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Iterative Synthesis of Deoxypropionate Units: The Inductor Effect in Acyclic Conformation Design

Stephen Hanessian,* Navjot Chahal, and Simon Giroux

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Centre-ville Montréal, P.Q. H3C 3J7

stephen.hanessian@umontreal.ca

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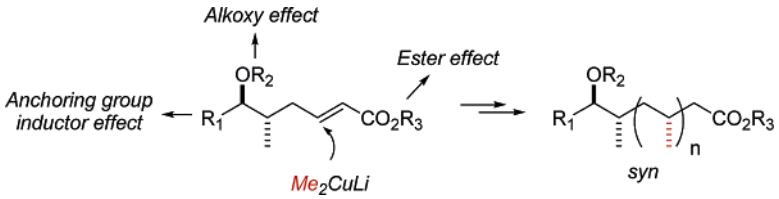

Conjugate addition of lithium dimethylcuprate to acyclic α,β-unsaturated esters of varying lengths bearing terminal alkyl or phenyl groups leads to a preponderance of syn 1,3-adducts when one methyl is already present. Conversion to enoates, and iteration of cuprate additions also favors syn adducts to give contiguous deoxypropionate units in a growing chain. The effect of end-group variation (Me, *i*-Pr, phenyl, *tert*-butyl) in conjunction with the nature of the ester group (Me, *tert*-butyl, etc.) on the diastereoselectivity of syn and anti products was studied. The results are rationalized in terms of inductor effects related to the minimization of the 1,5-pentane interactions in energetically favored folded conformations and corroborated by homodecoupling NMR studies.

The deoxypropionate motif is prevalent in many natural products that are biosynthetically derived from the so-called polypropionate pathway.[1] These units, consisting of an array of alternating *C*-methyl groups on an acyclic chain, are deployed in one of two relative orientations for a single deoxypropionate unit. Syn- and anti-methyl group orientations of a single deoxypropionate triad[2] originate from two propionate biosynthetic units, and they are present in a number of natural products.[3] On the other hand, two contiguous deoxypropionate units consisting of three alternating *C*-methyl groups on an acyclic chain within a molecule are much less prevalent. For example, a syn/syn-deoxypropionate unit can be found in only three natural products, TMC-151A,[4] pectinatone,[5] and siphonarienone (and its congeners),[6] and one macrocyclic lactone, doliculide.[7] Another macrocyclic lactone, borrelidin, harbors the only example of four alternating *C*-methyl groups with a syn/syn/anti orientation.[8] There are also two exceptions to the syn/syn "rule", in the C_4-C_8 segment of ionomycin[9] and in the segments of the cuticular hydrocarbon from cane beetle,[10] which have two and three contiguous deoxypropionate units with syn/anti orientations, respectively (Chart 1).

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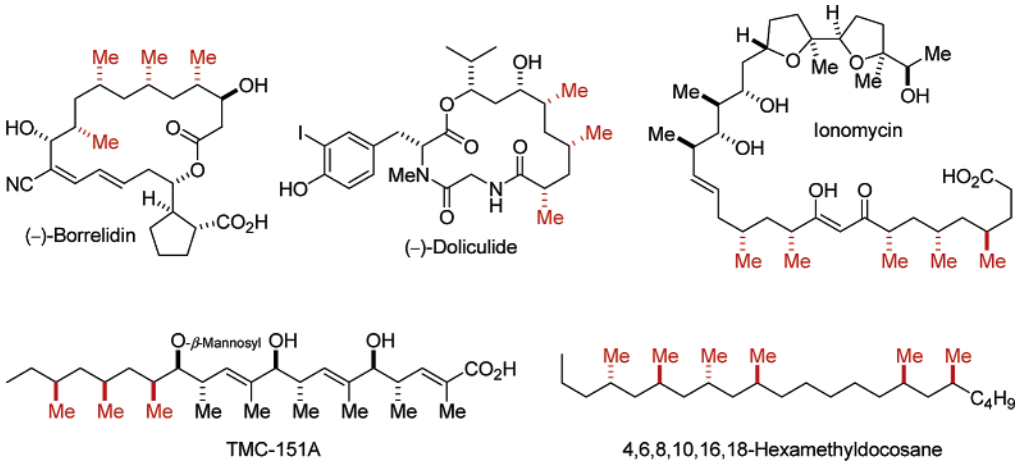
CHART 1. Representative Examples of Deoxypropionate Natural Products



The apparent preference for syn/syn deployment of *C*-methyl groups has been rationalized on the basis of conformation design in acyclic systems,[2,11] where 1,5-pentane interactions are minimized. Indeed the solid-state crystal structures of deoxypropionate-containing natural products such as pectinatone[5] and borrelidin[8] clearly show the nonstaggered orientation of the alternating *C*-methyl groups on the respective carbon frameworks. We have used a virtual diamond lattice to qualitatively visualize the three-dimensional structures of such deoxypropionate arrays.[12,13] The virtual superposition of the carbon chain backbone of such deoxypropionate arrays on the diamond lattice is also matched by NMR data.[12,13]

There are several methods for the *iterative* construction of deoxypropionate units with predisposed stereochemical orientations.[3] Until recently these methods relied on asymmetric induction due to resident chirality[12,13] or the presence of a chiral auxiliary.[14] Negishi[15] and Feringa[16] have now reported elegant catalytic methods for the elaboration of deoxypropionate units. Extension of these catalytic methods to the synthesis of complex polyfunctional natural products will no doubt follow.

Our approach to the iterative synthesis of the syn oriented deoxypropionate units found in borrelidin, doliculide, and siphonarienal relied on the conjugate addition of lithium dimethylcuprate to a "starter" enantiopure γ-alkoxy-α,β-unsaturated enoate.[17] The product resulting from a 1,2-induction obtained in very high diastereomeric purity, was extended to a second iteration via a 3-step sequence. A second cuprate addition took place to give a syn product in a ratio of 80:20. Surprisingly, a third iteration gave a seven carbon acid harboring three alternating syn/syn-C-methyl groups with a 91:9 diastereoselection (for the third addition). Thus, three stereocontrolled cuprate additions were done in an iterative manner on a growing acyclic chain. In the course of these studies, we introduced the 1-methyl-1-cyclopentyl (MCP) ester group, as a constrained steric variant to the *tert*-butyl group, which allowed the attainment of high syn selectivity compared to other esters.[12] We attributed this to an "ester" effect, which in conjunction with another anchoring group at the other extremity of the enoate, leads to energetically favorable folded conformations in which intervening 1,5-pentane interactions in the main carbon chain are minimized.[13]

In this paper, we studied the effect of placing different ester groups and a chain extremity "inductor" anchoring group, on the stereoselectivity of conjugate additions with lithium dimethylcuprate on a set of enoates. In this context, we also studied the effects of varying the nature of the alkoxy ether group (Figure 1).

We initially chose an isopropyl group as an anchoring extremity. Once the first *C*-methyl is introduced, it could, in principle, avoid a 1,5-pentane interaction with the two methyl groups of the isopropyl group in one or more energetically favored conformations by placing a hydrogen atom opposite to the *C*-methyl in the main chain (Figure 1, **A** versus **B** and **C**). It was anticipated that subsequent cuprate additions on iterated enoates would involve priviledged folded conformations which would undergo stereoselective syn additions in each cycle (Figure 1).

Chemistry. The readily available 2*R*-hydroxy-3-methyl butyrate **1**[17a] was protected as the BOM ether, reduced, then

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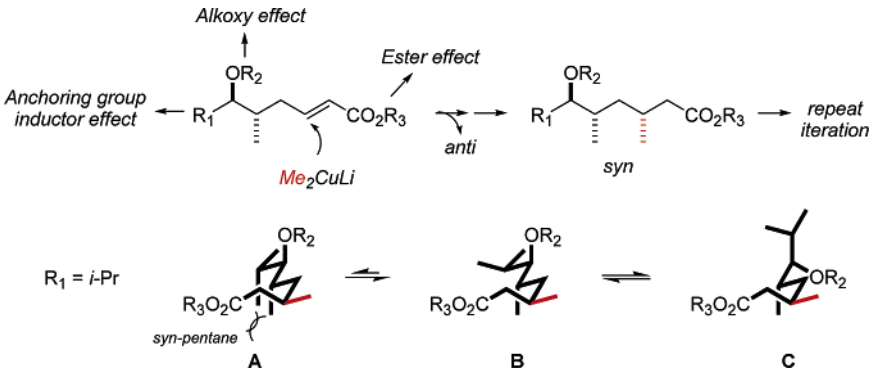
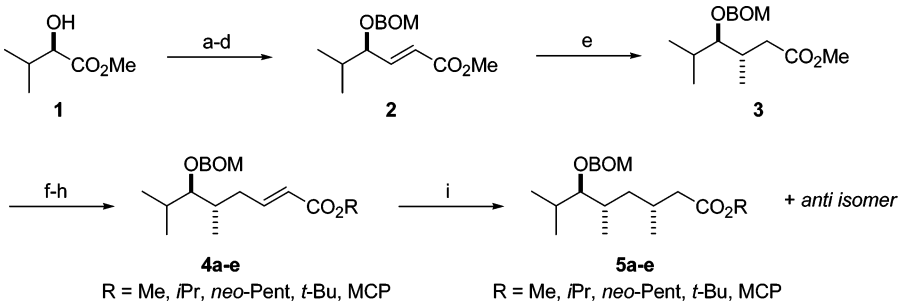


FIGURE 1. Functional group effects in enoate additions and possible preferred conformations of adducts.

SCHEME 1. Synthesis of 5a−e[a]



[a] (a) BOMCl, NEt(*i*Pr)$_2$, CH_2Cl_2, 85%; (b) Dibal-H, CH_2Cl_2, −78 °C, 92%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C, 97%; (d) PPh_3=C(H)CO_2Me, CH_2Cl_2, *E*/*Z* > 20:1, 91%; (e) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, syn/anti > 15:1, 96%; (f) repeat b, 93%; (g) repeat c, 97%, (h) PPh_3=C(H)CO_2R, CH_2Cl_2, for **4a**, 96%; **4b**, 85%; **4c**, 64%; **4d**, 91%; **4e**, 74%; (i) repeat i, see Table 1 for yields and syn/anti ratios. MCP = 1-methyl-1-cyclopentyl.

TABLE 1. Diastereoselective Cuprate Additions to Enoates 4a−e: The Ester Effect

entry	compd	product	R	syn/anti[a]	yield[b]
1	**4a**	**5a**	Me	75:25	80
2	**4b**	**5b**	*i*-Pr	77:23	96
3	**4c**	**5c**	*neo*Pent	78:22	93
4	**4d**	**5d**	*t*-Bu	89:11	87
5	**4e**	**5e**	MCP[c]	91:9	89

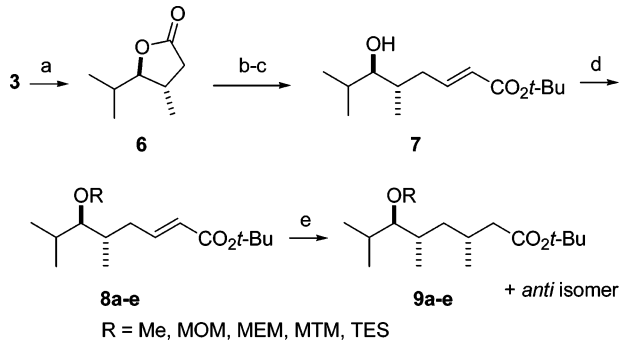
[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography. [c] MCP: methylcyclopentyl.

extended to the enoate **2** in an overall yield of 70% (Scheme 1). The addition of lithium dimethylcuprate in the presence of TMSCl at −78 °C[17a] gave the anti product **3** as a single isomer in quantitative yield.

A three-step extension was done with the appropriate phosphorane to give the corresponding enoates **4a−e** containing esters of increasing steric bulk. Cuprate additions afforded the corresponding adducts **5a−e** as mixtures of syn and anti diastereomers. The ratio increased in favor of the syn adduct in going from a methyl ester to the 1-methyl-1-cyclopentyl ester (MCP) without unduly affecting the yields (Table 1).

We next studied the influence of the alkoxy group on the diastereoselectivity of conjugate addition. The required substrates were prepared from precursor **3** by exchanging the BOM group (Scheme 2). Hydrogenolysis of **3** led to the lactone **6** which was partially reduced to the hemiacetal, and the latter was treated with *tert*-butyl(triphenylphosphoranylidene)acetate to afford the *trans*-enoate **7**. Attempted *O*-methylation in the presence of sodium hydride led to intramolecular cyclic ether formation. Alternatively, methylation with Meerwein's reagent

SCHEME 2. Synthesis of 9a−e[a]



[a] (a) H_2, 1 atm, Pd/C, MeOH, 99%; (b) Dibal-H, CH_2Cl_2, −78 °C; (c) PPh_3=C(H)CO_2*t*-Bu, CH_2Cl_2, *E*/*Z* > 20:1, 61% two steps; (d) for **8a**, Me_3OBF_4, proton sponge, CH_2Cl_2, 60%; for **8b**, MOMCl, NEt(*i*Pr)$_2$, CH_2Cl_2, 82%; for **8c**, MEMCl, NEt(*i*Pr)$_2$, DMAP (catalyst), CH_2Cl_2, 74%; for **8d**, benzoyl peroxide, dimethylsulfide, 48%; for **8e**, TESOTf, 2,6-lutidine, CH_2Cl_2, 44%; (e) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, see Table 2 for yields and syn/anti ratios.

in the presence of proton sponge[18] afforded the methyl ether **8a** in 61% yield. Other ethers **8b−d** were prepared under standard conditions from **7**. Addition of lithium dimethylcuprate to the individual enoates gave good to excellent yields of adducts with more or less the same diastereoselectivities favoring the syn isomers by a ratio of ca. 4:1 (Table 2). The methyl and BOM ethers were found to give a slightly higher ratio (Table 2, entries 1 and 6).

Having established that a bulky ester and a removable protective group such as a BOM ether were best suited to favor

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TABLE 2. Diastereoselective Cuprate Additions to Enoates 8a−f: The Alkoxy Effect

entry	compd	product	R[c]	syn/anti[a]	yield[b]
1	**8a**	**9a**	Me	90:10	60
2	**8b**	**9b**	MOM	86:14	78
3	**8c**	**9c**	MEM	86:14	81
5	**8d**	**9d**	TES	82:18	84
6	**4d**	**5d**	BOM	89:11	87

[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography. [c] MOM, methoxymethyl ether; MEM, methoxyethoxyether; TES, triethylsilyl ether; BOM, benzyloxymethyl ether.

TABLE 3. Cuprate Additions to Enoates 11a−c and 13a−b: The Third and Fourth Iterations

entry	compd	product	R	syn/anti[a]	yield[b]
1	**11a**	**12a**	Me	67:33	84
2	**11b**	**12b**	*t*-Bu	87:13	97
3	**11c**	**12c**	MCP	83:17	91
4	**13a**	**14a**	*t*-Bu	85:15	78
5	**13b**	**13b**	MCP	83:17	92

[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography.

the highest ratio of the syn adducts, we turned our attention to a third iteration. Thus, compound **5d** was reduced to the corresponding alcohol **10** and the pure syn isomer was oxidized and then treated with the appropriate phosphoranylidene ester to give **11a−c** (Scheme 3). Cuprate addition gave excellent yields of the corresponding adducts **12a−c** with diastereoselectivities favoring the syn/syn isomer (Table 3). After separation of the pure syn isomer, a fourth iteration was tried with *tert*-butyl and MCP esters **13a** and **13b** leading to diastereoselectivities in favor of the syn/syn/syn isomers **14a** and **14b** with average ratios of 4.2:1 (Table 3).

Our next objective was to probe the influence of the chain extremity "inductor" anchoring group on the stereoselectivity of cuprate addition on a γ-BOM enoate. Conjugate addition of lithium dimethylcuprate to the enoates **15a−c** obtained from (*R*)-mandelic acid led to **16a−c** in high selectivities[17d] and excellent yields (Scheme 4, Table 4).

A three-step chain extension of **16a−c** to the corresponding enoates **17a−c**, followed by cuprate addition gave the syn adducts **18a−c** in high selectivity. Separation of the syn isomer and further extension of the *tert*-butyl and MCP esters gave the pure syn isomers **19a** and **19b**. A third cuprate addition gave the corresponding syn/syn adducts **20a** and **20b** and the corresponding syn/anti adducts in ca. 4:1 diastereomeric ratio, respectively.

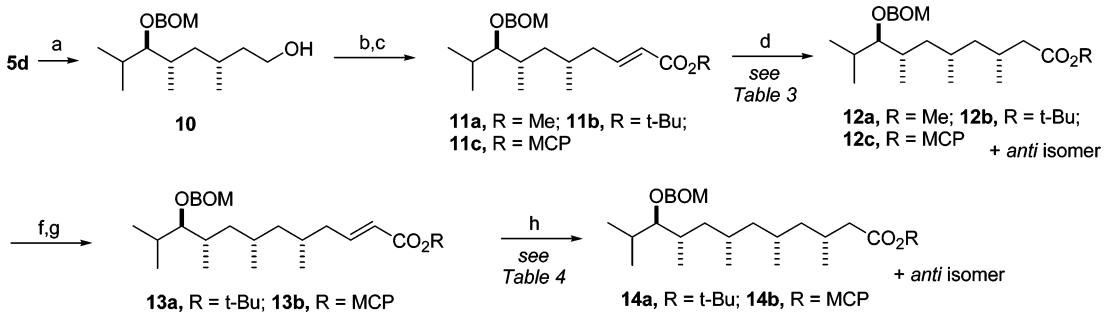
The terminal *tert*-butyl variant was also studied in a racemic substrate (Scheme 5, Table 5). Thus, pivalic aldehyde **21** was converted to (±)-enoate **22** in four uneventful steps. Cuprate addition to **22** followed by extension to **23a−c**, and a second iteration gave **24a−c** in relatively high diastereoselectivities (see Table 5). The third cuprate addition on the separated syn isomer was performed on the (±)-*tert*-butyl enoate **25** only, to give the corresponding adduct **26** in a 82:18 syn/anti ratio.

Finally, the effect of the chain extremity inductor group in these enoates was studied with the methyl series. Thus (*S*)-ethyl lactate **27** was converted to the enoates **28a−c**, and the latter was subjected to conjugate addition in the usual manner to give the corresponding adducts **29a−c** as single isomers in excellent yields after purification (Scheme 6). Extension of the *tert*-butyl ester to the enoate **30** and the addition of lithium dimethylcuprate gave the adduct **31** as a 2:1 mixture of syn and anti isomers (Table 6).

Iterative conjugate additions to enoates can also be extended in a bidirectional mode (Scheme 7). Thus, alcohol **32**[13] was elaborated to enoate **33** and subjected to a "third" cuprate conjugate addition in a bidirectional way. The anticipated 1,2-induction by the *O*-BOM group led to an excellent anti/syn ratio of >20:1 in **34**. A three-step extension, followed by conjugate addition, reduction to the corresponding alcohol, and removal of the minor isomer by chromatography led to enantiopure **35** (88:12, syn/anti). A similar extension led to **36** which was subjected to a third cuprate addition affording an 88:12 syn/anti ratio of *tert*-butyl ester **37**. All in all, five cuprate additions were effected starting from an enoate precursor of **32**.[13] Conversion of the *O*-BOM to the alcohol **38** by hydrogenolysis and treatment with MsCl in the presence of NEt_3 led to **39**. Subsequent treatment with $LiAlH_4$ with concomitant formation of the terminal alcohol, followed by etherification with MOMCl afforded the nonmeso compound **40** in addition to the minor anti isomer.

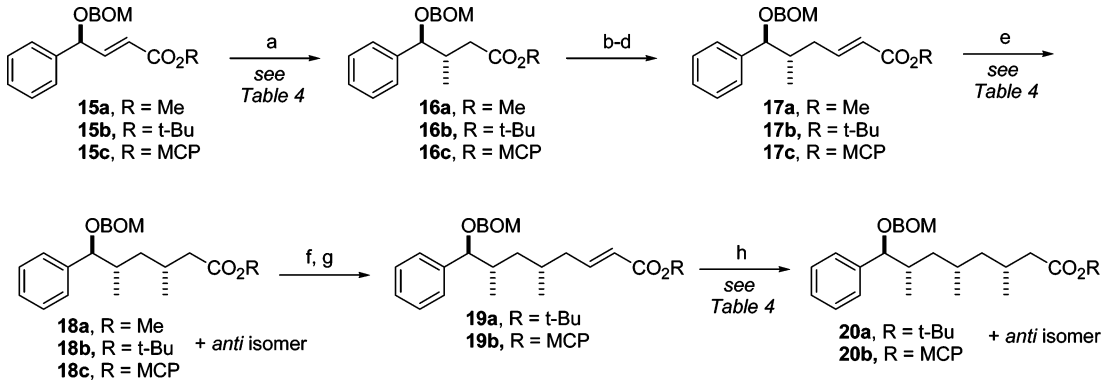
Deuterium Labeling and Isomer Ratios. The highly nonpolar nature of the cuprate adducts differing in the syn or anti dispositions of pendant *C*-methyl groups on growing acyclic chains rendered the determination of isomer ratio difficult by analytical methods such as HPLC or GC. ^{13}C inverse gated NMR spectroscopy which was used routinely in previous studies[12,13] was found to be a reliable method to estimate relative ratios of diastereomers. We sought to develop a method that would exploit ^1H NMR as an expedient method to determine isomer ratios and to corroborate the ^{13}C inverse gated NMR results. We surmised that incorporation of a deuterium atom on the carbon chain bearing each *C*-methyl group would

SCHEME 3. Third and Fourth Iterations[a]



[a] (a) Dibal-H, CH_2Cl_2, −78 °C, 74%; (b) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C; (c) $PPh_3{=}C(H)CO_2R$, CH_2Cl_2, for **11a**, 90% two steps, for **11b**, 94% two steps for **11c**, 85% two steps; (d) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, see Table 3; (f) repeat a with **12b**, 60%; (g) repeat b and c, for **14a**, 71% two steps, for **14b**, 70%; (h) repeat d, see Table 4. Iterations done on pure syn isomers.

SCHEME 4. Cuprate Additions in the Phenyl Series[a]



[a] (a) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, see Table 4; (b) Dibal-H, CH_2Cl_2, −78 °C, 75%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C; (d) $PPh_3{=}C(H)CO_2R$, CH_2Cl_2, for **17a**, 75% two steps, for **17b**, 87% two steps, for **17c**, 89% two steps; (e) repeat a, see Table 4; (f) repeat step b with **17a**, 60%; (g) repeat c and d, for **19a**, 99% two steps, for **19b**, 89% two steps; (h) repeat a, see Table 4. Iterations done on pure syn isomers.

TABLE 4. Cuprate Additions in the Phenyl Series

entry	compd	product	R	syn/anti[a]	yield[b]
1	**15a**	**16a**	Me	94:6	97
2	**15b**	**16b**	*t*-Bu	95:5	92
3	**15c**	**16c**	MCP	95:5	89
4	**17a**	**18a**	Me	69:31	86
5	**17b**	**18b**	*t*-Bu	84:16	85
6	**17c**	**18c**	MCP	85:15	86
7	**19a**	**20b**	*t*-Bu	79:21	90
8	**19b**	**20c**	MCP	79:21	74

[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography.

considerably simplify the interpretation of the ^1H spectra at the iterated enoate stage. Indeed, integration of methine peaks (bearing a *C*-methyl group and a deuterium atom), provided syn/anti ratios that were in excellent agreement with those determined by inverse gated ^{13}C NMR (Scheme 8).[19]

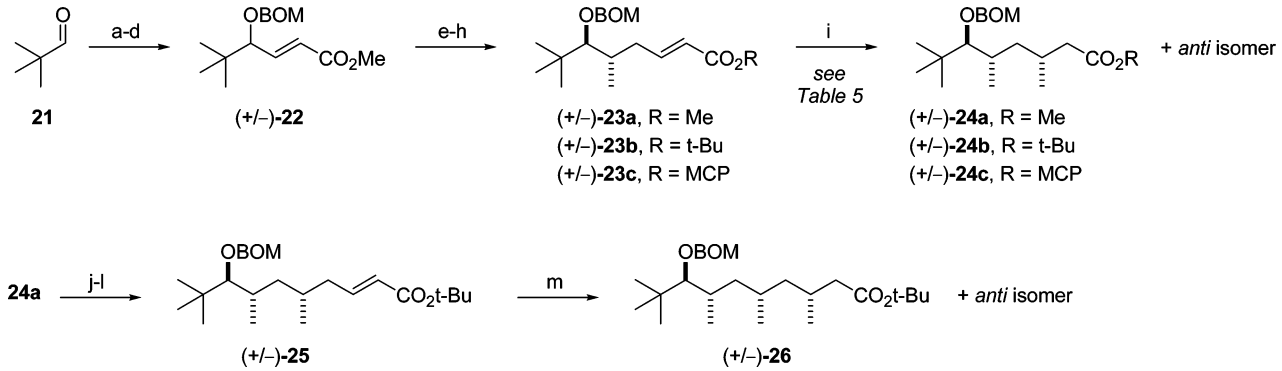
Discussion. The insightful studies by Hoffmann[2,11] demonstrated the importance of conformational design in acyclic carbon chains and the effect of a substituent like a *C*-methyl group as an "inductor group". Thus, a resident *C*-methyl group in an acyclic chain can serve as an inductor for an incoming second *C*-methyl group, leading to a preferred folded conformation which is best accommodated by an isotactic-type relationship of substituents. This observation was rationalized on the basis of the destabilization of those conformers where higher energy-level 1,5-pentane interactions are possible.[2,11] Accordingly, deoxypropionate units harboring two or more alternating *C*-methyl groups in a growing chain should adopt conformations favoring staggered orientations of such groups. We have extended this concept to the iterative synthesis of syn oriented deoxypropionates in functionalized enoates which were used as advanced intermediates in the total synthesis of doliculide[12] and borrelidin.[13] Thus, an enoate bearing an anchoring group at the extremity of the acyclic chain will adopt a conformation in solution allowing a preferential approach of the cuprate to give a syn adduct as the major isomer. Low energy conformations in which 1,5-pentane interactions are minimized in the main chain as well as with the extremity group will prevail, especially at low temperature. Despite the growing entropy of the system, and the presence of coordinating sites, this encoded bias for preferred folded conformations harboring predisposed *C*-methyl groups in the growing acyclic chain is operative for third and fourth cuprate additions so as to favor the syn adduct (Scheme 3). Detailed NMR studies[12,13] of first and second stage enoates such as **4a** and **11a** have corroborated this hypothesis, since homodecoupling measurements indicated the presence of a time-averaged folded conformation at 25 °C in each case that was in excellent agreement with values obtained from X-ray studies of natural products.[4] An overlay of the presumed folded conformation on a virtual diamond lattice provides a useful visual tool in such correlations in these new examples (Figure 2).

There is a clear "ester" effect in the conjugate additions to enoates, where syn isomers are favored over anti. Small ester moieties such as methyl lead to increasing amounts of anti adducts. *tert*-Butyl esters and 1-methyl-1-cyclopentyl (MCP) esters appear to be the best in favor of the syn isomers (Table 1, entry 5). This effect was more pronounced when the extremity was a $CH_2OTBDPS$ group (*t*-Bu 4:1, MCP 8:1).[12] Syn preference is also manifested in the third and fourth cuprate additions, especially in the presence of *tert*-butyl and MCP esters with ratios > 4:1 (Tables 3 and 4).

The chain extremity "inductor" effect was also studied with different anchoring groups. Diastereoselective preference for syn/syn over syn/anti isomers remained at > 4:1 especially with the *tert*-butyl and MCP esters. In substituting an isopropyl to a *tert*-butyl group as the chain extremity, we had anticipated a substantial drop in diastereoselectivity since a 1,5-pentane interaction could already exist with the first *C*-methyl group in the chain and one of the *tert*-butyl methyls (Figure 2, **23a**). However, a 9:1 selectivity for the second cuprate addition in the isopropyl series dropped only to 4:1 for the *tert*-butyl case (Scheme 5, Table 6, entries 1−3). The persistent syn selectivity in this case, despite potentially unavoidable 1,5-pentane interactions of *C*-methyl groups in the first and second stage cuprate additions may be rationalized by the existence of alternative conformations compared to the isopropyl series (Figure 2, **23a**). Indeed, homodecoupling studies showed a time-averaged coupling constant favoring folded conformation A (Figure 2, J_{F-E} = < 2.0 Hz), in which the *tert*-butyl group adopts a different orientation compared to B where the 1,5-pentane interaction is expected to be at a maximum (J_{F-E} expected > 9.0 Hz, see Figure 2, **4a** and **11a**). A potential *tert*-butyl/methyl and chain C−C interaction may still be operative in conformation A (Figure 2, **23a** red bonds). To corroborate these assumptions

(19) See Supporting Information.

SCHEME 5. Cuprate Additions in the *tert*-Butyl Series[a]



[a] (a) VinylMgBr, THF, 0 °C; (b) BOMCl, NEt(*i*-Pr)$_2$, CH_2Cl_2, 50% two steps; (c) OsO_4, $NaIO_4$, THF/H_2O; (d) PPh_3=C(H)CO_2Me, CH_2Cl_2, 54% two steps; (e) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, 80%; (f) Dibal-H, CH_2Cl_2, −78 °C, 82%; (g) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C; (h) PPh_3=C(H)CO_2R, CH_2Cl_2, for **23a**, 92%; for **23b**, 92%; for **23c**, 82%; (i) repeat e, see Table 5; (j) repeat f with **24a**, 64%; (k) repeat g; (l) repeat h with R = *t*-Bu, 70% two steps; (m) repeat e, syn/anti 82:18, 77%. Iterations done on pure syn isomers.

TABLE 5. Cuprate Additions in the *t*-Butyl Series

entry	compd	product	R	syn/anti[a]	yield[b]
1	**23a**	**24a**	Me	63:37	76
2	**23b**	**24b**	*t*-Bu	82:18	85
3	**23c**	**24c**	MCP	82:18	73

[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography.

based on NMR data, we also analyzed the methyl chain extremity analogue **30** (Figure 2). Here, coupling constants for FE protons are intermediate between vicinal and anti reflecting on the prevalence of equally populated conformations of the enoates A and B. Consequently, ratios of adducts are clearly diminished compared to branched extremity groups. It is reasonable to assume that at −78 °C, such energetically favored folded conformations are even more prevalent.

The mechanism of organocuprate additions to enoates is complex.[20] It is generally agreed that an initial π-complex **A** evolves to a β-cuprio(III) species **B** that delivers the alkyl methyl group. Thus, steric nonbonded interactions are manifested early in the transition states of a significant population of favorably folded conformations as depicted for the isopropyl series (**4e** and **11c**, Figure 3). With methyl esters, the relative differences in energies of conformers may be less significant than with bulkier esters such as *tert*-butyl or MCP. The nature of the alkoxy ether group is not important (Table 2), and it probably adopts a preferred orientation which exerts, however, only minor influence to the inductor effect of the chain extremity group. It is clear that the nature of the bulky ester overrides the effects of the chain extremity group, since syn selectivity up to four cuprate iterations was still observed in going from isopropyl, to phenyl, to *tert*-butyl (Schemes 3−5, Tables 3−6). These results are remarkable, considering the purely acyclic nature of the substrates.

(20) For mechanistic discussions see the following: (a) Bertz, S. H.; Carlin, C. M.; Deadwyler, D. A.; Murphy, M. D.; Ogle, C. A.; Seagle, P. H. *J. Am. Chem. Soc.* **2002**, *124*, 13650. (b) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393. (c) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288. (d) Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 1644. (e) Bertz, S. H.; Chopra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Chem.—Eur. J.* **1999**, *5*, 2680. (f) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900. (g) Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025. (h) Dorigo, A. E.; Wanner, J.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed.* **1995**, *34*, 476. (i) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381. (j) Bertz, S. H.; Smith, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 8276. (k) Dorigo, A, E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524. (l) Christensen, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523. (m) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133. (n) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. (o) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141. For a recent discussion on selectivity see the following: Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630. For the effect of TMSCl see (a) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023. (b) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283. (c) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (e) Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.

Experimental Section

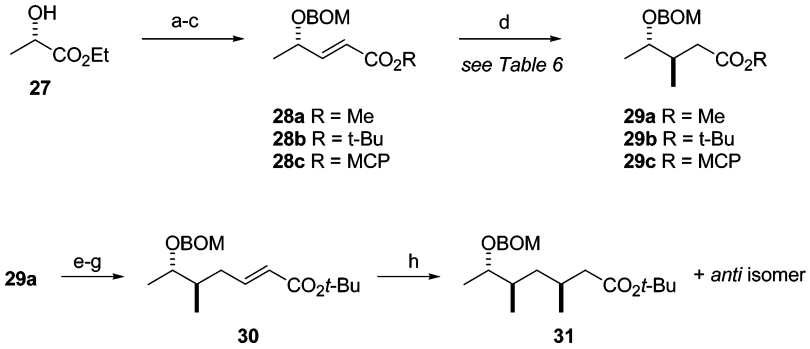
General Procedure for DIBAL-H Reduction (Procedure A). To a solution of the ester in CH_2Cl_2 cooled to −78 °C, DIBAL-H (3 equiv) was added. The reaction was stirred at −78 °C for 4 h before being quenched with a saturated Na/K tartrate solution. The reaction mixture was diluted with ethyl acetate and stirred for 30 min at room temperature until a clear biphasic solution was observed. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered. After concentration, the resulting residue was purified by flash chromatography. Syn isomers were separated and used in the next step.

General Procedure for Swern Oxidation (Procedure B). Oxalyl chloride (2.5 equiv) was slowly added to a solution of DMSO (5 equiv) in CH_2Cl_2 cooled to −78 °C. The reaction mixture was allowed to stir at −78 °C for 20 min before the addition of a solution of the alcohol in CH_2Cl_2. After 45 min, NEt_3 (10 equiv) was added, and the reaction was warmed to room temperature. The reaction was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and then concentrated. Flash chromatography afforded the desired aldehyde.

General Procedure for Wittig Olefination (Procedure C). A solution of the aldehyde in CH_2Cl_2, was charged with Ph_3P=$CHCO_2R$ (1.5 equiv). The reaction mixture was stirred at room temperature for 18 h and then evaporated to dryness. The crude solid was triturated with hexanes/Et_2O (3:1), and the resulting slurry was filtered over a pad of Celite. The filtrate was concentrated and purified by flash chromatography affording the enoate.

General Procedure for Cuprate Addition (Procedure D). To a slurry of CuI (6 equiv) in THF at −15 °C was added MeLi·LiBr (12 equiv). The resulting colorless solution was stirred at this temperature for 20 min and then cooled to −78 °C. Dropwise addition of TMSCl (18 equiv) was followed by cannulation of a

SCHEME 6. Cuprate Additions in the Methyl Series[a]



[a] (a) BOMCl, NEt(*i*-Pr)$_2$, CH_2Cl_2, 75%; (b) Dibal-H, CH_2Cl_2, −78 °C, 91%; (c) PPh_3═C(H)CO_2R, CH_2Cl_2, for **28a**, 96%; for **28b**, 94%; (d) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, see Table 6; (e) Dibal-H, CH_2Cl_2, −78 °C, 89% with **29a**; (f) Dess-Martin Periodinane, CH_2Cl_2; (g) PPh_3═C(H)CO_2-*t*-Bu, CH_2Cl_2, 52% two steps; (h) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, 90% 2:1 syn/anti. Iterations done on pure syn isomers.

TABLE 6. Cuprate Additions in the Methyl Series

entry	compd	product	R	syn/anti[a]	yield[b]
1	**28a**	**29a**	Me	73:27	99
2	**28b**	**29b**	*t*-Bu	85:15	91
3	**28c**	**29c**	MCP	80:20	92
4	**30**	**31**	*t*-Bu	66:33	90

[a] Determined by ^{13}C inverse gated NMR. [b] Isolated yields after chromatography.

solution of the α,β-unsaturated ester in THF at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and quenched with solution of NH_4OH/NH_4Cl (1:1). The mixture was diluted with Et_2O and warmed to room temperature. The aqueous layer was extracted three times with Et_2O, and the combined organic extracts were washed with NH_4OH/NH_4Cl (1:1) and brine and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography.

General Procedure for Swern Oxidation Followed by Wittig Reaction (Procedure E). Oxalyl chloride (2.5 equiv) was added to a solution of DMSO (5 equiv) in CH_2Cl_2 at −78 °C. After 15 min, a solution of the alcohol in CH_2Cl_2 was added and stirred at −78 °C for 45 min. Triethylamine (10 equiv) was then added, and the reaction mixture was warmed to room temperature over 45 min. A saturated solution of NH_4Cl was added, and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude aldehyde was added to a solution of Ph_3P═$CHCO_2R$ (1.5 equiv) in CH_2Cl_2, and the reaction was stirred at room temperature for 18 h and then evaporated to dryness. The crude solid was triturated with hexanes/Et_2O (3:1), and the resulting slurry was filtered over a pad of Celite. The filtrate was concentrated and purified by flash chromatography.

(3*S*,4*R*)-4-Benzyloxymethoxy-3,5-dimethyl-hexanoic Acid Methyl Ester (3). Following general procedure A, enoate **2**[17a] (2.5 g, 8.98 mmol) was subject to a cuprate addition providing product **3** (2.54 g, 96%): $[\alpha]_D$ −18.22 (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (m, 5H), 4.82 (d, 1H, *J* = 6.86 Hz), 4.79 (d, 1H, *J* = 6.89 Hz), 4.70 (d, 1H, *J* = 11.90 Hz), 4.65 (d, 1H, *J* = 11.84 Hz), 3.69 (s, 3H), 3.14 (t, 1H, *J* = 5.39 Hz), 2.63 (dd, 1H, *J* = 14.91, 3.21 Hz), 2.22 (m, 1H), 2.18 (dd, 1H, *J* = 9.76, 14.89 Hz), 1.79 (m, 1H), 1.00 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.49, 137.51, 128.81 (2C), 128.16 (2C), 128.03, 97.15, 89.34, 70.59, 51.82, 37.60, 33.31, 30.92, 20.55, 18.26, 18.05. IR (thin film): 2962, 2877, 1738, 1497, 1455, 1436, 1384, 1366, 1253, 1194, 1163 cm^{-1}. HRMS (EI): *m*/*z* 295.1917 (calcd for $C_{17}H_{26}O_4$, 295.1909).

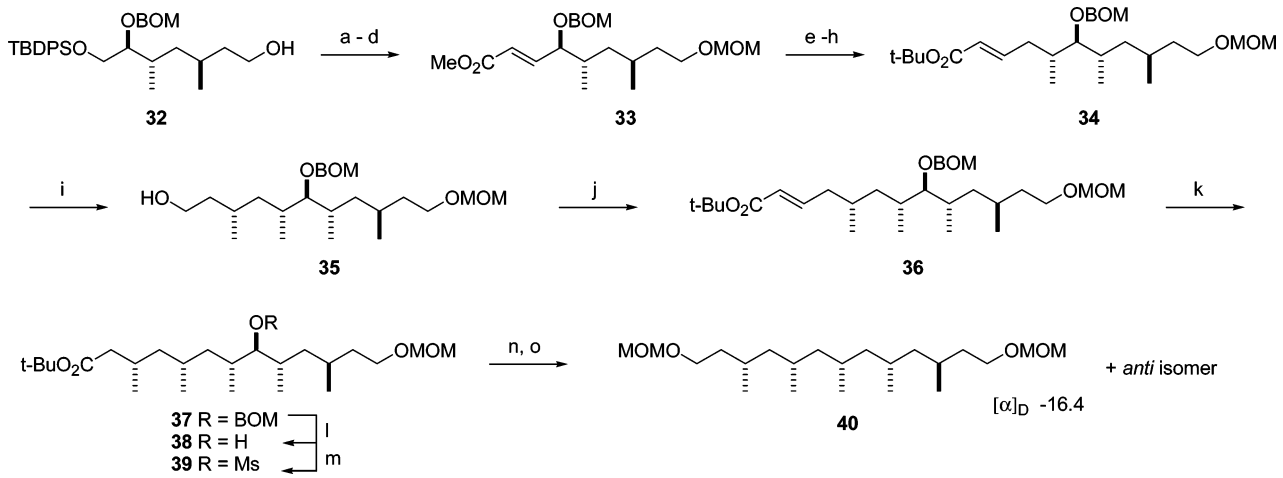
(*E*)−(5*S*,6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic Acid *tert*-Butyl Ester (4d). Following general procedure A, reduction of **3** (1.51 g, 5.13 mmol) afforded the corresponding alcohol (1.26 g, 93%) after flash chromatographic purification with 10% EtOAc/hexanes. Following general procedures B and C, oxidation of the alcohol (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%) and further Wittig homologation of the aldehyde (0.20 g, 0.77 mmol) gave **4d** (0.24 g, 85%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes: $[\alpha]_D$ −6.2 (*c* 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (m, 5H), 6.87 (m, 1H), 5.77 (d, 1H, *J* = 15.5 Hz), 4.82 (d, 1H, *J* = 6.9 Hz), 4.80 (d, 1H, *J* = 6.8 Hz), 4.69 (d, 1H, *J* = 11.9 Hz), 4.65 (d, 1H, *J* = 11.9 Hz), 3.11 (t, 1H, *J* = 5.4 Hz), 2.52 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.49 (s, 9H), 0.95 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 147.7, 138.3, 128.8 (2C), 128.5 (2C), 128.0, 124.6, 97.2, 89.7, 80.4, 70.6, 35.6, 35.2, 30.8, 28.6 (3C), 20.7, 18.0, 17.5. IR (thin film): 2967, 1712, 1651, 1455, 1366 cm^{-1}. HRMS (EI): *m*/*z* 363.2533 (calcd for $C_{22}H_{34}O_4$, 363.2535).

(3*R*,5*S*,6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic Acid *tert*-Butyl Ester (5d). Compound **4d** (0.10 g, 0.28 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**5d** and *anti*-**5d** (0.091 g, 87% combined yield) in a ratio of 89:11 syn/anti. $[\alpha]_D$ −14.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 (m, 5H), 4.82 (d, 1H, *J* = 6.9 Hz), 4.79 (d, 1H, *J* = 6.9 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 3.09 (t, 1H, *J* = 5.2 Hz), 2.30 (dd, 1H, *J* = 4.4, 14.3 Hz), 2.01 (m, 1H), 1.87 (m, 2H), 1.77 (m, 1H), 1.49 (m, 1H) 1.46 (s, 9H), 1.12 (m, 1H), 0.94 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.2 (173.9), 138.5, 128.8 (2C), 128.1 (2C), 128.0, 97.1, 97.0, (90.6) 90.1, 80.4, 70.4, (44.9) 42.5, 39.6 (38.8), 33.5 (33.2), (30.7) 30.6, 28.5 (3C), 21.7, 21.0 (20.8), (19.2) 18.8, 17.7 (17.3). IR (thin film): 2963, 2932, 2875, 1729, 14.56, 1367, 1257 cm^{-1}. HRMS (EI): *m*/*z* 379.2861 (calcd for $C_{23}H_{38}O_4$, 379.2848).

(3*R*,5*S*,6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctan-1-ol (10). Following general procedure A, **5d** (1.04 g, 2.76 mmol) was reduced to give a mixture of diastereomeric alcohols. Careful chromatographic separation provided *syn*-**10** (0.63 g, 74%) as a colorless oil. $[\alpha]_D$ −20.5 (*c* 0.73, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (m, 5H), 4.85 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.71 (d, 1H, *J* = 11.9 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 3.70 (m, 2H), 3.11 (t, 1H, *J* = 5.3 Hz), 1.87 (m, 2H), 1.69 (m, 2H), 1.49 (m, 2H), 1.27 (m, 1H), 1.10 (m, 1H), 0.97 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.5, 128.8 (2C), 128.1 (2C), 128.0, 97.0, 90.3, 70.5, 61.5, 40.3, 39.0, 33.4, 30.6, 27.7, 21.5, 21.1, 18.8, 17.84. IR (thin film): 3402 2960, 2931, 2875, 1456, 1382, 1158 cm^{-1}. HRMS (ESI): *m*/*z* 331.2238 (calcd for $C_{19}H_{32}O_3Na^+$, 331.2243).

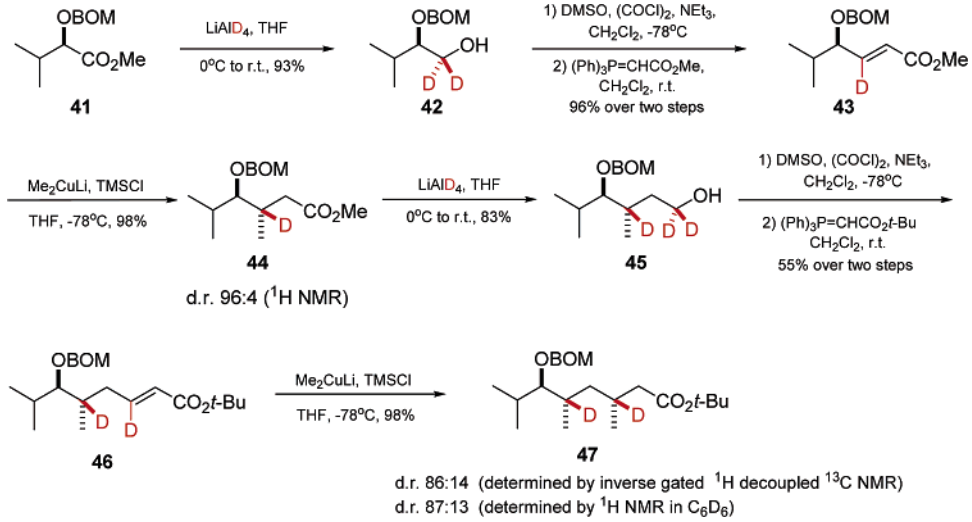
(*E*)−(5*S*,7*S*,8*R*)-8-Benzyloxymethoxy-5,7,9-trimedec-2-enoic Acid *tert*-Butyl Ester (11b). Following general procedure E, alcohol **10** (1.00 g, 3.24 mmol) provided **11b** ((*E*)- 1.07 g, (*Z*)- 0.150 g, 94%) after flash chromatographic purification with 2%

SCHEME 7. Bidirectional Cuprate Additions[a]



[a] (a) MOMCl, NE*t*-Pr_2, CH_2Cl_2, 93%; (b) TBAF, THF, 73%; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (d) PPh_3═C(H)CO_2Me, CH_2Cl_2, 93% for two steps; (e) MeLi·LiBr, CuI, TMSCl, THF, −78 °C, anti/syn > 20:1, 88%; (f) Dibal-H, CH_2Cl_2, −78 °C, 87%; (g) repeat c; (h) PPh_3═C(H)CO_2*t*-Bu, CH_2Cl_2, 69% for two steps; (i) repeat e, syn/anti > 10:1, 91%; repeat f, 72%; (j) repeat c and repeat d, 96% two steps; (k) repeat e syn/anti > 10:1, 83%; (l) H_2, 1 atm, Pd/C, MeOH/AcOH (4:1), 86%; (m) MsCl, NEt_3, CH_2Cl_2, 0 °C; (n) $LiAlH_4$, THF, 0 °C, 71% two steps; (o) repeat a, 73%. Iterations done on pure syn isomers.

SCHEME 8. Deuterium Labeling



EtOAc/hexanes. $[\alpha]_D$ −9.0 (*c* 0.63, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.36 (m, 5H), 6.87 (m, 1H), 5.78 (d, 1H, J = 15.5 Hz), 4.85 (d, 1H, J = 6.7 Hz), 4.82 (d, 1H, J = 6.8 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.68 (d, 1H, J = 11.9 Hz) 3.12 (t, 1H, J = 5.2 Hz), 2.31 (m, 1H), 1.97−1.90 (m, 3H), 1.64 (m, 1H), 1.52 (s, 9H), 1.53−1.52 (m, 1H), 1.14 (m, 1H), 0.99 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 147.2, 138.5, 128.7 (2C), 128.1 (2C), 128.0, 124.7, 97.0, 90.2, 80.3, 70.5, 39.5, 38.6, 33.4, 30.6, 30.5, 28.6 (3C), 21.5, 21.0, 18.8, 17.8. IR (thin film): 2961, 2931, 1715, 1653, 1457, 1368, 1321, 1256 cm^{-1}.

(3*R*,5*S*,7*S*,8*R*)-8-Benzyloxymethoxy-3,5,7,9-tetramethyldecanoic Acid *tert*-Butyl Ester (12b). Compound **11b** (0.055 g, 0.14 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**12b** and *anti*-**12b** (0.054 g, 97% combined yield) in a ratio of 87:13 syn/anti. $[\alpha]_D$ −21.10 (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.12 (t, 1H, J = 5.1 Hz), 2.29 (dd, 1H, J = 4.8, 14.3 Hz), 2.08 (m, 1H), 1.85 (m, 3H), 1.47 (s, 9H), 1.33 (m, 2H), 1.08 (m, 2H), 0.94 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.2 (172.9), 138.0, 128.2 (2C), 127.6 (2C), 127.4, 96.3, (90.3) 90.0, 79.8, 69.9, (44.7) 44.2, (43.1) 42.8, 40.0, 33.4 (33.1), 29.9 (2C), 28.0 (3C), 27.6, 21.1, 20.9, 20.6, (19.3) 18.9, 17.8 (17.5). IR (thin film): 2961, 2931, 2874, 1729, 1456 cm^{-1}.

(*E*)−(5*R*,7*S*,9*S*,10*R*)-10-Benzyloxymethoxy-5,7,9,11-tetramethyldodec-2-enoic Acid *tert*-Butyl Ester (13a). Following general procedure A, **12b** (0.23 g, 0.54 mmol) was reduced to give a mixture of diastereomeric alcohols. Careful chromatographic purification (2% EtOAc/hexanes) provided the pure all *syn*-alcohol (0.11 g, 60%) as a colorless oil. The alcohol obtained was then subject to general procedure E, providing **13a** (0.068, 71% over two steps) after flash chromatographic purification with 2% EtOAc/hexanes. $[\alpha]_D$ −17.9 (*c* 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (m, 5H), 6.89 (m, 1H), 5.76 (d, 1H, J = 15.5 Hz), 4.85 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.11 (t, 1H, J = 5.1 Hz), 2.24 (m, 1H), 1.86 (m, 4H), 1.57 (m, 1H), 1.50 (s, 9H), 1.42 (m, 1H), 1.32 (m, 1H), 1.06 (m, 1H), 0.93 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.6, 146.3, 137.7, 128.0 (2C), 127.4 (2C), 127.2, 123.9, 96.1, 89.3, 79.6, 69.7, 43.2, 39.8, 38.0, 32.6, 29.7, 29.5, 27.9 (3C), 27.4, 20.9, 20.5, 20.4, 18.1, 17.1. IR (thin film): 2960, 2930, 1715, 1653, 1457, 1368, 1321, 1288, 1250, 1158 cm^{-1}.

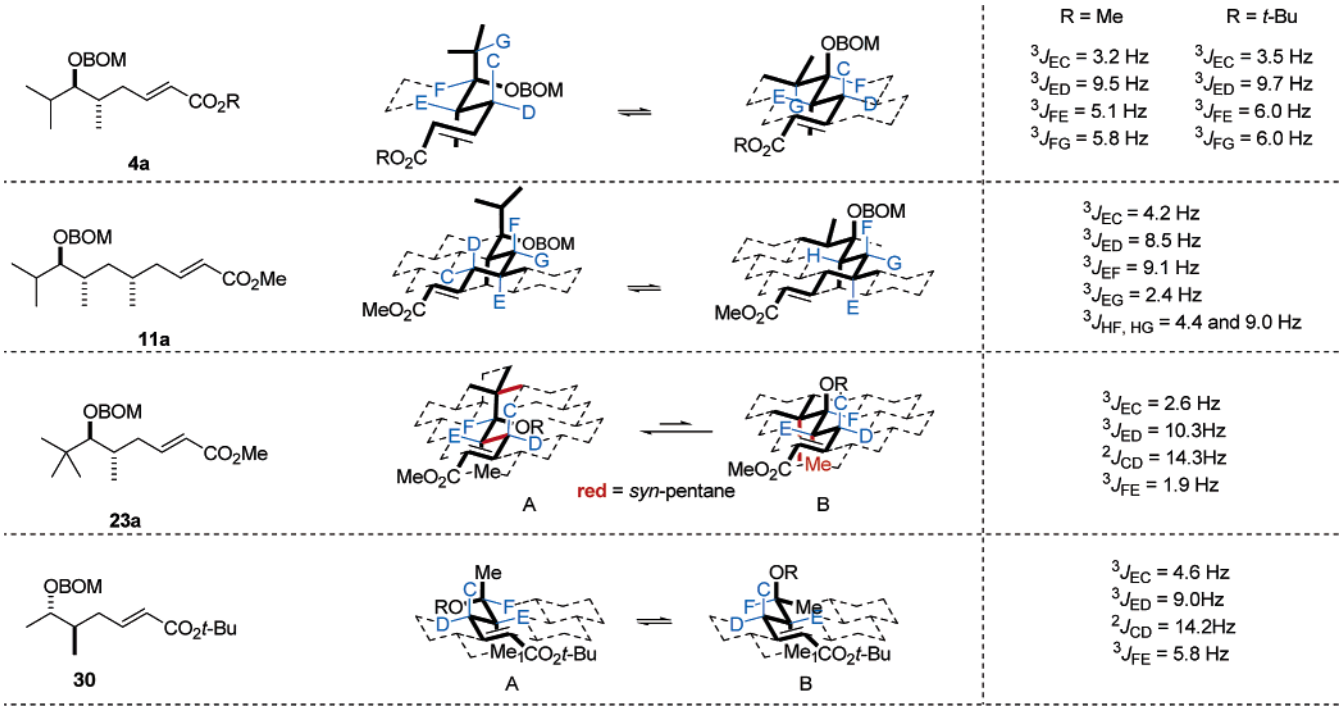


FIGURE 2. Possible conformations of enoates **4a**, **11a**, **23a**, and **30** on the basis of homodecoupling studies.

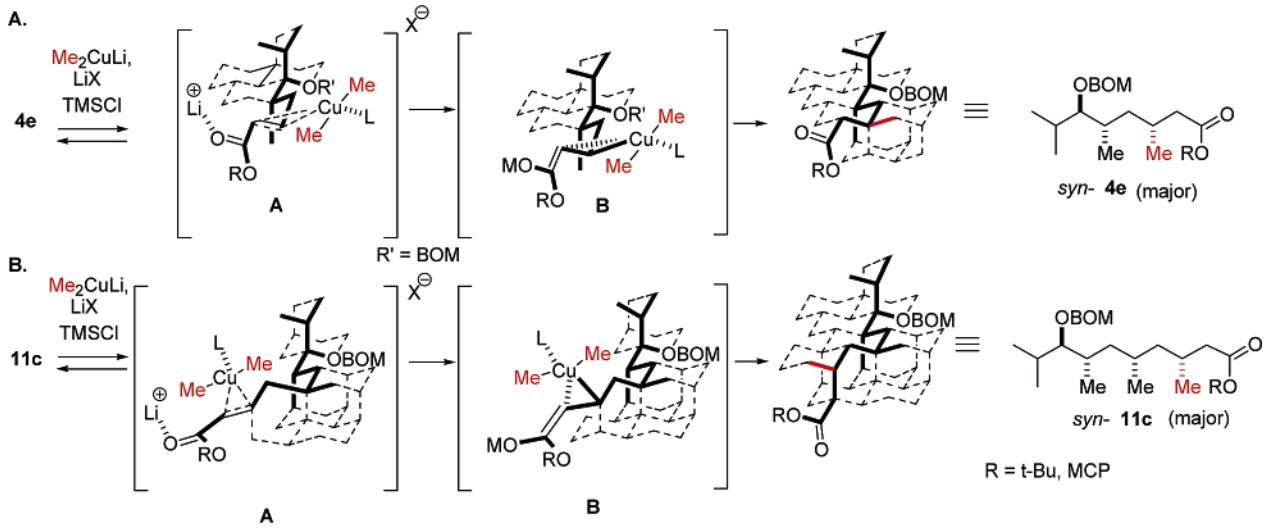


FIGURE 3. Proposed enoate/cuprate π-complexes, the corresponding β-cuprio(III) intermediates, and adducts. Cuprates are shown as monomers for simplicity: L = TMSCl or THF, M = Li or TMS.

(3*R*,5*R*,7*S*,9*S*,10*R*)-10-Benzyloxymethoxy-3,5,7,9,11-pentamethyldodecanoic Acid *tert*-Butyl Ester (14a). Compound **13a** (0.067 g, 0.15 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**14a** and *anti*-**14a** (0.057 g, 78% combined yield) in a ratio of 86:14 syn/anti. $[\alpha]_D$ −19.5 (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz). 4.81 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.12 (m, 1H), 2.28 (dd, 1H, J = 4.9, 14.2 Hz), 2.02 (m, 1H), 1.89 (m, 2H). 1.82 (m, 1H), 1.57 (m, 1H), 1.47 (s, 9H), 1.40 (m, 1H), 1.26 (m, 3H), 1.04 (m, 1H), 0.99−0.87 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.5 (172.2), 137.8, 128.0 (2C), 127.4 (2C), 127.2, 96.1, (89.3) 89.2, 79.5, 69.6, (44.6) 44.4, (44.0) 43.7, 39.8, 32.7 (32.6), 29.7, (29.7) 29.6, 27.8 (3C), 27.7, 27.4, 27.3, 21.2, (20.9) 20.9, 20.6, 20.4, (18.7) 18.2, 17.0 (16.8). IR (thin film): 2960, 2930, 1730, 1456, 1367 cm^{-1}.

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Supporting Information Available: Typical experimental procedures for key reactions and copies of selected ^{1}H and ^{13}C NMR spectras. This material is available free of charge via the Internet at http://pubs.acs.org.

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