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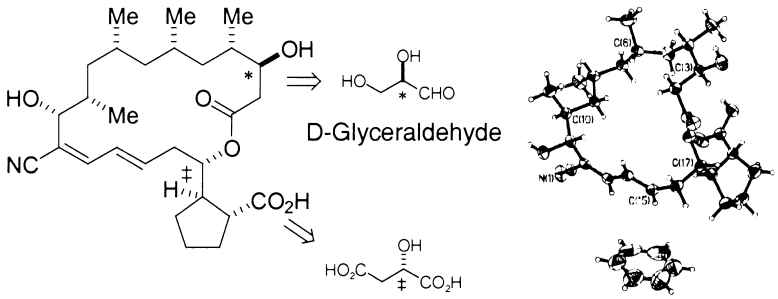

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Application of Conformation Design in Acyclic Stereoselection: Total Synthesis of Borrelidin as the Crystalline Benzene Solvate

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Abstract: The total synthesis of (−)-borrelidin (treponemycin), a structurally distinct 18-membered macrolide antibiotic, has been achieved. It was isolated as the crystalline benzene solvate, and its structure was confirmed by a single-crystal X-ray analysis. The deoxypropionate subunit consisting of four alternating *C*-methyl groups with a C_4-C_{10} syn/syn/anti orientation was elaborated by a new method of iterative cuprate additions to acyclic α,β-unsaturated esters relying on two consequtive 1,3-inductions and starting with D-glyceraldehyde as the chiral progenitor. The unique *Z/E* cyanodiene unit was obtained as a single isomer by application of the Still−Gennari olefination protocol. The γ-hydroxycyclopentane carboxylic acid subunit was prepared from L-malic acid utilizing a sequential introduction of *C*-vinyl and *C*-allyl groups, capitalizing on 1,2-induction in an acyclic α,β-unsaturated ester and carbocyclization by a Grubbs ring closure metathesis reaction. The prevalence of 1,3-syn-disposed deoxypropionate triads in the cuprate additions is rationalized on the basis of minimized syn-pentane interactions in the transition states. A virtual diamond lattice was used as a visual tool to portray the low-energy conformations of the acyclic substrates, and corroborated by ^{1}H NMR homodecoupling studies.

Borrelidin (treponemycin) is a structurally distinct, atypical macrolide antibiotic produced by a variety of *Streptomyces*.[1] In addition to its long-known inhibitory effect against experimental infections caused by *Borrelia*, the spirochete of relapsing fever,[2] it also exhibits a diverse spectrum of biological activities.[3] The inhibition of cyclin-dependent kinase of *Saccharomyces cerevisiae*[4] and the potent antiangiogenesis activity[5] in the rat aorta have attracted renewed attention to this structurally unique, albeit toxic, nitrile-containing natural product.[6] The structure of borrelidin (**1**, Figure 1), was elegantly determined by chemical degradation,[7] and its absolute configuration was deduced by X-ray crystallography of a (*S*)-2-methylbutanol solvate.[8] Morken and co-workers[9] have recently reported the first total synthesis of borrelidin utilizing enantioselective asymmetric methods of subunit construction and assembly. The synthesis of individual deoxypropionate subunits has been the subject of two reports,[10,11] relying on a Sharpless asymmetric epoxidation[12] and a Myers[13] enolate alkylation as key reactions, respectively.

Borrelidin (**1**) displays structural and functional features that distinguish it among macrolides and related natural products.[14] Thus, the C_1-C_{11} substructure encompasses four 1,3-alternating *C*-methyl groups as part of deoxypropionate segments with a distinctive syn/syn/anti relationship. Moreover, the *Z*/*E* cyanodiene unit at $C_{13}-C_{16}$ and the γ-hydroxy β-branched cyclopentane carboxylic acid unit have not been previously encountered in other natural products.

We describe herein the stereocontrolled total synthesis of crystalline (−)-borrelidin, isolated and characterized as its benzene solvate for the first time. Antithetic disconnections reveal acyclic and carbocyclic subunits that originate from D-glyceraldehyde and L-malic acid, respectively, as chiral progenitors, relying on a series of 1,2- and 1,3-inductions (Figure 1). The assembly plan would involve the coupling of a sulfone anion, prepared

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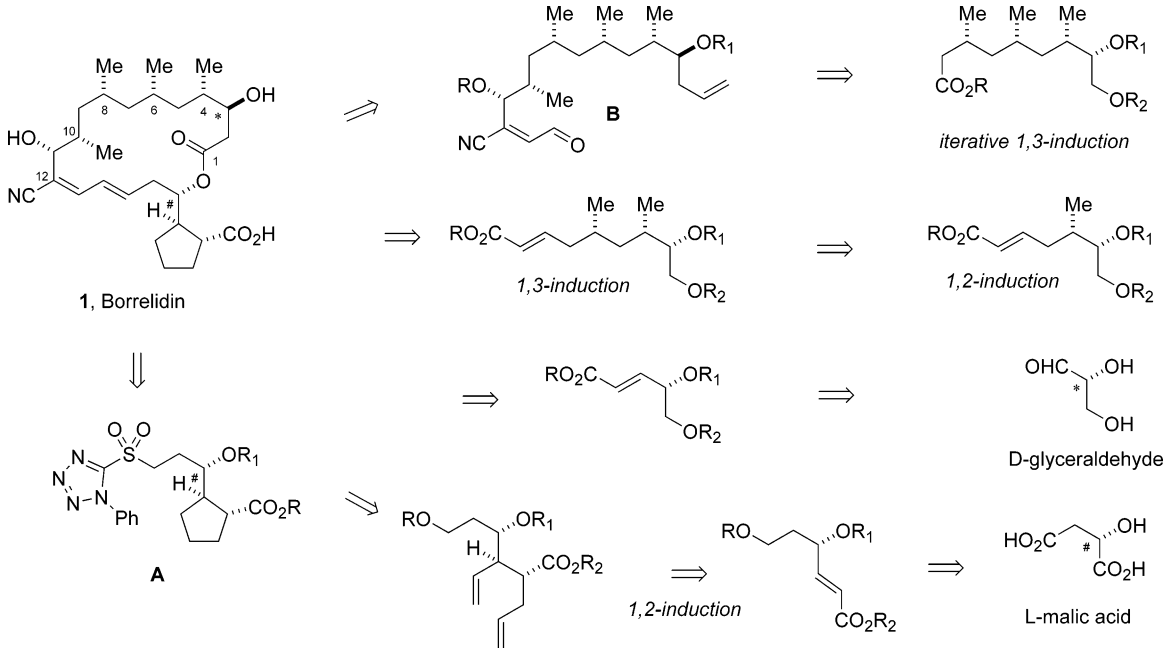

Figure 1. Borrelidin and its chiral progenitors.

from the cyclopentane carboxylic acid subunit A, to an acyclic cyanodiene aldehyde B, followed by cyclization to the 18-membered macrolactone and further elaboration to (−)-borrelidin.

C_1-C_{13} Substructure. Our first objective was to explore the prospects of a new synthesis of syn-disposed deoxypropionate subunits that could be applicable to borrelidin and other natural products. It is of interest that in the majority of natural products containing alternating 1,3-dimethyl groups on acyclic chains, their dispositions are invariably all-syn. Among those with two syn-disposed deoxypropionate units (two stereotriads)[15] for example are pectinatone,[16] lardolure,[17] TMC-151,[18] siphonarienolone,[19] and siphonarienal.[20] Doliculide[21] and borrelidin (**1**) are examples of macrolides that contain a syn-disposed 2,4,6-trimethylheptane motif in their macrolactone framework. Ionomycin,[22] zaragozic acid A,[23] rapamycin,[24] rakicidin C,[25] and several macrolides[26] and ionophores[27] contain substructures with syn-disposed 2,4-dimethylpentane motifs. The occurrence of deoxypropionate subunits in natural products has instigated many methods for their stereocontrolled synthesis.[13,28] In some cases, these methods have been utilized in an iterative manner to prepare acyclic motifs containing 2,4-dimethyl- and 2,4,6-trimethyldeoxypropionate subunits.[13,16,28a,b]

We have previously reported on the stereocontrolled synthesis of polypropionate subunits by an iterative protocol, whereby an enantiopure γ-alkoxy-α,β-unsaturated ester was subjected to a conjugate addition of lithium dimethylcuprate (Gilman cuprate), followed by hydroxylation of the corresponding potassium enolate.[29] Homologation to a new γ-alkoxy enoate, reiteration of the conjugate addition, and enolate hydroxylation afforded propionate triads of defined stereochemistry in a growing acyclic chain. This protocol of acyclic stereoselection relying on a series of sequential 1,2-inductions was successfully

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applied to the synthesis of the eight contiguous stereogenic centers in the polypropionate subunit of rifamycin S[30] and to the total synthesis of bafilomycin A_1.[31] We describe herein a new method for the synthesis of enantiopure acyclic esters containing the syn-4,6,8-trimethyl substitution pattern found in the C_1-C_9 substructure of borrelidin (Figure 1) and its further elaboration to the target itself.

Highly selective conjugate addition of lithium dimethylcuprate in the presence of TMSCl[32] to the readily available enoate **2** gave the adduct **3** as previously reported.[29a] Reduction of the methyl ester, followed by Swern oxidation and homologation, afforded the *tert*-butyl enoate **4** in excellent overall yield (Scheme 1). Cuprate addition to **4** led to a mixture of **5** and its anti isomer (not shown) in a ratio of 4:1 in favor of the desired syn isomer. Reduction to the respective alcohols afforded **6**, which was separated from the minor anti isomer and then homologated to the enoate **7**. A third cuprate addition afforded the C_3-C_7 syn/syn adduct **8** as the major product in 88% yield (syn/syn:anti/syn > 10:1 by 600 MHz ^{1}H NMR analysis of the homologated enoate). Its configurational identity was established by conversion to a known enantiopure product (see later). Although a fourth cuprate addition to the homologated enoate **10** proceeded in excellent yield, the resulting adduct harboring a terminal anti triad as required for C_{10} in borrelidin was obtained as the minor isomer compared to the seemingly favored all-syn configuration (syn/anti 2:1 for the last cuprate adduct). Therefore, a different approach was pursued to introduce the last *C*-methyl group at C_{10} with the desired stereochemistry. Thus, the trisubstituted ester **11**, prepared from the alcohol precursor **9** in two steps, was subjected to a variety of reduction conditions in an effort to secure the C_{10} methyl group. Unfortunately, none of the conditions tried gave satisfactory results.[33] We then decided to attempt a regioselective opening of the epoxide **12**. Reduction of the ester **11** and treatment of the resulting allylic alcohol with $VO(acac)_2$ in the presence of TBHP gave the desired epoxide as a 6:1 mixture of isomers. On the other hand, Sharpless−Katsuki epoxidation[12] led to **12** as the major product (20:1). The next challenge was to effect a regioselective ring opening of the epoxide **12** at the tertiary site. There are a number of examples of Lewis acid-catalyzed ring openings of epoxy alcohols.[34] Thus, use of $NaCNBH_3/BF_3\cdot Et_2O$, Dibal-H, or $LiBH_4/Ti(i\text{-}PrO)_4$ gave, after pivaloylation, the desired **13**, albeit with little or no selectivity. However, use of $LiBH_4/BF_3\cdot Et_2O$ afforded **13** as a major regioisomer in a ratio of 6:1. Protection of the hydroxyl group in **13** as a TBS ether, hydrogenolysis to remove the BOM ether, mesylation of the resulting alcohol, and selective cleavage of the TBDPS ether with Bu_4NF led to concomitant formation of the inverted epoxide **14**. Cleavage of the epoxide with vinylmagnesiocuprate and protection of the resulting alcohol as the TBS ether gave **15**, which was deesterified to the primary alcohol. Thus, the C_1-C_{13} substructure of borrelidin was secured in a stereocontrolled manner by two sequential conjugated additions of lithium dimethylcuprate to α,β-unsaturated esters relying on syn-selective 1,3-induction.

Z/E Cyanodiene Substructure. As previously mentioned, the *Z/E* diene unit in borrelidin is unique among natural products that contain a nitrile group.[6] Although cyanoolefins have been prepared from phosphorus-based reagents,[35] the necessity to have a *Z*-geometry presented an opportunity to apply the Still−Gennari olefination conditions.[36] Oxidation of the alcohol obtained from **15** to the corresponding aldehyde and treatment with TMSCN in the presence of $AlCl_3$[37] afforded the cyanohydrin **16** as a mixture of isomers (Scheme 1). Although several attempts to oxidize **16** to the corresponding cyanoketone (MnO_2, PCC, Swern) led to decomposition, oxidation was successfully achieved in excellent yield with the Dess−Martin periodinane reagent.[38] Olefination under the Still−Gennari conditions took place to give the *Z*-cyanomethoxycarbonylmethylene product **17** *as a single isomer* as evidenced by ^{1}H and ^{13}C NMR. Subsequent reduction to the alcohol **18** via the mixed anhydride and oxidation with the Dess−Martin reagent afforded the aldehyde intermediate **19**.

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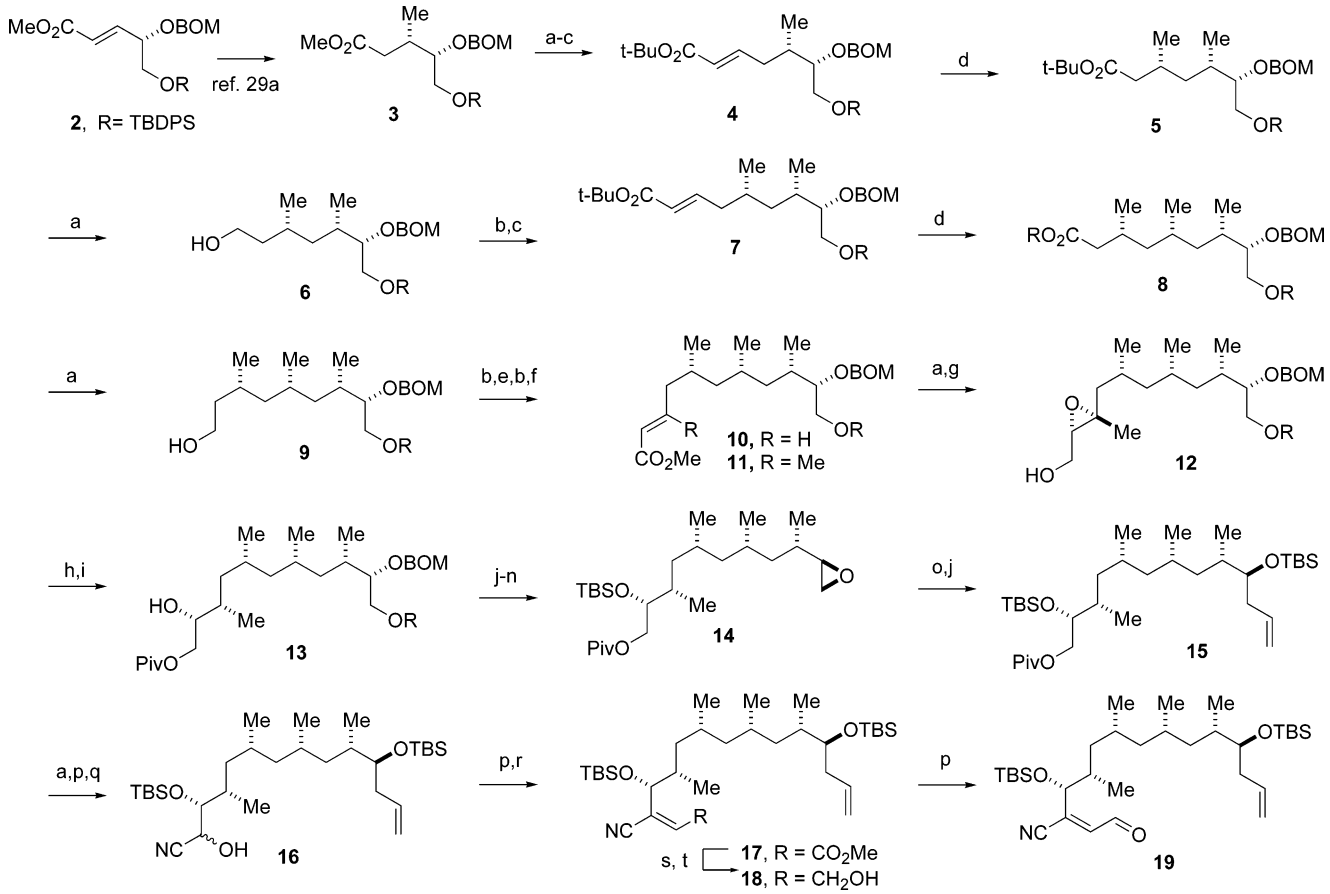
Scheme 1 [a]



[a] Reagents and conditions: (a) Dibal-H, CH_2Cl_2 (80%); (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C (96%); (c) $PPh_3CHCO_2{}^tBu$, CH_2Cl_2 (91%); (d) MeLi·LiBr, CuI, TMSCl, THF, −78 °C (93%, 4:1 *syn*-**6**/*anti*-**6a**); repeat a (82%); repeat b (88%); repeat c (90%); repeat d (88%) [syn/syn/syn > 90% by chiral GC analysis of a derivative]; repeat a (92%); repeat b (77%); (e) MeLi·LiBr, THF, −78 °C; repeat b (80% for two steps); (f) LiHMDS, $(MeO)_2P(O)CH_2CO_2Me$, THF, reflux, 12 h (88% 9:1 *E*/*Z*); repeat a (96%); (g) (+)-diethyl tartrate, $Ti(^iPrO)_4$, ^tBuOOH, CH_2Cl_2, −20 °C (86%, 20:1); (h) $LiBH_4$, $BF_3{\cdot}OEt_2$, THF (71%, 6:1); (i) PivCl, NEt_3, DMAP, CH_2Cl_2 (91%); (j) TBSOTf, 2,6-lutidine, CH_2Cl_2 (90%); (k) H_2, Pd/C 10%, MeOH (80%); (l) MsCl, NEt_3, CH_2Cl_2 (82%); (m) TBAF, THF; (n) K_2CO_3, MeOH (88% for two steps); (o) vinylMgBr, CuI, THF, −78 °C (82%); repeat j (91%); repeat a (98%); (p) Dess−Martin periodinane, CH_2Cl_2; (q) TMSCN, $AlCl_3$, CH_2Cl_2, then PPTS, MeOH (92% for three steps); repeat p; (r) KHMDS, 18-crown-6, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, −35 °C (70% for two steps); (s) LiOH, THF/MeOH/H_2O (3:1:1); (t) EtOCOCl, NEt_3,THF, then $NaBH_4$, MeOH (51% for two steps); repeat p (90%).

Cyclopentane Carboxylic Acid Substructure. Our strategy for the synthesis of the cyclopentane carboxylic acid with its γ-hydroxy appendage also relied on acyclic precursors. Thus, L-malic acid was easily converted to the chain-extended enoate **20**, which was subjected to conjugate addition with vinylmagnesiocuprate to afford the *C*-vinyl adduct **21** as the major isomer (5.5:1) (Scheme 2).[29b,39] Alkylation of the potassium enolate with allyl iodide gave the syn-allylated adduct **22** as previously reported for related vicinal 1,2-*C*-alkylations.[29b] Carbocyclization by the venerable Grubbs ring closure metathesis[40] led to **23** in excellent yield. Hydrogenation and further manipulations of the hydroxyl groups by well-precedented methodology[41] followed by separation of the minor isomer afforded the enantiopure sulfone intermediate **24** as the coupling partner to the previously obtained aldehyde **19**.

Assembly of Units and Completion of Synthesis. With the two subunits **19** and **24** in hand, we proceeded with their coupling under the conditions of the Julia reaction[42] as modified by Kocienski and co-workers (Scheme 3).[41] Thus, addition of the aldehyde **19** to a solution of the phenyltetrazole sulfone **24**, previously treated with NaHMDS and 15-crown-5 in THF at −78 °C, afforded the desired *Z*/*E* cyanodiene **25** and its isomeric *E*/*E* product in a ratio of 5:1, respectively. Various attempts to improve this ratio by varying the base and solvent were not successful.[43] We next addressed the selective oxidative cleavage of the terminal olefin. Under carefully controlled conditions of time and temperature, it was possible to achieve clean cleavage with OsO_4 and NMO in aqueous THF. Although the isolated yield of the aldehyde was modest (∼25%), the unreacted olefin could be easily recycled and an overall yield of 95% could be achieved. Evidently, the cyanodiene unit was also susceptible to prolonged exposure to the oxidant, hence a careful monitoring of the progress of the reaction was needed. Attempts to

(39) For examples of lithium dialkylcuprate additions to α,β-unsaturated esters having a γ-acetal group, see (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (b) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3814. (c) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. (d) Larcheveque, M.; Tamagau, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31. (e) Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett.* **1990**, *31*, 6205.

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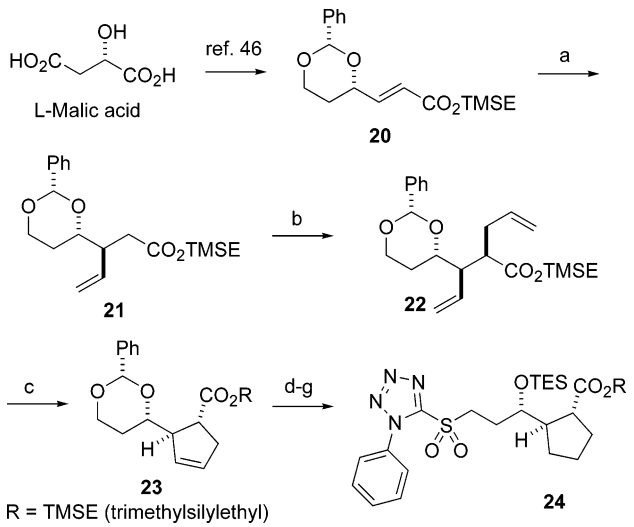
(42) (a) Julia, M.; Paris, J.-M., *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.

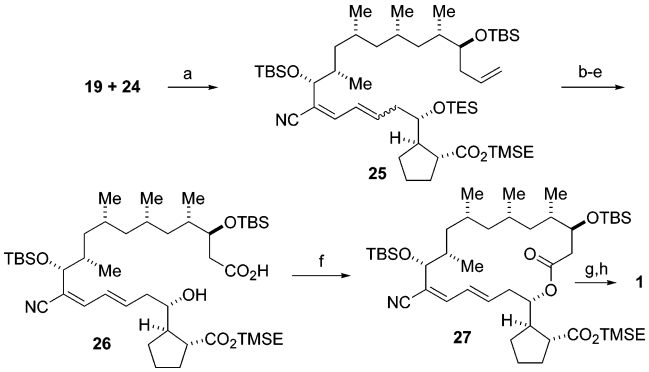
(43) The following conditions gave lower ratios: KHMDS/THF, −78 °C; KHMDS/18-crown-6/THF, −78 °C; KHMDS/DME, −78 °C; LiHMDS/THF, −78 °C; and NaHMDS/THF, −78 °C.

Scheme 2 [a]



[a] Reagents and conditions: (a) vinylMgBr, CuI, TMSCl, THF, −78 °C, (83%, 5.5:1 anti/syn); (b) KHMDS, THF, −78 °C, then allyl iodide (72%); (c) Grubbs' catalyst, CH_2Cl_2, rt (98%); (d) H_2, Pd/C 10%, MeOH/AcOH (4:1) (quant); (e) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DIAD, THF, 0 °C to rt (97%); (f) TESOTf, 2,6-lutidine, CH_2Cl_2 (85%); (g) m-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 12 h (71%).

Scheme 3 [a]



[a] Reagents and conditions: (a) NaHMDS, 15-crown-5, then **19**, THF, −78 °C to rt (5:1 *E/Z*, 66%); (b) OsO_4, NMO, THF/H_2O (25%, 95% after recycling); (c) $NaIO_4$, THF/H_2O; (d) $NaClO_2$, NaH_2PO_4, MeCN/H_2O (74% for two steps); (e) PPTS, MeOH/CH_2Cl_2 (93%); (f) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF/PhMe, 40 °C (73%); (g) HF, MeCN/H_2O (72%); (h) TBAF, THF (94%).

selectively cleave the terminal olefin with ozone by using Sudan red as an indicator[44] gave intractable mixtures.

Oxidation of the aldehyde to the carboxylic acid, selective cleavage of the TES ether, and separation of the minor *E/E*-cyanodiene isomer gave pure **26**. There remained to effect macrolactonization and deprotection to obtain the intended target. In the event, Yamaguchi lactonization [45] proceeded smoothly to afford **27** in 73% yield. The TBS ethers were cleaved with HF in aqueous acetonitrile, and the resulting TMSE ester was hydrolyzed with TBAF to afford crude borrelidin. Chromatographic purification and crystallization from benzene/hexane afforded X-ray quality crystals of borrelidin as the benzene solvate (Figure 2), identical with an authentic sample (mp, $[\alpha]_D$, LC/MS). It is interesting that the solvated benzene

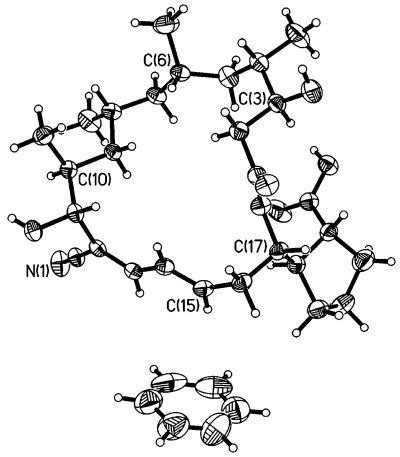


Figure 2. Synthetic borrelidin as its benzene solvate.

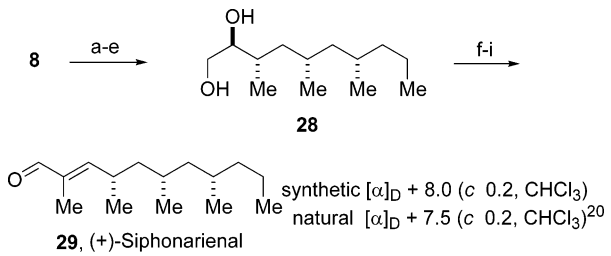
molecules were located near the cyanodiene portion in the unit cell in a 1:1 ratio.[46] This new benzene solvate is the second crystalline form of borrelidin since its initial isolation and X-ray structure elucidation as the (*S*)-2-methylbutanol solvate.[8]

Other Synthetic Applications of the Iterative *syn*-Deoxypropionate Method. As already outlined, it was our intention to explore the practicality of iterative conjugate addition of Gilman cuprates to acyclic δ-methyl-α,β-unsaturated esters as a method to access *syn*-deoxypropionate triads. The few reported examples utilize chiral auxiliaries as a means of asymmetric induction. Sakai and co-workers[47] showed a modest level of diastereoselectivity in the addition of lithium dimethylcuprate to α,β-unsaturated monoesters of (*R,R*)-1,2-cyclohexanediol prepared from *R*- and *S*-citronellal. Depending on the configuration of the resident *C*-methyl group, they obtained syn/anti ratios of 1:1 or 3:1 in 40−42% yields. Breit and Demel[48] reported conjugate addition of lithium dimethylcuprate to enantiopure α,β-unsaturated esters already containing a predisposed δ-*C*-methyl group and an adjacent directing group. They obtained a high preponderance of the *anti*-deoxypropionate isomer as determined by NMR. Williams et al.[49] described the stereoselective synthesis of syn- and anti-1,3-dimethyl arrays of deoxypropionates relying on the conjugate addition to enantiopure *N*-enoyloxazolidinones. Oppolzer et al.[50] synthesized anti-deoxypropionate units relying on stereoselective additions of an organocopper reagent already harboring a stereogenic *C*-methyl group to α,β-unsaturated camphosultam amides. To the best of our knowledge, these are the only known examples of a single-stage addition of lithium dimethylcuprate to δ-methyl α,β-unsaturated esters that lead to a 1,3-dimethyl deoxypropionate triad.

The present study has shown that *two* consequtive 1,3-syn-selective cuprate additions to enoates and their homologues that contain a δ-methyl group are possible. Although only minor amounts of the presumed C_3-C_7 anti/syn diastereomer could be detected in the third cuprate addition product **8** (Scheme 1) by ^{13}C and ^1H NMR, we sought to obtain further evidence for

(44) (a) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis*. **1980**, 807. (b) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 2699.
(45) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(46) See Supporting Information for details.
(47) Ogawa, T.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1993**, *41*, 1652.
(48) Breit, B.; Demel, P. *Tetrahedron* **2000**, *56*, 2833.
(49) Williams, D. R.; Kissel, W. S.; Li, J. J.; Mullins, R. J. *Tetrahedron Lett.* **2002**, *43*, 3723.
(50) Oppolzer, W.; Maretti, R.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4713.

Scheme 4 [a]



[a] Reagents and conditions: (a) Dibal-H, PhMe, −78 °C (92%); (b) TsCl, pyridine (88%); (c) MeLi, CuI, Et_2O, −40 °C (100%); (d) TBAF, THF; (e) H_2 (60 psi), Pd/C, MeOH/AcOH (87% for two steps); (f) $NaIO_4$, CH_2Cl_2/H_2O; (g) $PPh_3C(Me)CO_2Et$, PhMe/CH_2Cl_2, 80 °C (85% for two steps); (h) Dibal-H, CH_2Cl_2, −78 °C (100%); (i) MnO_2, hexane (94%).

its configurational identity by conversion to a known natural product before proceeding with the synthesis of borrelidin.[51]

Among the marine natural products isolated from the genus *Siphonarea griseo* are the metabolites siphonarienal **29**[20] and siphonarienone[28a] that harbor syn/syn-deoxypropionate triads (Scheme 4). Calter,[19] Norté,[20] and their co-workers have reported total syntheses of siphonarienal **29** utilizing catalytic and noncatalytic asymmetric methods, respectively. In both methods, the deoxypropionate motif was secured by a two-step deoxygenation of an initially obtained propionate triad to afford siphonarienal. Compound **8**, with the correct C_3-C_7-trimethyl substitution pattern and absolute stereochemistry already in place, was converted in five simple steps to **28** in 70% overall yield (Scheme 4). Cleavage of the terminal diol and Wittig olefination led to the corresponding trisubstituted ester, which upon reduction and allylic oxidation gave siphonarienal with physical constants identical to reported values.[20]

In an effort to demonstrate the viability of the iterative conjugate addition of cuprates to δ-methyl-α,β-unsaturated enoates, we show two additional examples of 1,3-syn-selective deoxypropionate motifs (Scheme 5). Homologation of **30**[29b] (>10:1 anti/anti-syn/anti) to the enoate **31**, followed by cuprate addition, afforded the C_3-C_5 syn isomer **32** as the preponderant product (syn/anti > 7:1 by 600 MHz ^{1}H NMR analysis of the homologated enoate).[46,52] Manipulation of functional groups in **32** by deoxygenation, reduction, and protection of the primary alcohols as MOM ethers afforded the meso compound **34**.[52] Homologation of **32** to the corresponding enoate followed by cuprate addition afforded **33** as the major isomer C_3-C_7 (syn/syn-anti/syn > 8:1 by 400 MHz ^{1}H NMR of the homologated enoate[46]). Further manipulation as for **32** gave the *meso*-diol derivative **35**.[52]

The ^{13}C chemical shifts of C_4, C_6, and C_8 of several enoates containing syn- and anti-deoxypropionate triads revealed interesting correlations (Table 1 and Figure 3). Thus, within a given pair of triads, the chemical shift value of C_4 in the syn isomer was at higher field compared to C_4 in the anti isomer (Table 1, entries 1−4). The reverse trend was observed for C_6 of the syn isomer compared to that of the anti isomer. Furthermore, within a single syn-dimethyl triad, the C_4 chemical shift value of the syn isomer was at higher field relative to C_6 of the same isomer. Again, the same trend was reversed in the anti isomer (Table 1, entries 1 and 2). These observations could be extended to syn/syn and anti/syn triads harboring three alternating *C*-methyl groups (Table 1, entries 3 and 4, compare C_4 and C_8). A similar trend, albeit with smaller chemical shift differences between a pair of syn and anti triads, has been observed by Breit and Demel.[48] Enoates containing 1,3-syn and anti triads can also be distinguished from a study of characteristic chemical shift differences between geminal methylene protons.[46] Chemical shift differences between methylene protons closest to the newly introduced methyl group in the enoate **10** are larger in the syn/syn compared to the anti/syn isomer (Figure 3B; compare H,I vs H′,I′ and E,F vs E′,F′). The same trend was observed in the case of syn-**7** and its minor anti isomer.[46] Thus, the chemical shift values in the ^{13}C and ^{1}H spectra of deoxypropionate triads of δ-methyl-α,β-unsaturated esters can be used as means of relative syn and anti stereochemical assignment.[53]

Syn-Selective Deoxypropionate Synthesis Based on Conformation Control. The most basic structural repetitive motif in a polydeoxypropionate chain is a 2,4-dimethylpentane unit. Despite its many degrees of rotational freedom, 2,4-dimethylpentane can be rendered monoconformational by anchoring an inductor group at one end of the chain, thereby orienting the two methyl groups so as to avoid 2,4-dimethylpentane interactions.[54] On a macroscopic scale, this preference is manisfested in the structure of all-syn homogeneously isotactic polypropylene,[55] which crystallizes in a helical conformation. Asymmetric 1,3-induction in the polymerization of methyl methacrylate was observed by Leitereg and Cram.[56] Insightful studies by R. W. Hoffmann[54a−c] have shown that the calculated preferences for extended conformations in derivatives of 1-*tert*-butyl-substituted isotactic oligodeoxypropionates are in the order 2,4-dimethylalkane (91% syn) > 2,4,6-trimethylalkane (76% syn) > 2,4,6,8-tetramethylalkane (58% syn).[54a] For entropic reasons, the preference for conformational control favoring syn-disposed methyl groups diminishes as 2,4-dimethylpentane units are added to existing triads.[54a,57] Nature appears to be using the same conformation principles to avoid syn-pentane interactions in the

(51) Compound **8** was also transformed to the corresponding *meso*-1,9-dimethoxymethyl-3,5,7-trimethyl-1,9-nonane diol **34**, $[\alpha]_D$ 0 (*c* 0.48, $CHCl_3$), as also corroborated by ^{13}C,^{1}H NMR. Chiral GC analysis indicated a diastereomeric purity >90%.

(52) It was not possible to obtain diastereomeric syn/anti ratios by chiral GC or LC for intermediates **32** and **33**. Transformation to the meso-hydrocarbons **34** and **35,** respectively, and analysis of *crude* products by chiral GC indicated a diastereomeric purity >80%.

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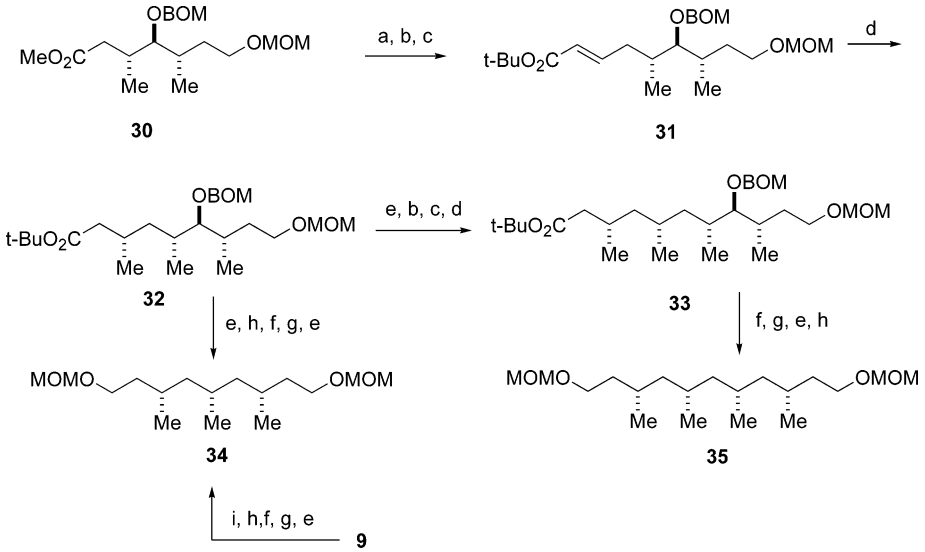
(57) It is estimated that an energy gap as high as 7 kJ/mol^{-1} can be created between the lowest and highest energy conformers of hydrocarbon backbones carrying alternating 1,3-dimethyl substituents and subject to destabilizing *syn*-pentane interactions. See for example: (a) Tsuzuki, S.; Schafer, L.; Goto, H.; Jemmis, E. D.; Hosoya, H.; Siam, K.; Tanabe, K.; Osawa, F. *J. Am. Chem. Soc.* **1991**, *113*, 4665. (b) Fărcaşiu, D.; Walter, P.; Sheils, K. *J. Comput. Chem.* **1989**, *10*, 520. (c) Pérez, J. J.; Villar, H. O.; Arteca, G. A. *J. Phys. Chem.* **1994**, *98*, 2318. (d) Flory, P. J. *Statistical Mechanics of Chain Molecules*; J. Wiley & Sons: New York, 1969.

Scheme 5 [a]



[a] Reagents and conditions: (a) Dibal-H, PhMe, −78 °C, (90%); (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (c) PPh_3CHCO_2t-Bu, CH_2Cl_2, (85% for two steps); (d) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, (91%). For **32** to **33**: (e) $LiAlH_4$, THF, 0 °C, (92%); repeat b and c (93% for two steps); repeat d (93%). For **33** to **35**: (f) H_2, Pd/C 10%, MeOH (99%) (g) MsCl, NEt_3, DMAP, CH_2Cl_2; repeat e; (h) MOMCl, Hunig's base, CH_2Cl_2 (84% for three steps). For **32** to **34**: step e (92%); step h (93%); step f (quant); step g (71%); repeat e (70%). For **9** to **34**: (i) TBAF, THF, rt; steps h and f (86% for three steps); steps g and e (85% for two steps).

Table 1: Comparison of Selected ^{13}C NMR Data of Syn and Anti Triads

entry	enoates	^{13}C NMR Shift (ppm)[a,b] 4	6	8	10
1	TBDPSO, OBOM, CO_2t-Bu, **7**	38.9	40.1	82.7	-
2	TBDPSO, OBOM, CO_2t-Bu, ***anti-7***	41.0	39.3	83.2	-
3	TBDPSO, OBOM, CO_2t-Bu, **10**	39.1	44.5	40.6	82.7
4[c]	TBDPSO, OBOM, CO_2t-Bu, ***anti-10***	41.2	43.8	40.8	82.9

[a] Data were recorded on a Bruker DMX600 at 303 K in CD_2Cl_2 calibrated at 53.8 ppm. [b] Chemical shifts were assigned on the basis of HMQC experiments. [c] Data from a 2:1 mixture of syn/syn-**10** and anti/syn-**10** by cuprate addition to **7** at −30 °C.

biosynthesis[58] of metabolites in which stereoregular single, double, or triple syn-1,3-dimethyldeoxypropionate triads are created.[54a] This preference is nicely corroborated in the X-ray crystal structures of (3*S*,5*R*,7*R*)-2,3,5-trimethyl-2,7-octanediol[54b] and of acyclic natural products such as pectinatone,[16] bourgeanic acid,[59] and TMC-151,[18] all of which harbor syn-related 1,3-deoxypropionate subunits, yet they adopt conformations that are devoid of syn-pentane interactions.

In considering the synthesis of syn-deoxypropionate units by an iterative addition of lithium dimethylcuprate to a growing chain of δ-methyl-α,β-unsaturated esters, we relied on the basic notion that transition-state conformations leading to intermediates in which syn-pentane interactions are minimized or avoided would be favored. We have used a virtual diamond lattice[60] as a hypothetical template upon which we superimposed the carbon backbone of several acyclic structures containing syn-1,3-dimethylpentane units, including pectinatone,[16] bourgeanic acid,[59] and TMC-151[18] from their X-ray coordinates. The diamond lattice was originally used in the context of macrolide conformational analysis.[61] More recently Kishi and co-workers used it to rationalize the conformations of *C*-glycosides[62a] and complex natural products.[62b] Other applications to the study of conformations of subunits in natural products have also been reported.[63]

The quasi perfect congruence of the X-ray structures on a diamond lattice exemplified by pectinatone (Figure 4A) encouraged us to use it as a visual aid to rationalize the observed prevalence of syn-1,3-dimethyl orientations after each cuprate addition. The 600 MHz ^1H NMR spectrum of enoate **7** showed unusually well-resolved individual signals for the methine and methylene protons within the triad, indicating the prevalence of a time-averaged preferred conformer in which the folding of the backbone was very similar to that of (−)-pectinatone in the crystal structure. The ^3J coupling constants determined by homodecoupling experiments corresponding to a conformation that is "anchored" by the *O*-BOM substituent[54a] are listed in Figure 4B. The same trend was observed in the case of **10** harboring a C_5-C_9 syn/syn-trimethyl motif, which closely simulates the pectinatone backbone conformation (Figure 4C). Low-energy conformations for **7** and **10** in accord with the NMR-derived results were also suggested by MM3 studies.[64]

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(63) See for example: (a) Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224 (epothilone); (b) Choy, N.; Shin, Y.; Nguyen, P. Q.; Curran, D. P.; Balachandran, R.; Madiraju, C.; Day, B. W. *J. Med. Chem.* **2003**, *46*, 2847 (discodermolide).

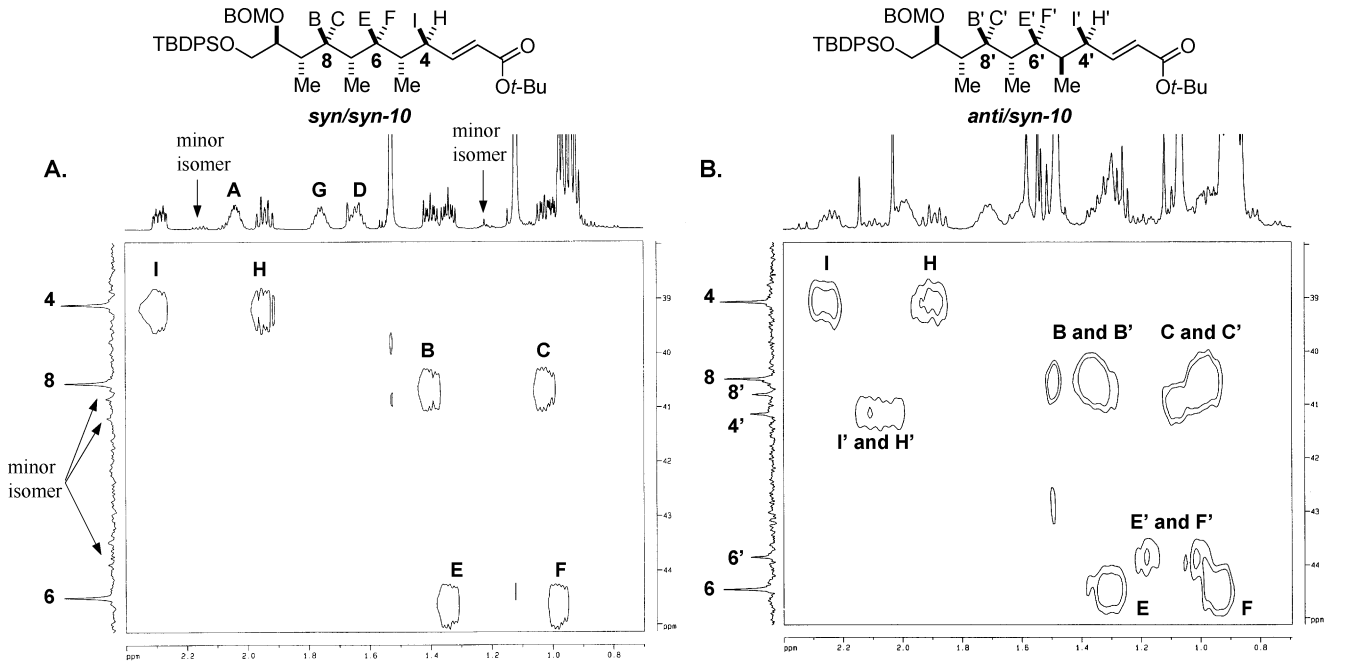

Figure 3. (A) Partial HMQC of *syn*/*syn*-**10** recorded on a Bruker DMX 600 in CD_2Cl_2 at 303 K. (B) Partial HMQC of an artificial mixture of *syn*/*syn*-**10** and *anti*/*syn*-**10** recorded on a Bruker AV 400 in CD_2Cl_2 at 293 K.

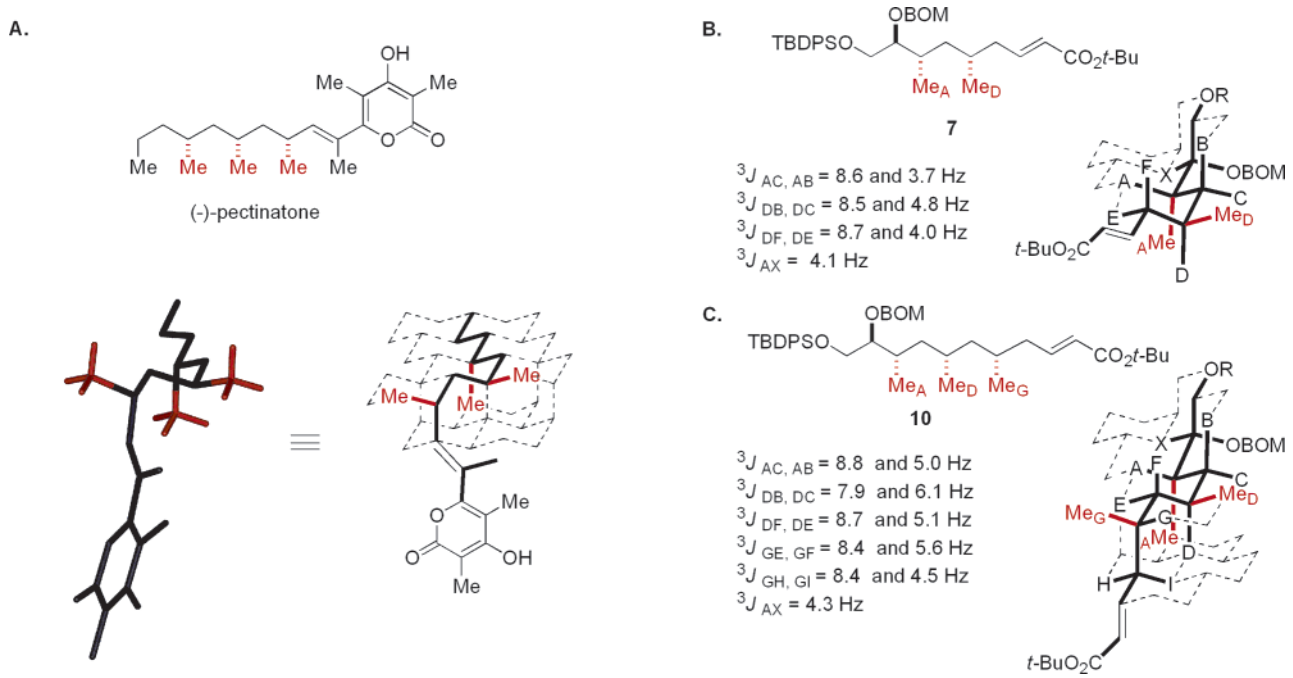

Figure 4. (A) X-ray crystal structure of (−)-pectinatone[16] and superposition of the carbon backbone on a virtual diamond lattice. (B, C) Possible conformations of **7** and **10** on the basis of relevant ^3J coupling constants.[46]

In Figure 5, we depict the intermediates along the reaction pathway[65,66] for enoates **4** and **7** leading to their respective syn adducts as major diastereomers. Starting with low-energy conformers in each case (corroborated by ^{1}H NMR homodecoupling experiments),[46] the spatial disposition of the δ-methyl group and the folding of the carbon backbone dictate the preferred directions of approach of the cuprate reagent, leading to the

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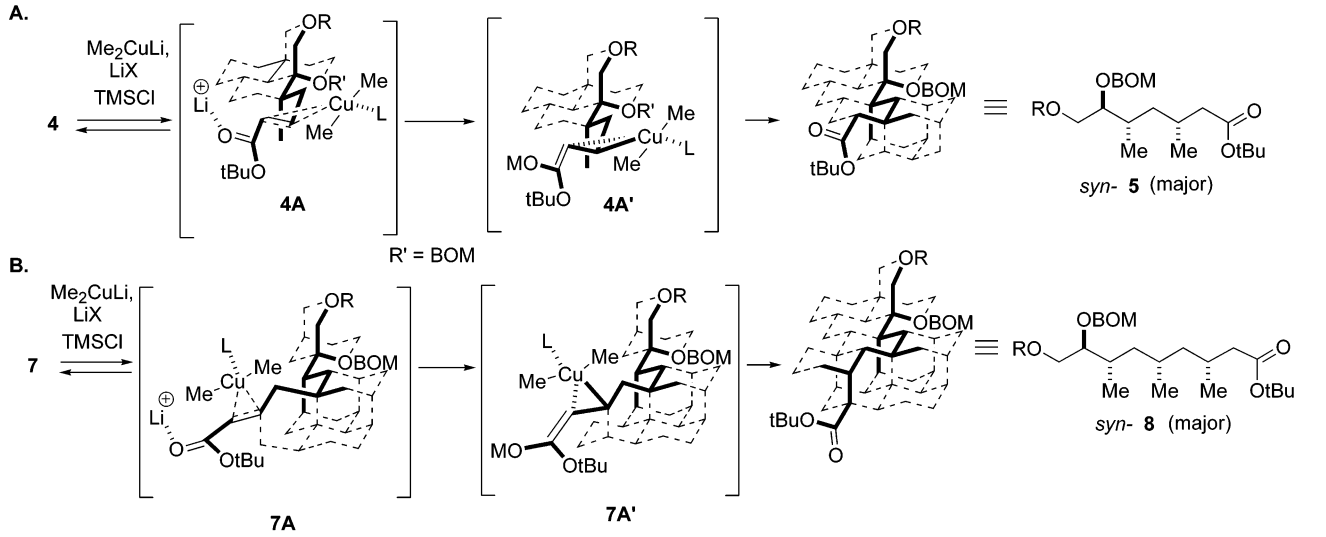

Figure 5. Proposed enoate/cuprate π-complexes and the corresponding β-cuprio(III) intermediates and adducts. Cuprates are shown as monomers for simplicity. L = TMSCl or THF, M = Li or TMS.

formation of enoate/cuprate π-complexes[66] **4A** and **7A** (Figure 5). The complexes evolve to the respective β-cuprio(III) transient intermediates[65−67] **4A′** and **7A′**, which are stabilized by coordination to TMSCl.[67] Transfer of a methyl group and reductive elimination of a copper species affords the respective products.[68] 1,5-Pentane-type interactions are minimized or avoided in **4A′** and **7A′**, leading to a preponderance of C_3-C_5 syn and C_3-C_7 syn/syn adducts **5** and **8**, respectively (Figure 5). Presumably, the transition state in the third cuprate addition to **7** is largely in favor of a conformer where the carbon backbone is already folded in an energetically biased conformation to accommodate the bulky cuprio(III) group (Figure 5B)[46] leading to the major syn/syn isomer **8**.[69,70]

The better syn selectivity in the second cuprate addition in the case of the enoate **31**(>7:1) (Scheme 5) compared to **4** is of interest. In the case of **31**, the propionate triad harboring anti/anti methyl groups flanking the *O*-BOM substituent acts as an internal anchor[54a,71] to bias a preferred conformation that favors a syn approach of the cuprate. The trend for syn/syn selectivity continues with the formation of **32** and **33** as the major products (Scheme 5). It is important to note that the highest ratios of the syn adducts in all cases were obtained with *tert*-butyl esters, which may further contribute to the prevalence of lower energy anchored conformations.[71]

Conclusion

A total synthesis of (−)-borrelidin, isolated as the crystalline benzene solvate, was achieved. The strategy involved the use of D-glyceraldehyde and L-malic acid as chiral progenitors and their elaboration into fully functionalized subunits capitalizing on 1,2- and 1,3-inductions in acyclic intermediates. A practical attribute of this iterative approach, compared to others mentioned earlier, particularly with regard to the C_1-C_{11} acyclic substructure of borrelidin, is that it generates advanced intermediates that also incorporate the C_3 and C_{11} hydroxyl groups.

Inspired by nature's preferences in conformational design,[54a] we were able to devise a new stereocontrolled synthetic protocol for the deployment of alternating 1,3-syn-disposed *C*-methyl groups encompassed within the C_1-C_{11} periphery of borrelidin. The same subunit was also utilized in a total synthesis of siphonarienal. The stereochemical outcome of iterative lithium dimethylcuprate additions to a growing chain of acyclic δ-methyl-α,β-unsaturated enoates has been rationalized on the basis of preferred conformations in which nonbonded syn-pentane interactions are minimized in the transition states. A virtual diamond lattice was used to qualitatively visualize the backbone conformation of acyclic chains and was corroborated by ^{1}H NMR homodecoupling studies.

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Supporting Information Available: Complete experimental procedures and NMR, X-ray, and other data (print/PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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(68) The corresponding ketene acetals could be isolated by avoiding any acidic workup. See also refs 32a,b.

(69) As previously discussed, a fourth cuprate addition to **10** was also syn-selective but only modestly (syn/anti 4:1), presumably due to entropic limitations of a growing deoxypropionate chain, as observed by Hoffmann.[54a]

(70) Cuprate addition to the enoate derived from C_5-C_7 *anti*-deoxypropionate (*anti*-**7**), under the same conditions led to a 2:1 mixture of isomers, indicating the preference for a syn-disposed deoxypropionate motif such as **7** for all-syn selectivity.

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