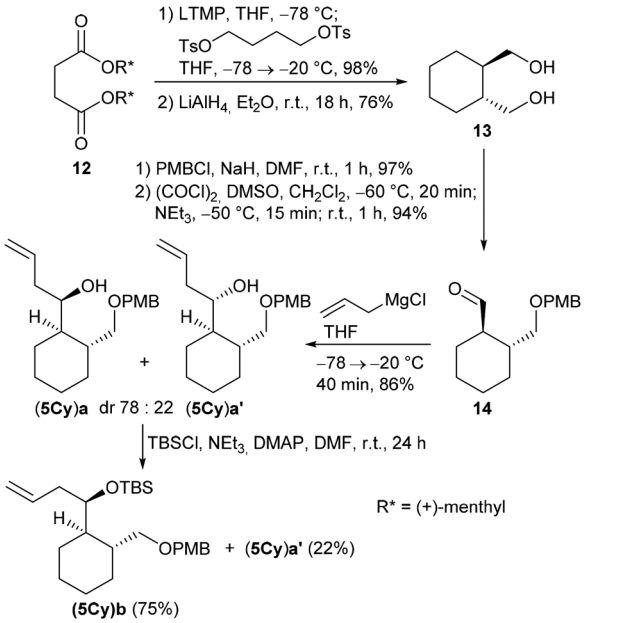


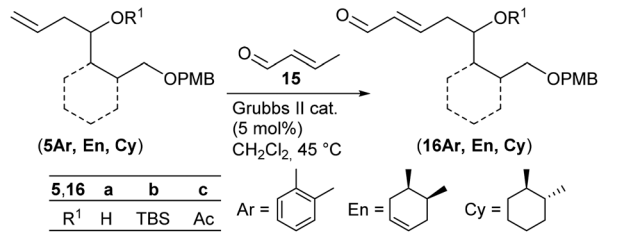
Scheme 4 Synthesis of cyclohexane-based homoallylic alcohols **(5Cy)a,b** and **(5Cy)a′**.

homoallylic alcohols **(5Cy)a** and **(5Cy)a′** (dr 78 : 22) in 86%. However, when **(5Cy)a** and **(5Cy)a′** were treated with TBSCl under our usual reaction conditions, only diastereomeric silyl-ether **(5Cy)b** was isolated in 75% while the diastereomeric alcohol **(5Cy)a′** remained unreacted and could be recovered in 22%. This diastereoselective kinetic resolution was rather unexpected, although some examples of diastereoselective Si–O couplings existed, *e.g.* employing silicon-stereogenic hydrosilanes and achiral Cu complexes.[31,32] Presumably, the reactivity of the OH group in diastereomer **(5Cy)a′** is diminished by hydrogen bonding between the OH group and the PMB group.

With homoallylic alcohols **5** in hand we investigated the cross metathesis with crotonaldehyde **15** (Table 1), which was reported to give better yields than acrolein when using the Grubbs II catalyst.[33]

Treatment of the aromatic TBS-protected cross metathesis (CM) precursor **(5Ar)b** with crotonaldehyde **15** in the presence of the second generation Grubbs catalyst (Grubbs II) (5 mol%) in CH_2Cl_2 at 45 °C provided 35% of the desired product **(16Ar)b** (entry 1). Cross metathesis of cyclohexane **(5Cy)b** afforded 80% of enal **(16Cy)b** on further addition of the Grubbs II catalyst after 18 h of reaction time (entry 7). Under these conditions the corresponding cyclohexene derivative **(5En)b** gave 92% of the diastereomeric CM product **(16En)b** (dr 83 : 17 by ^{1}H NMR of the C*H*O signal) (entry 4). As can be seen in Table 1, CM products **(16En)a** and **(16Cy)a′** with free hydroxy groups were isolated in high yields of 88% and 79%, respectively (entries 3 and 6). This observation is in good agreement with the previous reports by Fuwa *et al.*[34] and Lin and Davis[35] suggesting that free hydroxy groups have a beneficial influence on cross metathesis reactions due to hydrogen-bonding of the OH group with the chlorine atom of the ruthenium carbene

Table 1 Cross metathesis of homoallylic alcohol derivatives **5** with crotonaldehyde **15** to enals **16**

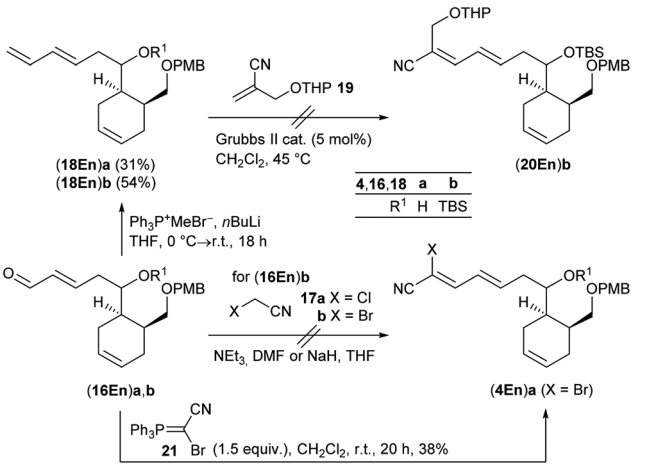


Entry[a]	5	R^1	Time (h)	16	Yield[b] (%)	dr
1	**(5Ar)b**	TBS	20	**(16Ar)b**	35	
2	**(5Ar)c**	Ac	18	**(16Ar)c**	89	
3	**(5En)a**	H	19	**(16En)a**	88	79 : 21
4[c]	**(5En)b**	TBS	20	**(16En)b**	92	83 : 17
5	**(5En)c**	Ac	18	**(16En)c**	84	73 : 27
6	**(5Cy)a′**	H	18	**(16Cy)a′**	79	
7[c]	**(5Cy)b**	TBS	20	**(16Cy)b**	80	

[a] Reaction conditions: **5** (1.0 equiv.), **15** (1.0 equiv.), cat. (5 mol%). [b] Isolated yield. [c] Further addition of Grubbs II catalyst (5 mol%) after 18 h.

complex.[36] Also the acetylated precursors **(5Ar)c** and **(5En)c** underwent cross metathesis under similar conditions providing the desired CM products **(16Ar)c** and **(16En)c** in comparable yields (entries 2 and 5).

The synthesis of cyanodiene fragments **4** was studied using first cross metathesis enals **(16En)a,b** (Scheme 5). Knoevenagel condensation of **(16En)b** with chloro- or bromoacetonitrile **17a,b**[37] to cyanodiene **(4En)b**, however, completely failed. An alternative strategy used a sequence of Wittig reaction/cross metathesis. While the Wittig olefination of enals **(16En)a,b** with methyltriphenylphosphonium bromide and *n*BuLi proceeded uneventfully to dienes **(18En)a** and **(18En)b** in 31% and 54% yield, respectively, the subsequent cross metathesis of **(18En)b** with substituted methacrylonitrile **19**[38] resulted in no conversion to cyanodiene **(20En)b**.



Scheme 5 Preliminary studies on olefination reactions of **(16En)a,b** to give fragments **(4En)a,b** (for details see the ESI†).

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Therefore, we decided to follow Omura's initial approach[13] by utilizing electron-poor bromocyanophosphorane **21**[39] or cyanophosphonates **22**[40] and again enals **(16En)a,b** as benchmark substrates for the olefination. While the reaction of the unprotected derivative **(16En)a** with phosphorane **21** at room temperature in CH_2Cl_2 yielded the desired olefination product **(4En)a** in 38%, the corresponding TBS-protected **(16En)b** resulted in no conversion (Scheme 5). Afterwards neither (**16Ar**) nor (**16Cy**) enals reacted under these conditions (ESI†), and the Wittig reaction was abandoned.

Next, the HWE olefination of enals **16** with α-chloro- and α-bromocyanophosphonate **22a,b**, respectively, was investigated. The results are summarized in Table 2. Deprotonation of α-chlorocyanophosphonate **22a** with NaH in DMF at 0 °C followed by addition of substrate **(16En)a** with the free OH group or the TBS-protected analogue **(16En)b** at 0 °C provided the respective cyanodienes **(4En)aCl** and **(4En)bCl** in 57% and 53% yield (entries 4 and 8). In both cases, however, the reaction with the corresponding α-bromocyanophosphonate **22b** under similar conditions did not lead to the olefination products **(4En)aBr** and **(4En)bBr** (entries 5 and 9). We surmised that α-bromocyanophosphonate **22b** underwent nucleophilic displacement of the bromide by hydride rather than deprotonation of the acidic α-hydrogen.

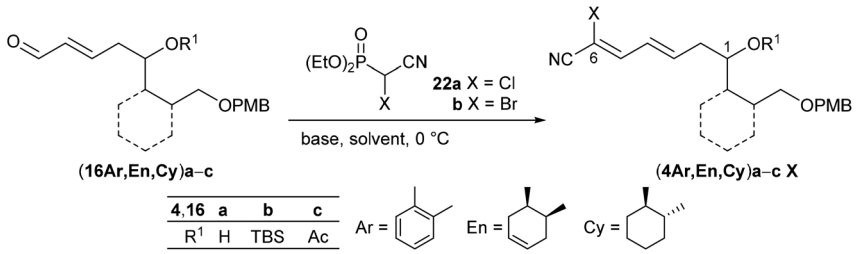
Following Omura's reaction conditions[13] we finally succeeded in the preparation of both chloro- and bromocyanodienes **4**. For this purpose, LiCl and subsequently DBU (1.5 equiv. each) were added to a solution of the respective substrate **16** and cyanophosphonate **22a** or **22b** in acetonitrile at 0 °C (Table 2). In this manner bromocyanodiene **(4En)bBr** could be isolated in 48% (entry 11). Similar yields were obtained for the unprotected enal **(4En)a** irrespective of the halide (entries 6 and 7). The HWE olefination of cyclohexane-based substrates **(16Cy)a′,b** resulted in good yields of bromocyanodienes **(4Cy)a′Br** (77%) and **(4Cy)bBr** (76%) (entries 15 and 19), while the yields of the corresponding chloro compounds **(4Cy)a′Cl** and **(4Cy)bCl** decreased to 43% and 27%, respectively (entries 14 and 18).

This difference in yields between chloro- and bromocyanodienes became even larger when the acetyl-protected enal **(16Ar)c** was olefinated to **(4Ar)cCl** (11%) and **(4Ar)cBr** (65%) (entries 2 and 3). A similar trend of increasing yield was observed for the olefination of acetylated **(16En)c** to **(4En)cBr** (99%) (entry 12).

Synthesis of borrelidin analogues 2

In order to optimize the reaction conditions for the envisioned cross coupling of fragments **3** and **4** we first studied the reaction of bromocyanodienes **(4)Br** with isobutyraldehyde **23** as a model substrate for fragment **3** (Table 3).

Table 2 HWE olefination of enals **16** with α-halogenocyanophosphonates **22** to cyanodienes **4**



Entry[a]	Enal	R^1	22	Base	Solvent	Time (h)	Product	Yield[b] (%)	dr[c]
1[d]	**(16Ar)a**	H	**22b**	NaH	THF	48	**(4Ar)aBr**	—	—
2	**(16Ar)c**	Ac	**22a**	DBU	MeCN	1.5	**(4Ar)cCl**	11	n.d.
3	**(16Ar)c**	Ac	**22b**	DBU	MeCN	1.5	**(4Ar)cBr**	65	n.d.
4	**(16En)a**	H	**22a**	NaH	DMF	2.5	**(4En)aCl**	57	80 : 20
5	**(16En)a**	H	**22b**	NaH	DMF	2.5	**(4En)aBr**	—[e]	—
6	**(16En)a**	H	**22a**	DBU	MeCN	1	**(4En)aCl**	49	82 : 18
7	**(16En)a**	H	**22b**	DBU	MeCN	1	**(4En)aBr**	49	80 : 20
8	**(16En)b**	TBS	**22a**	NaH	DMF	3	**(4En)bCl**	53	76 : 24
9	**(16En)b**	TBS	**22b**	NaH	DMF	2.5	**(4En)bBr**	—	—
10	**(16En)b**	TBS	**22a**	DBU	MeCN	1	**(4En)bCl**	51	78 : 22
11	**(16En)b**	TBS	**22b**	DBU	MeCN	1	**(4En)bBr**	48	78 : 22
12	**(16En)c**	Ac	**22b**	DBU	MeCN	1.5	**(4En)cBr**	99	82 : 18
13	**(16Cy)a′**	H	**22a**	NaH	DMF	3	**(4Cy)a′Cl**	—	—
14	**(16Cy)a′**	H	**22a**	DBU	MeCN	1	**(4Cy)a′Cl**	43	
15	**(16Cy)a′**	H	**22b**	DBU	MeCN	1	**(4Cy)a′Br**	77	
16	**(16Cy)b**	TBS	**22a**	NaH	DMF	2.5	**(4Cy)bCl**	—	—
17	**(16Cy)b**	TBS	**22b**	NaH	DMF	2.5	**(4Cy)bBr**	—	—
18	**(16Cy)b**	TBS	**22a**	DBU	MeCN	1	**(4Cy)bCl**	27	74 : 26[f]
19	**(16Cy)b**	TBS	**22b**	DBU	MeCN	1	**(4Cy)bBr**	76	85 : 15[f]

[a] Reaction conditions: **16** (1.0 equiv.), **22** (2.0 equiv.), LiCl (1.5 equiv.), DBU (1.5 equiv.); **16** (1.0 equiv.), NaH, **22** (1.25 equiv. each). [b] Isolated yield. [c] dr refers to stereocentre C-1 at the homoallylic ether position relative to the fixed *cis* or *trans* configuration in (**4En**) and (**4Cy**). [d] Temperature: −20 °C → r.t. [e] No conversion, starting materials were reisolated. [f] *E*/*Z* ratio at C-6.

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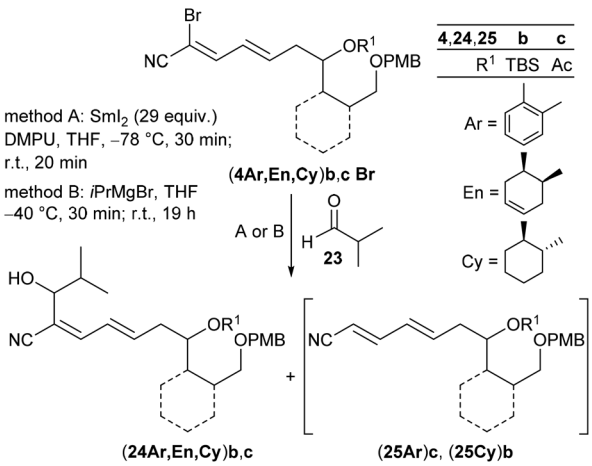
According to Omura's conditions,[13b] the aryl-substituted acetoxycyanodiene **(4Ar)cBr** was treated with aldehyde **23** and a large excess of SmI_2 (29 equiv.) in the presence of DMPU instead of HMPA in THF (method A). The secondary alcohol **(24Ar)c** could be isolated, albeit in a low yield of 18% (dr 66 : 34) (entry 1). In contrast, treatment of **(4Ar)cBr** with iPrMgBr in THF according to Iqbal's method,[24] followed by addition of **23** (method B) slightly increased the yield to 28% (dr 52 : 48), but alcohol **(24Ar)c** was accompanied by a byproduct **(25Ar)c** being isolated in 41% as an *E*/*Z* mixture (11 : 89) (entry 2). Its presence indicated that the initial attack of the isopropyl Grignard to fragment **(4Ar)cBr** and subsequent halogen metal exchange had indeed taken place, but subsequent addition of the *in situ* formed Grignard seemed to be too slow and thus, hydrolysis of the cyanodiene Grignard species occurred during workup giving byproduct **(25Ar)c**. Under both Grignard and SmI_2 conditions, cyanodienes **(4En)bBr** and **(4En)cBr** reacted to alcohols **(24En)b** and **(24En)c** which were isolated in low yields of 37% and 8%, respectively (entries 3 and 4). The Grignard addition of the cyclohexyl-substituted fragment **(4Cy)bBr** gave alcohol **(24Cy)b** in 48% yield (dr 89 : 11) together with 28% of the dehalogenated byproduct **(25Cy)b** (entry 5). The results in Table 3 revealed that intermolecular cross coupling could be achieved under both SmI_2 and Grignard mediated conditions, however, with less satisfactory yields for the SmI_2 method. We thus anticipated a poorer performance of SmI_2 in the intramolecular cyclization compared to the Grignard reaction.

Keeping the obtained results in mind we continued with the synthesis of the macrocyclic borrelidin analogues **2** as outlined in Scheme 6. Homoallylic alcohols **(5Ar)a** and **(5En)a** were esterified under Yamaguchi conditions[41] with the northern fragment **3** prepared in 99% yield by tetrahydropyranylation[38b] of 11-hydroxyundecanoic acid[42] to yield the corresponding carboxylates **(5Ar)d** and **(5En)d** in 86% and 91%, respectively. Cross metathesis with crotonaldehyde **15** in the presence of the Grubbs II catalyst under the optimized conditions provided enals **(16Ar)d** and **(16En)d** in 81% and 54% yield, respectively. The HWE reaction between the latter and bromocyanophosphonate **22b** gave the olefination products **(4Ar)dBr** and **(4En)dBr** in 59% and 42%, respectively. The decreased yields might be caused by a lower solubility of the less polar precursors **(16Ar)d** and **(16En)d** in acetonitrile compared to the model compound **(16Ar)c** having a simple acetate protecting group. THP deprotection with PPTS in EtOH proceeded uneventfully to afford alcohols (**26Ar**) and (**26En**) in 84% and 93% yield, which were subsequently oxidized with TPAP under Ley conditions[43] to yield aldehydes (**27Ar**) and (**27En**) in 88% and 78%, respectively, the key intermediates of the intramolecular cross coupling. The intermolecular cross coupling conditions (Table 3) were transferred to the intramolecular coupling reaction.

The SmI_2 mediated Reformatsky-type macrocyclization of (**27Ar**) under high dilution according to Omura (method A) failed to give the desired macrocycle (**2Ar**). Only the open-chain cyanodiene **(25Ar)e** (R^1 = $HO(CH_2)_{10}CO$–, see also

Table 3 Intermolecular cross coupling of cyanodienes **4** with isobutyraldehyde **23** to alcohols **24**



Entry[a]	Diene	Method	Product	Yield[b] (%)	dr[c]	25	Yield[b] (%)
1	**(4Ar)cBr**	A	**(24Ar)c**	18	66 : 34	—	—
2	**(4Ar)cBr**	B	**(24Ar)c**	28	52 : 48	**(25Ar)c**	41
3	**(4En)bBr**	B	**(24En)b**	37	83 : 17	—	—
4	**(4En)cBr**	A	**(24En)c**	8	67 : 33	—	—
5	**(4Cy)bBr**	B	**(24Cy)b**	48	89 : 11	**(25Cy)b**	28

[a] Reaction conditions: **4** (1.0 equiv.), **23** (1.0 equiv.), SmI_2 (29 equiv.), DMPU (19 equiv.); iPrMgBr (1.1 equiv.). [b] Isolated yield. [c] Determined by integration in ^1H NMR spectra.

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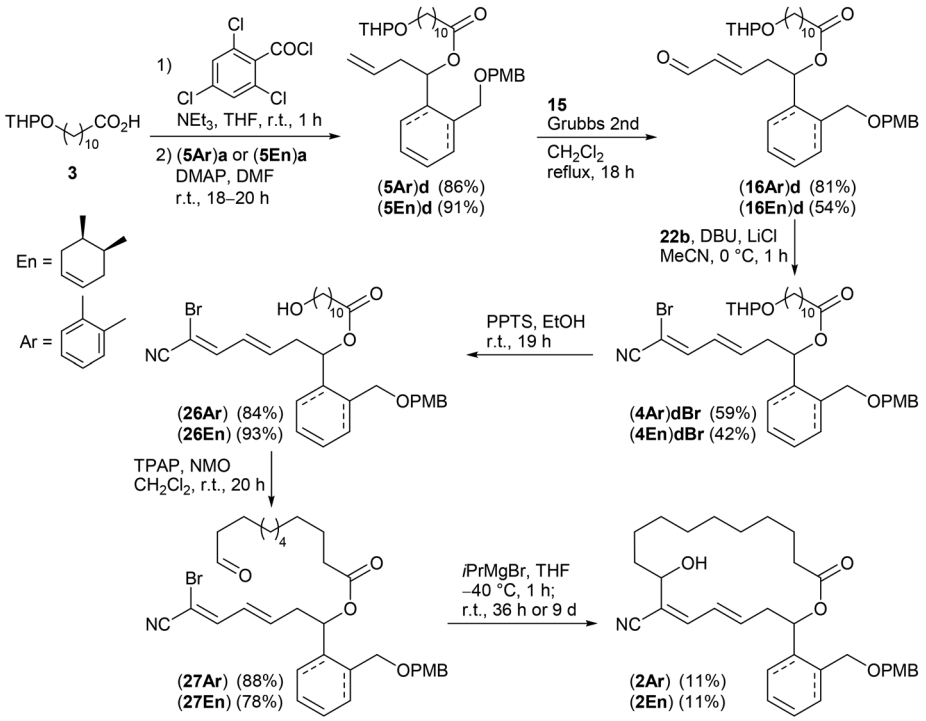

Scheme 6 Synthesis of borrelidin analogues (**2Ar**) and (**2En**). For attempts to assign the stereochemistry of the terminal C═C double bond in derivative **(4En)dBr** see the ESI.†

Table 3 and ESI†), resulting from SmI_2 induced reduction of the aldehyde moiety to the primary alcohol and simultaneous reductive debromination, was isolated in 27%. In contrast, the cross coupling of (**27Ar**) with iPrMgBr in THF (method B) by the Grignard reaction succeeded. The amount of iPrMgBr, however, was increased to 2 equivalents and the reaction time for halogen metal exchange prolonged to 1 h. After stirring at room temperature for 36 h followed by aqueous workup, the desired borrelidin analogue (**2Ar**) was isolated in 11% yield. In the case of cyclohexenyl-derived compound (**27En**), only small amounts of the target macrocycle (**2En**) were detected after 36 h reaction time under similar conditions. However, reaction time extension to 9 days resulted in the macrocyclic target compound (**2En**) in 11% yield.

We assume that the northern fragment **3** might be responsible for the moderate yields of the Grignard induced macrocyclization and the complete failure of SmI_2 promoted intramolecular reactions of aldehydes **27**. In comparison, Omura obtained 60% of the desired macrocycle with the 1,3,5,7-tetramethylated northern fragment in the case of the parent borrelidin synthesis.[13] These results might arise from the different conformations of the non-branched and the methyl-branched fragments. In order to investigate this aspect in detail, we have performed quantum-chemical calculations based on density functional theory (B3LYP/cc-pVDZ) for (**27Ar**). Out of a large number of conformers, we isolated **27A** and **27B** as shown in Fig. 1.

After correction for the zero-point vibrational energy, conformer **27A** was found to be 2.6 kcal mol^{-1} lower in energy

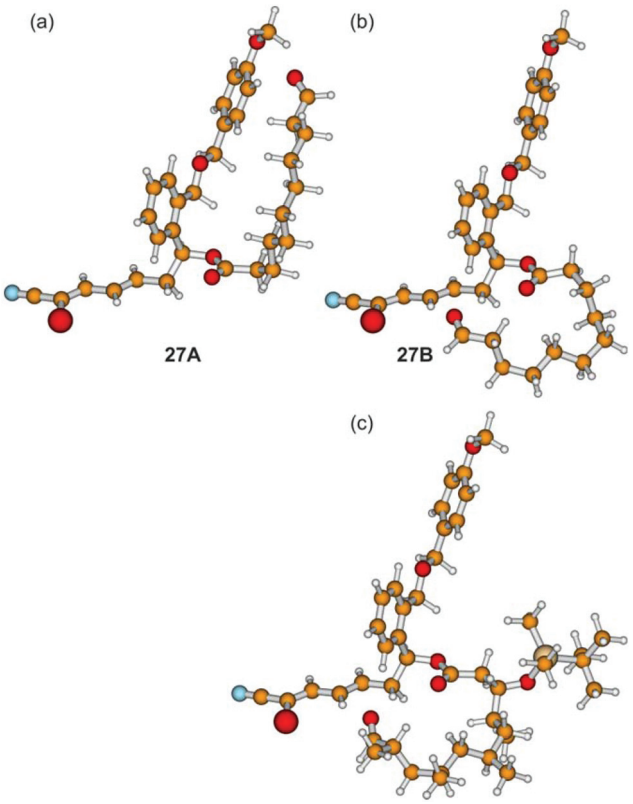

Fig. 1 Different conformations of (**27Ar**) (a, b). Conformer **27A** is about 2.6 kcal mol^{-1} lower in energy than **27B** (B3LYP/cc-pVDZ) (for further conformers see the ESI†). For comparison the methyl-branched borrelidin analogue of **27B** is depicted (c).

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than conformer **27B**, which constitutes a possible precursor to the cyclization reaction. As slight distortions in the **27B** structure led to conformer **27A**, the barrier between these two conformers must be very low. The opposite was found for the methyl-branched system: distortions of the analogue of conformer **27B** did not lead to the analogue of conformer **27A**, but the system was always trapped in the local minimum of the structure of the **27B** analogue. As a consequence, it is the occurrence of a multitude of conformations (including those with a linear northern fragment), which are lower in energy than the precursor **27B** shown in Fig. 1, and which are connected by low barriers, being responsible for low yields and/or long reaction times.

Biological studies of cyanodienes and borrelidin analogues 2

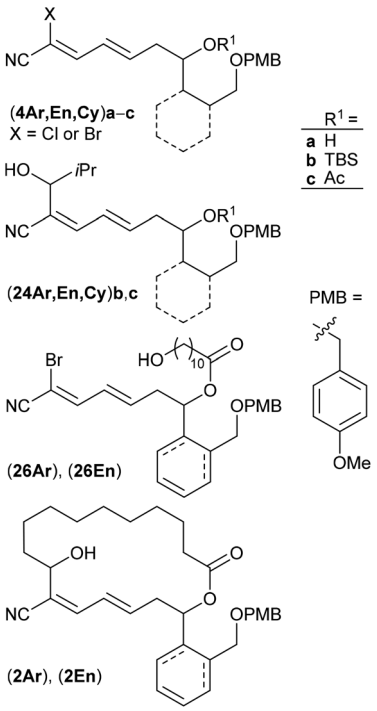
The ability of a set of cyanodiene derivatives **4**, **24**, **26**, and borrelidin analogues (**2Ar**) and (**2En**) to inhibit the proliferation of the L-929 mouse fibroblast cell line was examined using the WST-1 cytotoxicity assay according to the protocol given by the manufacturer.[44] The results are summarized in Table 4.

As can be seen from the data in Table 4, the studied derivatives **4**, **24**, and **26** generally revealed only moderate cytotoxicity against the L-929 mouse fibroblast cell line with IC_{50} values in the range of approximately 13–38 μM (entries 4, 5, 7, 8, 11–13, 15 and 17–20), which are approximately 2 orders of magnitude higher than the IC_{50} value of borrelidin itself (entry 1).

The cyclohexane-based fragment **(4Cy)a′Cl** with the free hydroxy group was the most active one in this series (IC_{50} 12.9 ± 2.7 μM). The presence of 11-hydroxyundecanecarboxylate in compound (**26Ar**) seems to influence the cytotoxic activity when compared with acetyl-protected **(4Ar)cBr** (entries 6 and 19), as only (**26Ar**) displayed potency against the cell line (IC_{50} 22.3 ± 9.8 μM). This effect was less pronounced for the corresponding cyclohexene-based derivatives **(4En)cBr** and (**26En**) (entries 11 and 20). Also the activity of cyanodienes **24** appeared to depend on the *O*-protecting group. While acetyl-protected **(24Ar)c** was inactive, TBS-ethers **(24En)b** and **(24Cy)b** revealed IC_{50} values between 15 and 17 μM, respectively (entries 16–18). Both borrelidin analogues (**2Ar**) and (**2En**) were inactive (entries 2 and 3) showing the relevance of the residue at C-17 for the biological activity of intact borrelidin. However, when only the southern fragment is present, the cytotoxicities seem to be only slightly affected by the kind of the six-membered ring system.

It should be noted that Sugawara *et al.* reported a significant decrease of cytotoxicity in the human diploid embryonic cell line MRC-5 when carboxylic acid at C-22 in borrelidin (**1**) was replaced by a methylester.[9a] Furthermore, the cytotoxic activity was almost lost upon acetylation of the 3-OH and 11-OH groups of **1**. Although comparison of these data should be handled with great care and taking into consideration that the mode of action of these analogues and the natural product might be different due to significant structural differences, the results in Table 4 suggest that an unbiased halogenocyanodiene moiety apparently favors cytotoxicity, whereas the macrocyclic ring deteriorates the activity (*e.g.* compare entries 2, 4 and 19). The increase of biological activity of borrelidin (**1**) by one order of magnitude upon hydrogenation of the C12–C15 diene moiety[9a] indicates that the contribution of the cyanodiene unit to the biological mode of action as well as the role of the northern fragment and the interplay between the northern and the southern fragment need to be further studied.

Table 4 Cytotoxic activities of cyanodienes **4**, **24**, and **26** and borrelidin analogues **2** against the L-929 mouse fibroblast cell line. For comparison the corresponding value of borrelidin (**1**) was determined



Entry[a]	Compound	IC_{50} (μM)	Entry[a]	Compound	IC_{50} (μM)
1	Borrelidin **1**	0.49 ± 0.19	11	**(4En)cBr**	27.1 ± 1.5
2	(**2Ar**)	>50	12	**(4Cy)a′Cl**	12.9 ± 2.7
3	(**2En**)	>50	13	**(4Cy)aBr**	16.9 ± 3.4
4	**(4Ar)aBr**	25.0 ± 0.7	14	**(4Cy)bCl**	>50
5	**(4Ar)cCl**	37.6 ± 10.8	15	**(4Cy)bBr**	37.8 ± 5.1
6	**(4Ar)cBr**	>50	16	**(24Ar)c**	—
7	**(4En)aCl**	23.3 ± 7.9	17	**(24En)b**	16.8 ± 4.7
8	**(4En)aBr**	20.5 ± 9.6	18	**(24Cy)b**	14.5 ± 4.4
9	**(4En)bCl**	—	19	(**26Ar**)	22.3 ± 9.8
10	**(4En)bBr**	—	20	(**26En**)	16.4 ± 3.9

[a] IC_{50} values were calculated by fitting the concentration dependence of the signals from the WST-1 cytotoxicity assay[44] with the 4-parameter equation and are given as mean ± S.D. of four replicates.

Conclusion

We have prepared a dedicated library of cyanodienes employing a sequence of cross metathesis and HWE olefination as key steps while alternative approaches met with little success. Cyanodienes were designed as structural analogues of the southern fragment of borrelidin (**1**). Attempts to cyclize cyanodienes (**27Ar**) and (**27En**) to the corresponding macrocyclic

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borrelidin analogues (**2Ar**) and (**2En**) by using Omura's SmI_2 method were not successful. However, this key transformation could be achieved by Grignard cross coupling providing the borrelidin analogues (**2Ar**) with an aryl side chain at C17 and the corresponding analogue (**2En**) with a cyclohexenyl side chain at C17 in 6 steps starting from fragments **(5Ar)a** and **(5En)a**. Quantum-chemical calculations were performed for (**27Ar**) to interpret the macrocyclization. The calculation suggests that the northern fragment, *i.e.* the 11-hydroxyundecanecarboxylate, makes the macrocyclization entropically less favorable due to a multitude of flexible conformations which are connected by low barriers. The opposite was found for the highly methyl-branched fragment in the natural product **1**. For the latter a helical conformation has already been reported[11,15a] which seems to facilitate the macrocyclization. SAR studies employing the L-929 mouse fibroblast cell line indicate a higher cytotoxicity for unbiased cyanodienes **4**, **24**, and **26** than for the truncated borrelidin derivatives **2**. Future work must demonstrate whether more rigid northern fragments are beneficial with regard to both macrocycle formation and biological activity.

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