JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

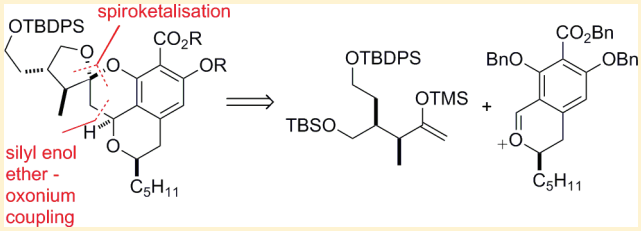
Formal Synthesis of Berkelic Acid: A Lesson in α-Alkylation Chemistry

Michael C. McLeod, Zoe E. Wilson, and Margaret A. Brimble*

School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

Supporting Information

ABSTRACT: The full details of our enantioselective formal synthesis of the biologically active natural product berkelic acid are described. The insertion of the C-18 methyl group proved challenging, with three different approaches investigated to install the correct stereochemistry. Our initial Horner–Wadsworth–Emmons/oxa-Michael approach to the berkelic acid core proved unsuccessful upon translation to the natural product itself. However, addition of a silyl enol ether to an oxonium ion, followed by a one-pot debenzylation/spiroketalisation/thermodynamic equilibration procedure, afforded the tetracyclic structure of the berkelic acid core as a single diastereoisomer.



INTRODUCTION

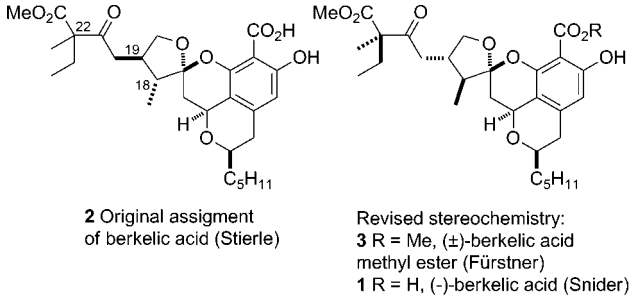
Extremophiles are organisms that can survive in extreme conditions and are currently of interest to the synthetic community due to a number of novel secondary metabolites that have been isolated from them.[1] To date, novel natural products have been isolated from organisms that inhabit environments of high and low pH, high and low temperature, high pressure, and high salt. Berkelic acid (**1**) was isolated as a secondary metabolite from a *Penicillium* species that inhabits Berkeley Pit Lake in Montana, USA.[2] This man-made lake was formed when an abandoned copper mine was flooded, and its waters are now both acidic (pH ∼2.5) and contain a number of heavy-metal ions in high concentrations. Berkelic acid (**1**) displays selective activity against the OVCAR-3 ovarian cancer cell line (GI_{50} 91 nM) as well as inhibiting caspase-1 (GI_{50} 98 μM) and metalloprotease-3 (GI_{50} 1.87 μM).[2]

Berkelic acid (**1**) was originally assigned as **2**, with the chirality at the C-22 center unknown. Through total synthesis of berkelic acid methyl ester (**3**), Fürstner proposed the reassignment of the C-18 and C-19 stereocenters.[3] This proposal and the absolute stereochemistry were confirmed by the first total synthesis of berkelic acid by the Snider group, who tentatively assigned the C-22 center as *S*.[4] This assignment was confirmed by further work undertaken by the Snider group[5] and further supported by a biomimetic total synthesis by De Brabander and co-workers.[6] A total synthesis by Fürstner et al.[7] and racemic formal synthesis by Pettus et al.[8] have since been reported.

We have previously reported an enantioselective formal synthesis of berkelic acid (**1**).[9] Herein we report the full results of our synthetic investigations.

RESULTS AND DISCUSSION

Retrosynthesis. We wished to synthesize berkelic acid via an efficient, modular approach that would be amenable to the synthesis of analogues to probe the biological activity of the natural product. We envisaged that this objective could be accomplished by effecting a Horner–Wadsworth–Emmons/oxa-Michael (HWE/oxa-M) coupling of phosphonate **6** with lactol **7** to obtain isochroman **5** (Scheme 1). Global debenzylation of isochroman **5** under acidic conditions should promote spiroketalization, which upon allyl protection of the free acid and phenol groups would lead to spiroketal **4**, an advanced intermediate in Snider's total synthesis of berkelic acid (**1**).[4] This proposed retrosynthetic strategy is based on previous work reported by our group, where a model tetracyclic core of berkelic acid was prepared using a similar HWE/oxa-M method.[10]



2 Original assigment of berkelic acid (Stierle)

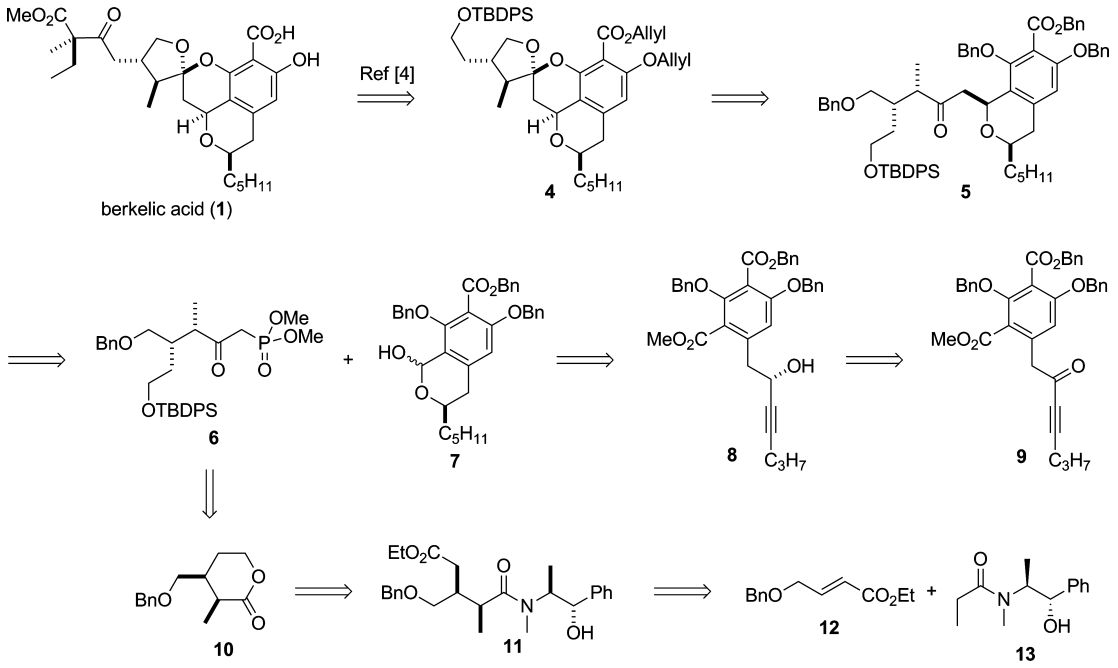
Revised stereochemistry:
3 R = Me, (±)-berkelic acid methyl ester (Fürstner)
1 R = H, (-)-berkelic acid (Snider)

Lactol **7** could be accessed by reduction of the corresponding lactone, which could be obtained by hydrogenation and lactonization of hydroxy ester **8**. The chirality of alcohol **8** could be introduced by enantioselective reduction of alkynyl ketone **9**. Phosphonate **6** could be prepared by ring opening of lactone **10**, which is available by reduction and cyclization of ester **11**. The key step of the phosphonate synthesis would be a syn-selective conjugate addition of pseudoephedrine-derived amide **13** to the α,β-unsaturated ester **12**.

Received: September 29, 2011
Published: November 11, 2011

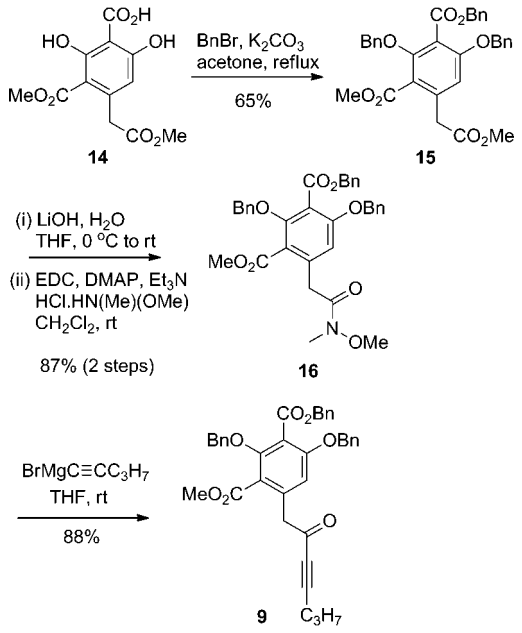
   dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400–416

Scheme 1. Original Retrosynthetic Strategy



Synthesis of Lactone 17. The synthesis of alkynyl ketone **9** as the key precursor to lactol **7** commenced with global benzyl protection of the known benzoic acid **14**[11] (Scheme 2).

Scheme 2. Synthesis of Alkynyl Ketone 9



Selective saponification of the aliphatic methyl ester was accomplished by treatment of **15** with lithium hydroxide. An EDC-mediated coupling of the resultant acid with *N*,*O*-dimethylhydroxylamine hydrochloride afforded the Weinreb amide **16**. Incorporation of the alkynyl chain proved problematic, with low levels of conversion observed at reduced temperatures and significant degradation resulting from use of extended reaction times. However, the addition of 4 equiv of 1-pentynylmagnesium bromide to amide **16** at room temperature with a short reaction time (2 min) resulted in the formation of alkynyl ketone **9** in a reproducible 88% yield.

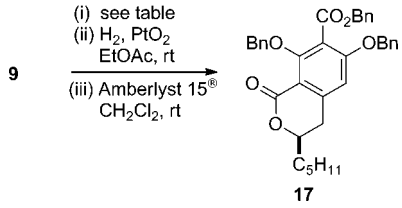
With an efficient route to alkynyl ketone **9** established, attention next turned to the key chiral reduction step (Table 1). The chiral reduction products were inseparable by HPLC; hence, they were immediately converted to lactone **17** by selective reduction of the alkyne moiety with Adam's catalyst[12] and lactonization with Amberlyst 15 (*R*). The two enantiomers of lactone **17** were readily separable by chiral HPLC (Chiralpak AD-H).

Previous model work by our group had identified (D)-TarB-NO_2[13] as the most enantioselective catalyst for the reduction of a similar substrate.[10] However, for the present substrate this reagent only effected reduction in 28% ee and poor yield (Table 1, entry 1). After screening several chiral reductants, we found that the Me-CBS[14] reagent provided the highest levels of enantiocontrol; however, some interesting effects were observed. When $BH_3{\cdot}SMe_2$ was employed as the stoichiometric reductant, a reversal of selectivity was observed upon raising the temperature of the reaction from −78 °C to −10 °C (entries 2 and 3). This effect was not observed with the use of catecholborane (entries 4 and 5). To the best of our knowledge, this temperature-dependent reversal of selectivity in the CBS reduction has not previously been reported and we can offer no explanation at this time. After extensive investigation, the enantioselectivity of the reduction could not be increased above 82% ee when the reaction was carried out in THF. It has recently been reported that the enantioselectivity of CBS reductions of allenyl and alkynyl ketones can be enhanced by the use of nitroethane as solvent.[15] Pleasingly, reduction of **9** with (*R*)-Me-CBS and catecholborane at −78 °C in nitroethane resulted in an increase in enantioselectivity to 99% ee (entry 6).

The absolute stereochemistry of the chiral reduction was determined by conversion to the formal synthesis target **4** (vide infra). The selectivity displayed by the Me-CBS catalyst (with the exception of entry 3) is the opposite to that predicted on the basis of existing chemical literature.[16] In this case, the $-CH_2Ar$ and alkynyl substituents are acting as the small and

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

Table 1. Chiral Reduction of Ketone 9



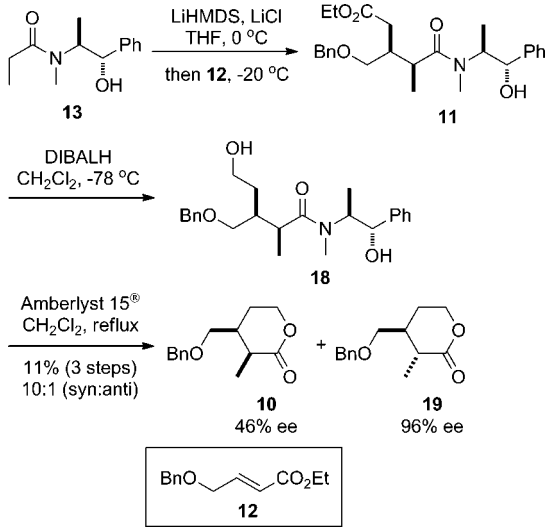
entry[a]	cat. (30 mol %)	stoichiometric reductant (1.1 equiv)	temp (°C)	yield (%)	ee (%)
1	(D)-TarB-NO_2	$NaBH_4$	−78 to rt	25	28
2	(*R*)-Me-CBS	$BH_3{\cdot}SMe_2$	−78	12	44
3	(*R*)-Me-CBS	$BH_3{\cdot}SMe_2$	−10	67	−82
4	(*R*)-Me-CBS	catecholborane	−78	52	72
5	(*R*)-Me-CBS	catecholborane	−10	75	70
6[b]	(*R*)-Me-CBS	catecholborane	−78	59	99

[a]Reactions carried out in THF unless stated. [b]Reaction in $EtNO_2$ with 2 equiv of catecholborane.

large groups, respectively, for the purposes of stereochemical prediction. The same selectivity has previously been reported with ketones bearing a $-CH_2Ar$ group.[17]

First-Generation Approach to Phosphonate 6. With a route to lactone **17** established, the synthesis of phosphonate **6** from lactone **10** was next investigated. A viable synthesis of lactone **10** was thus required. Pseudoephedrine acetamide enolates have been shown to undergo syn-selective Michael addition to a number of α,β-unsaturated esters in the presence of lithium chloride.[18] Pseudoephedrine derivative **13**[19] was therefore treated with LiHMDS and lithium chloride, and the resulting enolate was reacted with Michael acceptor **12** to afford **11** as an inseparable mixture of rotameric diastereoisomers (Scheme 3). To aid analysis of the Michael addition,

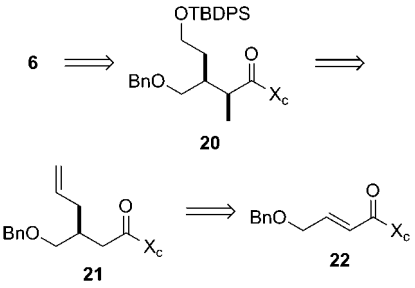
Scheme 3. Synthesis of Lactone 10



adduct **11** was reduced with DIBALH to afford alcohol **18**, which was treated with Amberlyst 15 (*R*) to promote cyclization. This procedure resulted in a separable 10:1 mixture of lactones **10** and **19**. The relative stereochemistry of the lactone products was established by analysis of NOE interactions. Chiral HPLC analysis revealed that the undesired trans lactone **19** was produced in 96% ee, whereas cis lactone **10** was formed in only 46% ee. After extensive screening of reaction conditions, no improvement in the enantioselectivity of the Michael addition could be obtained. The reason for this disappointing result may well be due to the fact that a propionyl ephedrine-enolate was used in the present work, whereas the literature precedent involved the use of ephedrine-enolates bearing an aryl substituent.[18] An alternative approach to phosphonate **6** was thus necessitated.

Second-Generation Approach to Phosphonate 6. Our second-generation retrosynthetic approach to phosphonate **6** is outlined in Scheme 4. Phosphonate **6** could be obtained by

Scheme 4. Second-Generation Retrosynthesis of Phosphonate 6

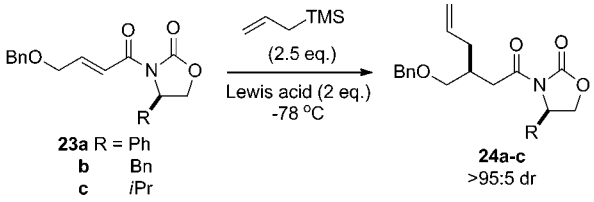


displacement of the chiral auxiliary in **20** with lithiated dimethyl methylphosphonate. In turn, **20** could be accessed by manipulation of the allyl chain and selective methylation of compound **21**. The allyl group could be introduced by conjugate addition to an α,β-unsaturated acyl derivative bearing the appropriate chiral auxiliary **22**.

The preparation of phosphonate **6** initially focused on conjugate addition of an allyl group to known α,β-unsaturated *N*-acyl oxazolidinones **23a−c**.[20] Despite extensive screening of reaction conditions, cuprate addition of an allyl group (allylmagnesium bromide, $CuBr{\cdot}SMe_2$) was unsuccessful. Additions without a Lewis acid returned unreacted starting material, whereas the use of TMSCl or $BF_3{\cdot}OEt_2$ resulted in complex mixtures. Attention next turned to the Lewis acid mediated conjugate addition of allyltrimethylsilane to **23a** (Table 2). Use of $BF_3{\cdot}OEt_2$ and $SnCl_4$ as Lewis acids returned unreacted starting material (entries 1 and 2). Use of $TiCl_4$ (2 equiv) resulted in adduct **24a** being isolated in 43% yield, but with considerable formation of byproduct (entry 3). Decreasing the amount of $TiCl_4$ resulted in a cleaner conversion to **24a**, albeit in lower yield (entry 4), while 4

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

Table 2. Conjugate Addition to α,β-Unsaturated *N*-Acyl Oxazolidinones 23a−c



entry	R	Lewis acid	solvent	yield (%)
1	Ph	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0
2	Ph	$SnCl_4$	CH_2Cl_2	0
3	Ph	$TiCl_4$	CH_2Cl_2	43
4[a]	Ph	$TiCl_4$	CH_2Cl_2	32
5[b]	Ph	$TiCl_4$	CH_2Cl_2	19
6	Ph	$TiCl_4$	Et_2O	0
7	Ph	$TiCl_4$	MeCN	0
8	Ph	$TiCl_4$	THF	0
9	Ph	$TiCl_4$	PhMe	0
10[c]	Ph	$TiCl_4$	CH_2Cl_2	76
11[c]	Bn	$TiCl_4$	CH_2Cl_2	24
12[c]	*i*Pr	$TiCl_4$	CH_2Cl_2	39

[a]1.1 equiv of $TiCl_4$. [b]4 equiv of $TiCl_4$. [c]With allyltributylstannane.

equiv of $TiCl_4$ significantly increased the formation of byproduct (entry 5). No reaction was observed when other solvents were used (entries 6−9). The byproducts could not be isolated but appeared to be the result of benzyl ether cleavage. We postulated that the trimethylsilyl cation formed during the conjugate addition could in some way be responsible for the observed cleavage. To test this hypothesis, the conjugate addition was repeated using allyltributylstannane. Pleasingly, adduct **24a** formed cleanly and was isolated in 76% yield (entry 10). Conjugate addition of allyltributylstannane to the benzyl (**23b**) and isopropyl (**23c**) oxazolidinones proceeded in lower yields (entries 11 and 12). The conjugate additions all took place with excellent selectivity, affording **24a−c** as a single diastereoisomer. The observed facial selectivity was opposite to that obtained from the corresponding cuprate additions and was in agreement with that observed for Lewis acid promoted allylations of similar substrates.[21,22]

With allyl adduct **24** in hand, attention next focused on its α-methylation to provide a precursor to phosphonate **6**. Our proposal for the introduction of an α-methyl group to **24** is based on a number of literature precedents where alkylation α to a carbonyl group has been shown to be directed by an existing chiral center at the β position.[23−25] For example, Fernández-Zertuche et al. have shown that alkylation of *N*-acyl oxazolidinones **25** and **27** proceeded with high diastereocontrol to afford the syn product, regardless of the chirality of the auxiliary (Scheme 5).[24] They rationalized this observation by the formation of enolate conformers **29** and **30** that minimize 1,3-allylic strain. They argue that the R group provides the overriding steric influence, directing the methyl group to add from the opposite face.

Alkylation of **24a** was attempted by enolate formation with LiHMDS in THF for 1 h followed by reaction with methyl iodide at −25 °C (Table 3). No reaction was observed with enolate formation at −78 °C, and reaction only occurred by generating the enolate with lithium chloride (4 equiv) at −25 °C to afford **31a** as a 5:1 mixture of diastereoisomers with the undesired anti isomer dominating (entries 1−4). Use of

Scheme 5. Literature Precedent for Syn α-Methylation of β-Substituted *N*-Acyl Oxazolidinones[24]

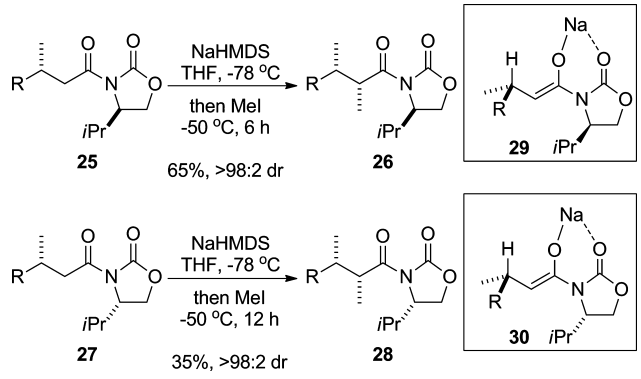
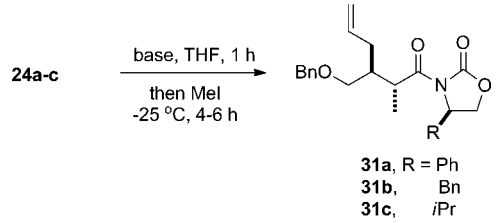


Table 3. Alkylation of *N*-Acyl Oxazolidinones 24a−c



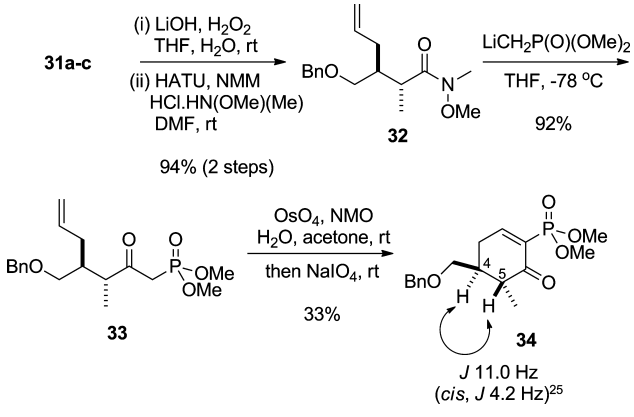
entry	R	base	additive	temp of enolate formation (°C)	conversn (%)	dr (anti:syn)
1	Ph	LiHMDS		−78	0	
2	Ph	LiHMDS	LiCl	−78	0	
3	Ph	LiHMDS		−25	0	
4	Ph	LiHMDS	LiCl	−25	80 (47)[a]	5:1
5	Ph	NaHMDS	LiCl	−25	30	6:1
6	Bn	LiHMDS	LiCl	−25	20	4:1
7	*i*Pr	LiHMDS	LiCl	−25	50	4:1

[a]Isolated yield in parentheses.

NaHMDS as base resulted in similar levels of diastereocontrol with a lower degree of conversion (entry 5). The benzyl and isopropyl oxazolidinones **24b,c** provided **31b,c** as a 4:1 mixture of anti and syn diastereoisomers (entries 6 and 7). It appears that, in this system, the stereochemistry of the oxazolidinone directs the facial selectivity of the alkylation.

The facial selectivity of the alkylation was determined by conversion of **31** to cyclic phosphonate **34** (Scheme 6). The

Scheme 6. Stereochemical Proof by Conversion to Phosphonate 34

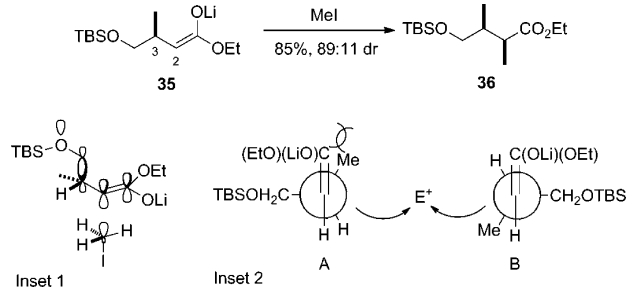


dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

chiral auxiliary was cleaved by treatment with lithium peroxide and the resulting carboxylic acid converted to Weinreb amide **32** by HATU-mediated coupling with *N,O*-dimethylhydroxylamine hydrochloride. Addition of lithiated dimethyl methylphosphonate to **32** afforded **33**. Oxidative cleavage of the terminal olefin with osmium tetroxide and sodium periodate afforded an aldehyde, which underwent in situ intramolecular Horner–Wadsworth–Emmons reaction to provide cyclic phosphonate **34**. The trans relationship of the substituents at C-4 and C-5 was confirmed by the magnitude of the vicinal coupling constant (J_{4-5} = 11.0 Hz), which was considerably larger than the corresponding coupling constant for the cis isomer (J_{4-5} = 4.2 Hz) that had previously been prepared by our group.[26]

α-Alkylation to esters has also been shown to be directed by a β-chiral center. McGarvey and Williams[25] showed that reaction of lithium enolate **35** with methyl iodide resulted in a 89:11 mixture of products **36** in favor of the syn diastereoisomer (Scheme 7). They postulate that this outcome is a

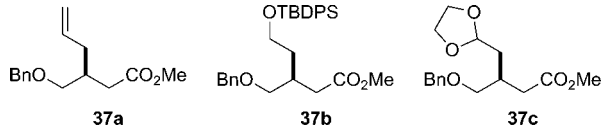
Scheme 7. Literature Precedent for Syn α-Methylation of β-Substituted Esters[25]

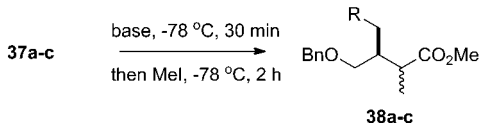


result of the electrophile approaching the enolate antiperiplanar to the substituent on the β carbon, thereby providing greater stabilization of the transition state through hyperconjugation. In the present work, this β substituent is the $-CH_2OBn$ group, where the oxygen lone pair can interact with the π system as shown (inset 1, Scheme 7). This leads to two possible conformations, as illustrated by Newman projections along the C2–C3 bond (inset 2, Scheme 7). Conformer A exhibits greater steric clashes so that conformer B is favored, leading to the observed syn methylation.

We proposed that this effect could be extended to our system to allow access to the desired syn arrangement between the allyl and methyl groups. To test this hypothesis, methyl esters **37a–c** were prepared from Michael adduct **24a**.[26] The esters **37a–c** were treated with base at −78 °C for 30 min to effect enolate formation and then reacted with an electrophile at −78 °C for 2 h (Table 4). Diastereoselectivities of 1.3:1 in favor of the desired syn isomer were observed with ester **37a**, independent of the metal counterion employed (entries 1–3). The choice of solvent had a profound effect on the reaction, with THF and DME favoring the syn product and toluene and Et_2O favoring the anti product (entries 1–6). The use of lithium chloride and DMPU as additives had a negligible effect on the reaction (entries 7 and 8). Employing dimethyl sulfate led to a slightly higher level of diastereocontrol than with methyl iodide (entries 1 and 9). Alkylation of silyl ether **37b** afforded a 1:1 mixture of diastereoisomers, while the use of acetal **37c** resulted in a 4:1 mixture in favor of the anti isomer (entries 10 and 11). The stereochemical outcome of this alkylation may be due to

Table 4. Alkylation of Esters 37a–c





entry	substrate	base	solvent	conversn (%)	dr (syn:anti)
1	**37a**	NaHMDS	THF	40	1.3:1
2	**37a**	LiHMDS	THF	20	1.3:1
3	**37a**	KHMDS	THF	50	1.3:1
4	**37a**	NaHMDS	PhMe	50	1:2
5	**37a**	NaHMDS	Et_2O	33	1:1.3
6[a]	**37a**	NaHMDS	DME	50	1.2:1
7[b]	**37a**	NaHMDS	THF	30	1.2:1
8[c]	**37a**	NaHMDS	THF	25	1.3:1
9[d]	**37a**	NaHMDS	THF	33	1.5:1
10	**37b**	NaHMDS	THF	81	1:1
11	**37c**	NaHMDS	THF	31	1:4

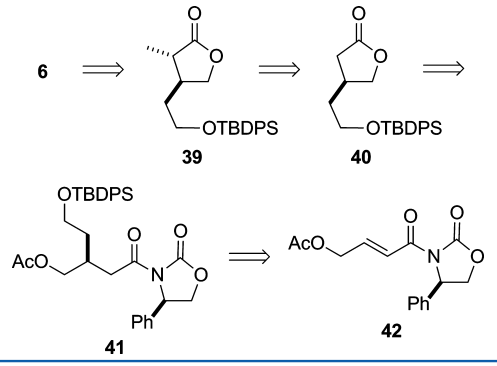
[a]Reaction at −20 °C. [b]With 4 equiv of LiCl. [c]With 4 equiv of DMPU. [d]With Me_2SO_4 as electrophile.

the difference in the chelating abilities of the bulky silyloxy group used in the present work compared to the substrates upon which this work is drawn that bear a benzyloxy group.

The relative stereochemistry of products originating from allyl compound **38a** were determined by comparison of the ^1H NMR resonances with the methyl ester derived from **31**. The stereochemistry of products originating from acetal **37c** were determined by conversion to a compound previously prepared in our group by addition of dimethyl methylphosphonate.[26] The mixture of diastereoisomers obtained from all three substrates **37a–c** were inseparable by chromatography. The corresponding β-ketophosphonates derived by addition of lithiated dimethyl methylphosphonate to the alkylation products were also found to be inseparable.

Third-Generation Approach to Phosphonate 6. The lack of stereochemical control in the above alkylation reactions and the coelution of the products by chromatography resulted in a third route to phosphonate **6** being investigated (Scheme 8).

Scheme 8. Third-Generation Retrosynthesis of Phosphonate 6



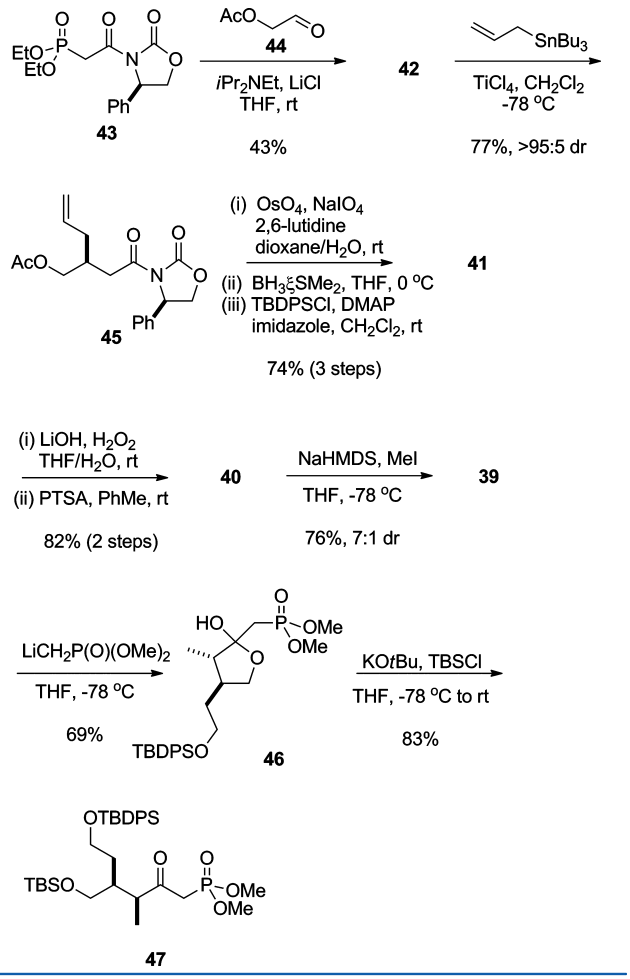
Phosphonate **6** could be accessed by ring opening of lactone **39** with dimethyl methylphosphonate. In this route, the methyl group would be introduced by alkylation of lactone **40**, which

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400–416

should proceed with high trans selectivity.[27] Cleavage of the acetate and oxazolidinone moieties of **41** should provide lactone **40**. Finally, silyl ether **41** could be obtained by allylation of α,β-unsaturated *N*-acyl oxazolidinone **42**, followed by appropriate functional group manipulation.

The third-generation synthesis of phosphonate **6** commenced with Horner–Wadsworth–Emmons coupling of the known phosphonate **43**[28] with aldehyde **44**[29] under Masamune–Roush conditions[30] (Scheme 9). $TiCl_4$-mediated allylation of **42** with

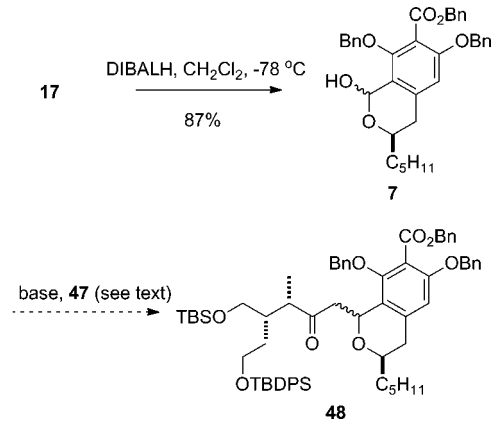
Scheme 9. Synthesis of Phosphonate 47



allyltributylstannane proceeded smoothly to afford **45** as a single diastereoisomer. The allyl moiety was converted into the TBDPS-protected alcohol **41** by oxidative cleavage with OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine,[31] reduction of the resulting aldehyde, and silyl ether formation. It was necessary to perform the TBDPS protection at concentrations of >0.4 M to avoid lactonization. The chiral auxiliary and acetate groups were next cleaved in one pot by reaction with lithium peroxide. The resulting hydroxyacid underwent lactonization spontaneously, but the rate of cyclization was significantly enhanced by treatment with PTSA. Methylation of lactone **40** with NaHMDS and methyl iodide at −78 °C proceeded with high diastereoselectivity to afford **39**. Lactone **39** has been prepared previously by Snider and co-workers by conjugate addition of a chiral phosphonamide anion to 2-butenolide.[4] Comparison of the optical rotation confirmed the facial selectivity of the conjugate addition to **42**. Addition of lithiated dimethyl methylphosphonate to lactone **39** afforded lactol **46**, which was opened by dianion formation with excess KO*t*Bu and trapping as the TBS ether **47** with TBSCl.[32] Attempts to form the analogous benzyl-protected compound **6** were unsuccessful.

Attempted Horner–Wadsworth–Emmons Coupling. With efficient routes to phosphonate **47** and lactone **17** established, the key HWE coupling was investigated (Scheme 10).

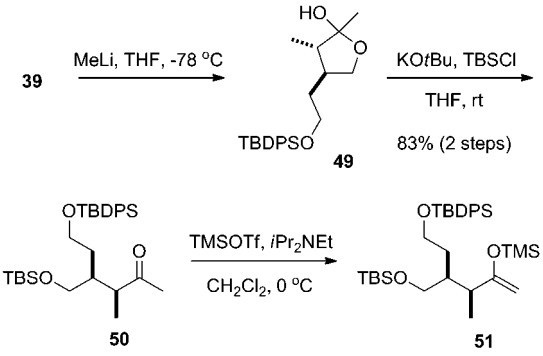
Scheme 10. Attempted HWE Coupling



Lactone **17** was reduced to lactol **7** with DIBALH at −78 °C, with careful monitoring of the reaction to avoid over-reduction. The HWE was carried out by deprotonation of lactol **7** followed by addition of phosphonate **47**. Disappointingly, none of the conditions screened (NaH, THF; K_2CO_3, Et_2O/H_2O; DBU, LiCl, MeCN, or THF; KO*t*Bu, THF) resulted in any of the desired product **48** being isolated. We postulate that the lack of reactivity in this case can be attributed to the lactol–hydroxyaldehyde equilibrium favoring the unreactive ring-closed form.

Silyl Enol Ether–Oxonium Ion Coupling Strategy. Faced with this lack of reactivity, we proposed that the two fragments could be unified by a coupling of a silyl enol ether with an oxonium ion derived from lactol **7**. We therefore prepared silyl enol ether **51** by addition of methyllithium to lactone **39** to afford lactol **49**, which was opened and trapped as the TBS ether **50** by treatment with KO*t*Bu and TBSCl (Scheme 11). Silyl enol ether formation proceeded smoothly by treatment of

Scheme 11. Synthesis of Silyl Enol Ether 51



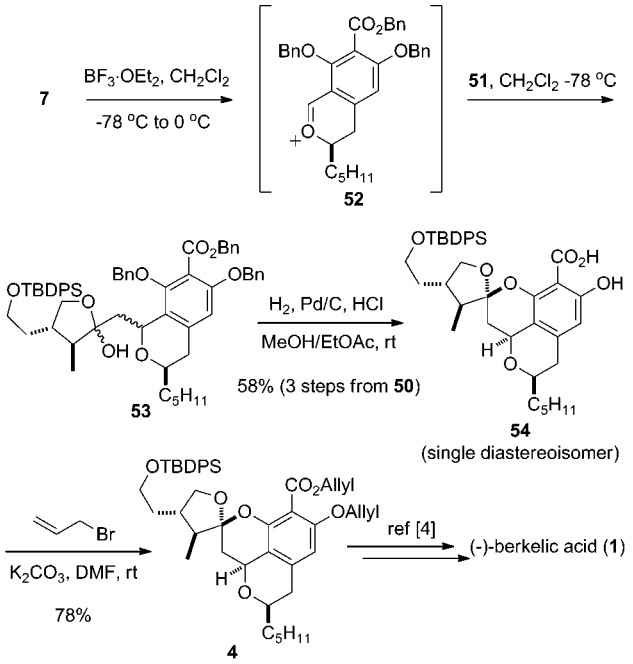
methyl ketone **50** with TMSOTf and Hünig's base to afford **51**, which was used without further purification.

Lactol **7** was treated with $BF_3{\cdot}OEt_2$ to afford oxonium ion **52**, which was reacted in situ by addition of silyl enol ether **51**

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400–416

at −78 °C to afford a diastereomeric mixture of lactols **53** (Scheme 12). Previous studies directed toward the synthesis of

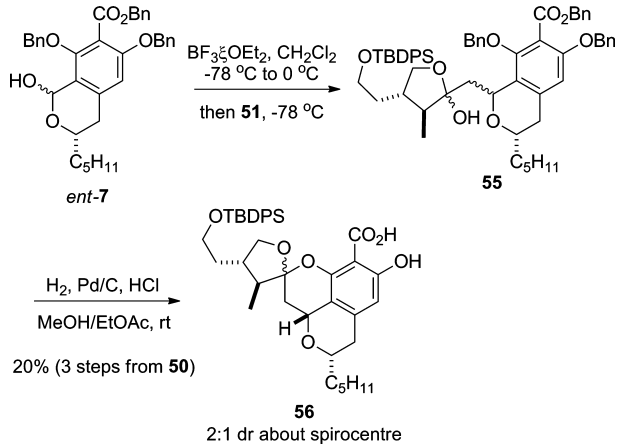
Scheme 12. Completion of Formal Synthesis



berkelic acid have demonstrated that, upon formation of the spiroketal moiety, the C-15 and C-17 stereocenters can be converted to the correct spiroketal configuration by acid-catalyzed equilibration. The mixture of lactol diastereoisomers **53** was therefore subjected to hydrogenolysis over Pd/C in the presence of HCl. Under these conditions, debenzylation, spiroketalization, and thermodynamic equilibration occurred in one pot to afford spiroketal **54** as a single diastereoisomer in 58% yield from methyl ketone **50** after purification by chromatography. To confirm that spiroketal **54** was indeed the most thermodynamically favored isomer, it was treated with TFA in $CDCl_3$ and the mixture monitored by ^1H NMR over a period of 3 days. After this period of time, no change in the ^1H NMR spectrum was observed, suggesting that **54** represents the most thermodynamically favored diastereoisomer and therefore contains the same configuration as the natural product. The formal synthesis of berkelic acid was completed by reaction of **54** with allyl bromide and K_2CO_3 to afford **4**, whose spectroscopic data and optical rotation matched those previously reported.[4]

To confirm unambiguously that we had prepared the correct spiroketal, and therefore to prove the absolute stereochemistry of the CBS reduction of ketone **9** (Table 1), we prepared the opposite enantiomer of lactol **7** by performing the CBS reduction with (*S*)-Me-CBS. Treatment of *ent*-**7** with $BF_3{\cdot}OEt_2$ followed by silyl enol ether **51** afforded a mixture of lactols **55** (Scheme 13). The debenzylation−spiroketalization−thermodynamic equilibration procedure afforded spiroketal **56** as an inseparable 2:1 mixture of diastereoisomers. Treatment with TFA in $CDCl_3$ resulted in the mixture slowly equilibrating to a 1:1.5 mixture of the two isomers after 2 days. This suggests that the two isomers of spiroketal **56** are close in energy and that **56** does not display the same configuration as the natural product.

Scheme 13. Oxonium−Silyl Enol Ether Coupling with *ent*-7



CONCLUSIONS

In conclusion, a full account of our synthetic efforts culminating in the successful completion of an enantioselective formal synthesis of berkelic acid has been described. Our original retrosynthetic strategy of a HWE/oxa-M cascade reaction proved unsuccessful, due to poor reactivity of the lactol coupling partner. This problem was overcome by the use of a silyl enol ether−oxonium ion coupling to unite the two fragments. Subsequent one-pot debenzylation, spiroketalization, and thermodynamic equilibration resulted in the formation of the desired spiroketal diastereoisomer. Other highlights from these synthetic studies include an unusual selectivity being observed in the CBS reduction of ketone **9**, which also displayed a temperature-dependent reversal of selectivity using $BH_3{\cdot}SMe_2$ as the stoichiometric reductant. The introduction of the methyl substituent on the phosphonate/silyl enol ether fragment proceeded with incorrect facial selectivity using acyclic substrates; hence, α-methylation of lactone **40** was used to obtain the correct stereochemistry. This route to Snider's advanced berkelic acid intermediate **4** is highly scalable and can be readily applied to the synthesis of analogues by simple reaction of any benzannulated lactols with a range of silyl enol ethers.

EXPERIMENTAL SECTION

General Methods. Unless stated, all solvents and reagents were used as supplied from commercial sources. Tetrahydrofuran was freshly distilled over sodium. Dichloromethane and diisopropylethylamine were freshly distilled over calcium hydride. Lithium chloride was dried for >24 h in an oven (110 °C) prior to use. Analytical thin-layer chromatography (TLC) was performed using Kieselgel F254 0.2 mm (Merck) silica plates with visualization by ultraviolet irradiation (254 nm) followed by staining with potassium permanganate or vanillin. Flash chromatography was performed using Kieselgel S 63−100 μm (Riedel-de-Hahn) silica gel. NMR spectra were recorded at the frequencies stated. Chemical shifts were referenced to δ 7.26 and 77.0 ppm from chloroform for ^1H and ^{13}C, respectively. The multiplicities of ^1H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. All coupling constants J = are reported in hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode, and assignments were determined using DEPT sequences. Mass spectra were obtained by electrospray ionization in positive ion mode. High-performance liquid chromatography (HPLC) was performed using an analytical 0.46 × 25 cm column with a guard column attached using the conditions outlined in the relevant experimental procedure.

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

1-Benzyl 3-Methyl 2,6-Bis(benzyloxy)-4-(2-methoxy-2-oxoethyl)isophthalate (15). Benzyl bromide (17.1 mL, 144 mmol) was added to a solution of acid **14**[11] (8.17 g, 28.7 mmol) and potassium carbonate (11.9 g, 86.1 mmol) in acetone (600 mL) at room temperature under argon. The mixture was heated at reflux for 19 h and then cooled, the solvent removed in vacuo, water (400 mL) added, and the reaction mixture extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 3/2 hexanes/ethyl acetate) to afford the title compound **15** (10.4 g, 65%) as a colorless solid: mp 58.5−59.0 °C; ν_{max} (film)/cm^{-1} 2953, 1724, 1600, 1295, 1197, 1098, 694; δ_H (400 MHz, $CDCl_3$) 7.40−7.22 (15H, m), 6.75 (1H, s), 5.30 (2H, s), 5.13 (2H, s), 5.07 (2H, s), 3.79 (3H, s), 3.75 (2H, s), 3.69 (3H, s); δ_C (100 MHz; $CDCl_3$) 170.5 (C), 166.8 (C), 165.1 (C), 157.2 (C), 155.5 (C), 136.7 (C), 136.6 (C), 135.6 (C), 135.2 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.0 (CH), 121.0 (C), 118.5 (C), 110.8 (CH), 77.9 (CH_2), 70.5 (CH_2), 67.2 (CH_2), 52.1 (CH_3), 52.0 (CH_3), 39.5 (CH_2); *m*/*z* (ESI+) 577 (MNa^+, 100%); *m*/*z* (ESI+) found $[M + Na]^+$ 577.1844, calcd for $C_{33}H_{30}NaO_8^+$ 577.1833.

1-Benzyl 3-Methyl 2,6-Bis(benzyloxy)-4-(2-(methoxy(methyl)amino)-2-oxoethyl)isophthalate (16). Lithium hydroxide hydrate (1.30 g, 30.6 mmol) was added to a solution of isophthalate **15** (8.50 g, 15.3 mmol) in water (150 mL) and tetrahydrofuran (150 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h and then concentrated in vacuo to remove the tetrahydrofuran and the resulting aqueous solution acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford 2-(3,5-bis(benzyloxy)-4-(benzyloxycarbonyl)-2-(methoxycarbonyl)-phenyl)acetic acid (8.27 g, 100%) as a colorless solid: mp <30 °C; ν_{max} (film)/cm^{-1} 3065, 2951, 1716, 1600, 1300, 1199, 1097, 733, 696; δ_H (400 MHz, $CDCl_3$) 7.40−7.21 (15H, m), 6.75 (1H, s), 5.28 (2H, s), 5.13 (2H, s), 5.02 (2H, s), 3.77 (3H, s), 3.75 (2H, s); δ_C (100 MHz; $CDCl_3$) 175.1 (C), 167.4 (C), 165.1 (C), 157.6 (C), 155.9 (C), 136.6 (C), 136.5 (C), 135.6 (C), 135.2 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 120.6 (C), 119.0 (C), 111.1 (CH), 78.1 (CH_2), 70.7 (CH_2), 67.4 (CH_2), 52.5 (CH_3), 14.0 (CH_2); *m*/*z* (ESI+) 563 (MNa^+, 100%); *m*/*z* (ESI+) found $[M + Na]^+$ 563.1683, calcd for $C_{32}H_{28}NaO_8^+$ 563.1676.

Triethylamine (0.36 mL, 2.6 mmol) was added to a solution of the above acid (1.07 g, 2.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.25 g, 2.6 mmol), 4-dimethylaminopyridine (0.26 g, 2.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.47 g, 2.5 mmol) in dichloromethane (12 mL) under argon. The resulting mixture was stirred at room temperature for 3 h and then washed successively with 1 M hydrochloric acid, brine, saturated aqueous sodium hydrogen carbonate, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 2/3 hexanes/ethyl acetate) to afford the title compound **16** (1.00 g, 87%) as a colorless solid: mp 91.0−91.5 °C; ν_{max} (film)/cm^{-1} 2949, 1725, 1663, 1600, 1301, 1200, 1096, 730, 696; δ_H (300 MHz, $CDCl_3$) 7.33−7.20 (15H, m), 6.74 (1H, s), 5.25 (2H, s), 5.11 (2H, s), 5.01 (2H, s), 3.84 (2H, s), 3.74 (3H, s), 3.57 (3H, s), 3.15 (3H, s); δ_C (100 MHz; $CDCl_3$) 171.0 (C), 167.1 (C), 165.3 (C), 157.1 (C), 155.4 (C), 137.7 (C), 136.8 (C), 135.9 (C), 135.3 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.92 (CH), 127.86 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 121.3 (C), 118.2 (C), 110.5 (CH), 77.9 (CH_2), 70.5 (CH_2), 67.2 (CH_2), 61.1 (CH_3), 52.1 (CH_3), 37.4 (CH_2), 32.2 (CH_3); *m*/*z* (ESI+) 584 (MH^+, 2%), 552 ($[M - HOCH_3]H^+$, 100); *m*/*z* (ESI+) found $[M + H]^+$ 584.2284, calcd for $C_{34}H_{34}NO_8^+$ 584.2279.

1-Benzyl 3-Methyl 2,6-Bis(benzyloxy)-4-(2-oxohept-3-ynyl)-isophthalate (9). Ethylmagnesium bromide (1 M in tetrahydrofuran, 37.9 mL, 37.9 mmol) was added to pentyne (3.85 mL, 37.9 mmol) at 0 °C under argon, and the mixture was stirred at this temperature for 15 min before heating to 50 °C for a further 2.5 h. The resulting solution of pentynylmagnesium bromide was cooled to room temperature, and a solution of amide **16** (5.52 g, 9.5 mmol) in tetrahydrofuran (50 mL) was added. The reaction mixture was stirred at room temperature for 2 min before cooling to 0 °C and addition of saturated ammonium chloride (100 mL). The reaction mixture was warmed to room temperature, diluted with water (100 mL), and extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 4/1 hexanes/ethyl acetate) to afford the title compound **9** (4.92 g, 88%) as a pale yellow solid: mp 71.0−71.7 °C; ν_{max} (film)/cm^{-1} 2963, 2211, 1722, 1671, 1599, 1301, 1254, 1208, 1179, 1100, 913, 735, 693; δ_H (400 MHz, $CDCl_3$) 7.38−7.18 (15H, m), 6.64 (1H, s), 5.25 (2H, s), 5.10 (2H, s), 5.01 (2H, s), 3.90 (2H, s), 3.75 (3H, s), 2.27 (2H, t, *J* = 7.0), 1.55−1.50 (2H, m), 0.94 (3H, t, *J* = 7.4); δ_C (100 MHz; $CDCl_3$) 183.4 (C), 166.8 (C), 165.2 (C), 157.4 (C), 155.8 (C), 136.7 (C), 136.4 (C), 135.7 (C), 135.3 (C), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.73 (CH), 127.67 (CH), 127.5 (CH), 126.9 (CH), 121.3 (C), 118.9 (C), 111.2 (CH), 96.4 (C), 80.5 (C), 78.1 (CH_2), 70.7 (CH_2), 67.3 (CH_2), 52.2 (CH_3), 50.3 (CH_2), 21.1 (CH_2), 20.9 (CH_2), 13.4 (CH_3); *m*/*z* (ESI+) 591 (MH^+, 80%), 559 ($[M - HOCH_3]H^+$, 100); *m*/*z* (ESI+) found $[M + H]^+$ 591.2386, calcd for $C_{37}H_{35}O_7^+$ 591.2377.

(*R*)-Benzyl 6,8-Bis(benzyloxy)-1-oxo-3-pentylisochroman-7-carboxylate ((*R*)-17). (*R*)-Me-CBS (0.10 mL, 1 M in tetrahydrofuran, 0.1 mmol) was added to ketone **9** (0.20 g, 0.3 mmol) and the solvent removed in vacuo. The resulting mixture of solids was placed under an atmosphere of argon, taken up in nitroethane (1 mL), and cooled to −78 °C. A solution of catecholborane (72 μL, 0.68 mmol) in nitroethane (0.5 mL) was added dropwise over 10 min. After 1.3 h at −78 °C, methanol (0.1 mL) was added and the reaction mixture warmed to room temperature. Ethyl acetate (20 mL) was added and the mixture washed with a 2:1 mixture of 1 M sodium hydroxide and saturated aqueous sodium hydrogen carbonate until the aqueous layer remained colorless. The organic layer was washed further with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant oil was dissolved in ethyl acetate (5 mL), and platinum dioxide (15 mg, 0.066 mmol) was added. The reaction mixture was placed under an atmosphere of hydrogen and stirred at room temperature for 3 h and then filtered through a pad of silica with ethyl acetate washings. The solvent was removed in vacuo and the resultant oil dissolved in dichloromethane (5 mL). Amberlyst 15 (200 mg) was added and the reaction mixture stirred at room temperature for 13 h. The resin was filtered with dichloromethane washings, and the filtrate was concentrated in vacuo. The resultant oil was purified by chromatography (silica gel, 3/2 hexanes/ethyl acetate) to afford the title compound (***R***)-**17** (110 mg, 59%, 99% ee) as a colorless solid: mp 120.5−121.0 °C; $[\alpha]_D^{20}$ = −45.7° (*c* 0.10, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2931, 1725, 1709, 1601, 1330, 1231, 1188, 1104, 729, 697; δ_H (400 MHz, $CDCl_3$) 7.48−7.16 (15H, m), 6.56 (1H, s), 5.28−5.11 (6H, m), 4.35−4.26 (1H, m), 3.14−2.74 (2H, m), 2.15−1.25 (8H, m), 0.97−0.85 (3H, m); δ_C (100 MHz; $CDCl_3$) 165.1 (C), 161.8 (C), 159.5 (C), 159.3 (C), 144.6 (C), 136.7 (C), 135.43 (C), 135.37 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 120.0 (C), 112.0 (C), 106.7 (CH), 77.43 (CH_2), 77.36 (CH), 70.6 (CH_2), 67.3 (CH_2), 34.9 (CH_2), 34.5 (CH_2), 31.5 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3); *m*/*z* (ESI+) 565 (MH^+, 2%), 181 ($C_{14}H_{13}^+$, 100); *m*/*z* (ESI+) found $[M + H]^+$ 565.2586, calcd for $C_{36}H_{37}O_6^+$ 565.2585. HPLC: column, Chiralpak AD-H; mobile phase, hexane/isopropyl alcohol (65/35 v/v); flow rate, 0.5 mL/min; retention times, 41.8 min (*S*), 46.0 min (*R*).

(*E*)-Ethyl 4-(Benzyloxy)but-2-enoate (12). Potassium carbonate (27.3 g, 198 mmol) was added to a solution of triethyl phosphonoacetate (19.8 mL, 99 mmol) in water (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then a solution of 2-(benzyloxy)acetaldehyde[33] (11.4 g, 76 mmol) in diethyl ether (60 mL) was added. The biphasic mixture was stirred vigorously at room temperature for 18 h, and then the aqueous layer was removed and extracted with ethyl acetate. The combined organics

dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400−416

were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 4/1 hexanes/ethyl acetate) to afford the title compound **12** (6.9 g, 33.5 mmol, 44%) as a colorless oil: δ_H (400 MHz, $CDCl_3$) 7.36−7.27 (5H, m), 6.99 (1H, dt, J = 15.5, 4.5), 6.14 (1H, dt, J = 15.5, 2.1), 4.56 (2H, s), 4.21 (2H, q, J = 7.2), 4.18−4.16 (2H, m), 1.29 (3H, t, J = 7.2). The ^{1}H NMR data closely matched those previously reported.[34]

(3*S*,4*S*)-4-(Benzyloxymethyl)-3-methyltetrahydro-2*H*-pyran-2-one (10). LiHMDS (1 M in tetrahydrofuran, 29.0 mL, 29.0 mmol) was added to a solution of amide **13**[19] (3.21 g, 14.7 mmol) and lithium chloride (4.32 g, 101.9 mmol) in tetrahydrofuran (30 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 30 min before cooling to −20 °C. α,β-Unsaturated ester **12** (3.00 g, 14.7 mmol) was added and the reaction mixture stirred at −20 °C for 13.5 h. Methanol (6 mL) and saturated aqueous ammonium chloride (60 mL) were added, and then the reaction mixture was warmed to room temperature and extracted with ethyl acetate. The combined organics were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant crude oil was partially purified by chromatography (silica gel, 2/3 hexanes/ethyl acetate) to afford a yellow oil (4.02 g). This oil was dissolved in dichloromethane (20 mL) and cooled to −78 °C. DIBALH (1 M in dichloromethane, 36.4 mL, 36.4 mmol) was added and the reaction mixture stirred at −78 °C for 1 h then at 0 °C for a further 1 h. Saturated aqueous Rochelle's salt (50 mL) was added and the reaction mixture stirred at room temperature for 15 min before extracting with dichloromethane. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was dissolved in dichloromethane (40 mL) and Amberlyst 15 (1.00 g) added. The reaction mixture was heated at reflux for 10 days without stirring. The resin was filtered, washed with dichloromethane, and concentrated in vacuo to afford an oil which was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford the title compound **10** (390 mg, 11%, 46% ee) as a colorless oil and the (3*R*,4*S*) isomer **19** (47 mg, 1%, 96% ee) as a colorless oil. **10**: $[\alpha]_D^{23}$ = +22.3° (c 0.10, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2975, 1734, 1559, 1457, 1387, 1113, 738, 698, 668; δ_H (400 MHz, $CDCl_3$) 7.36−7.26 (5H, m), 4.49 (2H, s), 4.42−4.22 (2H, m), 3.46−3.39 (2H, m), 2.80−2.73 (1H, m), 2.43−2.35 (1H, m), 2.05−1.90 (2H, m), 1.21 (3H, d, J = 7.0); δ_C (100 MHz; $CDCl_3$) 175.1 (C), 137.9 (C), 128.4 (CH), 127.6 (CH), 127.85 (CH), 73.3 (CH_2), 70.0 (CH_2), 66.7 (CH_2), 36.1 (CH), 35.3 (CH), 25.4 (CH_2), 12.4 (CH_3); m/z (ESI+) 235 (MH^+, 3%), 91 ($C_6H_5CH^+$, 100); m/z (ESI+) found $[M + H]^+$ 235.1322, calcd for $C_{14}H_{19}O_3^+$ 235.1329. HPLC: column, Chiralpak IC; mobile phase, hexane/isopropyl alcohol (65/35 v/v); flow rate, 0.5 mL/min; retention times, 33.3 min (*S*,*S*), 35.7 min (*R*,*R*). **19**: $[\alpha]_D^{23}$ = +4.1° (c 0.57, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2932, 1730, 1454, 1254, 1081, 737, 696; δ_H (400 MHz, $CDCl_3$) 7.37−7.28 (5H, m), 4.55 (1H, d, J = 12.0), 4.50 (1H, d, J = 12.0) 4.37−4.23 (2H, m), 3.54−3.46 (2H, m), 2.61−2.54 (1H, m), 2.09−1.91 (1H, m), 1.88−1.79 (2H, m), 1.25 (3H, d, J = 6.8); δ_C (75 MHz; $CDCl_3$) 175.4 (C), 138.0 (C), 128.5 (CH), 127.8 (CH), 127.6 (CH), 73.3 (CH_2), 71.7 (CH_2), 67.0 (CH_2), 38.3 (CH), 36.2 (CH), 26.7 (CH_2), 14.8 (CH_3); m/z (ESI+) 257 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 257.1149, calcd for $C_{14}H_{18}NaO_3^+$ 257.1148. HPLC: column, Chiralpak IC; mobile phase, hexane/isopropyl alcohol (65/35 v/v); flow rate, 0.5 mL/min; retention times, 32.1 min (3*S*,4*R*), 38.9 min (3*R*,4*S*).

General Procedure A: Lewis Acid Mediated Allylation. Titanium tetrachloride (1.0 M in dichloromethane, 2.5 equiv) was added dropwise over 10 min to a solution of α,β-unsaturated *N*-acyl oxazolidinone (1 equiv) in dichloromethane (0.07 M with respect to the oxazolidinone) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 15 min. Allyltributylstannane (2 equiv) was then added, and the resulting deep purple mixture was stirred at −78 °C for 3 h and then quenched with saturated aqueous ammonium chloride and warmed to room temperature. The organic layer was removed, and the aqueous phase was extracted with dichloromethane. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford the crude product, which was purified by chromatography (silica gel, 100% hexanes, then 2/1 hexanes/ethyl acetate).

*(R)-3-((S)-3-((Benzyloxy)methyl)hex-5-enoyl)-4-phenyloxazolidin-2-one (**24a**).* Following general procedure A, reaction with oxazolidinone **23a**[20] (1.0 g, 2.8 mmol) provided the title compound **24a** (810 mg, 76%) as a colorless oil: $[\alpha]_D^{20}$ = −47.6° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3032, 2865, 1777, 1703, 1383, 1195; δ_H (400 MHz, $CDCl_3$) 7.36−7.23 (10H, m), 5.78−5.68 (1H, m), 5.27 (1H, dd, J = 9.0, 4.0), 5.02−5.00 (1H, m), 4.97 (1H, br s), 4.51 (1H, dd, J = 9.0, 9.0), 4.39 (2H, s), 4.18 (1H, dd, J = 9.0, 4.0), 3.41 (1H, dd, J = 9.0, 5.0), 3.33 (1H, dd, J = 9.0, 6.5), 3.03 (1H, dd, J = 16.5, 6.5), 2.96 (1H, dd, J = 16.5, 7.0), 2.40−2.33 (1H, m), 2.20−2.04 (2H, m); δ_C (100 MHz, $CDCl_3$) 172.1 (C), 153.7 (C), 139.2 (C), 138.6 (C), 136.1 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.9 (CH), 116.9 (CH_2), 72.9 (CH_2), 72.4 (CH_2), 69.9 (CH_2), 57.7 (CH), 37.5 (CH_2), 35.8 (CH_2), 34.9 (CH); m/z (ESI+) 402 (MNa^+, 100%), 380 (MH^+, 8), 272 ($[M - BnOH]H^+$, 66); m/z (ESI+) found $[M + Na]^+$ 402.1675, calcd for $C_{23}H_{25}NO_4Na^+$ 402.1676.

*(R)-4-Benzyl-3-((S)-3-((benzyloxy)methyl)hex-5-enoyl)oxazolidin-2-one (**24b**).* Following general procedure A, reaction with oxazolidinone **23b**[20] (220 mg, 0.63 mmol) provided the title compound **24b** (60 mg, 24%) as a colorless oil: $[\alpha]_D^{20}$ = −44.6° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2971, 2902, 1777, 1698, 1384, 1205, 1058; δ_H (400 MHz, $CDCl_3$) 7.33−7.23 (8H, m), 7.17−7.14 (2H, m), 5.84−5.74 (1H, m), 5.10−5.02 (2H, m), 4.55−4.44 (3H, m), 4.07−4.00 (2H, m), 3.53 (1H, dd, J = 9.0, 5.0), 3.42 (1H, dd, J = 9.0, 7.0), 3.22 (1H, dd, J = 13.5, 3.5), 3.06 (1H, dd, J = 16.5, 7.5), 2.94 (1H, dd, J = 16.5, 6.0), 2.56−2.45 (2H, m), 2.27−2.11 (2H); δ_C (100 MHz, $CDCl_3$) 172.5 (C), 153.5 (C), 138.5 (C), 136.1 (CH), 135.5 (C), 129.4 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 117.0 (CH_2), 73.2 (CH_2), 72.9 (CH_2), 66.1 (CH_2), 55.3 (CH), 37.7 (CH_2), 37.5 (CH_2), 36.1 (CH_2), 35.0 (CH); m/z (ESI+) 432 (MK^+, 17%), 416 (MNa^+, 100); m/z (ESI+) found $[M + Na]^+$ 416.1827, calcd for $C_{24}H_{27}NO_4Na^+$ 416.1832.

*(R)-3-((S)-3-((Benzyloxy)methyl)hex-5-enoyl)-4-isopropyloxazolidin-2-one (**24c**).* Following general procedure A, reaction with oxazolidinone **23c**[20] (190 mg, 0.63 mmol) provided the title compound **24c** (84 mg, 39%) as a colorless oil: $[\alpha]_D^{20}$ = −48.1° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2971, 2922, 1778, 1697, 1383, 1195, 1078, 698; δ_H (400 MHz, $CDCl_3$) 7.33−7.26 (5H, m), 5.82−5.72 (1H, m), 5.07−5.00 (2H, m), 4.49 (1H, d, J = 12.0), 4.45 (1H, d, J = 12.0), 4.32−4.29 (1H, m), 4.15−4.08 (2H, m), 3.49 (1H, dd, J = 9.0, 5.0), 3.40 (1H, dd, J = 9.0, 7.0), 2.98 (2H, d, J = 6.8), 2.48−2.38 (1H, m), 2.35−2.27 (1H, m), 2.25−2.08 (2H, m), 0.87 (3H, d, J = 7.0), 0.82 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 172.5 (C), 154.1 (C), 138.5 (C), 136.1 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 116.9 (CH_2), 73.0 (CH_2), 72.7 (CH_2), 63.2 (CH_2), 58.5 (CH), 37.4 (CH_2), 35.9 (CH_2), 34.9 (CH), 28.4 (CH), 18.0 (CH_3), 14.6 (CH_3); m/z (ESI+) 368 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 368.1840, calcd for $C_{20}H_{27}NO_4Na^+$ 368.1832.

General Procedure B: Alkylation of *N*-Acyl Oxazolidinones. LiHMDS (1.0 M in tetrahydrofuran, 1.3 equiv) was added dropwise to a solution of the oxazolidinone (1 equiv) and lithium chloride (4 equiv) in tetrahydrofuran (0.03−0.13 M with respect to the oxazolidinone) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 10 min and then at −25 °C for 50 min. Methyl iodide (5 equiv) was then added, and the reaction mixture was stirred at −25 °C for a further 6 h and then quenched with saturated aqueous ammonium chloride, warmed to room temperature, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford the crude product.

*(R)-3-((2R,3S)-3-((Benzyloxy)methyl)-2-methylhex-5-enoyl)-4-phenyloxazolidin-2-one (**31a**).* Following general procedure B, reaction with oxazolidinone **24a** (750 mg, 2.0 mmol) provided the title compound **31a** (370 mg, 47%) as a colorless oil after purification by chromatography (silica gel, 4/1 hexanes/ethyl acetate): $[\alpha]_D^{21}$ = −81.9° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2915, 1778, 1708, 1382, 1199, 1100; δ_H (400 MHz, $CDCl_3$) 7.37−7.26 (8H, m), 7.19−7.16 (2H, m), 5.86−5.76 (1H, m), 5.07−5.01 (2H, m), 4.97 (1H, dd, J = 8.5, 3.0), 4.43 (1H, d, J = 11.5), 4.39 (1H, d, J = 11.5), 4.21 (1H, dd, J = 8.5, 8.5), 4.03 (1H, dd, J = 8.5, 3.0), 3.97−3.90 (1H, m), 3.51−3.44

(2H, m), 2.23−2.12 (3H, m), 1.05 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 175.7 (C), 153.6 (C), 139.7 (C), 138.6 (C), 136.8 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 125.6 (CH), 116.5 (CH_2), 73.2 (CH_2), 69.8 (CH_2), 69.7 (CH_2), 57.9 (CH), 40.8 (CH), 38.7 (CH), 34.2 (CH_2), 12.9 (CH_3); m/z (ESI+) 416 (MNa^+, 100%), 394 (MH^+, 32); m/z (ESI+) found $[M + H]^+$ 394.2001, calcd for $C_{24}H_{28}NO_4^+$ 394.2013.

*(R)-4-Benzyl-3-((2R,3S)-3-((benzyloxy)methyl)-2-methylhex-5-enoyl)oxazolidin-2-one (**31b**).* Following general procedure B, reaction with oxazolidinone **24b** (20 mg, 0.051 mmol) provided an inseparable 4/1 mixture of diastereoisomers, which were immediately converted to the corresponding carboxylic acid by cleavage with LiOH/H_2O_2 to determine the facial selectivity of the alkylation. The diastereomeric ratio of the initial alkylation was determined by integration of the CH_3 group: $\delta_{H,minor}$ 1.21 (d, J = 6.8), δ_{major} 1.17 (d, J = 6.8).

*(R)-3-((2R,3S)-3-((Benzyloxy)methyl)-2-methylhex-5-enoyl)-4-isopropyloxazolidin-2-one (**31c**).* Following general procedure B, reaction with oxazolidinone **24c** (10 mg, 0.029 mmol) provided an inseparable 4/1 mixture of diastereoisomers, which were immediately converted to the corresponding carboxylic acid by cleavage with LiOH/H_2O_2 to determine the facial selectivity of the alkylation. The diastereomeric ratio of the initial alkylation was determined by integration of the CH_3 group: $\delta_{H,minor}$ 1.16 (d, J = 6.8), δ_{major} 1.15 (d, J = 6.8).

*(2R,3R)-3-((Benzyloxy)methyl)-N-methoxy-N,2-dimethylhex-5-enamide (**32**).* Aqueous hydrogen peroxide (30%, 280 μL, 2.5 mmol) was added to a solution of oxazolidinone **31a** (195 mg, 0.50 mmol) in tetrahydrofuran (3 mL) and water (1 mL) at 0 °C. A solution of lithium hydroxide (42 mg, 0.99 mmol) in water (1 mL) was then added and the reaction mixture stirred at room temperature for 2 h. The reaction was quenched by addition of sodium sulfite (300 mg) in water (3 mL) and then acidified to pH ∼4 with 1 M hydrochloric acid and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 2/1 hexanes/ethyl acetate) to afford (2*R*,3*R*)-3-benzyloxymethyl-2-methylhex-5-enoic acid (124 mg, 100%) as a colorless oil: $[\alpha]_D^{20}$ = −15.0° (c 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2860, 1701, 1455, 1106; δ_H (400 MHz, $CDCl_3$) 7.34−7.23 (5H, m), 5.80−5.70 (1H, m), 5.06−5.01 (2H, m), 4.47 (2H, s), 3.47 (1H, dd, J = 9.5, 5.5), 3.44 (1H, dd, J = 9.5, 5.0), 2.67 (1H, qd, J = 7.0, 5.0), 2.23−2.04 (3H, m), 1.12 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 182.2 (C), 138.3 (C), 136.4 (CH), 128.3 (CH), 127.6 (2 × CH), 116.9 (CH_2), 73.2 (CH_2), 69.7 (CH_2), 40.6 (CH), 40.0 (CH), 33.9 (CH_2), 12.5 (CH_3); m/z (ESI+) 271 (MNa^+, 100%), 249 (MH^+, 25); m/z (ESI+) found $[M + H]^+$ 249.1481, calcd for $C_{15}H_{21}O_3^+$ 249.1485.

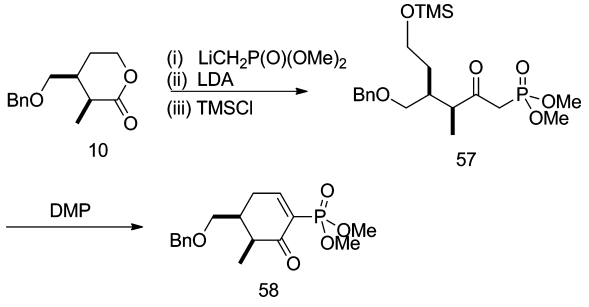
HATU (335 mg, 0.88 mmol) was added to a solution of the above acid (109 mg, 0.44 mmol) in DMF (3 mL) at 0 °C under nitrogen. *N*,*O*-Dimethylhydroxylamine hydrochloride (86 mg, 0.88 mmol) was then added, followed by *N*-methylmorpholine (97 μL, 0.88 mmol). The resulting colorless solution was stirred at 0 °C for 18 h and then diluted with ethyl acetate, washed sequentially with water, 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and concentrated in vacuo to afford the title compound **32** (120 mg, 94%) as a colorless oil, which was used without further purification: $[\alpha]_D^{19}$ = −18.1° (c 1.15, $CHCl_3$); ν_{max} (film)/cm^{-1} 2972, 2867, 1661, 1110, 996; δ_H (400 MHz, $CDCl_3$) 7.30−7.17 (5H, m), 5.73−5.62 (1H, m), 4.96−4.89 (2H, m), 4.43 (1H, d, J = 7.5), 4.38 (1H, d, J = 7.5), 3.77 (3H, s), 3.45 (1H, dd, J = 9.5, 4.0), 3.39 (1H, dd, J = 9.5, 5.0), 3.10 (3H, s), 2.98 (1H, br s), 2.23−2.16 (1H, m), 2.05−1.98 (1H, m), 1.97−1.89 (1H, m), 1.02 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 177.6 (br, C), 138.7 (C), 137.2 (CH), 128.3 CH), 127.6 (CH), 127.5 (CH), 116.3 (CH_2), 73.1 (CH_2), 69.0 (CH_2), 61.4 (CH_3), 40.8 (CH), 36.0 (CH), 34.6 (CH_2), 32.3 (br, CH_3), 14.5 (CH_3); m/z (ESI+) 314 (MNa^+, 100%), 292 (MH^+, 33); m/z (ESI+) found $[M + H]^+$ 292.1906, calcd for $C_{17}H_{26}NO_3^+$ 292.1907.

*Dimethyl (3R,4R)-4-((Benzyloxy)methyl)-3-methyl-2-oxohept-6-en-1-yl)phosphonate (**33**).* *n*-Butyllithium (880 μL, 1.23 mmol) was added to a solution of freshly distilled dimethyl methylphosphonate (133 μL, 1.23 mmol) in tetrahydrofuran (3 mL) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 1 h, and then a solution of amide **32** (120 mg, 0.41 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred for a further 4 h at −78 °C and then quenched by addition of saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **33** (134 mg, 92%) as a colorless oil: $[\alpha]_D^{21}$ = −59.9° (c 0.73, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2854, 1709, 1257, 1028; δ_H (400 MHz, $CDCl_3$) 7.35−7.25 (5H, m), 5.82−5.71 (1H, m), 5.07−5.02 (2H, m), 4.40 (1H, d, J = 12.5), 4.37 (1H, d, J = 12.5), 3.76 (3H, d, J = 11.0), 3.75 (3H, d, J = 11.0), 3.40−3.26 (3H, m), 3.02 (1H, dd, J = 22.0, 14.5), 2.84 (1H, qd, J = 7.0, 5.0), 2.34−2.28 (1H, m), 2.20−2.12 (1H, m), 2.07−2.00 (1H, m), 1.04 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 204.7 (C, d, J = 6.0), 138.1 (C), 136.3 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 117.0 (CH_2), 73.3 (CH_2), 69.5 (CH_2), 53.0 (CH_3, d, J = 6.5), 52.8 (CH_3, d, J = 6.5), 47.9 (CH, d, J = 1.5), 40.4 (CH), 39.6 (CH_2, d, J = 129.5), 34.2 (CH_2), 10.4 (CH_3); m/z (ESI+) 377 (MNa^+, 100%), 355 (MH^+, 60), 247 ($[M - HOBn]H^+$, 70); m/z (ESI+) found $[M + H]^+$ 355.1666, calcd for $C_{18}H_{28}O_5P^+$ 355.1669.

*Dimethyl ((4S,5R)-4-((Benzyloxy)methyl)-5-methyl-6-oxocyclohex-1-en-1-yl)phosphonate (**34**).* Osmium tetroxide (2.5 wt % in *t*BuOH, 32 μL, 0.0031 mmol) was added to a solution of phosphonate **33** (22 mg, 0.062 mmol) and *N*-methylmorpholine *N*-oxide (22 mg, 0.19 mmol) in water (1 mL) and acetone (3 mL). The resulting solution was stirred for 18 h at room temperature, then an additional aliquot of OsO_4 (32 μL, 0.0031 mmol) and NMO (22 mg, 0.19 mmol) were added, and the mixture was stirred for a further 18 h. A solution of sodium periodate (225 mg, 1.1 mmol) in water (1.5 mL) was then added and the resulting white precipitate was stirred at room temperature for 30 min and then filtered with dichloromethane washings. The filtrate was extracted with dichloromethane, and the combined organics were washed with saturated aqueous ammonium chloride, dried (Na_2SO_4), and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **34** (7 mg, 33%) as a colorless oil: $[\alpha]_D^{20}$ = +40.8° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2956, 2854, 1681, 1249, 1029; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, ddd, J = 20.5, 4.5, 3.5), 7.37−7.28 (5H, m), 4.53 (1H, d, J = 12.0), 4.49 (1H, d, J = 12.0), 3.79 (3H, d, J = 11.0), 3.76 (3H, d, J = 11.0), 3.53−3.47 (2H, m), 2.69−2.65 (2H, m), 2.54 (1H, dq, J = 11.0, 6.5), 2.10−2.02 (1H, m), 1.15 (3H, d, J = 6.5$_3$); δ_C (100 MHz, $CDCl_3$) 198.5 (C, d, J = 5.0), 162.4 (CH, d, J = 6.0), 138.0 (C), 129.5 (C, d, J = 183.0), 128.5 (CH), 127.8 (CH), 127.6 (CH), 73.4 (CH_2), 70.9 (CH_2), 53.1 (CH_3, d, J = 6.5), 53.0 (CH_3, d, J = 6.5), 43.9 (CH, d, J = 7.1), 40.7 (CH), 30.2 (CH_2, d, J = 16.0), 11.8 (CH_3); m/z (ESI+) 699 (M_2Na^+, 47%), 361 (MNa^+, 100), 339 (MH^+, 48); m/z (ESI+) found $[M + H]^+$ 339.1356, calcd for $C_{17}H_{24}O_5P^+$ 339.1356.

Proof of Stereochemistry of Phosphonate 34. The relative stereochemistry of phosphonate **34** was assigned by comparison of the spectral data with that of *cis*-phosphonate **58**, prepared from lactone **10** (Scheme 14).

Scheme 14. Synthesis of Phosphonate S-2



*Dimethyl (3S,4R)-4-(Benzyloxymethyl)-3-methyl-2-oxo-6-(trimethylsilyloxy)hexylphosphonate (**57**).* *n*-Butyllithium (1.6 M in

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

hexanes, 0.99 mL, 1.6 mmol) was added to a solution of dimethyl methylphosphonate (0.17 mL, 1.6 mmol) in tetrahydrofuran (6 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 15 min, and then a solution of lactone **10** (370 mg, 1.6 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, and then lithium diisopropylamine (1 M in tetrahydrofuran, 1.6 mL, 1.6 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h, and then trimethylsilyl chloride (400 μL, 3.2 mmol) was added and the reaction mixture was warmed to room temperature over 14 h. Saturated aqueous ammonium chloride (20 mL) was then added and the reaction mixture extracted with ethyl acetate. The combined organics were washed with saturated aqueous sodium bicarbonate, water, and brine, dried ($MgSO_4$), and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **57** (570 mg, 83%) as a colorless oil: ν_{max} (film)/cm^{-1} 2956, 1709, 1454, 1250, 1028, 839, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.27−7.16 (5H, m), 4.42−4.33 (2H, m), 3.66 (3H, d, J = 11.0), 3.65 (3H, d, J = 11.0), 3.52−3.38 (3H, m), 3.28−3.17 (2H, m), 2.98−2.89 (2H, m), 2.19−2.11 (1H, m), 1.46−1.26 (2H, m), 0.95 (3H, d, J = 6.8), 0.06−0.00 (9H, m); δ_C (100 MHz; $CDCl_3$) 205.0 (C, d, J = 6.2), 137.8 (C), 127.9 (CH), 127.22 (CH), 127.19 (CH), 72.6 (CH_2), 70.7 (CH_2), 60.0 (CH_2), 52.4 (CH_3, d, J = 6.4), 52.3 (CH_3, d, J = 6.4), 47.6 (CH, d, J = 1.9), 39.5 (CH_2, d, J = 130.0), 36.7 (CH), 30.3 (CH_2), 11.1 (CH_3), −1.0 (CH_3); δ_P (162 MHz, $CDCl_3$) 23.6; m/z (ESI+) 453 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 453.1840, calcd for $C_{20}H_{35}NaO_6PSi^+$ 453.1833.

*Dimethyl (4S,5S)-4-(Benzyloxymethyl)-5-methyl-6-oxocyclohex-1-enylphosphonate (**58**).* Dess−Martin periodinane (300 mg, 0.71 mmol) was added to a solution of **57** (150 mg, 0.35 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 18 h and then quenched by addition of water (10 mL) and extracted with dichloromethane. The combined organics were washed with saturated aqueous sodium thiosulfate, dried ($MgSO_4$), and concentrated in vacuo to afford an oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **58** (51 mg, 43%) as a yellow oil: ν_{max} (film)/cm^{-1} 2957, 1683, 1453, 1375, 1248, 1029, 828, 746; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, dt, J = 20.8, 4.0), 7.36−7.27 (5H, m), 4.46 (2H, s), 3.78 (3H, d, J = 11.4), 3.71 (3H, d, J = 11.4), 3.48−3.38 (2H, m), 2.75 (1H, dq, J = 7.2, 4.2), 2.69−2.50 (3H, m), 1.09 (3H, d, J = 7.2); δ_C (100 MHz; $CDCl_3$) 198.6 (C, d, J = 5.2), 161.7 (CH, d, J = 5.9), 137.8 (C), 129.5 (C, d, J = 181.1), 128.4 (CH), 127.7 (CH), 127.6 (CH), 73.3 (CH_2), 69.5 (CH_2), 53.0 (CH_3, d, J = 5.8), 52.8 (CH_3, d, J = 5.8), 43.4 (CH, d, J = 7.2), 38.3 (CH), 28.6 (CH_2, d, J = 15.7), 10.9 (CH_3); δ_P (162 MHz, $CDCl_3$) 16.7; m/z (ESI+) 339 (MH^+, 20%), 233 ($[M - BnOH]H^+$, 100), found MNa^+, 339.1360, calcd for $C_{17}H_{24}O_5P^+$ 339.1356.

*(S)-Methyl 3-((Benzyloxy)methyl)hex-5-enoate (**37a**).* Aqueous hydrogen peroxide (30%, 1.5 mL, 13.2 mmol) was added to a solution of oxazolidinone **24a** (1.0 g, 2.6 mmol) in tetrahydrofuran (18 mL) and water (6 mL) at 0 °C. A solution of lithium hydroxide (220 mg, 5.3 mmol) in water (6 mL) was then added and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was quenched by addition of sodium sulfite (1.5 g) in water (10 mL) and then acidified to pH ∼4 with 1 M hydrochloric acid and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 2/1 hexanes/ethyl acetate) to afford (*S*)-3-((benzyloxy)methyl)hex-5-enoic acid (575 mg, 95%) as a colorless oil: $[\alpha]_D^{20}$ = −1.2° (*c* 0.97, $CHCl_3$); ν_{max} (film)/cm^{-1} 2912, 2859, 1705, 1101; δ_H (400 MHz, $CDCl_3$) 7.36−7.26 (5H, m), 5.80−5.69 (1H, m), 5.08−5.03 (2H, m), 4.51 (1H, d, J = 12.0), 4.48 (1H, d, J = 12.0), 3.47 (1H, dd, J = 9.5, 5.0), 3.39 (1H, dd, J = 9.5, 6.5), 2.46 (1H, dd, J = 16.0, 7.0), 2.37 (1H, dd, J = 16.0, 6.0), 2.31−2.24 (1H, m), 2.24−2.07 (2H, m); δ_C (100 MHz, $CDCl_3$) 179.0 (C), 138.3 (C), 135.7 (CH), 128.4 (CH), 127.58 (CH), 127.56 (CH), 117.3 (CH_2), 73.1 (CH_2), 72.3 (CH_2), 36.1 (CH_2), 35.7 (CH_2), 35.2 (CH); m/z (ESI+) 257 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 257.1143, calcd for $C_{14}H_{18}NaO_3^+$ 257.1148.

(Trimethylsilyl)diazomethane (2.0 M in diethyl ether, 1.45 mL, 2.9 mmol) was added to a solution of the above acid (575 mg, 2.5 mmol) in tetrahydrofuran (30 mL) and methanol (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and then concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 6/1 hexanes/ethyl acetate) to afford the title compound **37a** (520 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ = −1.8° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2947, 2857, 1735, 1170, 1101; δ_H (400 MHz, $CDCl_3$) 7.36−7.26 (5H, m), 5.78−5.69 (1H, m), 5.06−5.01 (2H, m), 4.48 (2H, s), 3.62 (3H, s), 3.44 (1H, dd, J = 9.5, 5.0), 3.36 (1H, dd, J = 9.5, 6.0), 2.42−2.24 (3H, m), 2.24−2.07 (2H, m); δ_C (100 MHz, $CDCl_3$) 173.5 (C), 138.5 (C), 135.9 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 117.0 (CH_2), 73.0 (CH_2), 72.4 (CH_2), 51.5 (CH_3), 36.0 (CH_2), 35.8 (CH_2), 35.4 (CH); m/z (ESI+) 271 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 271.1303, calcd for $C_{15}H_{20}NaO_3^+$ 271.1305.

*(S)-Methyl 3-((Benzyloxy)methyl)-5-((tert-butyldiphenylsilyl)oxy)-pentanoate (**37b**).* Osmium tetroxide (2.5 wt % in *tert*-butyl alcohol, 760 μL, 0.075 mmol) was added to a solution of oxazolidinone **24a** (570 mg, 1.5 mmol) and *N*-methylmorpholine *N*-oxide (875 mg, 7.5 mmol) in water (10 mL) and acetone (30 mL). The reaction mixture was stirred for 18 h at room temperature, and then a solution of sodium periodate (5.4 g, 25.5 mmol) in water (15 mL) was added. The resulting white precipitate was stirred for 1 h at room temperature and then filtered with dichloromethane washings. The filtrate was extracted with dichloromethane, and the combined organics were washed with saturated aqueous ammonium chloride, dried (Na_2SO_4), and concentrated in vacuo to afford a black oil. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford (*S*)-3-((benzyloxy)methyl)-5-oxo-5-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)pentanal (397 mg, 69%) as a colorless oil: $[\alpha]_D^{25}$ = −36.4° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2861, 1778, 1705, 1385, 1202, 699; δ_H (400 MHz, $CDCl_3$) 9.69 (1H, br s), 7.38−7.24 (10H, m), 5.34 (1H, dd, J = 9.0, 4.0), 4.59 (1H, dd, J = 9.0, 9.0), 4.42 (2H, s), 4.23 (1H, dd, J = 9.0, 4.0), 3.43 (1H, dd, J = 9.0, 5.5), 3.38 (1H, dd, J = 9.0, 6.0), 3.07 (1H, dd, J = 17.0, 6.5), 3.02 (1H, dd, J = 17.0, 7.0), 2.85−2.79 (1H, m), 2.54 (1H, ddd, J = 17.0, 7.0, 2.0), 2.45 (1H, ddd, J = 17.0, 6.0, 1.5); δ_C (100 MHz, $CDCl_3$) 201.4 (CH), 171.3 (C), 153.7 (C), 139.0 (C), 138.1 (C), 129.2 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 125.9 (CH), 73.1 (CH_2), 72.4 (CH_2), 70.0 (CH_2), 57.6 (CH), 45.9 (CH_2), 37.2 (CH_2), 30.3 (CH); m/z (ESI+) 404 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 404.1462, calcd for $C_{22}H_{23}NNaO_5^+$ 404.1468.

Borane−dimethyl sulfide complex (48 μL, 0.50 mmol) was added dropwise to a solution of the above aldehyde (174 mg, 0.46 mmol) in tetrahydrofuran (10 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 10 min and then quenched by addition of saturated aqueous ammonium chloride (5 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 2/1 hexanes/ethyl acetate) to afford (*R*)-3-((*S*)-3-((benzyloxy)methyl)-5-hydroxypentanoyl)-4-phenyloxazolidin-2-one (176 mg, 100%) as a colorless oil: $[\alpha]_D^{21}$ = −39.1° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3430, 2927, 2865, 1777, 1704, 1384, 1201; δ_H (400 MHz, $CDCl_3$) 7.37−7.24 (10H, m), 5.28 (1H, dd, J = 9.0, 3.5), 4.56 (1H, dd, J = 9.0, 9.0), 4.44 (2H, s), 4.21 (1H, dd, J = 9.0, 3.5), 3.66−3.58 (2H, m), 3.45−3.38 (2H, m), 3.06 (1H, dd, J = 16.5, 7.0), 2.95 (1H, dd, J = 16.5, 6.4), 2.47−2.36 (1H, m), 1.71−1.49 (2H, m); δ_C (100 MHz, $CDCl_3$) 172.1 (C), 153.8 (C), 139.1 (C), 138.1 (C), 129.2 (CH), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 125.9 (CH), 73.5 (CH_2), 73.2 (CH_2), 70.0 (CH_2), 60.5 (CH_2), 57.7 (CH), 38.2 (CH_2), 35.3 (CH_2), 32.6 (CH); m/z (ESI+) 406 (MNa^+, 98%), 366 ($[M - H_2O]H^+$], 100); m/z (ESI+) found $[M + Na]^+$ 406.1628, calcd for $C_{22}H_{25}NNaO_5^+$ 406.1625.

TBDPSCl (76 μL, 0.54 mmol) was added to a solution of the above alcohol (174 mg, 0.45 mmol), imidazole (62 mg, 0.91 mmol), and DMAP (5.5 mg, 0.045 mmol) in dichloromethane (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 18 h, and then saturated aqueous ammonium chloride (5 mL) was added. The aqueous layer was extracted with

dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400−416

dichloromethane and the combined organics dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 9/1 hexanes/ethyl acetate) to afford (*R*)-3-((*S*)-3-((benzyloxy)methyl)-5-((*tert*-butyldiphenylsilyl)-oxy)pentanoyl)-4-phenyloxazolidin-2-one (192 mg, 69%) as a pale yellow oil: $[\alpha]_D^{21} = -46.4°$ (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3073, 3037, 2931, 2857, 1782, 1706, 1110, 702; δ_H (400 MHz, $CDCl_3$) 7.63 (4H, d, *J* = 6.0), 7.43−7.21 (16H, m), 5.23 (1H, dd, *J* = 9.0, 3.5), 4.45 (1H, dd, *J* = 9.0, 9.0), 4.33 (2H, s), 4.15 (1H, dd, *J* = 9.0, 3.5), 3.68 (2H, t, *J* = 6.5), 3.42 (1H, dd, *J* = 9.0, 5.0), 3.31 (1H, dd, *J* = 9.0, 7.0), 3.02 (2H, d, *J* = 6.5), 2.49−2.43 (1H, m), 1.70−1.57 (2H, m), 1.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 172.0 (C), 153.7 (C), 139.3 (C), 138.6 (C), 135.6 (CH), 133.9 (C), 129.5 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 125.8 (CH), 72.84 (CH_2), 72.75 (CH_2), 69.8 (CH_2), 62.0 (CH_2), 57.7 (CH), 37.9 (CH_2), 34.2 (CH_2), 32.4 (CH), 26.9 (CH_3), 19.2 (C); *m*/*z* (ESI+) 644 (MNa^+, 77%), 622 (MH^+, 100), 544 ($[M - C_6H_5]^+$, 36), 366 ([M − HOTBDPS]H^+, 78); *m*/*z* (ESI+) found $[M + H]^+$ 622.2973, calcd for $C_{38}H_{44}NO_5Si^+$ 622.2983.

Aqueous hydrogen peroxide (30%, 170 μL, 1.5 mmol) was added to a solution of the above oxazolidinone (185 mg, 0.30 mmol) in tetrahydrofuran (6 mL) and water (2 mL) at 0 °C. A solution of lithium hydroxide (25 mg, 0.60 mmol) in water (2 mL) was then added and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was quenched by addition of sodium sulfite (400 mg) in water (3 mL) and then acidified to pH ∼4 with 1 M hydrochloric acid and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a pale yellow oil. The crude product was purified by chromatography (silica gel, 2/1 hexanes/ethyl acetate) to afford (*S*)-3-((benzyloxy)-methyl)-5-((*tert*-butyldiphenylsilyl)oxy)pentanoic acid (130 mg, 91%) as a colorless oil: $[\alpha]_D^{21} = -5.4°$ (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3072, 2931, 2858, 1707, 1111, 701; δ_H (400 MHz, $CDCl_3$) 7.64 (4H, d, *J* = 7.0), 7.43−7.26 (11H, m), 4.48 (1H, d, *J* = 12.0), 4.44 (1H, d, *J* = 12.0), 3.70 (1H, t, *J* = 6.0), 3.49 (1H, dd, *J* = 9.0, 4.5), 3.37 (1H, dd, *J* = 9.0, 6.5), 2.51 (1H, dd, *J* = 17.0, 9.0), 2.43−2.39 (2H, m), 1.69−1.61 (2H, m), 1.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 177.1 (C), 138.2 (C), 135.6 (CH), 133.74 (C), 133.71 (C), 129.6 (CH), 128.4 (CH), 127.7 (CH), 127.6 (2 × CH), 73.1 (CH_2), 72.7 (CH_2), 61.7 (CH_2), 36.7 (CH_2), 34.0 (CH_2), 32.7 (CH), 26.9 (CH_3), 19.2 (C); *m*/*z* (ESI+) 499 (MNa^+, 100%), 477 (MH^+, 16), 291 ([M − C_6H_5 − HOBn]H^+, 22), 221 ([M − HOTBDPS]H^+, 56); *m*/*z* (ESI+) found $[M + H]^+$ 477.2450, calcd for $C_{29}H_{36}O_4Si^+$ 477.2456.

(Trimethylsilyl)diazomethane (2.0 M in diethyl ether, 270 μL, 0.54 mmol) was added to a solution of the above acid (130 mg, 0.27 mmol) in tetrahydrofuran (9 mL) and methanol (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo to afford the title compound **37b** (133 mg, 100%) as a yellow oil, which was used without further purification: $[\alpha]_D^{21} = -4.3°$ (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3072, 2932, 2858, 1737, 1111, 702; δ_H (400 MHz, $CDCl_3$) 7.65−7.64 (4H, m), 7.43−7.26 (11H, m), 4.46 (1H, d, *J* = 13.5), 4.42 (1H, d, *J* = 13.5), 3.69 (2H, t, *J* = 6.5), 3.60 (3H, s), 3.45 (1H, dd, *J* = 9.0, 4.0), 3.33 (1H, dd, *J* = 9.0, 5.5), 2.47−2.32 (3H, m), 1.70−1.58 (2H, m), 1.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 173.5 (C), 135.6 (CH), 133.8 (C), 129.6 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 73.0 (CH_2), 72.7 (CH_2), 61.8 (CH_2), 51.4 (CH_3), 36.7 (CH_2), 34.1 (CH_2), 32.9 (CH), 26.8 (CH_3), 19.2 (C); *m*/*z* (ESI+) 513 (MNa^+, 100%), 491 (MH^+, 31), 413 ($[M - C_6H_5]^+$, 53), 235 ([M − HOTBDPS]H^+, 79); *m*/*z* (ESI+) found $[M + H]^+$ 491.2607, calcd for $C_{30}H_{39}O_4Si^+$ 491.2601.

(S)-Methyl 3-((1,3-Dioxolan-2-yl)methyl)-4-(benzyloxy)butanoate (37c). *p*-Toluenesulfonic acid (187 mg, 0.98 mmol) was added to a solution of (*S*)-3-((benzyloxy)methyl)-5-oxo-5-((*R*)-2-oxo-4-phenyl-oxazolidin-3-yl)pentanal (750 mg, 2.0 mmol) and ethylene glycol (550 μL, 9.8 mmol) in dichloromethane (30 mL) at room temperature under argon. Silica (1.5 g) was then added, and the resulting slurry was stirred at room temperature for 18 h and then filtered with dichloromethane washings. The filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford (*R*)-3-((*S*)-3-(1,3-dioxolan-2-yl)methyl)-4-(benzyloxy)butanoyl)-4-phenyl-oxazolidin-2-one (**59**; 742 mg, 87%) as a colorless oil, which was used without further purification: $[\alpha]_D^{20} = -47.0°$ (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2883, 1776, 1703, 1200, 698; δ_H (400 MHz, $CDCl_3$) 7.36−7.22 (10H, m), 5.28 (1H, dd, *J* = 9.0, 3.5), 4.90 (1H, dd, *J* = 9.0, 9.0), 4.51 (1H, dd, *J* = 9.0, 9.0), 4.40 (2H, s), 4.17 (1H, dd, *J* = 9.0, 3.5), 3.95−3.87 (2H, m), 3.83−3.74 (2H, m), 3.48 (1H, dd, *J* = 9.0, 5.0), 3.39 (1H, dd, *J* = 9.0, 6.5), 3.17 (1H, dd, *J* = 17.0, 6.5), 3.03 (1H, dd, *J* = 17.0, 9.0), 2.55−2.48 (1H, m), 1.80 (1H, ddd, *J* = 14.0, 6.5, 4.5), 1.68 (1H, ddd, *J* = 14.0, 6.5, 5.5); δ_C (100 MHz, $CDCl_3$) 171.9 (C), 153.8 (C), 139.3 (C), 138.6 (C), 129.1 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.9 (CH), 103.5 (CH), 72.9 (CH_2), 69.9 (CH_2), 64.71 (CH_2), 64.68 (CH_2), 57.6 (CH), 37.9 (CH_2), 35.3 (CH_2), 31.5 (CH); *m*/*z* (ESI+) 448 (MNa^+, 100%), 318 ([M − BnOH)]H^+, 14), 274 ([M − BnOH − C_2H_4O]H^+, 65); *m*/*z* (ESI+) found $[M + Na]^+$ 448.1720, calcd for $C_{24}H_{27}NNaO_6^+$ 448.1731.

Aqueous hydrogen peroxide (30%, 990 μL, 8.7 mmol) was added to a solution of the above oxazolidinone (740 mg, 1.74 mmol) in tetrahydrofuran (18 mL) and water (6 mL) at 0 °C. A solution of lithium hydroxide (145 mg, 3.5 mmol) in water (6 mL) was then added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of sodium sulfite (1.5 mg) in water (6 mL) and then acidified to pH ∼4 with 1 M hydrochloric acid and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a pale yellow oil. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford (*S*)-3-((1,3-dioxolan-2-yl)methyl)-4-(benzyloxy)butanoic acid (145 mg, 30%) as a colorless oil: $[\alpha]_D^{20} = -7.1°$ (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3219, 2883, 1705, 1028; δ_H (400 MHz, $CDCl_3$) 7.34−7.23 (5H, m), 4.92 (1H, t, *J* = 5.0), 4.51 (1H, d, *J* = 12.0), 4.48 (1H, d, *J* = 12.0), 3.96−3.91 (2H, m), 3.85−3.79 (2H, m), 3.52 (1H, dd, *J* = 9.5, 5.0), 3.42 (1H, dd, *J* = 9.5, 6.0), 2.53−2.51 (2H, m), 2.46−2.40 (1H, m), 1.83 (1H, ddd, *J* = 14.0, 6.0, 4.5), 1.71 (1H, ddd, *J* = 14.0, 7.0, 5.0); δ_C (100 MHz, $CDCl_3$) 178.6 (C), 138.4 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 103.4 (CH), 73.0 (CH_2), 72.7 (CH_2), 64.7 (CH_2), 36.7 (CH_2), 35.2 (CH_2), 31.7 (CH); *m*/*z* (ESI+) 303 (MNa^+, 33%); *m*/*z* (ESI+) found $[M + Na]^+$ 303.1210, calcd for $C_{15}H_{20}NaO_5^+$ 303.1203.

(Trimethylsilyl)diazomethane (2.0 M in diethyl ether, 520 μL, 1.04 mmol) was added to a solution of the above acid (145 mg, 0.52 mmol) in tetrahydrofuran (5 mL) and methanol (1.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo to afford the title compound **37c** (150 mg, 100%) as a yellow oil, which was used without further purification: $[\alpha]_D^{20} = -5.7°$ (*c* 0.74, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954, 2884, 1733, 1088, 1028; δ_H (400 MHz, $CDCl_3$) 7.29−7.18 (5H, m), 4.85 (1H, t, *J* = 5.0), 4.42 (2H, s), 3.89−3.85 (2H, m), 3.77−3.73 (2H, m), 3.56 (3H, s), 3.44 (1H, dd, *J* = 9.0, 5.0), 3.35 (1H, dd, *J* = 9.0, 6.0), 2.43−2.36 (3H, m), 1.76 (1H, ddd, *J* = 14.0, 6.0, 4.5), 1.62 (1H, ddd, *J* = 14.0, 6.0, 5.0); δ_C (100 MHz, $CDCl_3$) 173.3 (C), 138.5 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 103.4 (CH), 73.0 (CH_2), 72.7 (CH_2), 64.8 (CH_2), 64.7 (CH_2), 51.4 (CH_3), 36.7 (CH_2), 35.4 (CH_2), 32.0 (CH); *m*/*z* (ESI+) 317 (MNa^+, 100%); *m*/*z* (ESI+) found $[M + Na]^+$ 317.1356, calcd for $C_{16}H_{22}NaO_5^+$ 317.1359.

General Procedure C: Alkylation of Methyl Esters. NaHMDS (1.0 M in tetrahydrofuran, 1.2 equiv) was added dropwise to a solution of ester **37** (1 equiv) in tetrahydrofuran (0.07−0.10 M with respect to the ester) at 78 °C under argon. The reaction mixture was stirred at −78 °C for 30 min and then methyl iodide (3 equiv) was added. The reaction mixture was stirred for 2 h at −78 °C and then quenched with saturated aqueous ammonium chloride, warmed to room temperature, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford the crude product.

(2S,3S)-Methyl 3-((Benzyloxy)methyl)-2-methylhex-5-enoate (38a). Following general procedure C, reaction with ester **37a**[26] (25 mg, 0.10 mmol) provided the title compound **38a** as a colorless oil as an inseparable 1.3:1 mixture of diastereoisomers after purification by chromatography (silica gel, 5/1 hexanes/ethyl acetate): δ_H (400 MHz, $CDCl_3$) 7.37−7.27 (5H, m), 5.79−5.68 (1H, m), 5.05−4.99 (2H, m), 4.45−4.42 (2H, m), 3.61 (3H, s), 3.45−3.34 (2H, m), 2.74−2.62 (1H, m),

dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400−416

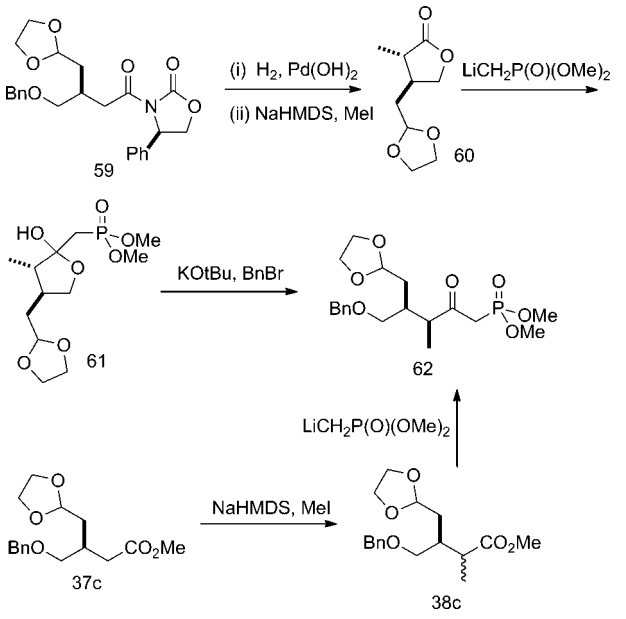
2.21−2.02 (3H, m), 1.12 and 1.11 (3H, 2*d*, *J*, 6.8, CH_3 of syn and anti diastereoisomers respectively).

*(2RS,3S)-Methyl 3-((Benzyloxy)methyl)-5-((tert-butyldiphenylsilyl)oxy)-2-methylpentanoate (**38b**).* Following general procedure C, reaction with ester **37b**[26] (50 mg, 0.10 mmol) provided the title compound **38b** as a colorless oil as an inseparable 1:1 mixture of diastereoisomers after purification by chromatography (silica gel, 9/1 hexanes/ethyl acetate): δ_H (400 MHz, $CDCl_3$) 7.66−7.64 (4H, m), 7.43−7.24 (11H, m), 4.46−4.36 (2H, m), 3.71−3.65 (2H, m), 3.59 and 3.57 (3H, 2s), 3.43−3.32 (2H, m), 2.75−2.68 (1H, m), 2.28−2.25 (1H, m), 1.65−1.40 (2H, m), 1.09 and 1.06 (3H, 2d, *J* = 7.2), 1.04 (9H, s).

*(2R,3S)-Methyl 3-((1,3-Dioxolan-2-yl)methyl)-4-(benzyloxy)-2-methylbutanoate (**38c**).* Following general procedure C, reaction with ester **37c**[26] (115 mg, 0.39 mmol) provided the title compound **38c** as a colorless oil as an inseparable 4/1 mixture of diastereoisomers after purification by chromatography (silica gel, 3/1 hexanes/ethyl acetate): δ_H (400 MHz, $CDCl_3$) 7.33−7.24 (5H, m), 4.93−4.90 (1H, m), 4.46 (2H, s), 3.96−3.90 (2H, m), 3.84−3.79 (2H, m), 3.61 and 3.60 (3H, 2s, CO_2Me of syn and anti diastereoisomers, respectively), 3.54−3.41 (2H, m), 2.82−2.73 (1H, m), 2.35−2.30 (1H, m), 1.80−1.62 (2H, m), 1.12 and 1.10 (3H, 2d, *J* = 7.2, $CHCH_3$ of anti and syn diastereoisomers, respectively).

Stereochemical Proof for Alkylation of 37c. To determine the stereochemical outcome for the alkylation of **37c**, ester **38c** was treated with lithiated dimethyl methylphosphonate and the spectral data of the resulting *β*-ketophosphonate compared to that of ***syn*-62**, prepared from oxazolidinone **59** (Scheme 15).

Scheme 15. Stereochemical Proof for Alkylation of 37c



*(3S,4S)-4-((1,3-Dioxolan-2-yl)methyl)-3-methyldihydrofuran-2(3H)-one (**60**).* A mixture of oxazolidinone **59** (590 mg, 1.39 mol) and 20% $Pd(OH)_2$ in ethyl acetate (20 mL) was placed under an atmosphere of hydrogen (balloon), stirred vigorously at room temperature for 2.5 h, and then filtered through Celite with ethyl acetate washing and concentrated in vacuo (water bath <30 °C) to afford a colorless oil. The oil was dissolved in ethyl acetate (20 mL), and then 0.5 M sodium hydroxide (10 mL) was added. The biphasic mixture was stirred vigorously at room temperature for 1 h, and then the organic layer was removed and the aqueous layer extracted with ethyl acetate. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo (water bath <30 °C) to afford a cream-colored solid. The crude product was purified by chromatography (silica gel, 95/5 to 90/10 dichloromethane/ethyl acetate) to afford volatile (*S*)-4-((1,3-dioxolan-2-yl)methyl)-dihydrofuran-2(3*H*)-one (55 mg, 23%) as a colorless oil, which was used immediately in the next step: δ_H (400 MHz, $CDCl_3$) 4.90 (1H, t, *J* = 4.0), 4.60 (1H, dd, *J* = 8.5, 8.5), 4.02−3.96 (3H, m), 3.90−3.80 (2H, m), 2.83−2.73 (1H, m), 2.65 (1H, dd, *J* = 17.0, 8.5), 2.29 (1H, dd, *J* = 17.0, 9.5), 1.92 (1H, ddd, *J* = 14.0, 6.5, 4.0), 1.83 (1H, ddd, *J* = 14.0, 7.5, 4.5).

NaHMDS (1.0 M in tetrahydrofuran, 680 μL, 0.68 mmol) was added dropwise to a solution of the above lactone (90 mg, 0.52 mmol) in tetrahydrofuran (5 mL) at −78 °C under argon. The reaction mixture was stirred for 45 min at −78 °C, and then methyl iodide (100 μL, 1.57 mmol) was added. The reaction mixture was stirred for a further 3 h at −78 °C and then quenched by addition of saturated aqueous ammonium chloride (3 mL), warmed to room temperature, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford the title compound **60** (50 mg, 52%) as a colorless oil: $[\alpha]_D^{20}$ = −17.0° (*c* 1.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 2975, 2888, 1773, 1007; δ_H (400 MHz, $CDCl_3$) 4.91 (1H, dd, *J* = 5.0, 3.5), 4.45 (1H, dd, *J* = 9.5, 7.5), 4.01−3.95 (2H, m), 3.92−3.83 (3H, m), 2.37−2.29 (1H, m), 2.26−2.18 (1H, m), 2.10 (1H, ddd, *J* = 14.5, 3.5, 3.5), 1.73 (1H, ddd, *J* = 14.5, 10.0, 5.0), 1.26 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 179.2 (C), 102.6 (CH), 72.1 (CH_2), 65.1 (CH_2), 64.9 (CH_2), 40.2 (CH), 39.3 (CH), 35.6 (CH_2), 13.5 (CH_3); *m*/*z* (ESI+) 209 (MNa^+, 100%), 187 (MH^+, 48), 143 ([M − C_2H_4O]H^+, 45); *m*/*z* (ESI+) found $[M + H]^+$ 187.0958, calcd for $C_9H_{15}O_4^+$ 187.0965.

*Dimethyl (((3S,4S)-4-((1,3-Dioxolan-2-yl)methyl)-2-hydroxy-3-methyltetrahydrofuran-2-yl)methyl)phosphonate (**61**).* *n*BuLi (1.4 M in hexanes, 92 μL, 0.13 mmol) was added dropwise to a solution of dimethyl methylphosphonate (14 μL, 0.13 mmol) in tetrahydrofuran (1 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 15 min, and then a solution of lactone **60** (24 mg, 0.13 mmol) in tetrahydrofuran (1 mL) was added. The reaction mixture was stirred at −78 °C for a further 1 h and then at room temperature for 1.5 h and was then quenched by addition of saturated aqueous ammonium chloride (1 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **61** (13 mg, 32%) as a colorless oil: $[\alpha]_D^{20}$ = −36.3° (*c* 1.10, $CHCl_3$); ν_{max} (film)/cm^{-1} 3390, 2957, 2885, 1030; δ_H (400 MHz, $CDCl_3$) 5.01 (1H, br s), 4.86 (1H, dd, *J* = 4.2, 4.2), 4.21 (1H, dd, *J* = 8.4, 8.4), 3.98−3.92 (2H, m), 3.85−3.80 (5H, m), 3.74 (3H, d, *J* = 11.0), 3.61 (1H, dd, *J* = 8.4, 8.4), 2.36−2.25 (2H, m), 2.16−1.94 (2H, m), 1.60−1.46 (2H, m), 1.05 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 103.6 (CH), 102.9 (C, d, *J* = 9.0), 72.5 (CH_2), 65.0 (CH_2), 64.9 (CH_2), 53.4 (CH_3, d, *J* = 6.0), 51.9 (CH_3, d, *J* = 6.0), 50.0 (CH, d, *J* = 13.0), 39.3 (CH), 36.8 (CH_2), 33.9 (CH_2, d, *J* = 134.0), 11.8 (CH_3); *m*/*z* (ESI+) 643 (M_2Na^+, 68%), 333 (MNa^+, 100), 293 ([M − H_2O]H^+, 76); *m*/*z* (ESI+) found [M + Na]$^+$ 333.1076, calcd for $C_{12}H_{23}NaO_7P^+$ 333.1074.

*Dimethyl ((3S,4S)-4-((1,3-Dioxolan-2-yl)methyl)-5-(benzyloxy)-3-methyl-2-oxopentyl)phosphonate (***syn*-62**).* Potassium *tert*-butoxide (22 mg, 0.20 mmol) was added to a solution of lactol **61** (25 mg, 0.081 mmol) in tetrahydrofuran (1.5 mL) at −78 °C under argon. The resulting yellow suspension was stirred at −78 °C for 15 min and then benzyl bromide (11 μL, 0.089 mmol) was added. The reaction mixture was warmed slowly to room temperature over 18 h and then quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil. The crude product was purified by preparative thin-layer chromatography (100% ethyl acetate, then 9/1 dichloromethane/methanol) to afford the title compound ***syn*-62** (3 mg, 10%) as a brown oily solid: $[\alpha]_D^{20}$ = +28.2° (*c* 0.38, $CHCl_3$); ν_{max} (film)/cm^{-1} 2923, 2853, 1710, 1251, 1029, 748; δ_H (400 MHz, $CDCl_3$) 7.36−7.28 (5H, m), 4.86 (1H, t, *J* = 5.0), 4.51 (1H, d, *J* = 12.0), 4.45 (1H, d, *J* = 12.0), 3.95−3.89 (2H, m), 3.83−3.78 (2H, m), 3.76 (3H, d, *J* = 11.0), 3.74 (3H, d, *J* = 11.0), 3.56 (1H, dd, *J* = 9.5, 5.0), 3.40−3.26 (2H, m), 3.31−2.99 (2H, m), 2.39−2.32 (1H, m), 1.63−1.51 (2H, m), 1.02 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$)

dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400−416

205.4 (C, d, J = 6.0), 138.2 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 103.2 (CH), 73.0 (CH_2), 71.3 (CH_2), 64.9 (CH_2), 64.6 (CH_2), 53.0 (CH_3, d, J = 6.5), 52.9 (CH_3, d, J = 6.5), 47.8 (CH), 39.9 (CH_2, d, J = 130.0), 36.2 (CH), 31.7 (CH_2), 11.3 (CH_3); m/z (ESI+) 423 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 423.1536, calcd for $C_{19}H_{29}NaO_7P^+$ 423.1543.

*Dimethyl ((3R,4S)-4-((1,3-Dioxolan-2-yl)methyl)-5-(benzyloxy)-3-methyl-2-oxopentyl)phosphonate (**anti-62**).* n-Butyllithium (260 μL, 0.36 mmol) was added dropwise to a solution of dimethyl methylphosphonate (38 μL, 0.36 mmol) in tetrahydrofuran (1 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 25 min and then a solution of ester **38c** (37 mg, 0.12 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at −78 ° C for 1 h and then at room temperature 2 h and was then quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **62** as an inseparable 4/1 mixture of anti and syn diastereoisomers. The ^1H and ^{13}C data for the minor syn isomer matched those obtained above. Data for ***anti*-62**: δ_H (400 MHz, $CDCl_3$) 7.34−7.25 (5H, m), 4.92 (1H, t, J = 5.0), 4.41 (1H, d, J = 11.0), 4.38 (1H, d, J = 11.0), 3.97−3.88 (2H, m), 3.83−3.79 (2H, m), 3.77 (3H, d, J = 11.5), 3.74 (3H, d, J = 11.5), 3.45 (1H, dd, J = 9.5, 5.0), 3.40−3.26 (2H, m), 3.03 (1H, dd, J = 22.0, 14.5), 2.94−2.89 (1H, m), 2.52−2.45 (1H, m), 1.77−1.63 (2H, m), 1.06 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 204.3 (C, d, J = 6.1), 138.1 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 103.4 (CH), 73.2 (CH_2), 70.0 (CH_2), 64.78 (CH_2), 64.76 (CH_2), 53.0 (CH_3, d, J = 6.5), 52.7 (CH_3, d, J = 6.5), 48.6 (CH), 39.5 (CH_2, d, J = 130.0), 36.6 (CH), 33.7 (CH_2), 10.6 (CH_3).

*(S,E)-4-Oxo-4-(2-oxo-4-phenyloxazolidin-3-yl)but-2-en-1-yl Acetate (**42**).* Diisopropylethylamine (9.8 mL, 56 mmol) was added to a solution of phosphonate **43**[28] (1.91 g, 5.6 mmol) and lithium chloride (360 mg, 8.4 mmol) in tetrahydrofuran (40 mL) at room temperature under nitrogen. The solution was stirred at room temperature for 20 min, and then a solution of aldehyde **44**[29] (1.24 g, 11.2 mmol) in tetrahydrofuran (20 mL) was added. The resulting yellow solution was stirred at room temperature for 18 h and then quenched with 1 M hydrochloric acid (30 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate to afford the title compound **42** (700 mg, 43%) as a colorless oil. $[\alpha]_D^{20}$ = −78.4° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3035, 2987, 2929, 1775, 1743, 1689, 1337, 1223, 1199; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, dt, J = 15.5, 2.0), 7.41−7.30 (5H, m), 7.03 (1H, dt, J = 15.5, 4.5), 5.49 (1H, dd, J = 9.0, 4.0), 4.78 (2H, dd, J = 4.5, 2.0), 4.72 (1H, dd, J = 9.0, 9.0), 4.31 (1H, dd, J = 9.0, 4.0), 2.14 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.4 (C), 163.8 (C), 153.6 (C), 143.4 (CH), 138.8 (C), 129.2 (CH), 128.8 (CH), 126.0 (CH), 120.8 (CH), 70.0 (CH_2), 62.9 (CH_2), 57.7 (CH), 20.7 (CH_3); m/z (ESI+) 312 (MNa^+, 100%); m/z (ESI+) found $[M + Na]^+$ 312.0842, calcd for $C_{15}H_{15}NO_5Na^+$ 312.0842.

*(S)-2-(2-Oxo-2-((S)-2-oxo-4-phenyloxazolidin-3-yl)ethyl)pent-4-en-1-yl Acetate (**45**).* Following general procedure A, reaction with oxazolidinone **42** (8.54 g, 29.5 mmol) provided the title compound **45** (7.56 g, 77%) as a pale yellow oil: $[\alpha]_D^{20}$ = −45.1° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2978, 2919, 1779, 1735, 1704, 1383, 1237, 1195; δ_H (400 MHz, $CDCl_3$) 7.41−7.29 (5H, m), 5.76−5.66 (1H, m), 5.42 (1H, dd, J = 9.0, 4.0), 5.04 (1H, br s), 5.02−4.99 (1H, m), 4.69 (1H, dd, J = 9.0, 9.0), 4.28 (1H, dd, J = 9.0, 4.0), 4.06 (1H, dd, J = 11.0, 5.0), 3.88 (1H, dd, J = 11.0, 6.5), 3.04 (1H, dd, J = 17.5, 6.5), 2.95 (1H, dd, J = 17.5, 6.5), 2.42−2.35 (1H, m), 2.16−2.03 (2H, m), 1.94 (3H, s); δ_C (100 MHz, $CDCl_3$) 171.4 (C), 171.0 (C), 153.7 (C), 139.1 (C), 135.3 (CH), 129.2 (CH), 128.8 (CH), 125.9 (CH), 117.4 (CH_2), 70.0 (CH_2), 66.1 (CH_2), 57.7 (CH), 36.9 (CH_2), 35.4 (CH_2), 33.4 (CH), 20.8 (CH_3); m/z (ESI+) 354 (MNa^+, 100%), 272 ($[M - HOAc]H^+$, 77); m/z (ESI+) found $[M + Na]^+$ 354.1307, calcd for $C_{18}H_{21}NO_5Na^+$ 354.1312.

*(S)-2-(2-tert-Butyldiphenylsilyloxyethyl)-4-oxo-4-((S)-2-oxo-4-phenyloxazolidin-3-yl)butyl Acetate (**41**).* Osmium tetroxide (2.5% in *tert*-butyl alcohol, 4.6 mL, 0.45 mmol) was added to a solution of **45** (7.44 g, 22.5 mmol) and 2,6-lutidine (5.2 mL, 44.9 mmol) in dioxane (250 mL) and water (100 mL) at room temperature. Sodium metaperiodate (19.1 g, 89.8 mmol) was then added and the resulting suspension stirred at room temperature for 2 h. The mixture was diluted with water (200 mL) and then extracted with dichloromethane. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil, which was used directly in the next step. An aliquot of aldehyde was purified for characterization by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford (*S*)-4-oxo-4-((*S*)-2-oxo-4-phenyloxazolidin-3-yl)-2-(2-oxoethyl)butyl acetate as a pale yellow oil: $[\alpha]_D^{20}$ = −57.7° (c 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2968, 2924, 1776, 1732, 1701, 1233, 1200, 1040; δ_H (400 MHz, $CDCl_3$) 9.69 (1H, t, J = 1.5), 7.41−7.28 (5H, m), 5.42 (1H, dd, J = 9.0, 3.5), 4.71 (1H, dd, J = 9.0, 9.0), 4.29 (1H, dd, J = 9.0, 3.5), 4.01 (2H, d, J = 6.0), 3.11 (1H, dd, J = 17.5, 6.0), 2.99 (1H, dd, J = 17.5, 7.0), 2.90−2.85 (1H, m), 2.53 (1H, ddd, J = 17.5, 7.0, 1.5), 2.46 (1H, ddd, J = 17.5, 6.5, 1.5), 1.99 (3H, s); δ_C (100 MHz, $CDCl_3$) 200.4 (CH), 170.9 (C), 170.8 (C), 153.7 (C), 138.9 (C), 129.3 (CH), 128.9 (CH), 125.9 (CH), 70.1 (CH_2), 66.1 (CH_2), 57.7 (CH), 45.4 (CH_2), 36.9 (CH_2), 28.8 (CH), 20.7 (CH_3); m/z (ESI+) 372 (MK^+, 100%), 356 (MNa^+, 35); m/z (ESI+) found $[M + Na]^+$ 356.1114, calcd for $C_{17}H_{19}NO_6Na^+$ 356.1105.

Borane−dimethyl sulfide complex (2.35 mL, 24.8 mmol) was added dropwise over 5 min to a solution of the above crude aldehyde in tetrahydrofuran (250 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 10 min and then quenched carefully with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a black oil. The crude product was purified by chromatography (silica gel, 1/3 hexanes/ethyl acetate) to afford (*S*)-2-(2-hydroxyethyl)-4-oxo-4-((*S*)-2-oxo-4-phenyloxazolidin-3-yl)butyl acetate (6.59 g, 87% over 2 steps) as a yellow oil: $[\alpha]_D^{20}$ = −55.7° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3457, 2924, 1775, 1732, 1704, 1385, 1234, 1200; δ_H (400 MHz, $CDCl_3$) 7.42−7.29 (5H, m), 5.43 (1H, dd, J = 9.0, 3.5), 4.71 (1H, dd, J = 9.0, 9.0), 4.29 (1H, dd, J = 9.0, 3.5), 4.07 (1H, dd, J = 11.0, 5.0), 3.96 (1H, dd, J = 11.0, 6.0), 3.65 (2H, t, J = 6.0), 3.03 (2H, br d, J = 6.5), 2.48−2.42 (1H, m), 1.98 (3H, s), 1.71−1.46 (2H, m); δ_C (100 MHz, $CDCl_3$) 171.8 (C), 171.0 (C), 153.7 (C), 138.9 (C), 129.2 (CH), 128.9 (CH), 126.0 (CH), 70.1 (CH_2), 66.7 (CH_2), 60.2 (CH_2), 57.7 (CH), 37.6 (CH_2), 34.3 (CH_2), 30.8 (CH), 20.8 (CH_3); m/z (ESI+) 358 (MNa^+, 100%), 318 ($[M - H_2O]H^+$, 54); m/z (ESI+) found $[M + Na]^+$ 358.1264, calcd for $C_{17}H_{21}NO_6Na^+$ 358.1261.

Imidazole (1.61 g, 23.6 mmol) was added to a solution of the above alcohol (6.59 g, 19.7 mmol), DMAP (240 mg, 1.97 mmol), and TBDPSCl (5.5 mL, 39.3 mmol) in dichloromethane (50 mL) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 18 h. Saturated aqueous ammonium chloride (30 mL) was added, and the organic layer was removed. The aqueous layer was extracted with dichloromethane, and then the combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. The crude product was purified by chromatography (silica gel, 3/1 hexanes/ethyl acetate) to afford the title compound **41** (9.63 g, 85%) as a pale yellow oil: $[\alpha]_D^{20}$ = −33.3° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2931, 2858, 1781, 1737, 1706, 1385, 1236, 1192, 1107, 703; δ_H (400 MHz, $CDCl_3$) 7.66−7.62 (4H, m), 7.42−7.27 (11H, m), 5.37 (1H, dd, J = 9.0, 3.5), 4.64 (1H, dd, J = 9.0, 9.0), 4.25 (1H, dd, J = 9.0, 3.5), 4.05 (1H, dd, J = 11.0, 5.0), 3.90 (1H, dd, J = 11.0, 6.0), 3.68 (2H, t, J = 6.5), 3.07 (1H, dd, J = 17.5, 7.0), 2.94 (1H, dd, J = 17.5, 6.5), 2.54−2.46 (1H, m), 1.91 (3H, s), 1.68−1.53 (2H, m), 1.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 171.4 (C), 171.0 (C), 153.7 (C), 139.1 (C), 135.6 (CH), 133.7 (C), 129.6 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 125.9 (CH), 70.0 (CH_2), 66.5 (CH_2), 61.7 (CH_2), 57.7 (CH), 37.3 (CH_2), 33.8 (CH_2), 31.1 (CH), 26.9 (CH_3), 20.8 (CH_3), 19.1 (C); m/z (ESI+) 596 (MNa^+, 100%), 496 ($[M - C_6H_5]^+$, 19); m/z (ESI+) found $[M + Na]^+$ 596.2428, calcd for $C_{33}H_{39}NNaO_6Si^+$ 596.2439.

dx.doi.org/10.1021/jo201988m | J. Org. Chem. 2012, 77, 400−416

*(4S)-4-(2-tert-Butyldiphenylsilyloxyethyl)dihydrofuran-2(3H)-one (**40**).* A solution of lithium hydroxide (2.82 g, 67.2 mmol) in water (50 mL) was added to a solution of protected diol **41** (9.63 g, 16.8 mmol) and 30% aqueous hydrogen peroxide solution (19.0 mL, 168 mmol) in tetrahydrofuran (150 mL) and water (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h and then quenched by addition of sodium sulfite (7.5 g) in water (20 mL). The mixture was acidified to ~pH 4 with 2 M hydrochloric acid and then extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a pale yellow oil. The crude product was dissolved in toluene (300 mL) and *p*-toluenesulfonic acid (640 mg, 3.36 mmol) added. The reaction mixture was stirred at room temperature for 2 h and then diluted with ethyl acetate (300 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford a colorless oily solid. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford the title compound **40** (6.03 g, 97%) as a pale yellow oil. The auxiliary could be isolated by flushing the column with 100% ethyl acetate to afford a colorless crystalline solid (2.30 g, 77%). Data for lactone **40**: $[\alpha]_D^{21}$ = +4.7° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2931, 2858, 1775, 1168, 1106, 1090, 703; δ_H (400 MHz, $CDCl_3$) 7.63 (4H, d, *J* = 7.0), 7.46−7.38 (6H, m), 4.42 (1H, dd, *J* = 8.5, 8.5), 3.94 (1H, dd, *J* = 8.5, 8.5), 3.72−3.66 (2H, m), 2.77−2.69 (1H, m), 2.57 (1H, dd, *J* = 17.0, 8.5), 2.17 (1H, dd, *J* = 17.0, 9.0), 1.75−1.65 (2H, m), 1.05 (9H, s); δ_C (100 MHz, $CDCl_3$) 177.1 (C), 135.5 (CH), 133.3 (C), 129.9 (CH), 127.8 (CH), 73.5 (CH_2), 61.9 (CH_2), 35.6 (CH_2), 34.6 (CH_2), 33.5 (CH), 26.9 (CH_3), 19.1 (C); *m*/*z* (ESI+) 391 (MNa^+, 41%), 386 (MNH_4^+, 13), 291 ($[M - C_6H_5]^+$, 100); *m*/*z* (ESI+) found $[M + Na]^+$ 391.1690, calcd for $C_{22}H_{28}O_3SiNa^+$ 391.1700.

*(3S,4S)-4-(2-tert-Butyldiphenylsilyloxyethyl)-3-methyldihydrofuran-2(3H)-one (**39**).* NaHMDS (1 M in THF, 9.0 mL, 8.95 mmol) was added dropwise over 10 min to a solution of lactone **40** (3.0 g, 8.14 mmol) in THF (120 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 1 h, and then methyl iodide (1.5 mL, 24.4 mmol) was added. The reaction mixture was stirred at −78 °C for a further 3 h and then quenched with saturated aqueous ammonium chloride (30 mL), warmed to room temperature, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a brown oil. The crude product was purified by chromatography (silica gel, 9/1 hexanes/ethyl acetate) to afford the title compound **39** (2.36 g, 76%) as a pale yellow oil: $[\alpha]_D^{20}$ = −13.4° (*c* 0.70, $CHCl_3$) (lit.[4] $[\alpha]_D^{22}$ = −15.5° (*c* 2.73, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.65−7.63 (4H, m), 7.47−7.37 (6H, m), 4.43 (1H, dd, *J* = 9.0, 7.5), 3.85 (1H, dd, *J* = 9.0, 9.0), 3.72−3.67 (2H, m), 2.33−2.15 (2H, m), 1.89−1.81 (1H, m), 1.65−1.56 (1H, m), 1.23 (3H, d, *J* = 7.0), 1.05 (9H, s); δ_C (100 MHz, $CDCl_3$) 179.6 (C), 135.5 (CH), 133.2 (C), 129.9 (CH), 127.8 (CH), 72.1 (CH_2), 62.1 (CH_2), 42.0 (CH), 40.4 (CH), 34.7 (CH_2), 26.9 (CH_3), 19.1 (C), 13.8 (CH_3); *m*/*z* (ESI+) found $[M + Na]^+$ 405.1869, calcd for $C_{23}H_{30}O_3SiNa^+$ 405.1856. The spectroscopic data closely matched thosepreviously reported.[4]

*Dimethyl ((3S,4S)-4-(2-tert-Butyldiphenylsilyloxyethyl)-2-hydroxy-3-methyltetrahydrofuran-2-yl)methylphosphonate (**46**).* *n*-Butyllithium (1.6 M in hexanes, 2.45 mL, 3.92 mmol) was added dropwise to a solution of dimethyl methylphosphonate (420 μL, 3.92 mmol) in tetrahydrofuran (10 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 20 min, and then a solution of lactone **39** (1.0 g, 2.61 mmol) in tetrahydrofuran (10 mL) was added. The resulting yellow solution was stirred at −78 °C for 2 h and then quenched by addition of saturated aqueous ammonium chloride (10 mL) and warmed to room temperature. The reaction mixture was extracted with ethyl acetate. The combined organics were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound **46** (912 mg, 69%) as a colorless oil: $[\alpha]_D^{21}$ = −27.3° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3391, 2956, 2932, 2857, 1030, 701; δ_H (400 MHz, $CDCl_3$) 7.66−7.63 (4H, m), 7.45−7.36 (6H, m), 5.00 (1H, s), 4.21 (1H, dd, *J* = 8.5, 8.5), 3.84 (3H, d, *J* = 11.0), 3.74 (3H, d, *J* = 11.0), 3.67−3.61 (2H, m), 3.57 (1H, dd, *J* = 8.5, 8.5), 2.31 (1H, dd, *J* = 18.0, 15.0), 2.23−2.15 (1H, m), 2.00 (1H, dd, *J* = 18.0, 15.0), 1.84−1.76 (1H, m), 1.50−1.42 (2H, m), 1.04 (9H, s), 1.02 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 135.6 (CH), 133.7 (C), 129.6 (CH), 127.7 (CH), 103.1 (C, d, *J* = 9.0), 72.6 (CH_2), 63.2 (CH_2), 53.3 (CH_3, d, *J* = 6.0), 52.0 (CH_3, d, *J* = 6.5), 50.1 (CH), 41.7 (CH), 35.8 (CH_2), 33.9 (CH_2, d, *J* = 134), 26.8 (CH_3), 19.1 (C), 12.0 (CH_3); *m*/*z* (ESI+) 529 (MNa^+, 100%); *m*/*z* (ESI+) found $[M + Na]^+$ 529.2129, calcd for $C_{26}H_{39}O_6PSiNa^+$ 529.2146.

*(3S,4S)-Dimethyl 4-tert-Butyldimethylsilyloxymethyl-6-tert-butyldiphenylsilyloxy-3-methyl-2-oxohexylphosphonate (**47**).* Potassium *tert*-butoxide (800 mg, 7.11 mmol) was added to a solution of lactol **46** (900 mg, 1.78 mmol) in tetrahydrofuran (50 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 15 min, and then TBSCl (1.61 g, 10.7 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 18 h, and then quenched by addition of saturated aqueous ammonium chloride (20 mL). The biphasic mixture was stirred vigorously for 15 min and then extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo to afford a colorless oil. The crude product was purified by chromatography (silica gel, 1/1 hexanes/ethyl acetate) to afford the title compound **47** (930 mg, 83%) as a colorless oil: $[\alpha]_D^{20}$ = +31.1° (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954, 2930, 2857, 1711, 1256, 1031, 836, 702; δ_H (400 MHz, $CDCl_3$) 7.66−7.63 (4H, m), 7.45−7.36 (6H, m), 3.77 (3H, d, *J* = 11.0), 3.75 (3H, d, *J* = 11.0), 3.65−3.61 (3H, m), 3.39−3.26 (2H, m), 3.04−2.93 (2H, m), 2.15−2.07 (1H, m), 1.54−1.46 (1H, m), 1.38−1.26 (1H, m), 1.04 (9H, s), 0.99 (3H, d, *J* = 7.0), 0.88 (9H, s), 0.02 (3H, s), 0.01 (3H, s); δ_C (100 MHz, $CDCl_3$) 205.7 (C, d, *J* = 6.0), 135.5 (CH), 133.7 (C), 129.6 (CH), 127.7 (CH), 63.5 (CH_2), 62.0 (CH_2), 53.0 (CH_3, d, *J* = 6.5), 52.8 (CH_3, d, *J* = 6.5), 47.4 (CH), 39.9 (CH_2, d, *J* = 130), 39.1 (CH), 29.9 (CH_2), 26.9 (CH_3), 25.9 (CH_3), 19.2 (C), 18.2 (C), 10.8 (CH_3), −5.5 (CH_3), −5.6 (CH_3); *m*/*z* (ESI+) 643 (MNa^+, 100%); *m*/*z* (ESI+) found $[M + Na]^+$ 643.2977, calcd for $C_{32}H_{53}O_6PSi_2Na^+$ 643.3011.

*(3R)-Benzyl 6,8-Bis(benzyloxy)-1-hydroxy-3-pentylisochroman-7-carboxylate ((**R**)-**7**).* DIBALH (1 M in toluene, 2.55 mL, 2.55 mmol) was added dropwise to a solution of lactone (***R***)-**17** (720 mg, 1.28 mmol) in dichloromethane (10 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 1 h and then quenched with methanol (1 mL) and saturated aqueous Rochelles' salt (10 mL) and stirred at room temperature for 3 h. The mixture was extracted with dichloromethane and the combined organics dried (Na_2SO_4) and concentrated in vacuo to afford a colorless solid. The crude product was purified by chromatography (silica gel, 3/1 hexanes/ethyl acetate) to afford the title compound (***R***)-**17** (631 mg, 87%) as a colorless oil: $[\alpha]_D^{21}$ = −29.6° (*c* 0.28, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3493, 2928, 1720, 1606, 1378, 1261, 1163, 1093, 1015, 733, 695; δ_H (400 MHz, $CDCl_3$) 7.38−7.22 (15H, m), 6.52 (1H, s), 6.14 (1H, d, *J* = 3.6), 5.31 (2H, s), 5.18 (1H, d, *J* = 10.8), 5.10 (2H, s), 4.99 (1H, d, *J* = 10.8), 4.29−4.23 (1H, m), 2.86 (1H, d, *J* = 3.6), 2.68−2.57 (2H, m), 1.70−1.26 (8H, m), 0.96−0.91 (3H, m); δ_C (100 MHz, $CDCl_3$) 166.1 (C), 156.2 (C), 154.8 (C), 138.7 (C), 137.3 (C), 136.4 (C), 135.5 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.93 (CH), 127.90 (CH), 127.6 (CH), 127.1 (CH), 122.1 (C), 118.8 (C), 108.0 (CH), 88.6 (CH), 77.2 (CH), 70.5 (CH_2), 67.3 (CH_2), 66.2 (CH_2), 35.4 (CH_2), 34.2 (CH_2), 31.8 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); *m*/*z* (ESI+) 589 (MNa^+, 65%), 389 ($[M - C_5H_{10} - OBn]^+$, 100); *m*/*z* (ESI+) found $[M + Na]^+$ 589.2568, calcd for $C_{36}H_{38}NaO_6^+$ 589.2561.

*(3S,4S)-4-(2-tert-butyldiphenylsilyloxyethyl)-2,3-dimethyltetrahydrofuran-2-ol (**49**).* Methyllithium (1.6 M in diethyl ether, 1.8 mL, 2.88 mmol) was added dropwise to a solution of lactone **39** (1.0 g, 2.61 mmol) in tetrahydrofuran (30 mL) at −78 °C under argon. The reaction mixture was stirred for 3 h at −78 °C, and then quenched with saturated aqueous ammonium chloride (10 mL), warmed to room temperature, and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentratred in vacuo to afford a colorless oil, which was used directly in the next step. An aliquot of aldehyde was purified for characterization by chromatography (silica gel, 3/1 hexanes/ethyl acetate) to afford the title compound **49** as a colorless oil: $[\alpha]_D^{19}$ = −30.9° (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3401, 2931, 2858, 1105, 1089, 700; δ_H (400 MHz, $CDCl_3$) 7.66−7.63 (4H, m),

dx.doi.org/10.1021/jo201988m | *J. Org. Chem.* 2012, 77, 400−416

7.44−7.36 (6H, m), 4.11 (1H, dd, J = 8.5, 8.5), 3.68−3.63 (2H, m), 3.48 (1H, dd, J = 8.5, 8.5), 2.18−2.10 (1H, m), 1.88−1.80 (1H, m), 1.53−1.41 (2H, m), 1.43 (3H, s), 1.04 (9H, s), 1.01 (3H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$) 135.6 (CH), 133.7 (C), 129.6 (CH), 127.8 (CH), 72.4 (CH_2), 63.2 (CH_2), 48.5 (CH), 42.1 (CH), 35.5 (CH_2), 26.8 (CH_3), 25.5 (CH_3), 19.1 (C), 12.1 (CH_3); m/z (ESI+) 421 (MNa^+, 35%), 381 ($[M - H_2O]H^+$, 22), 269 ($[M - (C_6H_5)_2]Na^+$, 100), 247 ($[M - (C_6H_5)_2]H^+$, 54); m/z (ESI+) found $[M + Na]^+$ 421.2145, calcd for $C_{24}H_{34}O_3SiNa^+$ 421.2169.

*(3S,4S)-4-tert-Butyldimethylsilyloxymethyl-6-tert-butyldiphenylsilyloxy-3-methylhexan-2-one (**50**).* TBSCl (787 mg, 5.22 mmol) was added to a solution of crude lactol **49** (~2.61 mmol) and imidazole (888 mg, 13.1 mmol) in dimethylformamide (20 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 4 h then diluted with diethyl ether, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to afford a pale yellow oil. The crude product was purified by chromatography (silica gel, 9/1 hexanes/ethyl acetate) to afford the title compound **50** (1.11 g, 83% over two steps) as a colorless oil: $[\alpha]_D^{20}$ = +16.8° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2930, 2857, 1710, 1105, 1084, 835, 700; δ_H (400 MHz, $CDCl_3$) 7.66−7.63 (4H, m), 7.44−7.35 (6H, m), 3.66−3.60 (3H, m), 3.55 (1H, dd, J = 10.0, 8.0), 2.87−2.79 (1H, m), 2.22−2.16 (1H, m), 2.13 (3H, s), 1.54−1.46 (1H, m), 1.37−1.29 (1H, m), 1.04 (9H, s), 0.95 (3H, d, J = 7.0), 0.87 (9H, s), 0.01 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 212.6 (C), 135.6 (CH), 133.8 (C), 129.6 (CH), 127.7 (CH), 63.6 (CH_2), 62.1 (CH_2), 47.1 (CH), 39.0 (CH), 30.0 (CH_2), 28.7 (C), 26.9 (CH_3), 25.9 (CH_3), 19.2 (C), 18.2 (C), 10.9 (CH_3), −5.5 (CH_3), −5.6 (CH_3); m/z (ESI+) 535 (MNa^+, 100%), 381 ($[M - TBSOH]H^+$, 55); m/z (ESI+) found $[M + Na]^+$ 535.3027, calcd for $C_{30}H_{48}O_3Si_2Na^+$ 535.3034.

*(3S,4S)-4-tert-Butyldimethylsilyloxymethyl-6-tert-butyldiphenylsilyloxy-3-methyl-2-trimethylsilyloxyhex-1-ene (**51**).* TMSOTf (26 μL, 0.15 mmol) was added to a solution of methyl ketone **50** (50 mg, 0.097 mmol) and diisopropylethylamine (51 μL, 0.29 mmol) in dichloromethane (1.5 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 1.5 h and then diluted with dichloromethane, washed with water, dried (Na_2SO_4), and concentrated in vacuo (water bath <30 °C) to afford **51** (78 mg) as a colorless oil, which was used directly in the next step.

*Snider's Acid **54**.* Boron trifluoride diethyl etherate (16 μL, 0.13 mmol) was added dropwise to a solution of lactol **7** (66 mg, 0.12 mmol) in dichloromethane (1.5 mL) at −78 °C under argon. The resulting yellow solution was stirred at −78 °C for 5 min and then at 0 °C for 10 min and then recooled to −78 °C and a solution of crude silyl enol ether **51** (78 mg) in dichloromethane (1.5 mL) added. The resulting yellow solution was stirred at −78 °C for 30 min and then quenched with saturated aqueous sodium hydrogen carbonate (2 mL), warmed to room temperature, and extracted with dichloromethane. The combined organics were dried (Na_2SO_4) and concentrated to afford lactol **53** (130 mg) as a pale yellow oil, which was used in the next step without further purification. A mixture of crude lactol **53**, 10% Pd/C (25 mg), 2 M hydrochloric acid (3 drops), methanol (3 mL), and ethyl acetate (3 mL) was placed under a balloon of hydrogen and stirred vigorously at room temperature for 4 h and then filtered through Celite with methanol washings and concentrated in vacuo to afford a yellow oil (85 mg). The crude product was purified by chromatography (silica gel, 19/1 hexane/ethyl acetate with 1.5% acetic acid) to afford the acid **54** (37 mg, 58% from methyl ketone **50**) as a colorless solid: mp 105−107 °C (hexane); $[\alpha]_D^{20}$ = −60.3° (c 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3238, 2956, 2931, 2858, 1695, 1429, 1111, 1074, 702; δ_H (400 MHz, $CDCl_3$) 11.86 (1H, s), 11.17 (1H, br s), 7.67−7.64 (4H, m), 7.45−7.38 (6H, m), 6.45 (1H, s), 4.80 (1H, dd, J = 12.0, 5.4), 4.28 (1H, dd, J = 8.7, 8.7), 3.87−3.80 (1H, m), 3.76 (1H, dd, J = 8.7, 8.7), 3.73−3.69 (2H, m), 2.81 (1H, dd, J = 17.7, 4.1), 2.63 (1H, dd, J = 17.7, 10.8), 2.30−2.21 (2H, m), 2.09 (1H, dd, J = 12.2, 12.2), 1.95−1.85 (2H, m), 1.68−1.33 (7H, m), 1.11 (3H, d, J = 6.9), 1.06 (9H, s), 0.91 (3H, t, J = 6.9); δ_C (100 MHz, $CDCl_3$) 170.6 (C), 162.6 (C), 149.9 (C), 142.2 (C), 135.5 (CH), 133.4 (C), 129.8 (CH), 127.8 (CH), 112.5 (C), 112.2 (C), 110.4 (CH), 98.7 (C), 75.2 (CH), 74.2 (CH_2), 67.4 (CH), 62.8 (CH_2), 48.8 (CH), 41.9 (CH), 36.3 (CH_2), 35.3 (CH_2), 34.4 (2 × CH_2), 31.8 (CH_2), 26.8 (CH_3), 25.0 (CH_2), 22.6 (CH_2), 19.1 (C), 14.0 (CH_3), 12.0 (CH_3); m/z (ESI+) found $[M + Na]^+$ 681.3178, calcd for $C_{39}H_{50}O_7SiNa^+$ 681.3218.

*Snider's Allyl Ester **4**.* The compound was prepared from acid **54** by the method reported in the literature:[4] $[\alpha]_D^{20}$ = −63.1° (c 0.50, $CHCl_3$) (lit.[4] $[\alpha]_D^{22}$ = −60.0° (c 2.31, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.67−7.64 (4H, m), 7.45−7.38 (6H, m), 6.23 (1H, s), 6.01−5.92 (2H, m), 5.36 (1H, ddd, J = 17.4, 3.2, 1.6), 5.32 (1H, ddd, 17.4, 2.8, 1.6), 5.22 (1H, ddd, J, 10.4, 2.8, 1.6), 5.14 (1H, ddd, J = 10.4, 2.8, 1.6), 4.82−4.68 (3H, m), 4.51 (2H, ddd, J = 4.8, 1.6, 1.6), 4.20 (1H, dd, J = 8.6, 8.6), 3.85−3.78 (1H, m), 3.70−3.62 (2H, m), 3.61 (1H, dd, J = 8.6, 8.6), 2.74 (1H, dd, J = 16.8, 4.0), 2.60 (1H, dd, J = 16.8, 10.8), 2.29−2.19 (1H, m), 2.14 (1H, dd, J = 12.2, 5.4), 1.96 (1H, dd, J = 12.2, 12.2), 1.88−1.81 (1H, m), 1.71−1.62 (2H, m), 1.54−1.25 (8H, m), 1.05 (9H, s), 1.00 (3H, d, J = 6.8), 0.90 (3H, t, J = 6.8); δ_C (400 MHz, $CDCl_3$) 165.6 (C), 155.6 (C), 149.1 (C), 135.9 (C), 135.6 (CH), 133.64 (C), 133.61 (C), 133.0 (CH), 132.4 (CH), 129.7 (CH), 127.7 (CH), 118.1 (CH_2), 117.1 (CH_2), 114.7 (C), 109.7 (C), 108.8 (C), 104.4 (CH), 75.4 (CH), 73.4 (CH_2), 69.5 (CH_2), 68.2 (CH), 65.6 (CH_2), 63.3 (CH_2), 49.0 (CH), 41.4 (CH), 36.4 (CH_2), 35.7 (CH_2), 34.6 (CH_2), 34.5 (CH_2), 31.8 (CH_2), 26.9 (CH_3), 25.2 (CH_2), 22.6 (CH_2), 19.1 (C), 14.1 (CH_3), 11.7 (CH_3). The spectroscopic data closely matched those previously reported.[4]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m.brimble@auckland.ac.nz.

■ ACKNOWLEDGMENTS

Financial assistance from the Royal Society of New Zealand Marsden Fund is gratefully acknowledged.

■ REFERENCES

(1) Wilson, Z. E.; Brimble, M. A. *Nat. Prod. Rep.* **2009**, *26*, 44.
(2) Stierle, A. S.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357.
(3) Buchgraber, P.; Snaddon, T. N.; Wirtz, C.; Mynott, R.; Goddard, R.; Furstner, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8450.
(4) Wu, X.; Zhou, J.; Snider, B. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1283.
(5) Wu, X.; Zhou, J.; Snider, B. B. *J. Org. Chem.* **2009**, *74*, 6245.
(6) Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350.
(7) Snaddon, T. N.; Buchgraber, P.; Schulthoff, S.; Wirtz, C.; Mynott, R.; Furstner, A. *Chem. Eur. J.* **2010**, *16*, 12133.
(8) Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 118.
(9) McLeod, M. C.; Wilson, Z. E.; Brimble, M. A. *Org. Lett.* **2011**, *13*, 5382.
(10) Wilson, Z. E.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 1284.
(11) Buechi, G.; Leung, J. C. *J. Org. Chem.* **1986**, *51*, 4813.
(12) Differing reactivities were observed, depending on the batch of PtO_2 used. Aldrich $PtO_2 \cdot H_2O$ gold label (cat. no. 22,905-9) resulted in significant hydrogenolysis of the benzyl groups, while that obtained from Strem (cat. no. 7-1890) selectively reduced the alkyne group with no observed debenzylation.
(13) Suri, J. T.; Truong, V.; Hernandez, A.; Congdon, J.; Bakthan, S. *Tetrahedron Lett.* **2002**, *43*, 3649.
(14) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(15) Yu, C.-M.; Kim, C.; Kweon, J.-H. *Chem. Commun.* **2004**, 2494.
(16) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(17) Gooding, O. W.; Bansal, R. P. *Synth. Commun.* **1995**, *25*, 1155.
(18) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903.
(19) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
(20) Henderson, J. R.; Parvez, M.; Keay, B. A. *Org. Lett.* **2009**, *11*, 3178.
(21) Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220.
(22) Wilding, E. E.; Gregg, J. J.; Mullins, R. J. *Synlett* **2010**, 793.
(23) Nakamura, S.; Kikuchi, F.; Hashimoto, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1059.
(24) Fernández-Zertuche, M.; Robledo-Pérez, R.; Meza-Avina, M. E.; Ordonez-Palacios, M. *Tetrahedron Lett.* **2002**, *43*, 3777.
(25) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.
(26) See the Supporting Information.
(27) Sibi, M. P.; Johnson, M. D.; Punniyamurthy, T. *Can. J. Chem.* **2001**, *79*, 1546.
(28) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237.
(29) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423.
(30) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(31) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
(32) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325.
(33) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847.
(34) Han, H.; Cho, C.-W.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565.