JOC Article

Approach toward the Total Synthesis of Orevactaene. 2. Convergent and Stereoselective Synthesis of the C18−C31 Domain of Orevactaene. Evidence for the Relative Configuration of the Side Chain

Michael G. Organ,* Yaroslav V. Bilokin, and Svetoslav Bratovanov

Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3

organ@yorku.ca

Received March 13, 2002

The synthesis of the C18−C31 subunit of orevactaene (**1**) in an enantioselective and convergent manner is reported. Four chiral centers in the structure (i.e., carbons 23, 25, 32, and 33) have unknown configuration; thus, a modular approach has been devised to link the two stereocenter-containing ends of the structure together via a trisubstituted olefin template to ultimately produce all possible diastereomers of the target. Keys to the success of this approach include (i) an efficient synthesis of four diastereomeric hydrophobic tails (C22−C29) of the molecule with two stereogenic centers at C23 and C25; (ii) the synthesis of three stereodefined trisubstituted olefins **37**, **38**, and **43** using palladium(0)-catalyzed hydrometalation and metallometalation; and (iii) the convergent assembly of the aforementioned sections by a 'one-pot' lithium/halogen exchange, boron/lithium exchange, borate ester saponification, and Suzuki cross-coupling followed by oxidative deprotection. The sequence provided the desired aldehydes **49** and **50** as single isomers in good yields. Compiled spectroscopic data from the literature and present work provides evidence that the relative configuration of the methyl groups in the side chain of orevactaene may be 1,3-*syn*, which will be confirmed when the total synthesis has been completed. These results have paved the way for a parallel synthesis approach to prepare all 16 possible stereoisomers of orevactaene so that the relative and absolute stereochemistry of this compound can be determined.

Introduction

Orevactaene (**1**), recently isolated from *Epicoccum nigrum* WC47880, is a novel polyene representing a new structural class of natural products.[1] It has been shown to be an effective binding inhibitor of the HIV-1 REV protein to REV response element (RRE). The potential importance of the biological implication, novelty, and complexity of its structure make it an attractive target for total synthesis.

There are three distinct components of **1**: (i) a sugar moiety fused with a pyrone substructure; (ii) a polyene segment; and (iii) a hydrophobic tail. Further adding to the intrigue of preparing **1** is the fact that four of the seven chiral centers in the structure (i.e., carbons 23, 25, 32, and 33) have yet to be confirmed relatively, which means that the absolute configuration also remains unknown. Thus, the synthetic route must be amenable to preparing all 16 diastereomers of **1** in order to confirm all questions surrounding its stereochemistry. We have had experience with the parallel synthesis of biologically active compounds,[2,3] and the modular/template approach[3] has proven to be an effective synthetic strategy for the simultaneous preparation of many diverse compounds. Here the target is divided into small fragments that can be varied readily and coupled together easily to a central template by one common series of transformations.[3] By using such a strategy, the complexity of generating the chiral centers in **1** can be reduced by preparing them as discrete units, where the control over stereocenter preparation can be maximized, and then coupling them to the rest of the structure by templates that have been designed for stereo- and regioselective bond construction with any reacting partner.

A key segment of orevactaene (**1**) is the stereodefined contiguous trisubstituted olefin section **2** (Figure 1) comprising the terminal chiral α,γ-dimethyl-substituted hexenyl chain (C22−C29) with unknown configuration at C23 and C25. A versatile method for making all four possible diastereomers of (*Z*)-4,6-dimethyl-2-[(*E*)-2-methyl-3-oxo-1-propenyl]-2-octenoate (**2**), representing the C18−C31 domain of orevactaene, has been developed, and this is the focus of this report.

(1) Shu, Y.-Z.; Ye, Q.; Li, H.; Kadow, K. F.; Hussain, R. A.; Huang, S.; Gustavson, D. R.; Lowe, S. E.; Chang, L.-P.; Pirnik, D. M.; Kodukula, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2295−2298.

(2) (a) Organ, M. G.; Dixon, C. E. *Biotechnol. Bioeng. (Combinatorial Chemistry)* **2000**, *71*, 71−77. (b) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Lavorato, D. J. *J. Comb. Chem.* **2001**, *3*, 473−476. (c) Organ, M. G.; Mayhew, D.; Cooper, J. T.; Dixon, C. E.; Lavorato, D. J.; Kaldor, S. W.; Siegel, M. G. *J. Comb. Chem.* **2001**, *31*, 64−67. (d) Organ, M. G.; Kaldor, S. W.; Dixon, C. E.; Parks, D. J.; Singh, U.; Lavorato, D. J.; Isbester, P. K.; Siegel, M. G. *Tetrahedron Lett.* **2000**, *41*, 8407−8411. (e) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288−1294.

(3) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959−7970.

10.1021/jo0201777 CCC: $22.00
Published on Web 06/20/2002

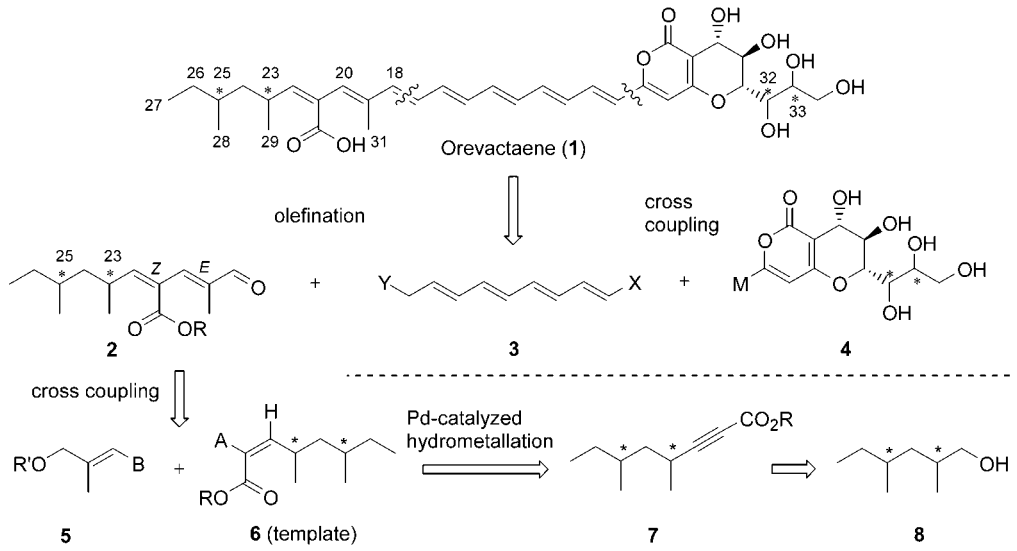


FIGURE 1. Retrosynthetic analysis of orevactaene (**1**).

Results and Discussion

Synthetic Plan. As the absolute stereochemistry of two asymmetric centers in a subunit **2** was not assigned in the original isolation work, our synthetic strategy grew (Figure 1) from the desire to have a versatile approach to make all four possible diastereomers of **2**, along with the defined stereochemistry of the contiguous trisubstituted olefin component. Stereodefined trisubstituted olefins are challenging to prepare as single entities; thus, preparing contiguous ones is an even greater task. Strategies that bring the olefinic carbons together during olefin formation often work with good selectivity for disubstituted targets, but this is not the case for trisubstituted olefins.[4−7] The route[8] we have opted for to prepare the stereodefined trisubstituted olefins **6** and **5** (Figure 1) is transition metal-catalyzed hydrometalation[9,10] and metallometalation,[11−13] respectively. Propargyl alcohol was elaborated to the requisite cross-coupling partner **5** by stannylcupration[8,11,13] followed electrophilic capture at the cuprate site. While stannanes are suitable partners for palladium-catalyzed cross-coupling reactions,[14,15] the substrates could also be transformed to other reactive species, like iodides or boronic acids.[15,16]

According to our retrosynthetic analysis (Figure 1), chiral alcohols **8** are focal intermediates to establish the two asymmetric centers at C23 and C25 positions in orevactaene (**1**). The γ-chiral center (C25) in the hydrophobic tail was set by starting the synthesis with (*R*)- or (*S*)-2-methyl-1-butanol. To install the second chiral center at C23, we employed a modification of the process first suggested by Evans in the total synthesis of the polyether antibiotic ionomycin.[17] This approach utilized chiral imide oxazolidinone substrates as chiral auxiliaries and triflates as electrophiles. Using chiral primary β-branched triflates as reactive alkylating agents,[18] we have been

(4) For Wittig approaches to stereodefined olefins, see: (a) Wittig, G.; Rieber, M. *Liebigs Ann. Chem.* **1949**, *562*, 187−192. (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616−8618. For reviews, see: (c) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recl.* **1997**, 1283−1301. (d) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1−85. (e) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369−379. (f) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1−157. (g) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(5) For Horner−Wadsworth−Emmons approaches to stereodefined olefins, see: (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499−2505. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99. (d) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624−2626. (e) Mori, Y.; Asai, M.; Kawade, J.-i.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315−5330. (f) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139−6152.

(6) For Peterson olefination approaches to stereodefined olefins, see: (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784. (b) Carey, F. A.; Court, A. C. *J. Org. Chem.* **1972**, *37*, 1926−1929. (c) Hurlick, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263−2264. For reviews, see: (d) Ager, D. J. *Org. React. (N. Y.)* **1990**, *38*, 1−223. (e) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M.; Flygare, J. A. *Synlett* **1991**, 764−770.

(7) For Julia olefination approaches to stereodefined olefins, see: (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833−4836. (b) Kocienski, P. J. *Chem. Ind. (London)* **1981**, 548−551. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178. (d) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285−296. (e) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345−9346.

(8) Preliminary communication: Organ, M. G.; Bratovanov, S. *Tetrahedron Lett.* **2000**, *41*, 6945−6949.

(9) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801−8824.

(10) (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867. (b) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621−6624. (c) Cochran, J. C.; Terrence, K. M.; Phillips, H. K. *Organometallics* **1991**, *10*, 2411−2418.

(11) For a leading list of references to this transformation, see: Cuadrado, P.; González-Nogal, A. M.; Sánchez, A. *J. Org. Chem.* **2001**, *66*, 1961−1965.

(12) Casson, S.; Kocienski, P.; Reid, G.; Smith, N.; Street, J. M.; Webster, M. *Synthesis* **1994**, 1301−1309.

(13) (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065−2068. (b) Thibonnet, J.; Prie, G.; Abarabri, M.; Duchene, A.; Parrain, J.-L. *Tetrahedron Lett.* **1999**, *40*, 3151−3154. (c) Thibonnet, J.; Abarbri, M.; Duchene, A.; Parrain, J.-L. *Synlett* **1999**, 141−143.

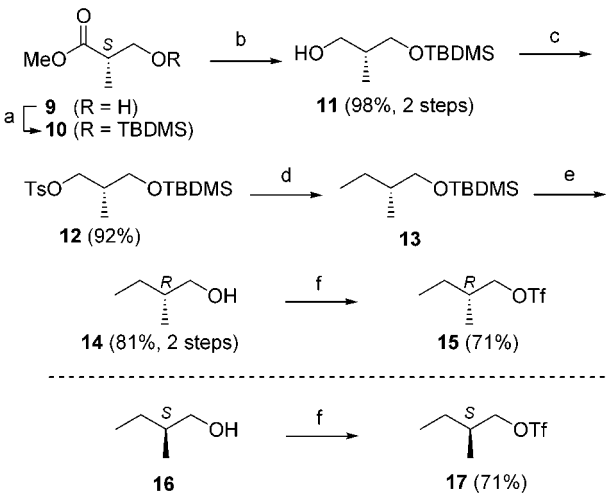
(14) (a) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500−7506. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1171−1780. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React. (N. Y.)* **1997**, *50*, 1−652. (e) Bellina, F.; Carpita, A.; Desantis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029−12046.

(15) (a) Tsuji, T. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, UK, 1995. (b) Marumoto, S.; Kogen, H.; Naruto, S. *J. Org. Chem.* **1998**, *63*, 2068−2069. (c) Marumoto, S.; Kogen, H.; Naruto, S. *Tetrahedron* **1999**, *55*, 7145−7156.

(16) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(17) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5313.

SCHEME 1[a]

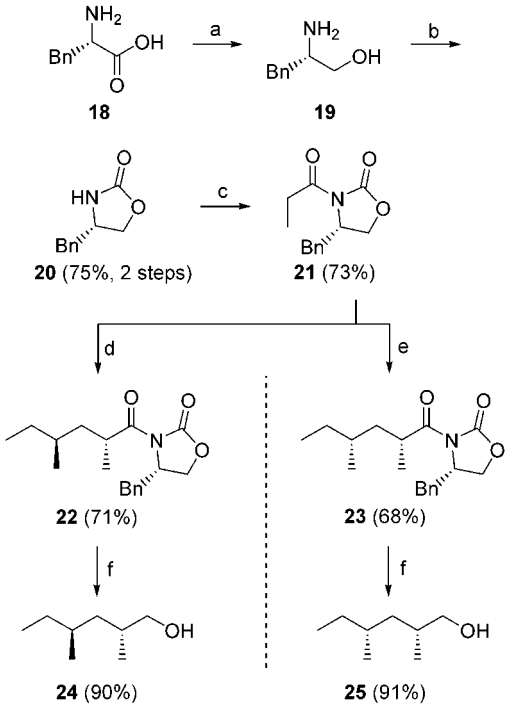


[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 0 °C to room temperature; (b) DIBALH, THF, PhMe, −78 °C to room temperature, then MeOH, −78 °C; (c) TsCl, pyridine, 0 °C to room temperature; (d) CuI/MeLi (Me_2CuLi), Et_2O, −78 °C to room temperature; (e) TBAF, THF, rt; (f) Tf_2O, pyridine, CH_2Cl_2, −78 °C.

able to install the adjacent α-chiral center (C23) and to make all four diastereomeric alcohols **8**. Finally, compounds **6**, required to cross-coupling with **5**, were obtained from chiral alcohols **8** via the corresponding alkyne esters **7**.

Synthesis of Four Possible Stereoisomers of 2,4-Dimethyl-1-hexanols (C22−C29 subunit). The development of an efficient, enantioselective synthesis of the acyclic 1,3-dimethyl segment poses a significant challenge in natural product chemistry.[19] For reliable enantioselective carbon−carbon bond formation, the asymmetric alkylation of the α-carbon of carboxylic acid derivatives is a reaction of fundamental importance in modern synthetic organic chemistry.[20] With a few exceptions, this type of transformation is accomplished using chiral auxiliary-based methodology. Foremost among these are the oxazolidinone auxiliaries introduced by Evans and co-workers.[21] (*R*)/(*S*)-2-Methylbutyl trifluoromethanesulfonates **15** and **17** were prepared from corresponding chiral 2-methyl-1-butanols **14** and **16** (Scheme 1). While *S*-(−)-2-methyl-1-butanol (**16**) is commercially available, albeit expensively, its *R*-(+) antipode **14** is not. Therefore, it is not surprising that a number of research groups have attempted to devise a practical synthesis of *R*-(+)-2-methyl-1-butanol (**14**).[22] Enatiomerically pure alcohol **14** was prepared starting from commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate (**9**) as shown in Scheme 1. Alcohols **14** and **16** were then converted to triflates **15** and **17**.[18]

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) $LiBH_4$, Me_3SiCl, THF, 0 °C to room temperature; (ii) MeOH, then 2.5 M NaOH, 0 °C; (b) $(EtO)_2CO$, K_2CO_3, 130−135 °C; (c) (i) *n*-BuLi, THF, −78 °C; (ii) EtCOCl, THF, −78 °C to room temperature; (d) LDA, (*S*)-**17**, THF, −78 °C to room temperature; (e) LDA, (*R*)-**15**, THF, −78 °C to room temperature; (f) $LiBH_4$, MeOH, Et_2O, rt.

Although both (4*S*)- and (4*R*)-propionyloxazolidinones **21** and **26** are commercially available, they can be synthesized in large scale much more economically using both (*S*)- and (*R*)-phenylalanine. As shown in Scheme 2, the reduction of amino acid **18** to amino alcohol **19** using $LiBH_4$/TMSCl proceeded smoothly and in high yield.[23] In turn, the oxazolidinone **20**[24] was prepared by heating **19** with diethyl carbonate followed by the low-temperature *N*-alkylation of the lithiate of 4-benzyloxazolidinone **20** with propionyl chloride to give **21**.[25]

Two general procedures for the diastereoselective alkylation of oxazolidinone amides have been tested. In the first, the alkylation was conducted using excess of alkyl triflate, and in the second, excess of enolate was used. In a typical protocol employing excess alkylating agent, the enolate suspension was treated with an alkylating agent (2−4 equiv) at −78 °C and then warmed to room

(18) For relevant examples and a list of leading references, see: Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534−3541.

(19) (a) For a review on synthetic strategies, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. (b) For a general review on conformational design of open-chain compounds, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054−2070.

(20) (a) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935−952. (b) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 1−63. (c) Crosby, J. *Tetrahedron* **1991**, *47*, 4789−4846. (d) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 213−274. (e) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1−110.

(21) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (b) For a review on using chiral oxazolidinones in asymmetric synthesis, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3−12.

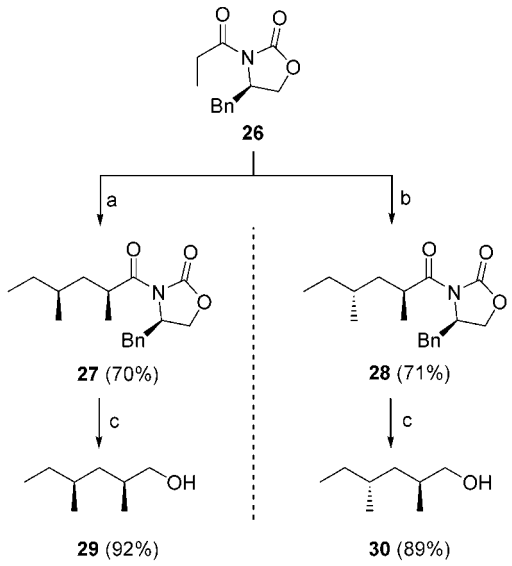
(22) (a) Logothetis, T. A.; Vleggaar, R. In *Proc. ECSOC-3, Proc. ECSOC-4, 1999, 2000*; Pombo-Villar, E., Ed.; Molecular Diversity Preservation International: Basel, 2000; pp 1064−1070. (b) Bell, L.; Brookings, D. C.; Dawson, G. J.; Whitby, R. J.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron* **1998**, *54*, 14617−14634. (c) Geresh, S.; Valiyaveettil, T. J.; Lavie, Y.; Shani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 89−96. (d) Mori, K.; Wu, J. *Liebigs Ann. Chem.* **1991**, 213−217. (e) Brown, H. C.; Naik, R. G.; Bakshi, R. K.; Pyun, C.; Singaram, B. *J. Org. Chem.* **1985**, *50*, 5586−5592. (f) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980−4983.

(23) Giannis, A.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 218−219.

(24) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−82.

(25) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83−91.

SCHEME 3[a]

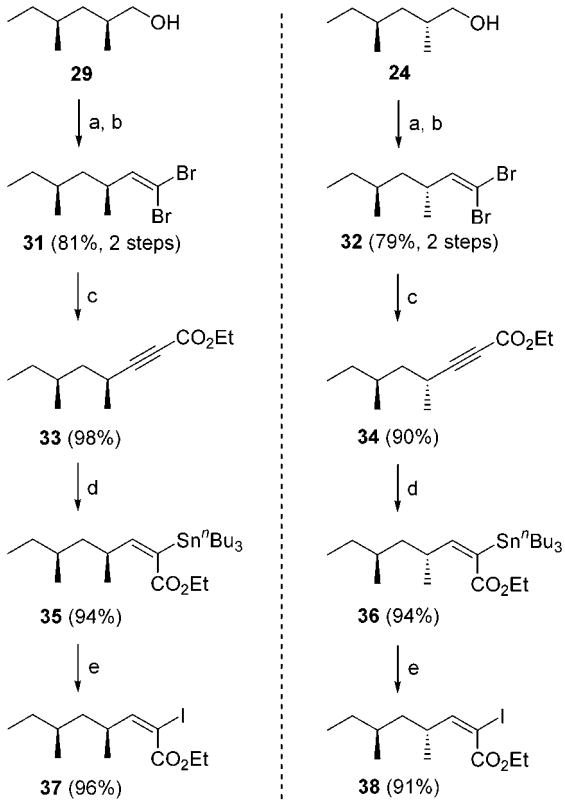


[a] Reagents and conditions: (a) LDA, (*S*)-**17**, THF, −78 °C to room temperature; (b) LDA, (*R*)-**15**, THF, −78 °C to room temperature; (c) $LiBH_4$, MeOH, Et_2O, rt.

temperature and held at that temperature for 16 h to give 60% yield (based on enolate). Reactions employing excess enolate were conducted similarly using 1.2 equiv of enolate. In this case, yields exceeded 70% (based on alkyl triflate). Ultimately, the alkylation of both enantiomers of oxazolidinone amides **21** and **26** with chiral triflates **15** and **17** was accomplished using the method employing excess enolate (Schemes 2 and 3). The corresponding 2,4-dimethyl-substituted oxazolidinones **22**, **23**, **27**, and **28**, accompanied by their C2 diastereomers, were obtained in a ca. 20:1 ratio. The diastereomers were readily separable by column chromatography to provide the oxazolidinones in good yields and diastereomeric purity.[26] Reduction of oxazolidinones **22**, **23**, **27**, and **28** with lithium borohydride in a mixture of methanol and ether[27] afforded the desired four optically pure alcohols **24**, **25**, **29**, and **30**,[28] accompanied by about 60−65% of recovered oxazolidinones.

Synthesis of Two Stereodefined Chiral Vinyl Iodides 37 and 38 (C21−C30 subunit) as Precursors for Cross-Coupling Experiments. Oxidation of **29** under standard Swern conditions[29] gave the corresponding aldehyde that was used immediately in the next step. Elaboration of the aldehyde to dibromoalkene **31** using a variation of Corey−Fuchs reaction[30] proceeded smoothly (Scheme 4).

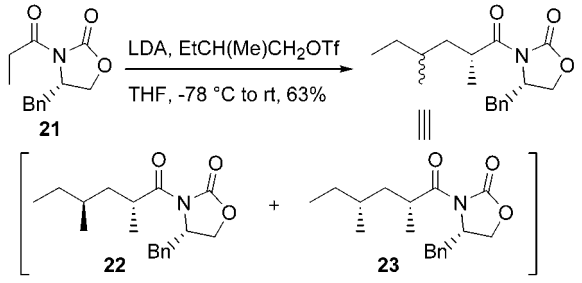
SCHEME 4[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C to room temperature; (c) (i) *n*-BuLi, THF, −78 °C to 0 °C; (ii) $ClCO_2Et$, −78 °C to room temperature; (d) *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, rt; (e) I_2, CH_2Cl_2, rt.

Treatment of **31** with *n*-butyllithium, followed by ethyl chloroformate, gave the desired alkyne ester **33**. Such electron-deficient alkynes are known to undergo regioselective palladium-catalyzed hydrostannylation to place the metal where necessary for the critical cross-coupling step.[9] Palladium(0)-catalyzed hydrostannylation with tributylstannane provided (*E*)-**35** in a regio- and stereoselective manner. The same sequence of reactions was repeated to provide vinyl iodide **38** with the anti arrangement of two methyl groups. Noteworthy, and further confirming the steric considerations for stannanes,[15] compounds with similar structure were found to be completely unreactive when cross-coupling reactions were attempted with vinyl[8] and (hetero)aryl iodides.[9] Thus, while the tin moieties were critical for obtaining the correct regio- and stereochemistry of the two trisubstituted olefin partners, the tin moieties could not be used to assemble them together.

(26) The possibility of using racemic 2-methylbutyl trifluoromethanesulfonate as an alkylating agent was examined with the idea that the two isomers **22** and **23** would be readily separable by flash chromatography. The diastereomers produced (below), which were epimeric at C4, proved to be inseparable in large scale using flash chromatography.



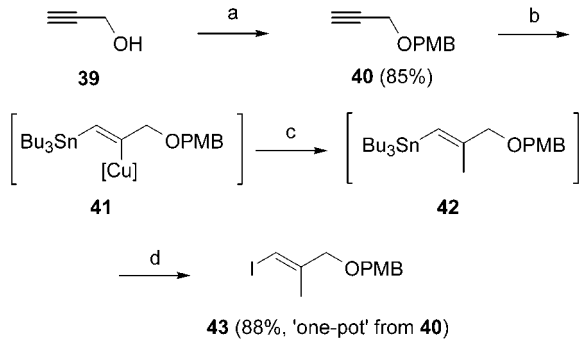
(27) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307−312.

(28) 2,4-Dimethyl-1-hexanols are volatile and must be recovered with care.

(29) (a) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148−4150. (b) For a review, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(30) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.

SCHEME 5[a]

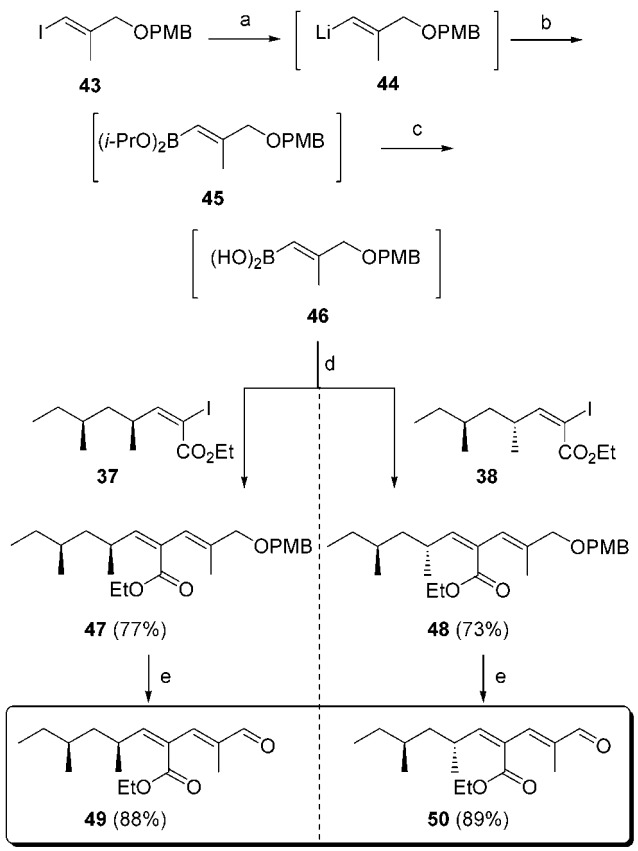


[a] Reagents and conditions: (a) (i) NaH, THF, rt; (ii) NaI, 4-methoxybenzyl chloride, reflux; (b) n-$Bu_3SnCu(n\text{-}Bu)CNLi_2$, THF, −78 °C; (c) MeI, HMPA, THF, −78 °C to room temperature; (d) I_2, THF, rt.

Final Assembly of the C18−C31 Fragment of Orevactaene Using Cross-Coupling (Suzuki reaction) as a Key Reaction. It is known that mixed alkyltributylstannylcuprate intermediates react *syn*-stereospecifically with monosubstituted alkynes to place the stannyl group at C1 and the copper atom at C2. The vinylcuprate intermediate reacts regiospecifically with some electrophiles to give a range of stereodefined stannylalkenes,[11] which could be converted to corresponding boronic acids[15,16] through intermediate iododerivatives. Thus, vinyl iodide **43** was successfully assembled through the synthetic steps depicted in Scheme 5.[8] Addition of the (tributylstannyl)butylcuprate reagent (n-$Bu_3SnCu(n\text{-}Bu)CNLi_2$)[31] to alkyne **40** followed by trapping of the intermediate alkenylcuprate **41** in situ with MeI afforded vinylstannane **42**, which was converted in the same operation to vinyl iodide **43** (Scheme 5). The iodide was activated later by lithium/halogen exchange.[32] The choice of protecting group for alcohol **39** proved to be more important than initially anticipated. Silyl protecting groups were found to be less stable to some transformations than *p*-methoxybenzyl (PMB).[8] Further, PMB offers the advantage of providing directly the desired aldehyde in **2** (e.g., Figure 1) during DDQ oxidative deprotection.[33]

With compounds **43** and **37**/**38** efficiently prepared and in hand, our attention shifted to the critical cross coupling that would join these two units together. Boronic acids are known to be less sterically demanding than the corresponding stannane. Thus, our attempts of coupling **43** and **37**/**38** were focused on using a boron derivative. Compound **43** does not contain any organolithium-sensitive groups, so we chose to install the metal on it. Treatment of **43** with *n*-butyllithium provided intermediate **44** that was quenched with triisopropylborate giving rise to borate ester **45** (Scheme 6), which was hydrolyzed to the corresponding acid **46**, and compounds **37** or **38** were added directly to the pot followed by the palladium(0) catalyst. The 'one-pot' lithium/halogen exchange, boron/lithium exchange, saponification, and cross-coupling sequence provided the desired products **47** and **48** as single isomers in good yields. The DDQ oxidative deprotection of the PMB group provided directly aldehydes **49** and **50** in excellent yields. The aldehydes represent the C18−C31 domain of orevactaene and are necessary to connect to the pyrone−polyene segment.

SCHEME 6[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; (b) $(i\text{-PrO})_3B$, −78 °C to room temperature; (c) NaOH, H_2O, rt; (d) **37** or **38**, $Pd(PPh_3)_4$, THF, 60 °C; (e) DDQ, 20:1 CH_2Cl_2/H_2O, 0 °C to room temperature.

Evidence for the Relative Configuration of the Side Chain of Orevactaene Based on ^{13}C NMR Shifts. Orevactaene (**1**) incorporates a terminal chiral α,γ-dimethyl-substituted heptenyl chain (C21−C29) in which the relative configuration of the two stereocenters (C23 and C25) is unknown. On the basis of computational[34] and experimental[35] data, it has been demonstrated that a series of compounds containing an α,γ-dimethylated heptenyl segment could serve as a valuable tool in relative structure elucidation of *syn* and *anti* arrangements of 1,3-skipped dimethyl groups. We were interested in analyzing the relation between relative configuration and ^{13}C NMR chemical shifts in unsaturated, 1,3-dimethylated hydrocarbon sequences, thus gaining some possible insight on the relative configuration of the side chain in **1**. We chose a set of compounds (Tables 1 and 2) with known 1,3-*syn* or -*anti* arrangements of terminal alkenyl chains to compare their

(31) For the preparation of $SnBu_3Cu(Bu)CNLi_2$ see: *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994; Chapter 12, p 279.

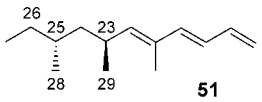
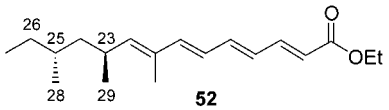
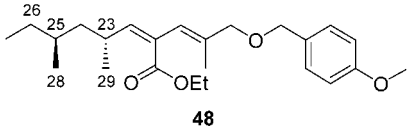
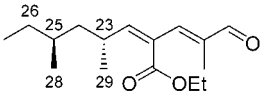
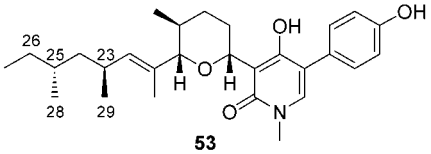
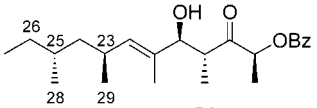
(32) Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, 2557−2562.

(33) Nakajima, N.; Uoto, K.; Yonemitsu, O. *Heterocycles* **1990**, *31*, 5−8.

(34) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem.* **1996**, *61*, 8083−8088.

(35) Clark, A. J.; Ellard, J. M. *Tetrahedron Lett.* **1998**, *39*, 6033−6036.

TABLE 1. Selected Experimental ^{13}C NMR Shifts of Some Side Chains Having C23/C25 *Anti* Arrangement[a]

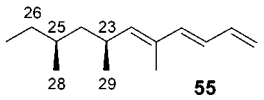
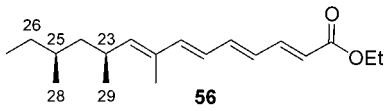
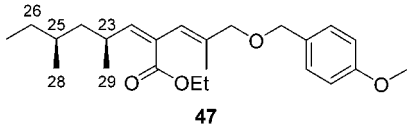
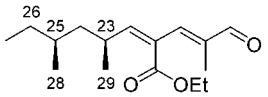
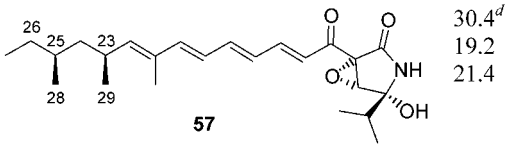
compounds	δC26 δC28 δC29
 **51**	29.5[b] 19.5 20.8
 **52**	29.5[b] 19.4 20.5
 **48**	29.2[c] 19.4 20.5
 **50**	29.2[c] 19.4 20.2
 **53**	28.9[d] 19.5 20.6
 **54**	28.9[d] 19.5 20.7

[a] The atom numbering of orevactaene (**1**) is used for all compounds. [b] Data from ref 35. [c] This work. [d] Data from ref 40.

measured ^{13}C NMR chemical shifts. It was reported[34,35] that for such compounds the most significant differences in chemical shifts might be expected for carbons analogous to C26, C28, and C29 on orevactaene. For simplicity, the numbering system of orevactaene has been adopted for this exercise. The most remarkable experimental feature found in compounds with 1,3-*syn* or 1,3-*anti* methyl arrangements is the shift difference between the methyl signals.[35] The shift difference is larger for *syn* compounds, a fact well reproduced by computational methods.[34]

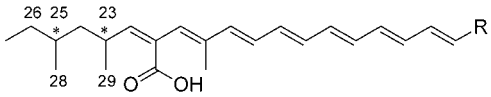
For compounds possessing a C23/C25 *anti* arrangement (Table 1), chemical shift intervals from 28.9 to 29.5 ppm appear for C26, from 19.4 to 19.5 ppm for C28, and from 20.2 to 20.8 ppm for C29. The chemical shift differences between C28 and C29 (on the same compound) range from 0.8 to 1.3 ppm. Different data and trends were observed for compounds with a C23/C25 *syn* arrangement (Table 2): chemical shift intervals from 30.0 to 30.4 ppm appear for C26, from 18.9 to 19.2 ppm for C28, and from 21.0 to 21.6 ppm for C29. The shift data for the *syn* compounds are close in agreement with that of orevactaene (Table 3). The chemical shift differences between C28 and C29 now fall between 2.1 and 2.5 ppm.

TABLE 2. Selected Experimental ^{13}C NMR Shifts of Some Side Chains Having C23/C25 *Syn* Arrangement[a]

compounds	δC26 δC28 δC29
 **55**	30.4[b] 19.1 21.6
 **56**	30.3[b] 19.0 21.3
 **47**	30.1[c] 19.0 21.4
 **49**	30.0[c] 18.9 21.0
 **57**	30.4[d] 19.2 21.4

[a] The atom numbering of orevactaene (**1**) is used for all compounds. [b] Data from ref 35. [c] This work. [d] Data from ref 41. [e] *Syn* relative configuration of the two methyl groups in the side chain of L-755,807 (**57**) was deduced by comparing the calculated and observed NMR spectra of model compounds.[34,35] The absolute stereochemistry of the epoxy-γ-lactam part is also unknown.

TABLE 3. Selected Experimental ^{13}C NMR Shifts of Orevactaene (1)[a]

compound	δC26 δC28 δC29
 Orevactaene (**1**)	29.7 18.9 21.4

[a] Data from ref 1.

These spectroscopic data suggest that the relative configuration of the methyl groups in the side chain of orevactaene is *syn*. Thus, the protected alcohol **47** and aldehyde **49** seem to be the most likely candidates to represent the relative configuration of the side chain of orevactaene, although the synthesis will need to be completed in order to confirm this tentative assignment.

Conclusions

In our effort directed toward the total synthesis of orevactaene, a recently isolated but yet to be synthesized natural product, we have successfully completed the synthesis of the C18−C31 subunit in an enantioselective

and convergent manner. Our convergent approach to this fragment was based on (i) a general strategy allowing us to synthesize four diastereomeric hydrophobic tails (C22−C29) of the molecule with two stereogenic centers at C23 and C25; (ii) the synthesis of two stereodefined trisubstituted olefins using palladium(0)-catalyzed hydrometalation and metallometalation as key reactions; and (iii) the final convergent assembly of these olefin templates to form the contiguous trisubstituted olefins of orevactaene using Pd coupling. The direct, convergent coupling of the two olefinic domains illustrated here allowed for the facile preparation of two of the diastereomers of compound **2**. Additionally, compiled spectroscopic data from the literature and the present study provide evidence that the relative configuration of the methyl groups in the side chain of orevactaene is *syn*, which will be confirmed once the total synthesis has been completed.

Experimental Section

General Methods. All reactions were carried out under a positive atmosphere of dry nitrogen unless otherwise indicated. Melting points were uncorrected. Solvents were distilled prior to use: THF and Et_2O were distilled from sodium benzophenone ketyl; CH_2Cl_2, pyridine, HMPA and Et_3N were distilled from CaH_2. Anhydrous DMF, DMSO, and MeOH were stored over 4 Å molecular sieves. Acetone was dried over drierite (anhydrous $CaSO_4$) for a few days and distilled under nitrogen from 4 Å molecular sieves prior to use. *p*-Toluenesulfonyl chloride was recrystallized from toluene/hexanes. Tetrakis(triphenylphosphine)palladium(0) was prepared by reduction of $PdCl_2(PPh_3)_2$ with hydrazine.[36] Chemical shifts are listed relative to residual $CHCl_3$ (δ 7.28) for ^{1}H NMR and relative to the middle peak for the triplet of $CDCl_3$ (δ 77.00) for ^{13}C NMR.

Representative Procedure for Preparation of 4-Benzyl-3-(2,4-dimethylhexanoyl)-1,3-oxazolidin-2-ones 22, 23, 27, and 28. Synthesis of (4*R*)-4-Benzyl-3-[(2*S*,4*S*)-2,4-dimethylhexanoyl]-1,3-oxazolidin-2-one (27). To a cold (−78 °C) solution of **26** (2.33 g, 10.0 mmol) in dry THF (50 mL) was added lithium diisopropylamide (5.8 mL, 11.6 mmol, 2 M solution in heptane/THF/ethyl benzene). After being stirred for 1 h, the resulting solution was treated with **17** (1.85 g, 8.4 mmol) and allowed to stir at −78 °C for 4.5 h and then at room temperature for 1.5 h. The reaction was quenched with ice-cold water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (anhydrous Na_2SO_4), concentrated in vacuo, and chromatographed (silica gel, 1:4 EtOAc/hexanes) to provide recovered starting material **26** (265 mg, 11.4%) and 1.78 g (70%) of pure **27**[37] as a yellow oil: R_f 0.58 (1:1 EtOAc/hexanes); $[\alpha]_D$ −28.9 (*c* 2.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.6 Hz, 3H), 0.93 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.13−1.25 (m, 2H), 1.34−1.48 (m, 2H), 1.89 (m, 1H), 2.76 (dd, J = 9.8, 13.3 Hz, 1H), 3.31 (dd, J = 2.7, 13.3 Hz, 1H), 3.96 (qdd, J = 6.8, 6.8, 6.8 Hz, 1H), 4.15−4.23 (m, 2H), 4.71 (m, 1H), 7.23−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.3 (−), 18.0 (−), 19.5 (−), 29.2 (+), 32.4 (−), 35.3 (−), 38.1 (+), 41.0 (+), 55.4 (−), 65.9 (+), 127.3 (−), 129.0 (−), 129.5 (−), 135.4 (+), 153.1 (+), 177.7 (+).

Representative Procedure for Preparation of 2,4-Dimethyl-1-hexanols 24, 25, 29, and 30. Synthesis of (2*S*,4*S*)-2,4-Dimethyl-1-hexanol (29). To a cooled (0 °C) solution of imide **27** (1.70 g, 5.593 mmol) in Et_2O (120 mL) was added 262 μL of methanol (6.43 mmol) followed by a solution of $LiBH_4$ (140 mg, 6.43 mmol) in 15 mL of THF/Et_2O (2:3). The reaction was stirred at 0 °C for 45 min and then allowed to warm to room temperature. After 1 h, NaOH (0.9 g, 22.5 mmol) in 10 mL of water was added, and stirring was continued until both phases were clear. The mixture was poured into a separatory funnel and washed successively with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, 2:3 Et_2O/pentane) yielded **29** (668 mg, 92%) as a clear, colorless liquid, and 624 mg of (4*R*)-4-benzyl-2-oxazolidinone (63%) was recovered. **29**: R_f 0.28 (1:5 EtOAc/hexanes); $[\alpha]_D$ −3.8 (*c* 1.65, $CHCl_3$) [lit.[38] $[\alpha]_D$ −3.9 (*c* 1.63, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3H), 0.88 (d, J = 6.2 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.86−0.97 (m, 1H), 1.10 (m, 1H), 1.21−1.49 (m, 3H), 1.71 (sx, J = 6.5 Hz, 1H), 3.39 (dd, J = 6.8, 10.3 Hz, 1H), 3.53 (dd, J = 5.0, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.1 (−), 17.3 (−), 19.8 (−), 29.0 (+), 31.6 (−), 33.2 (−), 40.6 (+), 68.4 (+).

These data agree with the literature data.[38,39]

(3*S*,5*S*)-1,1-Dibromo-3,5-dimethyl-1-heptene (31). To a stirring solution of oxalyl chloride (0.61 mL, 6.99 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added slowly dimethyl sulfoxide (0.89 mL, 12.54 mmol). After 15 min, **29** (657 mg, 5.045 mmol) in CH_2Cl_2 (10 mL followed by 2 ¥ 1 mL rinses) was added via cannula over 5 min. The reaction mixture was stirred for 30 min, and triethylamine (3.4 mL, 24.39 mmol) was added. The thick slurry was stirred for 30 min, warmed to 0 °C, further stirred for 45 min, and then quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with 4:1 Et_2O/pentane, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo using an ice-cold distilling bath on the rotory evaporator to give the crude aldehyde as a yellow oil: R_f 0.49 (1:9 EtOAc/hexanes). The crude aldehyde was used in the next step without further purification.

To a cold (0 °C) solution of Ph_3P (4.782 g, 18.23 mmol) in 10 mL of CH_2Cl_2 was added slowly a solution of CBr_4 (3.068 g, 9.25 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 15 min followed by dropwise addition of the crude aldehyde in CH_2Cl_2 (10 mL) over a 10 min period. The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2.5 h. Following dilution with 50 mL of Et_2O/pentane (4:1), the slurry was filtered through a plug of florisil and washed with a 4:1 Et_2O/pentane solution (4 × 50 mL). Organic solvents were evaporated and the residue was purified by flash chromatography (florisil, hexanes) to give dibromoalkene **31** (1.162 g, 81%, two steps from **29**) as a colorless oil: R_f 0.66 (hexanes); $[\alpha]_D$ +15.8 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.1 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.08−1.21 (m, 2H), 1.28−1.41 (m, 3H), 2.58 (m, 1H), 6.15 (d, J = 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.2 (−), 19.2 (−), 19.8 (−), 29.9 (+), 32.3 (−), 36.2 (−), 43.4 (+), 87.0 (+), 144.6 (−): HRMS (CI) calcd for $C_9H_{16}Br_2$ $[M]^+$ 281.9619, found 281.9648.

Ethyl (4*S*,6*S*)-4,6-Dimethyl-2-octynoate (33). To a solution of **31** (1.042 g, 3.67 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (6.88 mL, 11.01 mmol, 1.6 M solution in hexanes) after which the mixture was stirred for 1 h and then at 0 °C for 1 h. After the mixture was cooled to −78 °C, ethyl chloroformate (0.88 mL, 995 mg, 9.17 mmol) was added dropwise over 20 min. The reaction mixture was stirred for 1 h at −78 °C, 30 min at 0 °C, and 30 min at room temperature. The reaction mixture was quenched with a solution of saturated $NaHCO_3$ (20 mL) at 0 °C and was diluted with Et_2O (35

(36) (a) Coulson, D. R. *Inorg. Synth.* **1990**, *28*, 107−109. (b) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1985**, *292*, 19−28.

(37) The compound that was epimeric at C-2 (i.e., (2*R*,4*S*)-2,4-dimethylhexanoyloxazolidinone) was isolated (3.5% yield) and characterized. For details, see: Supporting Information.

(38) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115−9125.

(39) Nakamura, S.; Inagaki, J.; Kitaguchi, J.; Tatani, K.; Hashimoto, S. *Chem. Pharm. Bull.* **1999**, *47*, 1330−1333.

(40) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217−3220.

(41) Lam, Y. K. T.; Hensens, O. D.; Ransom, R.; Giazobbe, R. A.; Polishook, J.; Zink, D. *Tetrahedron* **1996**, *52*, 1481−1486.

mL). Following the separation of the two layers, the aqueous phase was additionally extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 1:9 Et_2O/hexanes) to afford alkyne **33** (706 mg, 98%) as a pale yellow oil: R_f 0.46 (1:9 Et_2O/hexanes); $[\alpha]_D$ +27.9 (*c* 1.78, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, $J = 6.7$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H), 1.14−1.36 (m, 3H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.59 (m, 2H), 2.67 (m, 1H), 4.23 (q, $J = 7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.1 (−), 14.0 (−), 18.6 (−), 20.5 (−), 23.8 (−), 29.8 (+), 32.3 (−), 43.1 (+), 61.7 (+), 73.3 (+), 93.2 (+), 154.0 (+); HRMS (CI) calcd for $C_{12}H_{21}O_2$ $[MH]^+$ 197.1542, found 197.1547.

Ethyl (*E*,4*S*,6*S*)-4,6-Dimethyl-2-(tributylstannyl)-2-octenoate (35). To a solution of alkyne **33** (577 mg, 2.94 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) in dry and degassed THF at room temperature was added dropwise *n*-Bu_3SnH (0.815 mL, 883 mg, 3.03 mmol) at room temperature over 1 h. The reaction mixture was stirred for 2 h, after which the solvent was removed in vacuo. The residue was filtered through a plug (10 cm) of silica gel using 1:4 benzene/hexanes (400 mL) as a wash. The organic phase was evaporated in vacuo, and the residue was purified by flash chromatography (silica gel, 1:4 benzene/hexanes) to give **35** (1.346 g, 94%) as a colorless oil: R_f 0.34 (3:7 benzene/hexanes); $[\alpha]_D$ +38.1 (*c* 2.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82−1.19 (m, 26H), 1.24−1.37 (m, 12H), 1.43−1.59 (m, 6H), 3.07 (m, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 5.69 (d, $J = 9.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 10.3 (+), 11.4 (−), 13.7 (−), 14.4 (−), 19.0 (−), 21.4 (−), 27.3 (+), 28.9 (+), 30.2 (+), 32.5 (−), 33.9 (−), 44.4 (+), 59.9 (+), 133.8 (+), 158.7 (−), 171.4 (+); HRMS (CI) calcd for $C_{24}H_{49}O_2Sn$ $[MH]^+$ 489.2759, found 489.2698; HRMS (CI) calcd for $C_{20}H_{39}O_2Sn$ $[M + H - C_4H_{10}]^+$ 431.1976, found 431.1939.

Ethyl (*E*,4*S*,6*S*)-2-Iodo-4,6-dimethyl-2-octenoate (37). To a solution of **35** (1.148 g, 2.356 mmol) in CH_2Cl_2 (45 mL) at room temperature was added iodine (608 mg, 2.395 mmol). The mixture was stirred for 3.5 h and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and stirred with semisaturated KF solution (110 mL) at room temperature for 2 h. The phases were separated, and the organic phase was additionally extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 3:7 benzene/hexanes) to afford **37** (733 mg, 96%) as a yellow oil: R_f 0.34 (3:7 benzene/hexanes); $[\alpha]_D$ +45.5 (*c* 2.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, $J = 5.9$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 1.02−1.20 (m, 2H), 1.03 (d, $J = 6.7$ Hz, 3H), 1.30 (m, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), 3.17 (m, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 6.60 (d, $J = 10.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.3 (−), 14.1 (−), 18.9 (−), 20.5 (−), 29.9 (+), 32.4 (−), 35.8 (−), 44.0 (+), 62.2 (+), 83.0 (+), 160.9 (−), 164.1 (+); HRMS (CI) calcd for $C_{12}H_{22}IO_2$ $[MH]^+$ 325.0655, found 325.0632.

1-({[(*E*)-3-Iodo-2-methyl-2-propenyl]oxy}methyl)-4-methoxybenzene (43). To a suspension of CuCN (832 mg, 9.29 mmol, dried at ca. 200 °C for 1 h under the stream of dry N_2) in THF (50 mL) at −78 °C was added *n*-BuLi (11.7 mL, 18.58 mmol, 1.6 M solution in hexanes). Upon completing the addition (10 min), the reaction mixture was stirred at room temperature for 30 min and cooled to −78 °C, and *n*-Bu_3SnH (5.408 g, 5.0 mL, 18.58 mmol) was added over 10 min. The mixture was kept at −78 °C for 1 h, and HMPA (4.31 mL, 4.44 g, 24.77 mmol) was added followed by **40** (1.091 g, 6.19 mmol). The reaction mixture was stirred at −78 °C for 45 min, MeI (3.85 mL, 8.79 g, 61.93 mmol) was added, and stirring was continued for 1 h at room temperature. The reaction mixture was cooled to 0 °C, and iodine (3.142 g, 12.38 mmol) was added. The mixture was stirred at room temperature for 16 h, quenched with saturated aqueous $Na_2S_2O_4$ (60 mL). The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (1:9 Et_2O/hexanes) to yield **43** (1.733 g, 88%, 'one-pot' from **40**) as a light brown oil: R_f 0.32 (1:9 Et_2O/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.88 (s, 3H), 3.83 (s, 3H), 4.00 (s, 2H), 4.44 (s, 2H), 6.30 (s, 1H), 6.91 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 21.6 (−), 55.3 (−), 71.7 (+), 73.7 (+), 78.6 (−), 113.9 (−), 129.4 (−), 130.0 (+), 145.0 (+), 159.3 (+).

Ethyl (*Z*,4*S*,6*S*)-2-{(*E*)-3-[(4-Methoxybenzyl)oxy]-2-methyl-1-propenyl}-4,6-dimethyl-2-octenoate (47). To a cold (−78 °C) solution of **43** (434 mg, 1.36 mmol) in 20 mL of dry THF was added *n*-BuLi (1.2 mL, 1.92 mmol, 1.6 M solution in hexanes). After stirring for 1 h, (*i*-PrO)$_3$B (0.45 mL, 366 mg, 1.94 mmol) was added. The mixture was warmed slowly to room temperature over 1 h, and NaOH (384 mg, 9.56 mmol) in 1.5 mL of degassed water was added dropwise. After 20 min, **37** (329 mg, 1.015 mmol) in 5 mL of THF and $Pd(PPh_3)_4$ (161 mg, 0.139 mmol) were added. The reaction mixture was heated at 60−65 °C for 2 h, cooled to 0 °C, and quenched with water (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 1:5 Et_2O/hexanes) to yield **47** (303 mg, 77%) as a yellow oil: R_f 0.28 (1:5 Et_2O/hexanes); $[\alpha]_D$ +30.7 (*c* 2.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, $J = 5.6$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 1.13 (m, 2H), 1.30 (m, 3H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.74 (s, 3H), 3.06 (m, 1H), 3.82 (s, 3H), 3.96 (s, 2H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.44 (s, 2H), 5.62 (d, $J = 10.3$ Hz, 1H), 6.11 (s, 1H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 11.3 (−), 14.2 (−), 15.1 (−), 19.0 (−), 21.4 (−), 30.1 (+), 31.5 (−), 32.5 (−), 44.6 (+), 55.2 (−), 60.5 (+), 71.3 (+), 75.7 (+), 113.7 (−), 124.9 (−), 128.8 (+), 129.4 (−), 130.5 (+), 134.7 (+), 148.8 (−), 159.1 (+), 168.2 (+); HRMS (CI) calcd for $C_{24}H_{37}O_4$ $[MH]^+$ 389.2692, found 389.2681.

Ethyl (*Z*,4*S*,6*S*)-4,6-Dimethyl-2-[(*E*)-2-methyl-3-oxo-1-propenyl]-2-octenoate (49). To a solution of **47** (259 mg, 0.67 mmol) in CH_2Cl_2 (16 mL) and water (0.8 mL) at 0 °C was added DDQ (378 mg, 1.67 mmol). The mixture was stirred for 15 min and then further stirred at room temperature for 1.5 h. Then the reaction mixture was quenched at 0 °C by simultaneous addition of water (40 mL) and Et_2O (40 mL). The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 1:5 Et_2O/hexanes) to give **49** (156 mg, 88%) as a yellow oil: R_f 0.30 (1:5 Et_2O/hexanes); $[\alpha]_D$ +62.2 (*c* 2.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, $J = 5.6$ Hz, 3H), 0.86 (t, $J = 7.1$ Hz, 3H), 1.07 (d, $J = 6.4$ Hz, 3H), 1.16 (m, 2H), 1.24−1.41 (m, 3H), 1.35 (t, $J = 7.3$ Hz, 3H), 1.80 (s, 3H), 3.05 (m, 1H), 4.30 (q, $J = 7.3$ Hz, 2H), 6.01 (d, $J = 10.5$ Hz, 1H), 6.90 (s, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (−)) δ 10.2 (−), 11.2 (−), 14.1 (−), 18.9 (−), 21.0 (−), 30.0 (+), 32.3 (−), 32.6 (−), 44.3 (+), 61.1 (+), 129.1 (+), 137.6 (+), 147.0 (−), 154.3 (−), 166.9 (+), 195.1 (−); HRMS (CI) calcd for $C_{16}H_{27}O_3$ $[MH]^+$ 267.1960, found 267.1952.

Acknowledgment. This work was supported by funding from the Ontario Research and Development Challenge Fund (ORDCF) and NSERC (Canada).

Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds prepared in this study. Experimental details for preparation of compounds **10**−**15**, **17**, **19**−**25**, **28**, **30**, **32**, **34**, **36**, **38**, **40**, **48**, and **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0201777