Synthesis of the Aliphatic Depside (+)-Bourgeanic Acid

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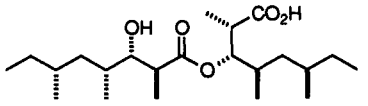
The lichen metabolite (+)-bourgeanic acid (1) was synthesized in 12 steps and 3.4% overall yield from (*R*)-2-methyl-1-iodobutane (**53**) by a sequence which confirmed that this aliphatic depside is the self-esterification product of (2*S*,3*S*,4*R*,6*R*)-2,4,6-trimethyl-3-hydroxyoctanoic acid. Alkylation of the enolate of (*S*)-*N*-propionylprolinol (**48**) with **53** gave the amide **60** which was transformed to (2*R*,4*R*)-2,4-dimethylhexanal (**4**). The latter was reacted with the crotylboronate **68**, prepared from (*S*,*S*)-(−)-diisopropyl tartrate, to afford (3*R*,4*S*,5*R*,7*R*)-3,5,7-trimethyl-1-nonen-4-ol (**65**) as the major diastereomer. Protection followed by ozonolysis and oxidation furnished (−)-hemibourgeanic acid (**2**). The β-lactone **73** derived from **2** was used to acylate **65**, and the resulting ester **74** was subjected to oxidative ozonolysis to yield (+)-**1**.

In 1973 Bodo reported the isolation of a new substance which he named bourgeanic acid from several *Ramalina* species of lichen.[1] Degradation and spectroscopic analysis established the relative stereochemistry of this novel lichen metabolite as **1**.[2] More recently, the absolute configuration of (+)-**1** was announced[3] after an X-ray crystallographic study was completed on a derivative of (−)-hemibourgeanic acid (**2**). Bourgeanic acid has the distinction among lichen metabolites of being the first member of a new class of naturally occurring aliphatic depsides.



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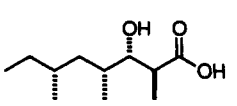
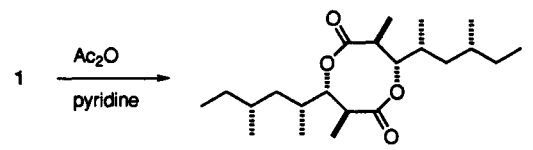


2

Degradative studies on bourgeanic acid carried out by Bodo[2] led to the surprising discovery of the eight-membered dilactone **3** (bourgeanic lactone). First isolated as a side product in the dehydration of **1** with acetic anhydride in refluxing pyridine, milder conditions (0 °C for 24 h) afforded a 53% yield of **3**. In view of the difficulty usually associated with the synthesis of eight-membered cyclic structures, the facility with which formation of **3** occurs is remarkable.



3

As the condensation product of two molecules of hemibourgeanic acid (**2**), a strategy for the synthesis of **1** simplifies to construction of (2*S*,3*S*,4*R*,6*R*)-2,4,6-trimethyl-3-hydroxyoctanoic acid as the initial target. Implicit in this approach is the need for a method of achieving the self-esterification of **2** to give **1**, a process which seemed likely to present a significant challenge in view of the sterically hindered nature of both the carboxyl and hydroxyl groups. This feature together with the opportunity to test certain stereochemical paradigms in the context of the syn and anti relationships of the substituents within **1** prompted us to examine synthetic routes to this depside. We also hoped to gain insight into the cyclization pathway which affords the dilactone **3**. Herein, we describe an enantioselective synthesis of natural (+)-**1**.[4]

Of several options considered for the enantioselective synthesis of **2**, a route proceeding through (2*R*,4*R*)-2,4-dimethylhexanal (**4**) appeared to offer the best prospect for success. A primary consideration behind this plan was the fact that methodology for elaborating the 2,3-anti-3,4-syn configuration of **2** from this aldehyde was available by means of either an aldol construction or via crotylmetalation chemistry. Aldehyde **4** thus became a pivotal intermediate in our scheme and access to this substance was explored from both chiral and achiral starting materials. In the latter case, our objective was to establish the correct configuration of the C4 methyl substituent of **4** through directed saturation of an olefinic (trisubstituted) bond which would be introduced in the form of tiglaldehyde (**5**) or a related precursor. The alternative strategy in which C4 configuration was incorporated at the outset as a (*R*)-2-methylbutyl synthon **6** was initially deemed less attractive since the preparation of (*R*)-**6**, in contrast to its *S* enantiomer, would require several steps. Ultimately, however, we were forced to accept this longer route.

An attribute of the plan departing from **5** was the fact that the known alcohol **8**[5] is readily prepared in pure form by the condensation of **5** with the *N*-propionyl-2-oxazolidone **7**[6] obtained from (−)-ephedrine. The alcohol **8** became the focal intermediate for directed saturation of the C=C bond and, as shown previously by Evans,[5] hydrogenation of **8** at atmospheric pressure in the presence of rhodium(I) (NBD)(DIPHOS-4) catalyst[7] gave **9** accompanied by a minor quantity of **10**. Although the 84:16 ratio of **9**:**10** can be improved by increasing the pressure of hydrogen, subsequent difficulties in removing the

• Abstract published in *Advance ACS Abstracts*, May 1, 1994.

(1) Bodo, B.; Hebrord, P.; Molho, L.; Molho, D. *Tetrahedron Lett.* **1973**, 1631.
(2) Bodo, B. *Bull. Mus. Natl. Hist. Nat. (Paris)* **1975**, *349*, 23.
(3) Bodo, B.; Trowitzch-Kienast, W.; Schomberg, D. *Tetrahedron Lett.* **1986**, *27*, 847.
(4) Preliminary communication: White, J. D.; Johnson, A. T. *J. Org. Chem.* **1990**, *55*, 5938.
(5) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(6) Evans, D. A.; Ennis, M. O.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(7) Brown, J. M.; Naik, R. *J. Chem. Soc., Chem. Commun.* **1982**, 348.

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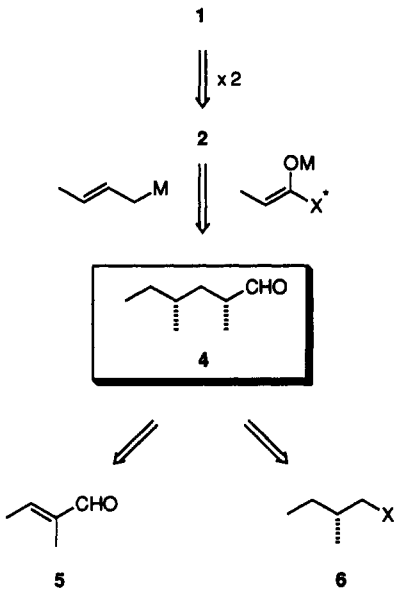
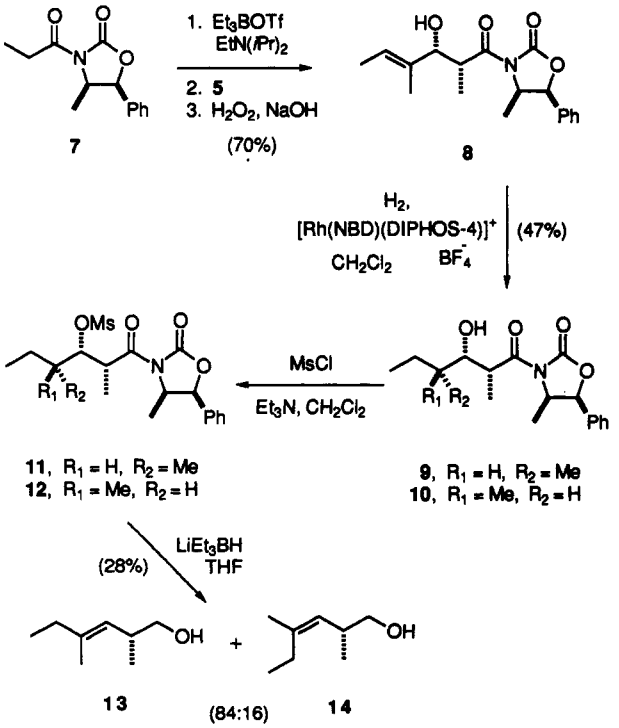
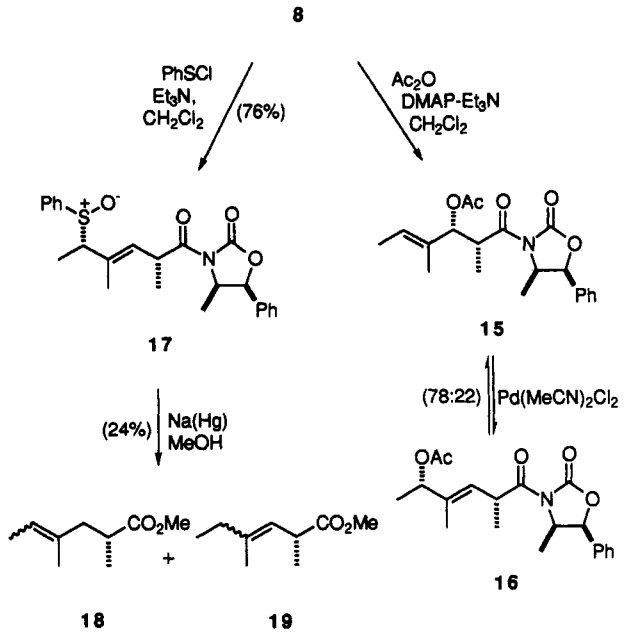


hydroxyl group from **9** made this exercise moot. Thus, although the mixture of **9** and **10** was readily converted to the corresponding mesylates **11** and **12**, attempted reduction of these derivatives with lithium triethylborohydride[8] led only to elimination products **13** and **14** (84:16, respectively). The fact that these alkenols were produced in a ratio which exactly matched the precusors **9** and **10** suggested that stereospecific anti elimination occurred from each of the mesylates **11** and **12**. Elimination rather than reductive displacement of hindered mesylates is a commonly observed phenomenon[9] which, in the present circumstances, rendered **9** unusable as a progenitor of **4**.



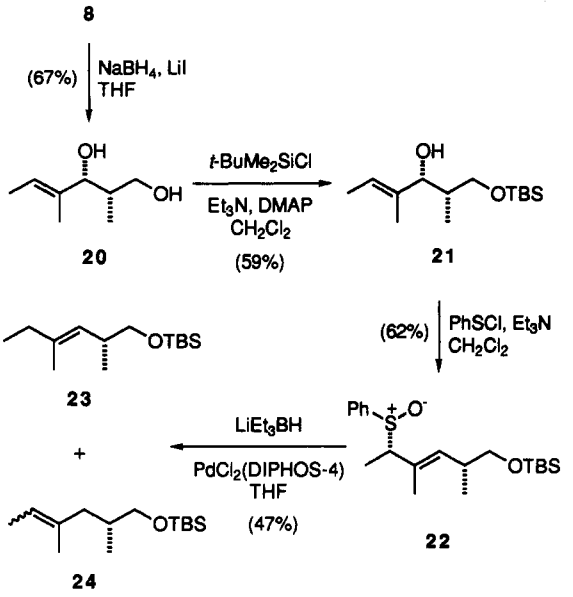
In the hope of making the hydroxyl function more accessible for reduction, two schemes for effecting allylic transposition of **8** were investigated. Acetylation of **8** afforded **15** in excellent yield but transposition of this acetate, which on the basis of precedent[10] should be facile, met unanticipated difficulties. Among these was the fact that an equilibrium was established between **15** and its isomer **16** in the presence of palladium(II) bis(acetonitrile) dichloride which was heavily in favor of the former. A [2,3]-sigmatropic rearrangement of the allylic sulfenate from **8** initially appeared more promising, leading to a mixture of sulfoxide diastereomers **17** in good yield.[11] However, the sulfoxide function proved to be ineffective as a directing group in the hydrogenation of **17** with rhodium(I)(NBD)(DIPHOS-4) catalyst and its reductive removal with sodium amalgam in methanol[12] resulted in a low yield of an intractable mixture of structural and stereoisomeric olefinic esters **18** and **19**.



It was surmised that the oxazolidinone moiety in **17** was a possible source of these problems, and it was therefore decided to remove the chiral auxiliary by reduction. Lithium borohydride was the reagent of choice for this purpose and gave **20** in reproducibly good yield. The primary hydroxyl group of **20** was protected selectively as the *tert*-butyldimethylsilyl ether **21** which was treated with benzenesulfenyl chloride to give sulfoxide **22** directly as a mixture of diastereomers. Reductive cleavage of the mixture, in this instance with lithium triethylborohydride in the presence of a palladium(II) complex,[13] again showed poor selectivity, affording a 1:1:1 mixture of **23** together with *E* and *Z* isomers of **24**. This unappealing mixture of olefins clearly nullified any realistic approach to **4** by means of stereoselective saturation of the double bond. However, it appeared likely that if one of these substances could be prepared in pure form a method for installing the C4 methyl group of **4** could be developed. The most readily accessible candidate proved to be the *E* isomer **29**

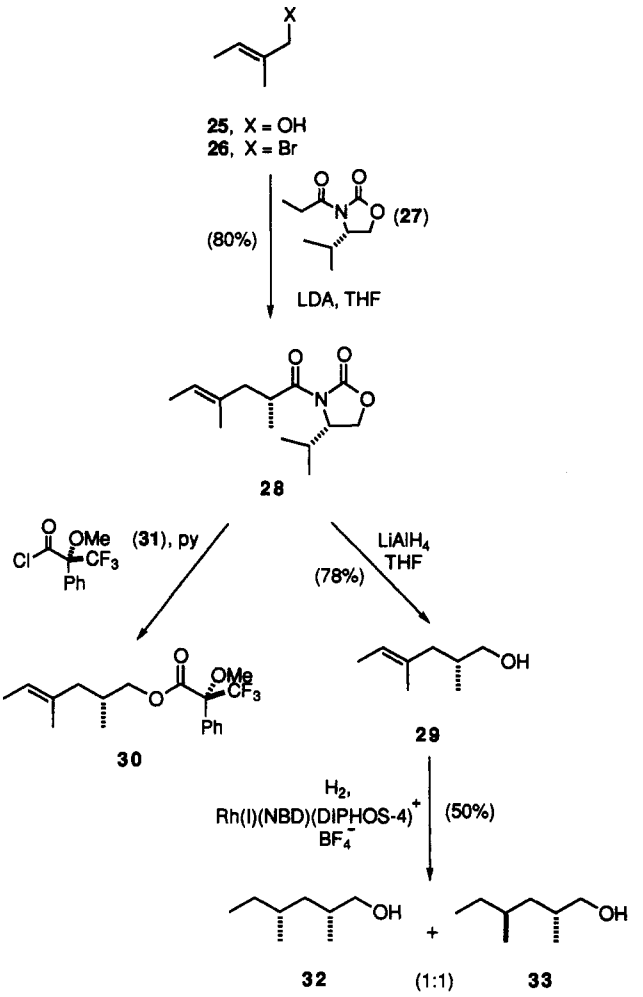
(8) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669.
(9) White, J. D. In *Strategies and Tactics in Organic Synthesis*; Ludberg, T., Ed.; Academic: Orlando, FL, 1984; Vol. 1, p 354.
(10) (a) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200. (b) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (c) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.
(11) (a) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100. (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
(12) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(13) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H.; Takagaki, H.; Yamazaki, K. *Chem. Lett.* **1986**, 1177.

corresponding to 24 which was prepared from geometrically pure 2-methyl-2-butenol (25).[14]

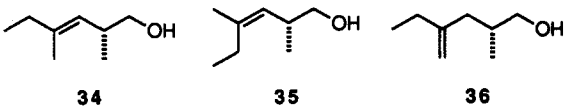


Bromination of 25 with NBS afforded 26,[15] which was used to alkylate the enolate derived from (*S*)-*N*-propionyl-4-isopropyl-2-oxazolidinone (27).[6] The latter was prepared by selenium-catalyzed carbonylation of (*S*)-valinol,[16] followed by acylation of the lithium anion of the resulting oxazolidinone with propionyl chloride. Analysis of the alkylation product 28 by ^1H and ^{13}C NMR spectroscopy indicated that within the limits of detection this substance was a pure diastereomer, a result in accord with the high de's (>98%) observed by Evans in asymmetric alkylations with 27.[6] Reduction of 28 gave alcohol 29 whose optical purity was ascertained by conversion to its methoxy(trifluoromethyl)phenyl acetate (30) with (+)-acyl chloride 31.[17] A separate experiment in which racemic 29 was prepared from (±)-27 and then converted to diastereomeric Mosher esters with (+)-31 established the fact that these esters were spectroscopically distinguishable; one stereoisomer exhibited an AB quartet in the ^1H NMR spectrum (δ 4.02 and 4.24) and the other a simple doublet (δ 4.13) for the CH_2 group adjacent to oxygen. The ^1H NMR spectrum of 30 corresponded to the former splitting pattern. Assignment of configuration to 28 and hence to 29 is based on well-established precedent[6] which stipulates that attack by the alkylating agent (26) occurs at the face of the *E* enolate of 27 opposite the isopropyl substituent.

The acquisition of 29 afforded an opportunity to test the limits of directed hydrogenation with the rhodium(I)(NBD)(DIPHOS-4) catalyst[18] since, although high stereoselectivity has been obtained with allylic and even homoallylic alcohols possessing an intervening stereogenic center,[19] its application to bishomoallylic alcohols has not been reported. In principle, coordination of rhodium(I) to the hydroxyl substituent and olefin of 29 can lead to a rigid template which should result in the delivery of



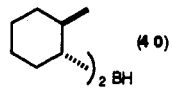
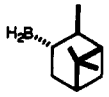
hydrogen stereoselectively to the double bond. It was found, however, that a 1:1 mixture of 32 and 33 resulted from this hydrogenation. Closer examination of the reaction revealed that the absence of stereoselectivity was not due to failure of the catalyst to complex with 29 but rather to competitive isomerization of the double bond. Recovered alkene at an intermediate stage of the reaction was found to consist not only of 29 but also 34, 35, and 36.[20]



The failure to effect stereoselective hydrogenation of 29 prompted us to turn to hydroboration as a means for setting the configuration at C4 of hexanol 32. Precedent suggested that the existing stereogenic center in 29 would be sufficient to guide a sterically demanding but achiral hydroborating agent preferentially to one face of the olefin.[21] If this failed, there remained the option of employing a chiral borane.[22] In the event, hydroboration of silyl ether 37 with either borane–dimethyl sulfide or with thexylborane gave, after an oxidative workup, a 1:1

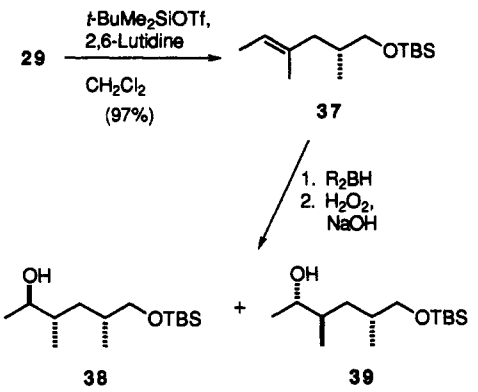
(14) Kleveland, K.; Skattebol, L.; Sydnes, L. K. *Acta Chem. Scand.* **1977**, *B31*, 463.
(15) Grdina, M. B.; Orfanopoulos, M.; Stephenson, L. M. *J. Org. Chem.* **1979**, *44*, 2936.
(16) Sonada, N.; Yamamoto, G.; Natsukawa, K.; Kondo, K.; Murai, S. *Tetrahedron Lett.* **1975**, 1969.
(17) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(18) Brown, J. M. *Angew Chem., Int. Ed. Engl.* **1987**, *26*, 190.
(19) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.
(20) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134.
(21) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577.
(22) Brown, H. C.; Jadhar, P. K.; Mandol, A. K. *J. Org. Chem.* **1982**, *47*, 5074.
(23) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257 and references cited therein.

Table 1. Hydroboration–Oxidation of 37

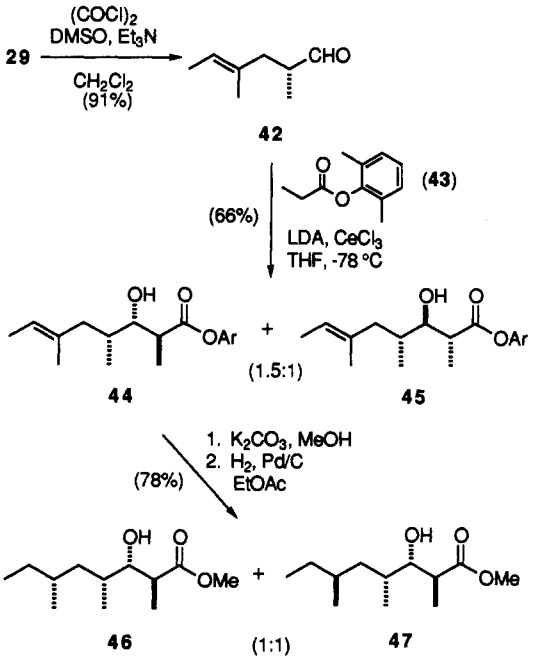
hydroborating agent (R_2BH)	yield (%)	ratio 38:39[a,b]
BH_3·Me_2S	67	1:1
$Me_2CHCMe_2BH_2$	77	1:1
 (40)	15	1:1
 (41)	76	5.5:1

[a] Ratios were determined by ^1H NMR spectroscopy. [b] Stereochemical assignments are based on the mechanistic model proposed by Houk (see ref 23).

mixture of alcohols **38** and **39**. A similar ratio of products was obtained in low yield with the borane **40** prepared by hydroborating 1-methylcyclohexene. Modest stereoselectivity was observed in the hydroboration–oxidation of **37** with monoisopinylcampheylborane (**41**) prepared from (−)-α-pinene,[22] but the difficult separation of **38** from **39** together with the need for subsequent removal of a hydroxyl group made this approach to **4** impractical. The results of these hydroboration studies are summarized in Table 1.



Although the objective of preparing **4** by stereoselective reduction of an olefinic precursor had not been attained, we nevertheless believed that access to hemibourgeanic acid (**2**) might be possible if the reduction were accomplished at a later stage with the full octanoate skeleton of **2** assembled. Consequently, **29** was carefully oxidized under Swern conditions[24] to afford **42** in high yield, and this aldehyde was then subjected to condensation with the propionate ester **43** of 2,6-dimethylphenol. Heathcock has shown that the enolate of **43** undergoes highly antiselective aldol condensation with a variety of aldehydes,[25] and **42** did not disappoint us in this regard. Unfortunately, facial selectivity in the reaction of **43** with an α-chiral aldehyde is often poor[26] and this proved to be the case with **42**, resulting in a 1.5:1 mixture of **44** and **45**. In practice, it was necessary to add an equivalent of cerium(III) chloride[27] to the lithium enolate of **43** to obtain a satisfactory yield of aldol products. The ^1H NMR spectra of **44** and **45** permitted a ready distinction between these 3,4-syn and anti isomers, **44** displaying the methine proton at C3 as a doublet of doublets (J = 9 and 3 Hz) at δ 3.75 whereas the corresponding proton signal in **45** appeared as a triplet (J = 6 Hz) at δ 3.52. In this respect, the major stereoisomer **44** was clearly more similar to **2**, for which the C3 portion is reported as a doublet of doublets (J = 8.5 and 2.5 Hz) at δ 3.72,[2] and it was therefore this ester which was advanced toward **2**. Transesterification of **44** in methanol gave the corresponding methyl ester but, unsurprisingly in light of our previous experience, hydrogenation of this alkene under all conditions produced both methyl hemibourgeanate (**46**) and its C6 epimer **47** in equal quantity. Moreover, no method could be found for clean separation of **46** from 6-epihemibourgeanate **47**. This result persuaded us that the C6 configuration of **2** should be introduced unambiguously at the outset of the route and thus led to a reexamination of **6** for this purpose.



In contemplating **6** as the source of the terminal segment of hemibourgeanic acid, we were, of course, cognizant of its shortcoming as an alkylating agent. Thus, whereas allylic halides such as **26** react readily with the enolate of **27**, a saturated halide is inert. Indeed, it was this limiting property of *N*-acyloxazolidinones which had initially convinced us to start from unsaturated materials such as tiglaldehyde **5** and alcohol **25**. Fortunately, an attractive alternative to the oxazolidinone family of chiral auxiliaries is available for asymmetric alkylation in the form of *N*-acylprolinol **48** which has been shown by Evans[28] and by Sonnet[29] to afford good levels of stereoselectivity with *saturated* halides. However, the data available on the scope of alkylation with **48** together with uncertainty regarding the compatibility of its dianion with **6** suggested that a prudent experiment would be reaction of **48** with readily available (*S*)-2-methyl-1-iodobutane (**49**). Amide **48**, prepared from (*S*)-prolinol and propionic anhydride,[28] was converted to its dianion with 2 equiv of LDA and then treated with **49**. The results, shown in Table 2, entries 1–3, indicate that good diastereoselectivity can be achieved

(24) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(25) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.
(26) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(27) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233.
(28) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.
(29) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

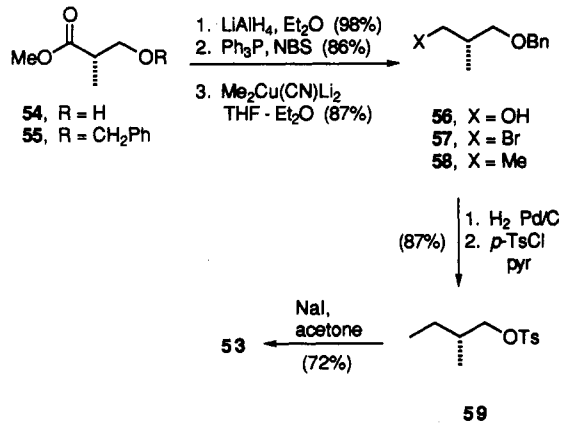
Table 2. Alkylation of (*S*)-*N*-Propionylprolinol (48) with (*R*)- and (*S*)-1-Iodo-2-methylbutanes (49 and 53)

entry	alkylating agent	conditions	products	ratio[a]	yield (%)
1	49	LDA, THF	50:51	7:1	65
2	49	LDA, THF-HMPA, −78 °C → rt	50:51	12:1	54
3	49	LDA, THF-HMPA, −78 °C	50:51	17:1	24
4	53	LDA, THF-HMPA, −78 °C, 5 h	60:61	17:1	34
5	53	LDA, THF-HMPA, −78 °C, 65 h	60:61	19:1	49
6	53	LDA, THF-TMEDA, −78 °C, 65 h	60:61	11.5:1	17

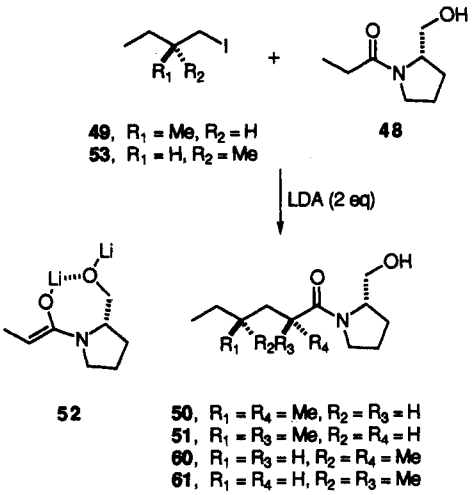
[a] Ratios were measured by ^{13}C NMR spectroscopy.

in this alkylation providing low temperature is maintained and the reaction medium is made homogeneous by adding a sufficient quantity of HMPA. However, there is a compensatory effect leading to reduced yield at higher levels of stereoselectivity. Assignment of configuration to the new stereogenic center of the major isomer **50** is based on the assumption that alkylation occurs at the face of the *Z* enolate of the dianion **52** opposite the alkoxymethyl substituent attached to the pyrrolidine.[30]

It seemed likely that similar diastereoselectivity could be anticipated in the alkylation of **48** with (*R*)-iodide **53**,[31] and the latter was therefore prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate (**54**). Thus, **54** was converted to **55** with benzyl trichloracetimidate[32] and the ester function was reduced to alcohol **56**. The corresponding bromide **57**[33] was treated with lithium cyanomethylcuprate[34] to give **58** which, after hydrogenolysis of the benzyl ether, was transformed to tosylate **59** and then to **53** with sodium iodide.[35] The seven-step sequence from (*S*)-**54** makes (*R*)-**53** available in an overall 38% yield.



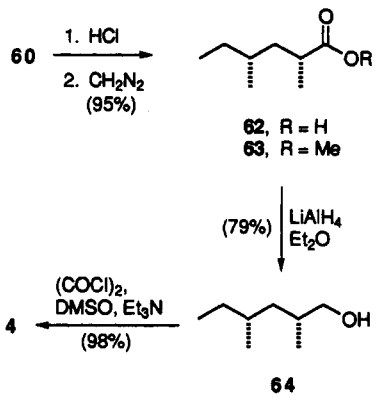
Alkylation of **48** with **53** was carried out under conditions similar to those employed with **49** and was found to give **60** in moderate yield but with good stereoselectivity (Table 2 entries 4–6). The reaction was noticeably slower than that between **48** and **49** but the apparent "mismatch" did not impact on stereoselectivity, providing the requirements of low temperature and the presence of HMPA were maintained. It was found that TMEDA could not be substituted satisfactorily for HMPA in this process (entry 6) nor could the dilithio species **52** be replaced by its dipotassio counterpart. Optimal conditions are those expressed in entry 5, although it was found that stereoselectivity dropped to ca. 10:1 upon scale up (>25 mmol) under these conditions.



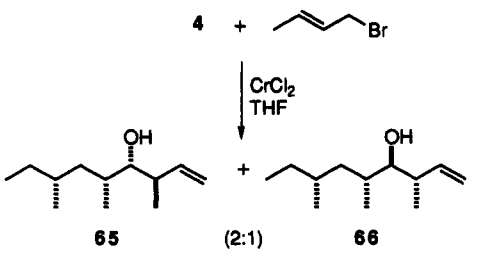
In addition to providing good stereoselection in alkylation with saturated alkyl halides, a further attribute of the chiral auxiliary **48** is its ease of removal from the product. This is presumably a consequence of rapid reversible intramolecular acyl transfer from amine to alcohol which, although heavily favoring the amide, permits hydrolysis to take place via the ester of **48**.[36] In practice, treatment of **60** with 1 M HCl at reflux led to the carboxylic acid **62** in excellent yield. This acid was purified to optical homogeneity by recrystallization of its cinchonidine salt and then was esterified with diazomethane to afford **63**. Reduction of **63** gave (2*R*,4*R*)-2,4-dimethylhexanol (**64**) which, after Swern oxidation, furnished aldehyde **4**. This substance proved to be unstable, being especially prone to epimerization at C2 as well as to cyclotrimerization (^{13}C NMR, δ 112), and was characterized as its (2,4-dinitrophenyl)hydrazone.

In principle, elaboration of **4** toward hemibourgeanic acid (**2**) requires only a stereoselective aldol construction. However, for reasons associated with the need to block the carboxyl terminus of **2** before its assembly into the complete structure of **1**, we chose to homologate **4** via crotylation, intending to unmask the carboxyl group of bourgeanic acid (**1**) in a final ozonolysis. This strategy circumvents possible complications arising from selective cleavage of the terminal over the internal ester in the finished bourgeanate. Initially, the crotylchromium species prepared from *trans*-crotyl bromide and chromium(II) chloride was explored for this purpose since this reagent is known to give the anti product with high stereoselectivity in its reaction with aldehydes.[37] Facial selectivity with

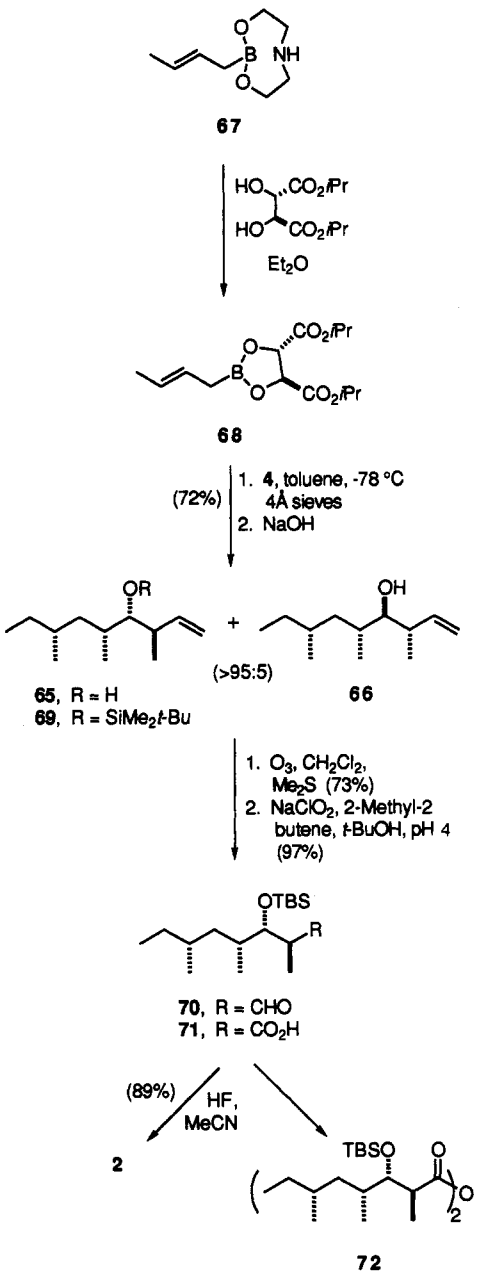
(30) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.
(31) Mori, K. Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439.
(32) White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624.
(33) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374.
(34) Lipshutz, B. E.; Parker, D.; Kozlowski, J. A. *J. Org. Chem.* **1983**, *48*, 3334.
(35) Longone, D. T. *J. Org. Chem.* **1963**, *28*, 1770.
(36) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63.
(37) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.



this achiral reagent would, of course, be vested in the α-chiral aldehyde, and there appeared to be encouraging precedent for expecting predominantly *re* face attack at the carbonyl group of **4**.[37] Disappointingly, the reaction of *trans*-crotyl bromide with **4** in the presence of $CrCl_2$ gave only a 2:1 ratio of **65** and **66** regardless of the conditions under which the reaction was run. Hence, it must be concluded that the difference in steric size between the substituents attached to the α carbon of **4** is simply not large enough to provide good facial bias with the relatively nondiscriminating crotylchromium(II) nucleophile. This result implied that reagent-based stereocontrol would be required if the 3,4-syn orientation of substituents in **2** was to be secured in a satisfactory manner. For this reason we turned to the asymmetric crotylboronate methodology developed by Roush[38] and others[39] for completion of the route to hemibourgeanic acid.



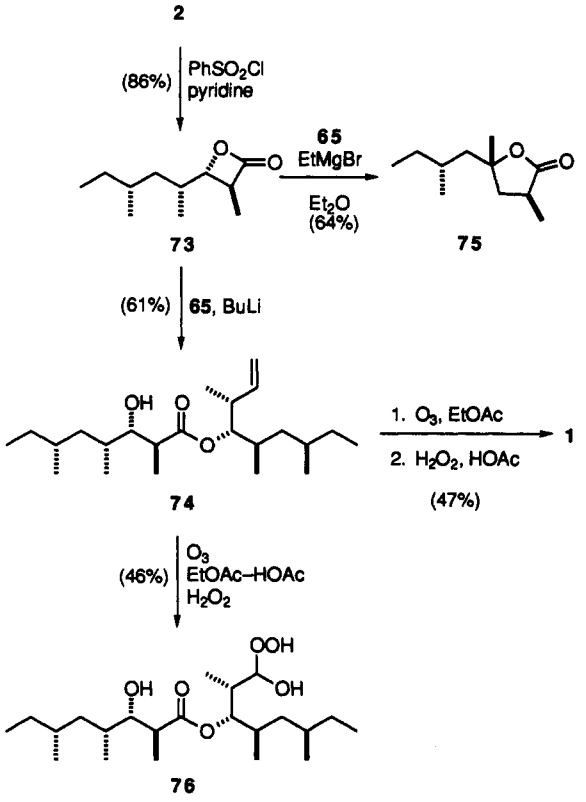
The crystalline crotyl aminoboronate **67**,[40] prepared from the anion of *trans*-2-butene[41] by treatment with tris(isopropoxy)borane and then with diethanolamine,[42] was converted to *trans*-crotyl boronate **68** with (*S*,*S*)-(−)-diisopropyl tartrate. Boronate **68** was treated with **4** in toluene at low temperature to give **65** and **66** in a ratio which consistently exceeded 95:5, indicating that excellent *re* face selectivity prevailed in this coupling. The 3,4-anti-4,5-syn relationship in the major non-1-ene **65** follows from precedent established by Roush in similar double stereodifferentiating reactions of **68** with chiral aldehydes.[38] Although the preparation of a rigorously pure sample of **65** required gas chromatography, separation from minor quantities of **66** proved unnecessary for the subsequent transformation to **2**. This was achieved by first protecting **65** as its *tert*-butyldimethylsilyl ether **69** before a reductive ozonolysis of the terminal olefin gave **70**. The aldehyde was oxidized to carboxylic acid **71** which, after deprotection with fluoride, furnished (−)-hemibourgeanic acid (**2**). The latter was identical in all respects including optical rotation with a sample of (−)-**2** derived from alkaline hydrolysis of natural (+)-bourgeanic acid (**1**), thus confirming the structural assignment made to **2** by Bodo.[3]



Bourgeanic acid (**1**), the self-esterification product of **2**, would be accessible in principle via coupling of **65** with the carboxylic acid **71**. However, the steric impedance attached to the hindered hydroxyl group of **65** defeated all attempts at its esterification with activated versions of **71**. This included the (acyloxy)pyridinium derivative of **71** obtained by Mukaiyama's protocol,[43] the mixed trichloroacetic anhydride,[44] and the acyl phosphate prepared with diethyl phosphorochloridate,[45] all of which led to anhydride **72** as the sole product. The latter was also unreactive

(38) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(39) Hoffmann, R. W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* **1988**, *121*, 2225.
(40) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
(41) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.
(42) Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1986**, *51*, 4526.
(43) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.
(44) Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927.
(45) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268.

with 65 even under the forcing conditions recommended by Hassner.[46] The solution to this problem was eventually found in β-lactone 73, a derivative of hemibourgeanic acid initially prepared by Bodo[2] and acquired by treatment of 2 with benzenesulfonyl chloride.[47] Vederas has shown that β-lactones are particularly effective acylating agents with "hard" nucleophiles such as methoxide,[48] and when 73 was reacted with the lithio alkoxide obtained from 65 and n-butyllithium, the ester 74 was formed in ca. 60% yield. Other alkali metal alkoxide derivatives of 65 were much less satisfactory, and it appears that lithium has a dual role in this esterification which involves coordination to the β-lactone carbonyl as well as enhancement of the nucleophilicity of 65. This conjecture is supported by the observation that the bromomagnesio alkoxide obtained by reacting 65 with ethylmagnesium bromide promotes rearrangement of 73 to 75. A similar rearrangement of a β-lactone in the presence of magnesium bromide was reported by Black.[49]



With 74 in hand, it appeared that ozonolytic cleavage of the vinyl group followed by an oxidative workup would yield bourgeanic acid (1) in straightforward fashion. Unexpectedly, the sole product obtained upon ozonolysis of 74 in ethyl acetate containing acetic acid followed by addition of hydrogen peroxide was the hydroperoxide 76. Although 76 could subsequently be transformed into 1 by exposure to p-toluenesulfonyl chloride in pyridine,[50] a more direct route to bourgeanic acid was realized through a minor modification of the ozonolysis conditions. Thus, ozonolysis of 74 in ethyl acetate at low temperature and then treatment of the ozonide with 30% H_2O_2 in acetic acid gave (+)-1, identical with a sample of natural (+)-bourgeanic acid. The 12-step sequence from 53 to 1 proceeds in an overall yield of 3.4% and establishes that natural (+)-bourgeanic acid is the self-esterification product of (2S,3S,4R,6R)-2,4,6-trimethyl-3-hydroxyoctanoic acid.

Finally, (+)-1 was converted to dilactone 3 by treatment with benzenesulfonyl chloride under the conditions described by Bodo.[2] The crystalline dilactone, obtained in 96% yield, possessed a melting point and optical rotation virtually identical to those reported by Bodo. The ease with which 1 closed to 3 was underscored by allowing a sample of synthesized bourgeanic acid to stand in $CDCl_3$. After less than 1 day, a significant quantity of the dilactone was present. The conformational properties of 3 and a rationale for its formation from 1 will be presented in a forthcoming paper.

Experimental Section

Starting materials and reagents purchased from commercial suppliers were generally used without purification. Toluene, tetrahydrofuran (THF), and ether were distilled from potassium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, diisopropylethylamine, 2,6-lutidine, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), tetramethylethylenediamine (TMEDA), and dichloromethane were distilled from calcium hydride under argon. Pyridine was distilled from barium oxide under argon. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon.

Concentration under reduced pressure refers to the use of a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at pressures less than 2 Torr. Reaction flasks were flame dried under a stream of argon. Syringes were oven dried at 160 °C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Analytical thin layer chromatography (TLC) was conducted using 1.5 × 5.0 cm precoated aluminum TLC plates (0.2-mm layer thickness of silica gel 60 F-254). Spots were visualized by ultraviolet light, exposure to iodine vapor, or by heating the plate after dipping in a 3–5% solution of phosphomolybdic acid in ethanol, or a 1% solution of vanillin in 0.1M H_2SO_4 in methanol. Flash chromatography was carried out using silica gel 60 (230–400-mesh ASTM).

Melting points were measured using a capillary melting point apparatus and are uncorrected. Optical rotations were measured on a polarimeter at ambient temperature using a 1 dm cell of 1-mL capacity. Infrared (IR) spectra were recorded with a Nicolet spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using an 80-, 300-, or 400-MHz spectrometer. Mass spectra (MS) were obtained at an ionization potential of 70 eV.

(2′*R*,3′*RAR*,5*S*)-(*E*)-3-(2,4-Dimethyl-3-hydroxy-4-hexenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (8). To a solution of triethylborane (231 mg, 2.36 mmol) in 1.5 mL of CH_2Cl_2 at 0 °C was slowly added neat trifluoromethanesulfonic acid (354 mg, 2.36 mmol). After 1 h of stirring at room temperature, 7[6] (500 mg, 2.14 mmol) was added as a solution in 3.0 mL of CH_2Cl_2 followed by the addition of ethyldiisopropylamine (333 mg, 2.58 mmol) in 0.5 mL of CH_2Cl_2. The solution was stirred at 0 °C for 30 min and cooled to −78 °C, and (*E*)-2-methyl-2-butenal (5) (200 mg, 2.38 mmol) was added as a solution in 0.5 mL of CH_2Cl_2. Stirring for 30 min at −78 °C was followed by 2 h at room temperature, at which time the reaction was quenched by pouring the solution into 10 mL of MeOH and 4 mL of an aqueous pH 7 phosphate buffer at 0 °C. Addition of 6 mL of 30% aqueous H_2O_2 to this mixture and stirring for 1 h at 0 °C was followed by extraction with CH_2Cl_2, washing of the combined organic layers with saturated aqueous NaCl, and drying over $MgSO_4$. Concentration of the dried solution under reduced pressure and column chromatography (2–5% EtOAc/CH_2Cl_2) afforded 477 mg (70%) of 8 as a viscous oil. Crystallization from Et_2O/hexane

(46) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* 1978, *34*, 2069.
(47) Krapcho, A. P.; Jahnyer, G. E., Jr. *J. Org. Chem.* 1974, *39*, 1322.
(48) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* 1985, *107*, 7105.
(49) Black, T. H.; Hall, J. A.; Sheu, R. G. *J. Org. Chem.* 1988, *53*, 2371.
(50) Thompson, Q. E. *J. Org. Chem.* 1962, *27*, 4498.

provided colorless needles: mp 86–87 °C (Et_2O/hexane), R_f 0.28 (2% EtOAc/CH_2Cl_2); $[\alpha]^{22}_D$ +35.5° (*c* 1.70, $CHCl_3$); IR (neat) 3490, 2984, 1779, 1699, 1364, 1196, 989, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m), 5.68 (1H, d, *J* = 7.2 Hz), 5.64 (1H, m, *J* = 1.3, 6.6 Hz), 4.78 (1H, m, *J* = 6.7 Hz), 4.38 (1H, m), 3.98 (1H, dq, *J* = 3.8, 7.0 Hz), 1.65 (6H, m), 1.16 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 152.6, 134.3, 133.1, 128.8, 128.7, 125.6, 120.5, 78.9, 75.5, 54.9, 40.7, 14.3, 13.04, 13.02, 10.4; MS *m/z* (rel intensity) 317 (M^+, 8), 233 (44), 134 (33), 118 (64), 57 (100). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.04; H, 7.33; N, 4.48.

(2′*R*,3′*R*,4*R*,5*S*)-(*E*)-3-(3′-Acetoxy-2′,4′-dimethyl-4-hexenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (15). A solution of 8 (71 mg, 0.22 mmol), acetic anhydride (46 mg, 0.45 mmol), Et_3N (45 mg, 0.45 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (7 mg, 0.06 mmol) in 0.5 mL of CH_2Cl_2 was stirred for 11 h at room temperature. Dilution with CH_2Cl_2 was followed by washing with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and H_2O and drying over $MgSO_4$. Concentration under reduced pressure gave a viscous oil which on trituration with 20% EtOAc–hexane afforded 78 mg (96%) of **15** as colorless needles: mp 107.5–108 °C (Et_2O/hexane), R_f 0.45 (30% EtOAc/hexane); $[\alpha]^{22}_D$ +9.0° (*c* 1.20, $CHCl_3$); IR (KBr) 2977, 1782, 1720, 1700, 1235, 1195, 957, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (3H, m), 7.32 (2H, m), 5.70 (1H, d, 7.1 Hz), 5.59 (1H, m, *J* = 6.8 Hz), 5.57 (1H, d, *J* = 5.2 Hz), 4.62 (1H, m, *J* = 6.6 Hz), 4.23 (1H, dq, *J* = 5.2, 6.9 Hz), 2.09 (3H, s), 1.68 (3H, d, *J* = 0.8 Hz), 1.64 (3H, m, *J* = 6.7 Hz), 1.13 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.8, 170.3, 153.1, 133.2, 131.5, 128.7 (×2), 125.6, 122.1, 79.0, 55.4, 40.2, 21.0, 14.4, 13.1, 12.8, 10.8; MS *m/z* (rel intensity) 359 (M^+, 0.6), 299 (54), 240 (72), 134 (65), 118 (100). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.72; H, 6.94; N, 4.02.

(2′*R*,5′*S*,4*R*,5*S*)-(*E*)-3-(2′,4′-Dimethyl-5-acetoxy-3-hexenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (16). A solution of 15 (47 mg, 0.13 mmol) and $PdCl_2(CH_3CN)_2$ (22 mg, 0.08 mmol) in 2.0 mL of THF was stirred at room temperature for 18 h. The brown solution was filtered through a short plug of silica gel and concentrated under reduced pressure, and the residue was chromatographed on silica gel (hexane–EtOAc–CH_2Cl_2, 16:3:1) to give 24.7 mg (53%) of recovered **15**, 3.7 mg (9%) of **16**, and 13 mg of a 1:1 mixture of **15** and **16**. Compound **16**: R_f 0.27 (hexane–EtOAc–CH_2Cl_2, 8:2:1); $[\alpha]^{22}_D$ −30.3° (*c* 0.37, $CHCl_3$); IR (neat) 2984, 1783, 1734, 1701, 1238, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m), 5.65 (2H, dd, *J* = 7.3 Hz), 5.26 (1H, q, *J* = 6.4 Hz), 4.75 (1H, m, *J* = 6.7 Hz), 4.68 (1H, dq, *J* = 6.9, 9.4 Hz), 2.06 (3H, s), 1.72 (3H, d, *J* = 1.3 Hz), 1.31 (3H, d, *J* = 6.5 Hz), 1.27 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 170.2, 152.6, 136.9, 133.3, 128.8, 128.7, 125.6, 125.2, 78.9, 74.6, 55.1, 36.9, 21.4, 19.1, 18.2, 14.4, 12.7; MS *m/z* (rel intensity) 299 (48), 240 (M^+ − CH_3-CH=CHPh, 100), 134 (33), 118 (57). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 67.00; H, 6.91; N, 3.92.

(2′*R*,5′*S*,4*R*,5*S*)-(*E*)-3-[2′,4′-Dimethyl-5′-(phenylsulfinyl)-3′-hexenoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (17). To a solution of 8 (215 mg, 0.68 mmol) in 3.4 mL of CH_2Cl_2 was added Et_3N (137 mg, 1.35 mmol). The solution was cooled to −78 °C and benzenesulfenyl chloride (157mg,1.07 mmol) added as a solution in 0.2 mL of CH_2Cl_2. Stirring at −78 °C for 15 min was followed by warming to room temperature. The reaction was quenched after 30 min by the addition of 3 mL of an aqueous pH 7 phosphate buffer. Extraction with CH_2Cl_2, drying of the organic phase over $MgSO_4$, and concentration under reduced pressure gave a clear viscous oil. Column chromatography (10% EtOAc/CH_2Cl_2) afforded 220 mg (76%) of **17** as an inseparable 9:5:2:1 mixture of diastereomers: R_f 0.17 (5% EtOAc/CH_2Cl_2); IR (neat) 2977, 1781, 1701, 1137, 1041 cm^{-1}; major diastereomer ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.28 (5H, m), 5.67 (1H, d, *J* = 6.7 Hz), 5.28 (1H, d, *J* = 9.6 Hz), 4.72 (1H, m, *J* = 6.7 Hz), 4.61 (1H, m, *J* = 2.5, 7.0 Hz), 3.38 (1H, q, *J* = 7.0 Hz), 1.75 (3H, d, *J* = 1.3 Hz), 1.44 (3H, d, *J* = 7.0 Hz), 1.32 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.8, 152.5, 143.1, 134.0, 133.1, 131.0 , 130.1, 129.7, 128.8, 128.7, 125.5, 125.1, 78.8, 70.7, 55.0, 37.1, 17.9, 15.4, 14.4, 12.1; MS *m/z* (rel intensity) 300 (M^+ − PhSO, 62), 218 (43), 125 (65), 109 (100).

(2*S*,3*R*)-(*E*)-2,4-Dimethyl-3-hydroxy-4-hexen-1-ol (20). To a solution of 8 (125 mg, 0.39 mmol) in 4.0 mL of THF at 0 °C was added anhydrous LiI (116 mg, 0.87 mmol) followed by $NaBH_4$ (33 mg, 0.87 mmol). Stirring for 1 h at 0 °C was followed by quenching with H_2O and addition of NaCl to give two layers. Extraction of the aqueous phase with EtOAc, drying of the combined organic layers over $MgSO_4$, concentration under reduced pressure, and column chromatography (30–50% EtOAc–CH_2Cl_2) of the residual oil afforded 38 mg (67%) of **20** as a colorless oil: R_f 0.26 (EtOAc–CH_2Cl_2, 1:1); $[\alpha]^{22}_D$ +15.0° (*c* 1.82, $CHCl_3$); IR (neat) 3363, 2967, 1422, 1032, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, m, *J* = 1.2, 6.7 Hz), 4.09 (1H, d, *J* = 3.7 Hz), 3.26 (2H, d, *J* = 4.3 Hz), 2.31 (1H, bs), 2.16 (1H, bs), 1.88 (1H, m, *J* = 1.9, 5.2 Hz), 1.64 (3H, m, *J* = 1.1, 6.7 Hz), 1.60 (3H, s), 0.91 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 119.8, 78.9, 66.6, 37.7, 12.9, 12.7, 10.8; MS *m/z* (rel intensity) 144 (M^+, 7), 126 (14), 111 (15), 85 (100). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.51; H, 10.99.

(4*R*,5*R*)-(*E*)-3,5-Dimethyl-6-[(1,1-dimethylethyl)dimethylsiloxy]-2-hexen-4-ol (21). A solution of **20** (94 mg, 0.65 mmol), *tert*-butyldimethylsilyl chloride (108 mg, 0.72 mmol), Et_3N (79 mg, 0.78 mmol), and DMAP (3 mg, 0.03 mmol) in 6.5 mL of CH_2Cl_2 was stirred overnight (18 h) at room temperature. The solution was washed with 10% aqueous NH_4Cl and saturated aqueous NaCl and was dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (15% EtOAc–hexane) of the residual oil afforded 99 mg (59%) of **20** as a colorless oil: R_f 0.70 (10% EtOAc–CH_2Cl_2); $[\alpha]^{22}_D$ +9.9° (*c* 1.41, $CHCl_3$); IR (neat) 3436, 2957, 1254, 1099, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, m, *J* = 1.3, 6.8 Hz), 4.13 (1H, bs), 3.64 (2H, dq, *J* = 5.4, 10.0 Hz), 2.74 (1H, d, *J* = 2.9 Hz), 1.81 (1H, m, *J* = 2.6, 7.0 Hz), 1.63 (3H, m, *J* = 1.1, 6.8 Hz), 1.57 (3H, s), 0.90 (9H, s), 0.87 (3H, d, *J* = 6.9 Hz), 0.06 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.9, 119.3, 78.6, 67.5, 37.6, 25.8, 18.2, 13.0, 10.5, −5.6; MS *m/z* (rel intensity) 258 (M^+, 5), 201 (31), 109 (77), 75-(100).

(2*S*,5*R*)-(*E*)-6-[(1,1-Dimethylethyl)dimethylsiloxy]-2-(phenylsulfinyl)-3,5-dimethyl-3-hexene (22). To a solution of **21** (32 mg, 0.12 mmol) and Et_3N (63 mg, 0.62 mmol) in 1 mL of CH_2Cl_2 at −78 °C was added benzenesulfenyl chloride (27 mg, 0.19 mmol) as a solution in 0.05 mL of CH_2Cl_2. The solution was warmed to room temperature after 15 min and the reaction was quenched by the addition of 1 mL of an aqueous pH 7 phosphate buffer. Extraction with CH_2Cl_2 and drying of the organic layers over $MgSO_4$ was followed by concentration under reduced pressure to a viscous oil. Column chromatography (10% EtOAc/CH_2Cl_2) afforded 28 mg (62%) of **22** as an inseparable 9:6:2:1 mixture of diastereomers: R_f 0.13 (2% EtOAc/CH_2Cl_2); IR (neat) 2956, 1254, 1087, 1046, 837, 776 cm^{-1}; major diastereomer ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.44 (5H, m), 4.87 (1H, d, *J* = 9.5 Hz), 3.32 (2H, m), 3.17 (1H, m), 2.47 (1H, m), 1.70 (3H, d, J = 1.4 Hz), 1.45 (3H, d, *J* = 7.0 Hz), 0.87 (9H, s), 0.80 (3H, d, *J* = 6.7 Hz), 0.02 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.3, 135.1, 130.9, 130.4, 128.6, 125.5 , 124.8, 71.2, 67.5, 35.5, 25.8, 18.3, 16.7, 12.6, −5.4 (×2); MS *m/z* (rel intensity) 241 (M^+ − PhSO, 42), 109 (26), 89 (100), 73 (71).

(2′*R*,4*S*)-(*E*)-3-(2,4-Dimethyl-4-hexenoyl)-4-isopropyl-1,3-oxazolidin-2-one (28). A solution of LDA was prepared at 0 °C by the addition of *n*-BuLi (4.3 mL, 6.9 mmol; 1.6 M in hexanes) to a solution of diisopropylamine (0.70 g, 6.9 mmol) in 10.0 mL of THF. Cooling to −78 °C was followed by the addition of **27**[6] (1.20 g, 6.47 mmol) as a solution in 2.0 mL of THF. After 30 min **26** (2.80 g, 18.8 mmol) was added as a solution in 2.0 mL of THF. Stirring for 15 min at −78 °C was followed by stirring for an additional 2 h at −10 °C. The reaction was quenched with 10% aqueous NH_4Cl, the solution was extracted with Et_2O, and the combined extracts were washed with saturated aqueous NaCl before being dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (25% EtOAc–hexane) of the residual oil afforded 1.27 g (80%) of **28** as a clear colorless oil: R_f 0.40 (30% EtOAc–hexane); $[\alpha]^{22}_D$ +64.8° (*c* 2.11, CH_2Cl_2); IR (neat) 2968, 1781, 1702, 1388, 1238, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, m, *J* = 1.3, 6.4 Hz), 4.46 (1H, m), 4.22 (2H, m), 4.03 (1H, dd, *J* = 7.1 Hz), 2.50 (1H, dd, *J* = 6.9, 13.3

Hz), 2.29 (1H, m), 1.98 (1H, dd, J = 7.6, 13.3 Hz), 1.64 (3H, s), 1.55 (3H, d, J = 6.6 Hz), 1.08 (3H, d, J = 6.7 (Hz), 0.90 (3H, d, J = 7.3 Hz), 0.84 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.8, 132.9, 121.2, 63.0, 58.4, 44.2, 35.7, 28.4, 17.9, 16.3, 15.3, 14.5, 13.4; MS m/z (rel intensity) 253 (M^+, 36), 124 (100), 109 (43), 96 (97), 81 (55). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.35; H, 8.98; N, 5.60.

(2*R*)-(*E*)-2,4-Dimethyl-4-hexen-1-ol (29). To a solution of **28** (1.00 g, 3.95 mmol) in 22 mL of THF at 0 °C was added $LiAlH_4$ (0.45 g, 11.8 mmol), and the mixture was stirred at 0 °C for 30 min. This was followed by careful addition of 1.0 mL of H_2O at 0 °C, warming to room temperature, and drying over $MgSO_4$. Filtration through a pad of Celite, concentration under reduced pressure, and column chromatography using 5–10% EtOAc–CH_2Cl_2 afforded 398 mg (74%) of **29** as a colorless oil: R_f 0.45 (10% EtOAc–CH_2Cl_2); $[\alpha]^{22}_D$ +4.8° (c 2.64, CH_2Cl_2); IR (neat) 3345, 2957, 1668, 1453, 1038, 806 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, dd, J = 6.0, 6.6 Hz), 3.44 (2H, m), 2.06 (1H, m), 1.82 (2H, m), 1.58 (6H, m), 0.86 (3H, d, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 120.2, 68.5, 44.2, 33.7, 16.7, 15.6, 13.3; MS m/z (rel intensity) 128 (M^+, 43), 97 (45), 95 (64), 81 (26), 70 (63), 58 (100). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 75.11; H, 12.63.

The enantiomeric excess of **28** was assessed by ^{1}H and ^{13}C NMR analysis of the α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA ester)[17] prepared by stirring **28** in pyridine with an excess of the (*S*)-MTPA acid chloride (**31**) at room temperature. Aqueous workup and purification by column chromatography afforded **30** as a colorless oil: $[\alpha]^{22}_D$ +36.1° (c 2.38, CH_2Cl_2); IR (neat) 2964, 1749, 1273, 1170, 1024, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, m), 7.41 (3H, m), 5.18 (1H, m, J = 5.7 Hz), 4.24 (1H, dd, J = 4.5, 10.6 Hz), 4.02 (1H, dd, J = 6.0, 10.6 Hz), 3.55 (3H, s), 2.02 (2H, m), 1.83 (1H, m), 1.56 (6H, d, J = 6.0 Hz), 0.86 (3H, d, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 133.0, 128.6, 128.4, 127.4, 124.4 (q, CF_3), 121.9, 121.0, 70.9, 55.4, 43.7, 30.5, 16.7, 15.4, 13.3.

(2*R*)-(*E*)-2,4-Dimethyl-4-hexenal (42). To a solution of $(COCl)_2$ (236 mg, 1.86 mmol) in 2.0 mL of CH_2Cl_2 at −78 °C was added a solution of DMSO (290 mg, 3.71 mmol) in 2.0 mL of CH_2Cl_2. After 5 min **29** (119 mg, 0.93 mmol) was added as a solution in 3.0 mL of CH_2Cl_2. After an additional 10 min Et_3N (564 mg, 5.57 mmol) was added in 2.0 mL of CH_2Cl_2. Stirring for 20 min at −78 °C was followed by stirring at 0 °C for 30 min. The reaction was quenched by the addition of an aqueous pH 7 phosphate buffer followed by warming to room temperature. The mixture was filtered and the solid was washed with pentane. The filtrate was washed with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (20% Et_2O–pentane) of the residual oil afforded 107 mg (91%) of **42** as a pale yellow oil: R_f 0.46 (20% EtOAc–hexane); $[\alpha]^{22}_D$ −9.5° (c 5.61, $CHCl_3$); IR (neat) 2975, 2716, 1729, 1455, 1383 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (1H, d, J = 2.2 Hz), 5.26 (1H, m), 2.50 (1H, m), 2.43 (1H, dd), 1.98 (1H, m, J = 2.2), 1.58 (6H, m), 1.03 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 132.2, 121.5, 44.4, 40.8, 15.5, 13.4, 13.2; MS m/z (rel intensity) 126 (M^+, 7), 111 (22), 84 (47), 69 (100).

(2*S*,3*S*,4*R*)-(*E*)-2′,6′-Dimethylphenyl 3-Hydroxy-2,4,6-trimethyl-6-octenoate (44) and (2*R*,3*R*,4*R*)-(*E*)-2′,6′-Dimethylphenyl 3-Hydroxy-2,4,6-trimethyl-6-octenoate (45). A solution of LDA was prepared at 0 °C by the addition of n-BuLi (0.92 mL, 1.47 mmol) to a solution of diisopropylamine (148 mg, 1.47 mmol), in 4.0 mL of THF. The solution was cooled to −78 °C and 2,6-dimethylphenyl propionate (**43**)[25] (250 mg, 1.40 mmol) added as a solution in 1.0 mL of THF. After 1 h a slurry of anhydrous $CeCl_3$ (618 mg, 1.66 mmol) in 3.0 mL of THF was added to the enolate, and the resulting mixture was stirred for 30 min at −78 °C. A solution of **42** (161 mg, 1.27 mmol) in 1.0 mL of THF was added and after 45 min the reaction was quenched with 2 mL of 10% aqueous NH_4Cl. Extraction with Et_2O, drying of the organic phase ($MgSO_4$), concentration under reduced pressure, and column chromatography of the residue using CH_2Cl_2 afforded 255 mg (66%) of the aldol product as a 1.5:1.0 mixture of diastereomers. Separation of the diastereomers was achieved by HPLC using two 7.8mm × 30 cm μ-Porosil columns in tandem and 5% EtOAc–hexane as eluant (flow rate 3.4 mL/min, chart speed 5 mm/min, UV detection at 295 nm). Major diastereomer (**44**): t_R = 18.0 min; $[\alpha]^{22}_D$ −14.6° (c 2.15, $CHCl_3$); IR (neat) 3529, 1741, 1142, 769 cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (3H, m), 5.28 (1H, m, J = 5.3 Hz), 3.75 (1H, dd, J = 2.9, 9.0 Hz), 2.94 (1H, dq, J = 1.7, 7.0 Hz), 2.17 (7H, m), 2.00 (1H, dd, J = 7.8, 12.9 Hz), 1.91 (1H, m, J = 2.8, 6.9 Hz), 1.59 (6H, m), 1.34 (3H, d, J = 7.2 Hz), 0.88 (3H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 148.0, 133.6, 130.0, 128.6, 125.8, 120.1, 74.9, 44.4, 43.7, 32.0, 16.4, 15.4, 14.5, 13.3, 12.1; MS m/z 304 (M^+, 3), 286 ($M^+ - H_2O$, 1.4), 234 (18), 178 (9), 127 (38), 122 (100), 69 (90). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.00; H, 9.33.

Minor diastereomer (**45**): t_R = 18.7 min; $[\alpha]^{22}_D$ −6.6° (c 1.20, $CHCl_3$); IR (neat) 3535, 2973, 2928, 1741, 1456, 1151, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (3H, m), 5.25 (1H, m, J = 5.5 Hz), 3.52 (1H, t, J = 6.0 Hz), 3.07 (1H, dq, J = 1.4, 7.2 Hz), 2.43 (1H, d, J = 13.1 Hz), 2.17 (6H, s), 1.18 (1H, m, J = 3.6, 6.8, 10.5 Hz), 1.77 (1H, dd, J = 10.5, 13.1 Hz), 1.58 (6H, m), 1.47 (3H, d, J = 7.2 Hz), 0.93 (3H, d, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 147.9, 134.0, 130.0, 128.7, 126.0, 120.6, 78.2, 42.3, 41.5, 34.3, 16.4 (×2), 15.5, 15.4, 13.4.

(5*R*)-(*E*)-3,5-Dimethyl-6-[(1,1-dimethylethyl)dimethylsiloxy]-2-hexene (37). To a solution of **28** (200 mg, 1.56 mmol) and 2,6-lutidine (334 mg, 3.12 mmol) in 6.2 mL of CH_2Cl_2 at 0 °C was added *tert*-butyldimethylsilyl triflate (619 mg, 2.34 mmol). The solution was warmed to room temperature and after 20 min was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl and dried ($MgSO_4$) before being concentrated under reduced pressure. Column chromatography (2% Et_2O–hexane) of the residual oil afforded 366 mg (97%) of **37** as a colorless oil: R_f 0.64 (10% EtOAc–hexane); $[\alpha]^{22}_D$ −1.1° (c 3.58, $CHCl_3$); IR (neat) 2960, 2887, 1670, 1470, 1254, 1090, 837, 776, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (1H, m, J = 5.7 Hz), 3.38 (2H, m, J = 5.4, 10.6 Hz), 2.10 (1H, dd, J = 5.2, 12.4 Hz), 1.73 (1H, m), 1.65 (1H, dd, J = 8.7, 12.4 Hz), 1.56 (6H, m), 0.89 (9H, s), 0.80 (3H, d, J = 6.5 Hz), 0.03 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 134.3, 119.8, 68.2, 43.8, 33.8, 25.7, 18.3, 16.5, 15.5, 13.3, −3.0; MS m/z (rel intensity) 185 (M^+ − t-Bu′, 0.2), 109 (65), 75 (100), 69 (32).

Methyl (2*S*)-3-(Benzyloxy)-2-methylpropionate (55). To a stirred solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (18.8 g, 0.158 mol) in 370 mL of cyclohexane and 190 mL of CH_2Cl_2 (2:1 v/v) was added benzyl 2,2,2-trichloroacetimidate (50.0 g, 0.198 mol) followed by trifloromethanesulfonic acid (2.40 g, 0.016 mol). After 24 h the mixture was filtered, and the solid was washed with CH_2Cl_2. The combined filtrates were washed with H_2O, saturated aqueous $NaHCO_3$, H_2O, and finally saturated NaCl before being dried over $MgSO_4$. Column chromatography (15% EtOAc–hexane) afforded 27.4 g (83%) of **55** as a clear colorless oil: R_f 0.38 (20% EtOAc–hexane) $[\alpha]^{22}_D$ +11.3° (c 3.80, $CHCl_3$) [lit.[32] $[\alpha]^{22}_D$ +9.7° (c 3.40, $CHCl_3$)]; IR (neat) 2979, 1742, 1455, 1201, 1097, 739, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (5H, m), 4.52 (2H, s), 3.69 (3H, s), 3.65 (1H, dd, J = 1.7, 9.3 Hz), 3.49 (1H, dd, J = 4.9, 9.3 Hz), 2.79 (1H, m, J = 7.1 Hz), 1.18 (3H, d, J = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3, 138.1, 128.3, 127.6, 127.5, 73.0, 71.9, 51.7, 40.1, 13.9; MS m/z (rel intensity) 208 (M^+, 12), 122 (12), 107 (60), 91 (100), 77 (35).

(2*R*)-3-(Benzyloxy)-2-methyl-1-propanol (56). To a suspension of $LiAlH_4$ (5.0 g, 0.132 mol) in 130 mL of Et_2O at 0 °C was added a solution of **55** (27.4 g, 0.132 mol) in 130 mL of Et_2O dropwise with stirring. The mixture was warmed to room temperature and after 30 min the excess $LiAlH_4$ was quenched by the careful addition of 5.0 mL of H_2O, 5.0 mL of 15% aqueous NaOH, and 15 mL of H_2O. After 15 min anhydrous $MgSO_4$ was added and stirring was continued for 15 min. The mixture was filtered, the solid washed with Et_2O, and the combined filtrates were concentrated under reduced pressure to give 23.9 g (98%) of **56** as a clear yellow oil of sufficient purity for the subsequent experiment. An analytical sample was obtained by column chromatography (30% EtOAc–hexane) as a clear colorless oil: R_f 0.15 (20% EtOAc/hexane); $[\alpha]^{22}_D$ +16.8° (c 4.31, $CHCl_3$) [lit.[51] $[\alpha]^{22}_D$ +16.4° (c 4.50, $CHCl_3$)]; IR (neat) 3396, 3030, 2873, 1095,

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737, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (5H, m), 4.52 (2H, s), 3.64–3.53 (3H, m, J = 4.7, 9.1 Hz), 3.42 (1H, dd, J = 8.2, 9.1 Hz), 2.62 (1H, dd, J = 4.7, 6.7 Hz), 2.03 (1H, m, J = 7.0 Hz), 0.88 (3H, d, J = 7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 127.6, 75.4, 73.3, 67.8, 35.5, 13.4; MS m/z (rel intensity) 180 (M^+, 100), 165 (25), 107 (22), 91 (51). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.92.

(2*S*)-3-(Benzyloxy)-2-methyl-1-bromopropane (57). To a solution of **56** (23.7 g, 0.131 mol) in 260 mL of CH_2Cl_2 was added PPh_3 (36.2 g, 0.138 mol). The solution was cooled to 0 °C and *N*-bromosuccinimide (24.6 g, 0.138 mol) added in four 6.15-g portions over 10 min. A vigorous effervescence was observed with each addition. The clear yellow solution was then warmed to room temperature and stirred overnight. After 20 h at room temperature an additional 0.1 equiv each of PPh_3 (3.4 g) and NBS (2.3 g) were added and the solution was stirred for 3 h. The solution was washed with 5% aqueous $NaHCO_3$ and the organic layer concentrated under reduced pressure to a dark blue oil. Treatment of the oil with 150 mL of hexane and 150 mL of H_2O gave a mixture containing a blue solid. This mixture was stirred at room temperature for 20 min and filtered, and the solid was washed with hexane. The organic layer was separated from the aqueous layer and dried over $MgSO_4$. Concentration of the dry solution under reduced pressure and column chromatography of the residual oil (10% EtOAc–hexane) afforded 27.7 g (86%) of **57** as a clear colorless oil: R_f 0.53 (30% EtOAc–hexane); $[\alpha]^{22}_D$ +12.7° (*c* 5.44, EtOH) [lit.[33] $[\alpha]^{22}_D$ +13.0° (*c* 1, EtOH)]; IR (neat) 3030, 2965, 1454, 1099, 736, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m), 4.51 (2H, s), 3.50 (2H, m, J = 1.2, 5.1 Hz), 3.40 (2H, m, J = 2.1, 5.6 Hz), 2.13 (1H, m, J = 1.2, 5.6, 6.9 Hz), 1.02 (3H, d, J = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 127.5, 73.1, 72.7, 38.2, 35.6, 15.8; MS m/z (rel intensity) 243 (M^+, 0.7), 180 (100) 165 (21), 91 (60).

(2*R*)-1-(Benzyloxy)-2-methylbutane (58). A flask charged with 4.79 g (53.5 mmol) of CuCN was gently heated with a flame under argon to drive off residual moisture. After cooling to room temperature under argon, the solid was suspended in 100 mL of THF and the mixture was cooled to −78 °C. To this suspension was added via cannula MeLi (1.4 M solution in Et_2O) (76.4 mL, 106.9 mmol) from a 100-mL graduated cylinder using a positive pressure of argon. After the addition was completed, the opaque mixture was warmed to 0 °C and stirred for 5 min. The slightly opaque solution was then cooled to −78 °C and **57** (10.0 g, 41.6 mmol) added via cannula as a solution in 50 mL of THF. The resulting yellow solution was warmed to −20 °C, stirred for 4 h, and then left to come to room temperature overnight. After a total time of 20 h, the reaction was quenched by the addition of 50 mL of 10% NH_4OH in saturated aqueous NH_4Cl (CAUTION: addition of the first few milliliters was accompanied by a vigorous reaction) followed by 50 mL of H_2O. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography using 2% EtOAc–hexane afforded 6.43 g (87%) of **58** as a clear colorless oil: R_f 0.38 (5% EtOAc–hexane); $[\alpha]^{22}_D$ −4.5° (*c* 3.23; $CHCl_3$); IR (neat) 2961, 1455, 1099, 734, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (5H, m), 4.50 (2H, s), 3.29 (2H, ddd, J = 5.1, 6.3, 15.5 Hz), 1.69 (1H, m, J = 1.2, 6.6 Hz), 1.49 (1H, m, J = 5.4, 7.5 Hz), 1.15 (1H, m, J = 5.4, 7.5 Hz), 0.91 (3H, d, J = 6.7 Hz), 0.88 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 75.7, 72.9, 35.0, 26.3, 16.6, 11.3; MS m/z (rel intensity) 178 (M^+, 1.3), 91 (100). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.30.

(*R*)-2-Methyl-1-butanol 4-Methylbenzenesulfonate (59). To a solution of **58** (12.2 g, 68.4 mmol) in 70 mL of THF were added 4 drops of 10% HCl and 610 mg of 10% Pd–C. The mixture was stirred for 3 h under H_2 (1 atm) and then filtered through a plug of $MgSO_4$ using pentane as a wash. The resulting solution was concentrated by fractional distillation using a 25-cm Vigreaux column and a gradual increase in the oil bath temperature to 115 °C. The resulting solution, a 1:1:1 mixture of (*R*)-2-methyl-1-butanol, toluene, and THF, was used directly in the next experiment.

The alcohol solution was combined with 100 mL of pyridine and cooled to 0 °C. To this solution was added *p*-toluenesulfonyl chloride (16.9 g, 88.4 mmol) in small portions. The resulting solution was stirred at 0 °C for 10 min before being warmed to room temperature and stirred for 15 h. The reaction was diluted with one volume of Et_2O and the resulting mixture was filtered, the solid being washed with Et_2O. The filtrate was washed with 0.1 M aqueous HCl, H_2O, and finally saturated aqueous NaCl before being dried over $MgSO_4$. The dry solution was concentrated under reduced pressure and the residual oil chromatographed using 15% EtOAc–hexane to afford 14.4 g (87%) of **59** as a colorless oil: R_f 0.43 (20% EtOAc–hexane); $[\alpha]^{22}_D$ −4.7° (*c* 1.06, $CHCl_3$) [lit.[52] $[\alpha]^{22}_D$ −3.4° (neat) ≥ 96% ee); IR (neat) 2966, 1359, 1176, 963, 843, 665, 555 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, m, J = 8.3 Hz); 7.35 (2H, m, J = 7.8 Hz), 3.84 (2H, m, J = 5.7, 9.3 Hz), 2.46 (3H, s), 1.70 (1H, m, J = 6.5 Hz), 1.38 (1H, m, J = 7.5 Hz), 1.14 (1H, m, J = 7.5 Hz), 0.88 (3H, d, J = 6.7 Hz), 0.83 (3H, t, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.6, 133.0, 129.7, 127.8, 74.8, 34.2, 25.3, 21.6, 15.9, 10.9; MS m/z (rel intensity) 242 (M^+, 0.9), 155 (15), 91 (48), 70 (100).

(2*R*)-2-Methyl-1-iodobutane (53). A solution of **59** (14.3 g, 59.0 mmol) and NaI (18.6 g, 123.9 mmol; dried 24 h at 70 °C at <1 mmHg) in 295 mL of acetone was heated at reflux for 5 h. Upon cooling to room temperature, the mixture was diluted with 300 mL of pentane and filtered, and the solid was washed with 100 mL of pentane. The combined organic layers were washed with H_2O (1 L) and saturated aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. The solution was concentrated at atmospheric pressure by distillation using a 25-cm Vigreaux column and a maximum bath temperature of 120 °C. The still pot residue was further distilled at reduced pressure to give 8.4 g (72%) of **53** as a pale yellow oil: bp 105 °C/130 mm [lit.[31] bp 59–60 °C/38mm]; $[\alpha]^{22}_D$ −6.0° (*c* 8.55, $CHCl_3$) [lit.[31] $[\alpha]^{22}_D$ −5.6° (neat)]; IR (neat) 2966, 1456, 1193, 601, 580, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (2H, m, J = 4.5, 9.5, 14.1 Hz), 1.39 (2H, m), 1.26 (1H, m, J = 7.5 Hz), 0.97 (3H, d, J = 6.4 Hz), 0.89 (3H, t, J = 7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 36.3, 29.1, 20.1, 17.5, 11.3; MS m/z (rel intensity) 198 (M^+, 7), 70 (100).

(2*S*,2′*R*,4′*R*)-2-(Hydroxymethyl)-1-(2′,4′-dimethylhexanoyl)pyrrolidine (60). A solution of LDA was prepared in 5.0 mL of THF at 0 °C from diisopropylamine (1.42 g, 14.0 mmol) and *n*-BuLi (8.40 mL, 13.4 mmol; 1.6 M in hexanes). After 10 min a solution of **48**[30] (1.00 g, 6.36 mmol) in 8.0 mL of THF was added and the resulting solution was warmed to room temperature. Stirring for 1 h gave a heavy white precipitate. To this mixture was added hexamethylphosphoramide (HMPA) (2.20 mL, 12.7 mmol). The resulting clear yellow solution was cooled to −78 °C and a solution of **53** (1.38 g, 6.97 mmol) in 3.0 mL of THF was added. The flask was fitted with a second septum and placed into a precooled jar containing Drierite and allowed to stand at −78 °C (freezer) for 3 days. The reaction was quenched at −78 °C by the addition of a saturated aqueous solution of NH_4Cl. Upon reaching room temperature, the mixture was extracted with Et_2O, and the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was chromatographed using MeOH–EtOAc–hexane (1:3:6) to give 706 mg (49%) of **60**: R_f 0.27 (MeOH–EtOAc–hexane, 1:3:6); IR (neat) 3396, 2962, 1618, 1464, 1435, 1055, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (1H, dd, J = 2.4, 7.6 Hz), 4.26 (1H, m), 3.70–3.47 (4H, m), 2.67 (1H, m, J = 6.4 Hz), 2.04 (1H, m), 1.91 (2H, m), 1.73 (1H, m), 1.60 (1H, m), 1.36 (2H, m), 1.14 (3H, d, J = 6.8 Hz), 1.09 (2H, m), 0.87 (3H, t, J = 7.2 Hz), 0.86 (3H, d, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.5, 67.8, 60.9, 47.8, 40.7, 35.6, 32.1, 29.4, 28.2, 24.4, 19.4, 18.2, 11.2; MS m/z (rel intensity) 227 (M^+, 2), 196 (8), 70 (100); HRMS calcd for $C_{13}H_{25}NO_2$ 227.1885, found 227.1885.

(2*R*,4*R*)-2,4-Dimethylhexanoic Acid (62). A suspension of **60** (632 mg, 2.78 mmol) in 16.5 mL of 1.0 M aqueous HCl was heated to reflux (bath temperature 110 °C) for 2 h. The mixture was cooled to room temperature and extracted with Et_2O, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 379 mg (95%) of virtually pure **62** as a pale yellow oil. Distillation (125 °C/20 mm) afforded **62** as a colorless oil: IR (neat) 3475–2353 (br s), 2986, 1708, 1465, 1241, 942 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (1H, m, J =

(52) Sonnet, P. E.; Carney, R. L.; Henrick, C. *J. Chem. Ecol.* **1985**, *11*, 1371.

6.1, 7.1 Hz), 1.74 (1H, m, J = 5.2, 9.0, 13.7 Hz), 1.36 (2H, m), 1.18 (3H, d, J = 7.1 Hz), 1.15 (2H, m), 0.89 (3H, d, J = 6.5 Hz), 0.87 (3H, t, J = 7.3Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.8, 40.8, 37.3, 32.2, 29.4, 18.9, 17.8, 11.1; MS m/z (rel intensity) 145 (M^+, 7), 127 (1), 74 (100), 71 (80). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.32; H, 11.26.

An optically pure sample of **62** was obtained via recrystallization of its cinchonidine salt. Thus, a mixture of **62** (56.0 mg, 0.39 mmol) and cinchonidine (114.0 mg, 0.39 mmol) was dissolved with heating in 50% aqueous acetone. Standing at 0 °C afforded 93.6 mg of a crystalline solid. Recrystallization of the salt (mp 78–82 °C) to a constant specific rotation $[\alpha]^{22}_D$ −86.8° (c 1.12, $CHCl_3$) was followed by decomposition with 2 M aqueous HCl and extraction with Et_2O. Concentration of the dried solution ($MgSO_4$) under reduced pressure afforded 31.5 mg (56%) of optically pure **62** as a colorless oil: $[\alpha]^{22}_D$ −30.6° (c 3.01, $CHCl_3$).

(2*R*,4*R*)-2,4-Dimethylhexan-1-ol (64). A solution of **62** (3.40 g, 23.6 mmol) in 50 mL of Et_2O was treated with an excess of CH_2N_2 at room temperature. The solution was concentrated under reduced pressure to half the original volume and added dropwise to a slurry of $LiAlH_4$ (0.94 g, 23.6 mmol) in 50 mL of Et_2O at 0 °C. The reaction was quenched after 1.5 h by the careful addition of 0.95 mL of H_2O at 0 °C, followed by 0.95 mL of 15% aqueous NaOH at room temperature, and finally 3 mL of H_2O. The resulting mixture was stirred with $MgSO_4$, filtered, and concentrated to an oil. Column chromatography using 15% Et_2O–pentane afforded 2.43 g (79%) of **64** as a colorless oil: R_f 0.28 (20% EtOAc–hexane); $[\alpha]^{22}_D$ +3.7° (c 1.67, $CHCl_3$); IR (neat) 3334, 2961, 1462, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, m, J = 5.5, 10.4 Hz), 3.39 (1H, m, J = 5.5, 10.4 Hz), 1.72 (1H, m, J = 1.5, 6.7 Hz), 1.62–1.27 (4H, m), 1.07 (1H, m, J = 1.2 Hz) 0.98–0.83 (10H, m); ^{13}C NMR (75.5 MH, $CDCl_3$) δ 68.4, 40.5, 33.1, 31.5, 28.9, 19.8, 17.3, 11.1; MS m/z 112 (M^+ − OH, 1.1), 83 (69), 70 (100); HRMS calcd for C_8H_{17} (M^+ − OH) 113.1330, found 113.1330. Anal. Calcd for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.84; H, 13.88.

(2*R*,4*R*)-2,4-Dimethylhexanal (4). To a solution of $(COCl)_2$ (0.974 g, 7.68 mmol) in 5.0 mL of CH_2Cl_2 at −78 °C was added a solution of DMSO (1.20 g, 15.4 mmol) in 5.0 mL of CH_2Cl_2. Stirring for 5 min was followed by the addition of **64** (500 mg, 3.84 mmol) as a solution in 5.0 mL of CH_2Cl_2. After 10 min Et_3N (2.33 g, 23.0 mmol) was added as a solution in 5.0 mL of CH_2Cl_2. Stirring for 20 min was followed by warming to 0 °C. After 30 min at 0 °C, the mixture was diluted with pentane and filtered, and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O–pentane) afforded 484 mg (98%) of **4** as a pale yellow oil: R_f 0.49 (10% EtOAc–hexane); IR (neat) 2964, 2705, 1728, 1461, 1379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, d, J = 2.5 Hz), 2.43 (1H, m, J = 2.5, 6.8 Hz), 1.72 (1H, m), 1.39 (2H, m) 1.18–1.07 (2H, m), 1.08 (3H, d, J = 6.8 Hz), 0.89 (3H, d, J = 7.0Hz), 0.88 (3H, t, J = 7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.5, 44.1, 37.8, 31.9, 29.1, 19.2, 14.1, 11.1. (2,4-Dinitrophenyl)hydrazone: mp 112–113°C (EtOH) [lit.[2] mp 96–96.5 °C (EtOH); $[\alpha]^{22}_D$ −37.6° (c 0.25, $CHCl_3$) [lit.[2] $[\alpha]^{22}_D$ −16.1° (c 0.70. $CHCl_3$)]; MS m/z (rel intensity) 308 (M^+, 7), 238 (8), 220 (22), 203 (44), 117 (30), 69 (100). Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.72; H, 6.38; N, 17.97.

(3*R*,4*S*,5*R*,7*R*)-3,5,7-Trimethyl-1-nonen-4-ol (65). A suspension of **67**[39] (1.01 g, 6.00 mmol) in a solution of (−)-diisopropyl tartrate (1.41 g, 6.00 mmol) and 7.5 mL of Et_2O was stirred rapidly at room temperature while 7.5 mL of saturated aqueous NaCl was added. After 5 min the layers were separated, and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered under argon, and concentrated under reduced pressure to give **68** as a clear viscous oil. This material was used without further purification in the next step.

A solution of **68** in 25.0 mL of toluene was stirred with 900 mg of powdered 4-Å molecular sieves at −78 °C and **4** (481 mg, 3.74 mmol) was added as a solution in 6.0 mL of toluene. After the solution was stirred for 4 h at −78 °C, the reaction was quenched by the addition of 15 mL of 2 N aqueous NaOH. The resulting mixture was warmed to 0 °C and stirred for 20 min before being filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the Et_2O was removed under reduced pressure. The toluene solution was placed on a short column of silica gel packed in hexane. Elution with hexane removed the toluene and further elution with 5% EtOAc–hexane afforded 491 g (71%) of **65** as a colorless oil. An analytical sample of **65** was obtained by preparative gas chromatography (20 m 4% Carbowax column, He carrier gas and a flow rate of 75 mL/min, chart speed 2 cm/min) under isothermal conditions (120 °C): t_R = 6.4 min; R_f 0.32 (10% EtOAc–hexane); $[\alpha]^{22}_D$ −4.31° (c 1.02, $CHCl_3$); IR (neat) 3481, 3077, 2963, 1639, 997, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, m, J = 8.4, 10.5, 16.3 Hz), 5.13 (2H, m, J = 2.0, 10.5, 16.3 Hz), 3.18 (1H, m, J = 3.2, 6.7 Hz), 2.28 (1H, m, J = 8.1 Hz), 1.74 (1H, m, J = 3.4, 6.9 Hz), 1.49 (1H, d, J = 3.4 Hz), 1.46–1.34 (3H, m), 1.13–1.00 (2H, m), 0.98 (3H, d, J = 6.6 Hz), 0.83 (3H, t, J = 7.4 Hz), 0.86 (6H, overlapping d, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.7, 116.3, 76.3, 42.4, 41.4, 31.4, 31.3, 29.2, 19.6, 16.6, 13.1, 11.2; MS m/z (rel intensity) 184 (M^+, 2), 167 (14), 111 (100), 97 (89), 69 (65). Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.03; H, 13.30.

(3*R*,4*S*,5*R*,7*R*)-4-[(1,1-Dimethylethyl)dimethylsiloxy]-3,5,7-trimethylnon-1-ene (69). To a solution of **65** (934 mg, 5.06 mmol) in CH_2Cl_2 containing 2,6-lutidine (1.09 g, 10.12 mmol) at 0 °C was added (1.47 g, 5.57 mmol) *tert*-butyldimethylsilyl triflate. The solution was warmed to room temperature and stirred for 4.5 h before the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. Separation of the layers, extraction of the aqueous layer with CH_2Cl_2, drying ($MgSO_4$), and concentration under reduced pressure afforded a viscous oil. Column chromatography (2% Et_2O–hexane) afforded 1.26 g (83%) of **69** as a colorless oil: R_f 0.63 (5% EtOAc–hexane); $[\alpha]^{22}_D$ +13.0° (c 1.47, $CHCl_3$); IR (neat) 3077, 2961, 1642, 1254, 910, 836, 813, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, m, J = 7.7, 10.4, 17.0 Hz), 4.97 (2H, m, J = 7.7, 17.0 Hz), 3.36 (1H, dd, J = 3.6, 4.8 Hz), 2.34 (1H, m, J = 4.8, 7.1 Hz), 1.67 (2H, m), 1.37 (2H, m), 1.24 (1H, m, J = 5.0, 7.1 Hz), 0.99 (3H, d, J = 6.9 Hz), 0.90 (9H, s), 0.89–0.78 (9H, m), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.3, 113.7, 79.3, 42.8, 42.0, 33.8, 31.7, 28.7, 26.2, 19.8, 18.5, 17.6, 15.5, 11.2, −3.6, −3.7; MS m/z (rel intensity) 242 (M^+ − t-Bu$^\cdot$, 14), 167 (22), 136 (25), 112 (19), 73 (100). Anal. Calcd for $C_{18}H_{38}OSi$: C, 72.41; H, 12.83. Found: C, 72.38; H, 12.86.

(2*S*,3*S*,4*R*,6*R*)-3-[(1,1,-Dimethylethyl)dimethylsiloxy]-2,4,6-trimethyloctanal (70). A solution of **69** (1.26 g, 4.22 mmol) in 60 mL of CH_2Cl_2 was cooled to −78 °C and treated with O_3 until a faint blue color persisted. The solution was flushed with argon while being warmed to room temperature and then was treated with a large excess of Me_2S and refluxed for 8 h. After cooling to room temperature, the solution was concentrated under reduced pressure. Column chromatography of the residual oil (2–4% EtOAc–hexane) afforded 0.865 g of **70** and 122 mg of the unreacted ozonide, each as a colorless oil. The ozonide was again subjected to the reduction conditions, followed by column chromatography as above, to afford an additional 66 mg of **70** for a total of 931 mg (73%): R_f 0.33 (5% EtOAc–hexane); $[\alpha]^{21}_D$ +53.0° (c 1.00; $CHCl_3$); IR (neat) 2960, 2712, 1728, 1463, 1036, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, d, J = 2.8 Hz), 3.74 (1H, dd, J = 3.7, 4.7 Hz), 2.55 (1H, m, J = 2.8, 4.7, 7.3 Hz), 1.74 (1H, m, J = 4.9, 6.9 Hz), 1.44–1.28 (3H, m, J = 4.9, 8.9 Hz), 1.07 (3H, d, J = 7.1 Hz), 0.99 (2H, m), 0.89 (9H, s), 0.88 (3H, d, J = 7.0 Hz), 0.85 (6H, m), 0.07 (3H, s), 0.05 (3H, s); ^{13} C NMR (75.5 MHz, $CDCl_3$) δ 205.4, 78.1, 50.0, 40.5, 35.0, 31.7, 28.3, 25.9, 19.9, 18.3, 15.2, 12.4, 11.1, −3.9, −4.3; MS m/z (rel intensity) 301 (M^+, 2), 259 (61), 243 (4), 217 (12), 131 (31), 75 (100).

(2*S*,3*S*,4*R*,6*R*)-3-[(1,1-Dimethylethyl)dimethylsiloxy]-2,4,6-trimethyloctanoic Acid (71). To a solution of **70** (845 mg, 2.81 mmol) in 23 mL of *t*-BuOH and 17.5 mL of an aqueous pH 4 phosphate buffer cooled to 0 °C was added 2-methyl-2-butene (1.97 g, 28.1 mmol). The resulting solution was stirred at 0 °C while a 1 M aqueous solution of $NaClO_2$ (540 mg, 4.78 mmol) was added dropwise. Stirring for 15 min at 0 °C was followed by 2.5 h at room temperature. The reaction was diluted with saturated aqueous NH_4Cl and extracted wtih CH_2Cl_2, and the separated organic layer was dried ($MgSO_4$) before being concentrated under reduced pressure. The residual oil was chromatographed using 10% EtOAc–hexane to give 866 mg (97%) of **71** as a colorless oil: R_f 0.12 (5% EtOAc–hexane); $[\alpha]^{20}_D$ +15.6° (c 0.93, $CHCl_3$); IR (neat) 3382–2347 (broad) 2960, 1711, 1073, 835 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 3.75 (1H, dd, J = 3.3, 5.1 Hz), 2.66 (1H, dq, J = 5.1, 7.2 Hz), 1.75 (1H, m), 1.38 (3H, m), 1.21 (3H, d, J = 7.4 Hz), 1.00 (2H, m), 0.91 (9H, s), 0.92–0.83 (9H, m), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 78.3, 43.3, 39.9, 34.3, 31.5, 28.3, 25.9, 19.9, 18.3, 15.8, 14.9, 11.1, -4.0, -4.4; MS *m/z* (rel intensity) 317 (M^+, 0.4), 259 (100), 217 (26), 75 (29). Anal. Calcd for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46. Found: C, 64.60; H, 11.45.

(-)-Hemibourgeanic Acid (2). To a solution of **71** (849 mg, 2.68 mmol) in 26 mL of THF–CH_3CN (1:1) at room temperature was added 2.4 mL of 48% aqueous HF. After 48 h the reaction was diluted with 0.1 M aqueous HCl (40 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil. This material was dissolved in Et_2O and extracted with 5% $NaHCO_3$. The combined aqueous layers were acidified with 10% aqueous HCl to pH 1, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration under reduced pressure afforded 484 mg (89%) of **2** as a colorless oil: R_f 0.22 (MeOH/EtOAc/hexane 1:3:6); $[\alpha]^{20}_D$ -4.4° (*c* 0.22, $CHCl_3$) [lit.[2] $[\alpha]^{20}_D$ -3.2° (*c* 1.08; $CHCl_3$)]; IR (neat) 3660–2400, 3436, 3964, 1714, 1464, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (1H, dd, J = 3.2, 8.6 Hz), 2.66 (1H, m, J = 1.0, 7.2 Hz), 1.75 (1H, m, J = 3.2, 6.8 Hz), 1.48–1.30 (4H, m), 1.19 (3H, d, J = 7.2 Hz) 1.09 (3H, m), 0.87 (3H, d, J = 6.9 Hz), 0.87 (3H, t, J = 7.2Hz), 0.86 (3H, d, J = 6.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.6, 75.2, 43.3, 40.9, 31.5, 31.2, 29.2, 19.4, 14.1, 12.9, 11.2; MS *m/z* (rel intensity) 202 (M^+, 0.5), 129 (8), 111 (11), 103 (100), 85 (64), 74 (43), 69 (33).

(1′*R*,3*R*,3′*R*)-3-Methyl-4-(1′,3′-dimethylpentyl)-2-oxetanone (β-Lactone 73). To a solution of **2** (109 mg, 0.54 mmol) in 5.4 mL of pyridine at 0 °C was added benzenesulfonyl chloride (285 mg, 1.61 mmol). The reaction was allowed to stand at 0 °C overnight (22 h) before being quenched with ice-cold H_2O. The mixture was extracted with Et_2O and the combined organic layers were washed with ice-cold saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography of the residual oil (5% EtOAc–hexane) afforded 85 mg (86%) of **73** as a colorless oil: R_f 0.33 (10% EtOAc–hexane); $[\alpha]^{21}_D$ -32.6° (*c* 1.08, $CHCl_3$); IR (neat) 2963, 1827, 1461, 1123, 867 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (1H, dd, J = 4.1, 8.3 Hz), 3.24 (1H, dq, J = 4.1, 7.5 Hz), 1.86 (1H, m), 1.45 (1H, m), 1.39 (3H, d, J = 7.5 Hz), 1.22 (2H, m), 1.05 (2H, m), 1.01 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.7 Hz), 0.87 (3H, t, J = 7.1 Hz), 0.85 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1, 83.8, 48.9, 38.7, 34.9, 31.2, 28.1, 20.0, 15.6, 12.9, 10.9; M/S *m/z* (rel intensity) 184 (M^+, 12), 167 (24), 112 (11), 84 (38), 69 (100).

Ester 74. To a solution of **65** (975 mg, 0.407 mmol) in 2.5 mL of THF at 0 °C was added *n*-BuLi (0.26 mL, 0.41 mmol) in hexane. Stirring for 10 min at 0 °C was followed by addition of **73** (75.0 mg, 0.407 mmol) as a solution in 2.0 mL of THF. The reaction was quenched after 5.5 h at 0 °C by the addition of saturated aqueous NH_4Cl. Extraction with Et_2O, concentration of the dried ($MgSO_4$) organic layers under reduced pressure, and column chromatography of the residual oil (7% EtOAc–hexane) afforded 91.2 mg (61%) of **74** as a colorless oil: R_f 0.35 (10% EtOAc–hexane); $[\alpha]^{21}_D$ -11.8° (*c* 0.45, $CHCl_3$); IR (neat) 3535, 2964, 1717, 1461, 1179, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, m, J = 8.8, 10.3, 16.9 Hz), 4.99 (2H, m, J = 1.5, 14.5, 16.9 Hz), 4.80 (1H, dd, J = 4.0, 7.7 Hz), 3.59 (1H, m, J = 3.3, 4.8 Hz), 2.58 (1H, m, J = 7.2 Hz), 2.49 (1H, d, J = 4.8 Hz, exchanges with D_2O), 2.47 (1H, m), 1.88 (1H, m, J = 4.1 Hz), 1.71 (1H, m, J = 3.3, 6.9 Hz), 1.43 (3H, m), 1.27 (3H, m), 1.14 (3H, d, J = 7.2), 1.10–1.02 (4H, m), 0.99 (3H, d, J = 7.0 Hz), 0.96–0.81 (18H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.2, 140.7, 115.3, 78.9, 74.9, 43.8, 41.2, 40.8, 40.4, 31.6, 31.4, 31.3, 31.1, 29.3, 28.9, 19.7, 19.5, 17.2, 14.4, 14.3, 13.0, 11.3, 11.1; MS *m/z* (rel intensity) 369 (M^+, 28), 357 ($M^+ - H_2O$, 0.4), 287 (11), 203 (2), 185 (100), 167 (39), 97 (26), 69 (42). Anal. Calcd for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03. Found: C, 74.55; H, 11.86.

Hydroperoxide 76. A solution of **74** (10.6 mg, 0.029 mmol) in 1 mL of EtOAc–HOAc (1:1 v/v) was cooled to -10 °C and treated with O_3 until all of the starting material had been consumed. The solution was flushed with argon while warming to room temperature and then 1 mL of 30% aqueous H_2O_2 was added. After stirring for 1 h at room temperature, the solution was diluted with 1 mL of 10% aqueous HCl and extracted with EtOAc. Concentration of the dried ($MgSO_4$) solution and column chromatography (10–30% EtOAc–hexane) afforded 5.5 mg (46%) of **76** as a colorless oil: R_f 0.64 (MeOH–EtOAc–hexane, 1:3:6); IR (neat) 3409, 2963, 1713, 1460, 1183, 984 cm^{-1}; $[\alpha]^{21}_D$ -15.0° (*c* 0.42, $CHCl_3$) δ 10.55 (1H, bs, exchanges with D_2O), 9.82 (1H, bs, exchanges with D_2O), 5.23 (1H, d, J = 5.9 Hz), 4.94 (1H, dd, J = 1.9, 10.3 Hz), 3.91 (1H, dd, J = 2.2, 10.3 Hz), 2.93 (1H, d, J = 4.6 Hz, exchanges with D_2O), 2.71 (1H, dq, J = 2.8, 7.2 Hz), 2.27 (1H, dq, J = 6.1, 7.0 Hz), 1.90 (1H, m, J = 6.6 Hz), 1.79 (2H, bs + m, singlet exchanges with D_2O), 1.46 (3H, m), 1.26 (3H, m), 1.12 (3H, d, J = 7.2 Hz), 1.09 (3H, m), 0.99 (3H, d, J = 7.0 Hz), 0.94–0.81 (18H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.4, 112.3, 75.9, 75.1, 43.9, 41.0, 40.8, 36.8, 31.3, 31.0, 30.9, 30.4, 29.6, 29.5, 19.3 (×2), 14.5, 13.4, 12.4, 11.3, 11.2, 11.1; MS *m/z* (rel intensity) 387 ($M^+ - H_2O$, 2), 287 (3), 185 (43), 111 (36), 83 (58), 69 (100).

(+)-Bourgeanic Acid (1). A solution of **74** (8.3 mg, 0.023 mmol) in 1 mL of EtOAc was cooled to -78 °C and O_3 was bubbled through the solution until the starting material had been consumed as shown by TLC. The solution was flushed with argon while warming to room temperature and was concentrated under reduced pressure to give 12.0 mg of a viscous oil. The oil was dissolved in 0.5 mL of glacial acetic acid and 0.5 mL of 30% aqueous H_2O_2, and the mixture was stirred for 72 h at room temperature. The solution was diluted with 1 mL of 10% aqueous HCl and extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (MeOH–EtOAc–hexane, 1:3:6) afforded 7.2 mg of an amorphous solid. This material was dissolved in HOAc, diluted with 0.1 M aqueous HCl, and extracted with EtOAc. Concentration of the dried solution ($MgSO_4$) under reduced pressure afforded 4.2 mg (47%) of **1** as a colorless crystalline solid: mp 124.5–125 °C (hexane) [lit.[2] mp 125–126 °C (hexane)]; $[\alpha]^{21}_D$ +7.3° (*c* 0.40, $CHCl_3$), [lit.[2] $[\alpha]^{21}_D$ +7.0° (*c* 1.00, $CHCl_3$)]; IR (KBr) 3418, 2963, 1745, 1720, 1462, 1265, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (1H, dd, J = 2.6, 9.6 Hz), 3.71 (1H, dd, J = 2.5, 9.4 Hz), 2.79 (1H, m, J = 7.1, 9.6 Hz), 2.60 (1H, m, J = 7.2, 9.4 Hz), 1.90 (1H, m, J = 2.6, 7.1 Hz), 1.71 (1H, m, J = 2.3, 6.8 Hz), 1.45 (3H, m), 1.29 (4H, m), 1.17 (3H, d, J = 7.1 Hz), 1.09 (3H, d, J = 7.2 Hz), 1.08 (3H, m), 0.96–0.81 (20H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.0, 175.8, 76.4, 74.7, 44.1, 42.1, 41.0, 40.7, 31.2, 30.9, 30.8, 29.4, 29.2, 19.4, 19.3, 14.4, 13.8, 13.7, 12.7, 11.3, 11.1; MS *m/z* (rel intensity) 387 (M^+, 0.7), 287 (9), 185 (100), 167 (51), 111 (18), 83 (39), 69 (42).

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