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Catalytic Enantioselective Synthesis of Vicinal Dialkyl Arrays

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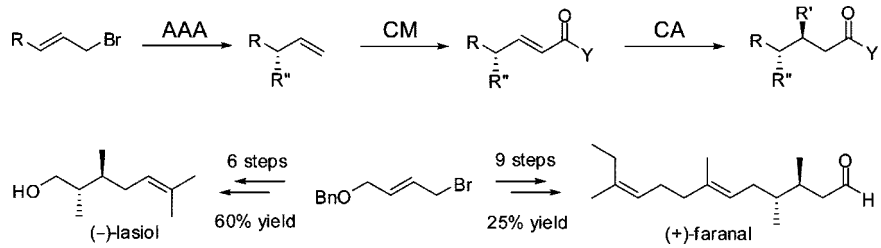

With a consecutive "asymmetric allylic alkylation (AAA)/cross-metathesis (CM)/conjugate addition (CA)" protocol it is possible to synthesize either stereoisomer of compounds containing a vicinal dialkyl array with excellent stereoselectivity. The versatility of this protocol in natural product synthesis is demonstrated in the preparation of the ant pheromones faranal and lasiol.

Introduction

In the synthesis of chiral natural products, it is imperative that the stereochemistry of each of the stereogenic centers can be controlled. Therefore, methods that allow the introduction of each stereochemical element independently (reagent or catalyst control), as opposed to being dependent on chirality introduced previously (substrate control), are an invaluable addition to the synthetic chemist's tool box.[1] The Cu-catalyzed asymmetric allylic alkylation (AAA)[2] and conjugate addition (CA)[3] are two powerful C−C bond forming reactions enabling the formation of stereogenic centers with alkyl substituents. Recently, we reported catalysts based on copper and diphosphine ligands (Figure 1), which perform both the Cu-catalyzed allylic alkylation[4] and conjugate addition[5,6] using Grignard reagents providing the chiral products in high yields and with excellent regioselectivity and enantiomeric excess.[7]

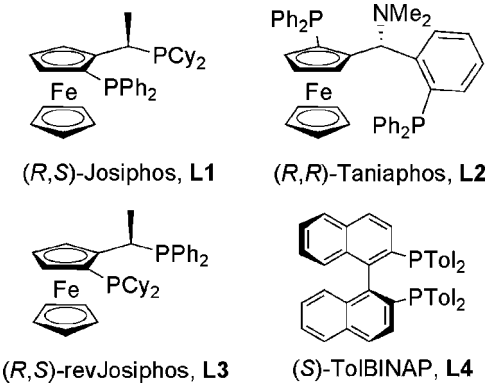

FIGURE 1. Diphosphine ligands for asymmetric Cu-catalyzed conjugate addition and allylic alkylation with Grignard reagents.[8]

Iterative protocols based on the enantioselective Cu-catalyzed conjugate addition for the synthesis of compounds with two or

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(1) Taylor, M. S.; Jacobsen, E. N. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5368–5373.
(2) (a) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025–1037. (b) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780. (c) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435–4439. (d) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124–130.
(3) (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300. (b) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. *Copper-Catalysed Enantioselective Conjugate Addition Reactions of Organozinc Reagents in Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 7. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (d) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
(4) (a) van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558–2563. (b) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572–15573. (c) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409–411.
(5) (a) Maciá Ruiz, B.; Geurts, K.; Fernández-Ibáñez, M. A.; ter Horst, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2007**, *9*, 5123–5126. (b) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.

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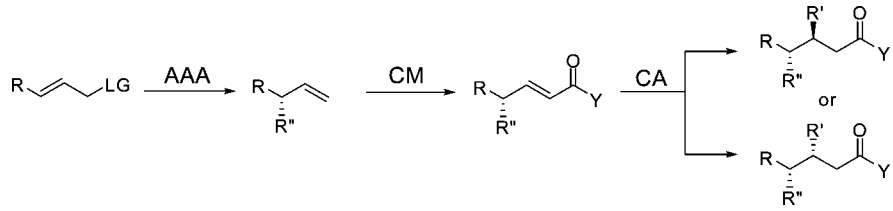
SCHEME 1. Synthetic Protocol Providing Vicinal Dialkyl Compounds (LG = Leaving Group)



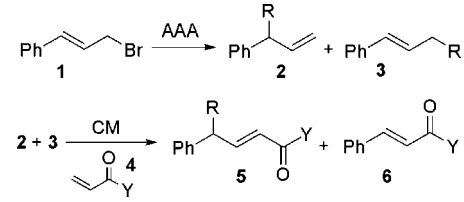
more stereocenters in a 1,3-relation[9] or 1,5-relation[10] to each other have been developed in our group, recently. The utility of these protocols has been demonstrated in the total synthesis of several natural products.[11] However, these approaches do not provide for the stereoselective synthesis of vicinal (1,2-relation) dialkyl arrays.[12]

Herein we report a versatile protocol for the synthesis of such vicinal 1,2-dialkyl arrays based on three successive modern catalytic transformations (Scheme 1). The strategy consists of an initial Cu-catalyzed asymmetric allylic alkylation (AAA) to build the first stereogenic center, a subsequent cross-metathesis (CM) reaction,[13] which transforms the generated terminal alkene moiety into an α,β-unsaturated system, and finally a Cu-catalyzed enantioselective conjugate addition (CA) of a Grignard reagent which delivers the desired 1,2-dialkyl motif. In this manner, adjacent stereocenters with simple alkyl substituents are introduced with independent control over the stereochemistry.[14] Furthermore, we applied this protocol in the synthesis of the two ant pheromones, lasiol and faranal.

Results and Discussion

The Cu-catalyzed allylic alkylations were performed as reported previously, with cinnamyl bromide **1** as a model substrate and MeMgBr or EtMgBr as Grignard reagents. The reactions were performed in CH_2Cl_2 at −75 °C in the presence of a copper catalyst, which was preformed in situ from $CuBr\cdot SMe_2$ and ligand **L2**.[4c,8] The enantioselective allylic alkylation is high yielding and gives the chiral product with excellent enantioselectivity (Table 1). In the AAA with methylmagnesium bromide, the regioselectivity is very high (>97:3). However, the AAA with ethylmagnesium bromide provided a mixture of S_N2' and S_N2 products **2** and **3** in a ratio of 80:20. Since **2** and **3** were inseparable by standard column chromatography, the cross-metathesis reactions were performed on the mixture. Consequently, the cross-metathesis reaction leads to both products **5** and **6** from **2** and **3**, respectively (Scheme 2).

SCHEME 2. Formation of Distinct Products in AAA and subsequent CM



Our previous reports on the enantioselective Cu-catalyzed conjugate addition have focused on three types of acyclic substrates: α,β-unsaturated esters, ketones, and thioesters. Therefore, three different electron-deficient olefins **4** were used in the cross-metathesis reactions: methyl acrylate **4a**, methyl vinyl ketone **4b**, and *S*-ethyl thioacrylate **4c**. The results of the two-step syntheses of **5a**−**e** are summarized in Table 1.

Compounds **5a** and **5b**, an α,β-unsaturated ester and ketone, respectively, with R = Me, could be obtained readily (Table 1, entries 1 and 2). The reactions were performed in CH_2Cl_2 at rt using 5 equiv of olefin **4** and 2 mol % of the Hoveyda−Grubbs second-generation catalyst (**HG-2**, Figure 2). Compound **5c** was obtained by a similar route using 2 equiv of **4c** and two portions of 5 mol % of catalyst (Table 1, entry 3).[15]

Despite the different reactivities of terminal and internal olefins, under the aforementioned conditions the S_N2-product **3** was transformed into the cinnamic acid derivative **6** quantita-

(6) **L4**'s performance in conjugate addition was first reported by Loh and co-workers: Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276–277.

(7) For reviews on the use of Grignard reagents in asymmetric allylic alkylation and conjugate addition, see: (a) López, F.; Minnaard, A. J.; Feringa, B. L. In *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2008; Part 2, Chapter 17. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, . in press. (c) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188.

(8) The correct stereochemistry of (+)-Taniaphos **L2** is (R,R_{Fc}), as depicted in Figure 1. Based on information from the literature, our previous articles (refs 2a, 4, 5b, and 7) have erroneously depicted the ligand as its (R,S_{Fc}) diastereomer; in ref 4b, (−)-(R,S_{Fc})-Taniaphos should be (+)-(R,R_{Fc})-Taniaphos. See also: (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 3666. (b) Fukuzawa, S.-i.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, 5540–5545. (c) Fukuzawa, S.-i.; Yamamoto, M.; Kikuchi, S. *J. Org. Chem.* **2007**, *72*, 1514–1517.

(9) (a) Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967. (b) Schuppan, J.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 792–793.

(10) van Summeren, R. P.; Reijmer, S. J. W.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2005**, 1387–1389.

(11) (a) Casas-Arce, E.; ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Eur. J.* **2008**, *14*, 4157–4159. (b) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2007**, *9*, 3013–3015. (c) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 489–491. (d) van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 4546–4547.

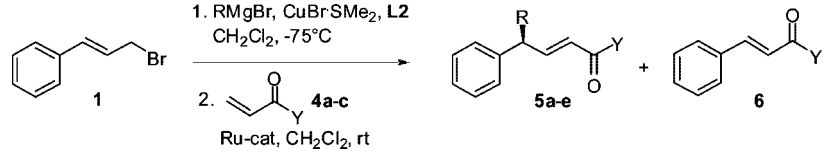
(12) For representative approaches to the asymmetric synthesis of vicinal dialkyl arrays through asymmetric catalysis, see for example: desymmetrization: (a) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514–4518. (b) Chen, Y.; Tian, S.-K.; Deng, L., *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543. Michael reactions: (c) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491. For representative approaches through chiral pool and chiral auxiliaries or reagents, see for example: tiglylation/hydroboration: (d) Coleman, R. S.; Gurrala, S. R.; Mitra, S.; Raao, A. *J. Org. Chem.* **2005**, *70*, 8932–8941. 1,4-addition on chiral substrates: (e) Morita, M.; Ishiyama, S.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1675–1678. (f) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505–5508. 1,4-addition/enolate trapping: (g) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477–5480. (h) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763–7772. (i) White, J. D.; Lee, C.-S.; Xu, Q. *Chem. Commun.* **2003**, 2012–2013. Michael reactions: (j) Brebion, F.; Delouvrié, B.; Nájera, F.; Fensterbank, L.; Malacria, M.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5342–5345. (k) Liang, B.; Carroll, P. J.; Joullié, M. M. *Org. Lett.* **2000**, *2*, 4157–4160. Ireland-Claisen rearrangement: (l) Oishi, T.; Shoji, M.; Kumahara, M.; Hirama, M. *Chem. Lett.* **1997**, 845–846, See also refs 20−28.

(13) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

(14) A single example of this protocol was reported previously by our group; see ref 4c.

(15) van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 5651–5653.

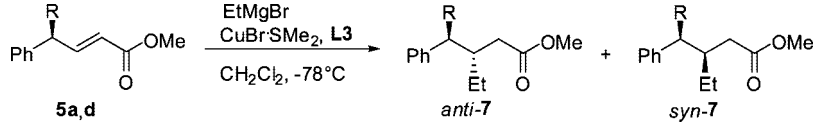
TABLE 1. Synthesis of 5a−e through Allylic Alkylation Followed by Cross-Metathesis[a]



	R	4		Ru-cat. (Figure 2)		5	yield[b] (%)	(ee[c]) (%)	5:6[d]
1[d]	Me	**4a**	(Y = OMe) 5 equiv	**HG-2**	(2 mol %)	**5a**	66	(n.d.)	>97:3
2	Me	**4b**	(Y = Me) 5 equiv	**HG-2**	(2 mol %)	**5b**	80	(99)	>97:3
3	Me	**4c**	(Y = SEt) 2 equiv	**HG-2**	(10 mol %)[f]	**5c**	74	(97)	>97:3
4	Et	**4a**	(Y = OMe) 5 equiv	**HG-2**	(2 mol %)	**5d**	67[g]	(98)	80:20
5	Et	**4a**	(Y = OMe) 5 equiv	**G-2**	(1.5 mol %)	**5d**	49[g]	(98)	90:10
6	Et	**4c**	(Y = SEt) 2 equiv	**HG-2**	(10 mol %)[f]	**5e**	67[g]	(97)	80:20

[a] Reaction conditions: (1) **1** (1.0 equiv), CuBr·SMe_2 (1.0 mol%), (+)-(R,R_{Fc})-**L2** (1.2 mol%), RMgBr (1.2 equiv), CH_2Cl_2, −75 °C, (2) **2** (1.0 equiv), **4a−c** (2−5 equiv), Ru-cat. (1.5−10 mol%), CH_2Cl_2, rt. [b] Isolated yield of **5** after two steps. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR spectroscopy. [e] Reference 4c. [f] Catalyst added in two portions of 5.0 mol %. [g] Calculated yield of **5** from **1** after two steps, based on overall yield and ratio of **5** and **6**.

TABLE 2. Conjugate Additions on α,β-unsaturated Esters 5a and 5d[a]



entry	R	5	ligand		yield[b] (%)	dr (*anti:syn*)[c]	ee[c] (%)
1[d]	Me	**5a**	(*R,S*)-**L3**	*anti*-**7a**	81	99:1	>99.5
2[d]	Me	**5a**	(*S,R*)-**L3**	*syn*-**7a**	84	4:96	>99.5
3	Et	**5d**	(*R,S*)-**L3**	*anti*-**7b**	77	91:9	>99.5
4	Et	**5d**	(*S,R*)-**L3**	*syn*-**7b**	30[e]	4:96	99

[a] Reaction conditions: **5** (1.0 equiv), CuBr·SMe_2 (5.0 mol %), **L3** (6.0 mol %), EtMgBr (5.0 equiv), CH_2Cl_2, −78 °C, 18 h. [b] Isolated yield of the mixture of diastereomers. [c] Determined by chiral GC or HPLC. [d] Reference 4c. [e] Conv. = 50%.[18]

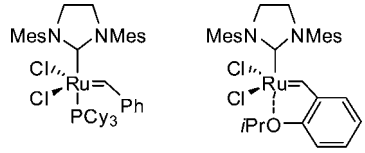


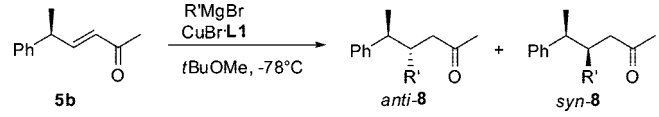
FIGURE 2. Ruthenium-based metathesis catalysts: Grubbs second generation (**G-2**) and Hoveyda−Grubbs second generation (**HG-2**).

tively. This gave, in the case of **5d** and **5e**, where R = Et, a mixture of **5** and **6** (80:20) which was not separable (Table 1, entries 4 and 6).[16] The reaction with the Grubbs second-generation catalyst (**G-2**, Figure 2) was more selective (90:10); however, this decreased the total yield of **5** (Table 1, entry 5).

The results of the subsequent asymmetric 1,4-addition reactions with EtMgBr on the α,β-unsaturated esters **5a** and **5d** are summarized in Table 2. Stereoselective synthesis of a 1,2-methyl,ethyl motif was accomplished readily. Thus, depending on the enantiomer of ligand **L3** used, either *anti*-**7a** or *syn*-**7a** was obtained in good yield and diastereoselectivity from substrate **5a** (Table 2, entries 1 and 2). The synthesis of *anti*-**7b**, which has a diethyl motif, proceeded in good yield and diastereoselectivity from **5d** (Table 2, entry 3).[16] The reaction using the ligand (*S,R*)-**L3** was slower, however, providing *syn*-**7b** in 30% yield, albeit with excellent diastereoselectivity (Table 2, entry 4). Introduction of a methyl substituent at the β-position with methyl Grignard reagent was not possible with this catalyst system, due to the insufficient reactivity of oxo esters.[17]

The results of the asymmetric 1,4-addition reactions on the α,β-unsaturated ketone **5b** are summarized in Table 3. Enones are more active Michael acceptors than esters, which allows

TABLE 3. Conjugate Additions on α,β-Unsaturated Ketone 5b[a]



entry	R′MgBr	ligand		yield[b] (%)	dr (*anti:syn*)[c]	ee[c] (%)
1	MeMgBr	(*R,S*)-**L1**	*anti*-**8a**	73	98:2	> 99.5
2	MeMgBr	(*S,R*)-**L1**	*syn*-**8a**	46	14:86	66
3	EtMgBr	(*R,S*)-**L1**	*anti*-**8b**	89	92:8	> 99.5
4	EtMgBr	(*S,R*)-**L1**	*syn*-**8b**	64	40:60	97

[a] Reaction conditions: **5** (1.0 equiv), CuBr·**L1** (7.0 mol %), RMgBr (1.3 equiv), *t*-BuOMe, −78 °C, 18 h. [b] Isolated yield of the mixture of diastereomers. [c] Determined by chiral GC or HPLC.

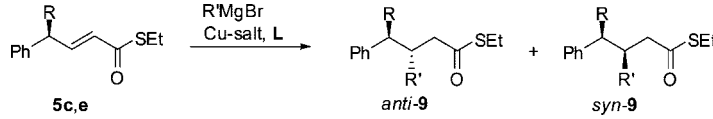
for the introduction of a second methyl group through 1,4-addition with this catalyst system. Thus, stereoselective synthesis of a 1,2-dimethyl motif was accomplished through 1,4-addition with MeMgBr (Table 3, entries 1 and 2). The product *anti*-**8a** could be obtained in high yield and excellent diastereoselectivity and enantiomeric excess, in contrast to the *syn*-product, which was obtained in lower yield and with reduced diastereoselectivity. Interestingly, the enantiomeric excess of the product was

(16) All conjugate additions with substrates **5d** and **5e** were performed on their mixtures with **6**. The conjugate addition products of **6** were separated by column chromatography from the products of **5**.

(17) During preparation of this manuscript Loh and co-workers reported that the use of MeMgBr was possible under certain reaction conditions with their catalyst system: (a) Wang, S.-Y.; Lum, T.-K.; Ji, S.-J.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 673–677. (b) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 761–764.

(18) Extended reaction times to allow completion of the reaction did not improve the yield but did lead to a reduction in diastereoselectivity and enantiomeric excess.

TABLE 4. Conjugate Additions on α,β-Unsaturated Thioesters 5c and 5e[a]



5c,e *anti*-**9** *syn*-**9**

entry	R		R′MgBr	catalyst		yield[b] (%)	dr (*anti:syn*)[c]	ee[c] (%)
1	Me	**5c**	MeMgBr	CuBr•(*R*,*S*)-**L1**	*anti*-**9a**	59	99:1	99
2[d]	Me	**5c**	MeMgBr	CuBr•(*S*,*R*)-**L1**	*syn*-**9a**	17	61:39	nd
3	Me	**5c**	MeMgBr	CuI/(*R*)-**L4**	*anti*-**9a**	96	99.5:0.5	99
4	Me	**5c**	MeMgBr	CuI/(S)-**L4**	*syn*-**9a**	82	5:95	>99.5
5	Me	**5c**	EtMgBr	CuI/(*R*)-**L4**	*anti*-**9b**	91	98:2	94%
6	Me	**5c**	EtMgBr	CuI/(*S*)-**L4**	*syn*-**9b**	58	64:36	>99.5
7[d]	Et	**5e**	MeMgBr	CuBr•(*R*,*S*)-**L1**	*anti*-**9c**	67	98:2	>99.5
8[d]	Et	**5e**	MeMgBr	CuBr•(*S*,*R*)-**L1**	*syn*-**9c**	6[c]	45:55	nd
9	Et	**5e**	MeMgBr	CuI/(*R*)-**L4**	*anti*-**9c**	<5[c]	nd	nd
10	Et	**5e**	MeMgBr	CuI/(*S*)-**L4**	*syn*-**9c**	71	12:88	>99.5

[a] Reaction conditions: **5** (1.0 equiv), CuBr•**L1** (6.0 mol %) or CuI (3.0 mol %) and **L4** (3.3 mol %), RMgBr (3.0−4.0 equiv), *t*-BuOMe, −75 °C, 18 h. [b] Isolated yield of the mixture of diastereomers. [c] Determined by chiral GC or HPLC. [d] Reaction time: 40 h.

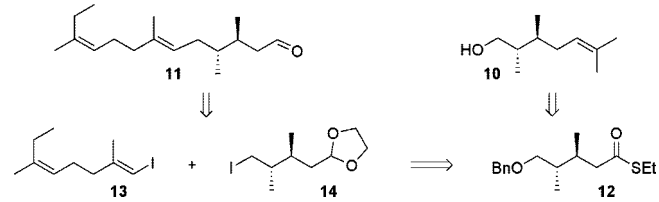
found to be 66%, which implies that racemization of the substrate occurs under the reaction conditions. When the reaction was performed with EtMgBr the same trend was observed (Table 3, entries 3 and 4), although substantial racemization was not observed.

Compounds containing an α,β-unsaturated thioester are more active electrophiles than their corresponding oxo esters. Nevertheless, their synthetic versatility is similar. In our earlier contributions, two catalysts that perform the 1,4-addition on thioesters effectively and selectively, Cu/JosiPhos **L1** and Cu/Tol-BINAP **L4**, were reported. The results of the 1,4-additions are summarized in Table 4. Conjugate addition with methyl Grignard to the methyl-containing substrate **5c** gave product **9a** with a 1,2-dimethyl motif. The performance of Tol-BINAP **L4** was better in all aspects (Table 4, entries 1−4). Although the use of **L1** provided *anti*-**9a** in good yield and excellent stereoselectivity, **L4** provided the compound in higher yield and equally excellent selectivity. The other diastereomer *syn*-**9a** could be obtained in good yield and excellent stereoselectivity with ligand **L4**, whereas a catalyst system with ligand **L1** was significantly less active and selective (entry 4 vs entry 2).

The *anti*-diastereomer of product **9b** could be obtained in excellent selectivity using ligand **L4** and EtMgBr. However, product *syn*-**9b** could not be obtained selectively by this route (Table 4, entries 5 and 6). Curiously, stereoselective synthesis of *anti*-**9c**, which contains a 1,2-ethyl,methyl motif, could be accomplished with ligand **L1**, while the use of **L4** was necessary to obtain the other diastereomer *syn*-**9c**.[16] Hence, the two ligand systems are complementary in this case (Table 4, entries 7−10).

In natural products, the 1,2-dimethyl motif is the most common of the vicinal dialkyl arrays. It is present, for example, in the two ant pheromones lasiol (**10**) and faranal (**11**) (Scheme 3). Lasiol is a volatile compound which was isolated from the mandibular glands of male *Lasius meridionalis* ants.[19] Shortly after its discovery and racemic synthesis by Lloyd et al.,[19] both enantiomers of the pheromone lasiol were synthesized by Kuwahara et al. from the chiral pool[20] and by Mori and co-workers using a desymmetrization mediated by a chiral base.[21] Since then, several total syntheses and formal syntheses have followed.[22]

SCHEME 3. Retrosynthetic Analysis of Lasiol (10) and Faranal (11) to a Common Intermediate 12



Faranal is the trail pheromone of *Monomorium pharaonis*, the pharaoh's ant, a common pest in households, food storage facilities, and hospitals.[23] The absolute configuration of natural faranal was established through biological tests with diastereomeric mixtures of faranal, where one of the stereogenic centers was set using an enzymatic condensation.[23a] Some stereoselective but racemic syntheses have been published.[24] The first truly asymmetric total synthesis of natural (+)-faranal (**11**) involved the resolution of a racemate[25] and was followed by other routes which made use of the chiral pool,[26] chiral bases,[27] or enzymatic desymmetrization.[28]

Importantly, in both natural products the vicinal 1,2-dimethyl motif has an *anti* configuration. Retrosynthetic analysis shows that they can be derived from a common intermediate **12**, which

(19) Lloyd, H. A.; Jones, T. H.; Hefetz, A.; Tengö, J. *Tetrahedron Lett.* **1990**, *31*, 5559–5562.

(20) Kuwahara, S.; Shibata, Y.; Hiramatsu, A. *Liebigs Ann. Chem.* **1992**, 993–995.

(21) Kasai, T.; Watanabe, H.; Mori, K. *Bioorg. Med. Chem.* **1993**, *1*, 67–70.

(22) Catalytic asymmetric desymmetrizations: (a) Vasil'ev, A. A.; Vielhauer, O.; Engman, L.; Pietzsch, M.; Serebryakov, E. P. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 481–487. (b) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610–6618. Chiral auxiliary-based: (c) Asano, S.; Tamai, T.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2003**, 2252–2254. (d) Schneider, C. *Eur. J. Org. Chem.* **1998**, 1661–1663.

(23) (a) Kobayashi, M.; Koyama, T.; Ogura, K.; Seto, S.; Ritter, F. J.; Brüggemann-Rotgans, I. E. M. *J. Am. Chem. Soc.* **1980**, *102*, 6602–6604. (b) Ritter, F. J.; Brüggemann-Rotgans, I. E. M.; Verwiel, P. E. J.; Persoons, C. J.; Talman, E. *Tetrahedron Lett.* **1977**, *18*, 2617–2618.

(24) (a) Vasil'ev, A. A.; Engman, L.; Serebryakov, E. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2211–2216. (b) Baker, R.; Billington, D. C.; Ekanayake, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1387–1393. (c) Knight, D. W.; Ojhara, B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 955–960.

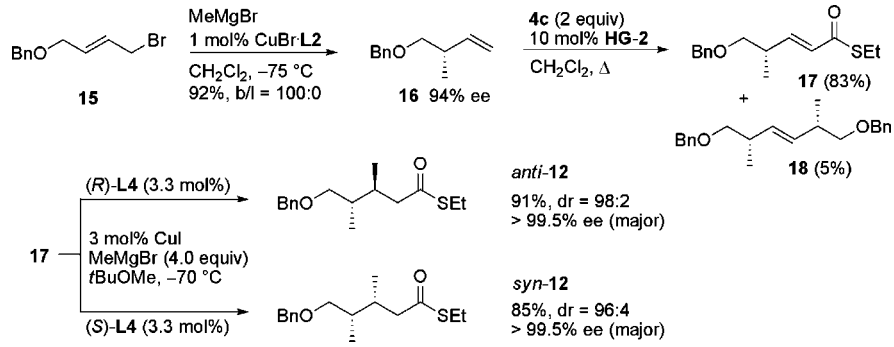
(25) Mori, K.; Ueda, H. *Tetrahedron* **1982**, *38*, 1227–1233.

(26) Wei, S.-Y.; Tomooka, K.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5973–5974.

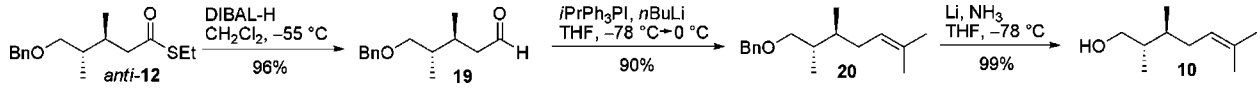
(27) (a) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 3531–3534. (b) Mori, K.; Murata, N. *Liebigs Ann.* **1995**, 2089–2092.

(28) Poppe, L.; Novák, L.; Kolonits, P.; Bata, Á.; Szántay, C. *Tetrahedron* **1988**, *44*, 1477–1487.

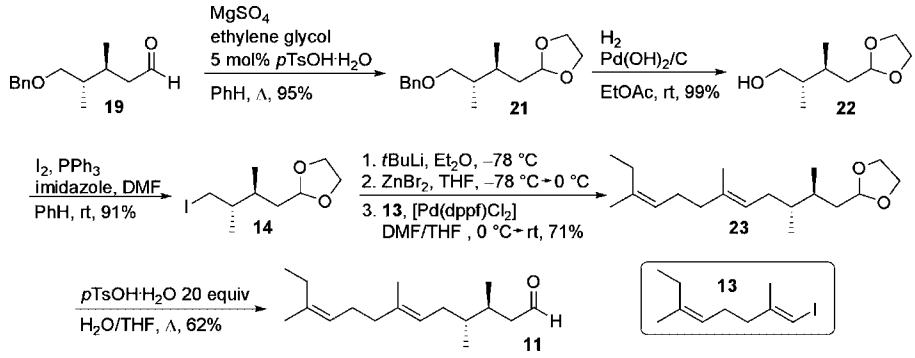
SCHEME 4. Synthesis of Common Intermediate 12



SCHEME 5. Synthesis of (−)-Lasiol (10) from Common Intermediate *anti*-12



SCHEME 6. Synthesis of (+)-Faranal (11) from Precursor 19



can be obtained in turn through the allylic alkylation/cross-metathesis/conjugate addition protocol.

Allylic alkylation of compound **15**[29] with MeMgBr using the preformed complex CuBr·(*R*,R_{Fc})-**L2** as the catalyst gave product **16** in excellent yield, regioselectivity, and enantioselectivity (Scheme 4). Cross-metathesis with thioacrylate **4c** gave α,β-unsaturated thioester **17** in good yield together with a small percentage of the dimer **18** (ratio = 94:6).[30] Conjugate addition to **17** with MeMgBr and (*R*)-**L4** as the ligand gave *anti*-**12** in good yield and excellent diastereoselectivity. The other diastereomer *syn*-**12** could be obtained in high diastereoselectivity by using ligand (*S*)-**L4** instead. In both cases the opposite enantiomer of the major diastereomer could not be detected, which highlights the potential of this protocol in synthesis.

(−)-Lasiol (**10**), which has the absolute (2*S*,3*S*)-configuration,[31] was synthesized from the common intermediate *anti*-**12**. The thioester was first reduced to aldehyde **19** using DIBAL-H (Scheme 5). A Wittig reaction with isopropyltriphenylphosphonium iodide was performed to obtain benzyl ether **20**, followed by quantitative deprotection of the alcohol using a dissolving metal reduction. Thus, (−)-lasiol (**10**) was synthesized in six steps from **15** in an overall yield of 60%.

The synthesis of (+)-faranal (**11**) from compound *anti*-**12** started with its reduction to aldehyde **19** (Scheme 5). The aldehyde was subsequently protected as its acetal with ethylene glycol to give dioxolane **21** (Scheme 6). The benzyl ether was cleaved through hydrogenolysis with $Pd(OH)_2$ to furnish alcohol **22**,[32] which was converted to the alkyl iodide **14** using iodine, triphenylphosphine, and imidazole. Compound **14** was converted in situ to the corresponding zinc bromide with *t*-BuLi and $ZnBr_2$ and used in a Negishi-coupling reaction[33] with alkenyl iodide **13**, a known compound which was synthesized according to the methods of Baker et al.[24b] and Mori et al.,[27b] and catalytic [Pd(dppf)Cl_2] to obtain faranal precursor **23**. Hydrolysis of the acetal in THF and water under dilute conditions completed the synthesis of (+)-faranal (**11**) in nine steps and an overall yield of 25% from the achiral precursor **15**.

Conclusions

In summary, a new protocol for the stereoselective synthesis of vicinal dialkyl arrays is reported. The protocol, which combines enantioselective allylic alkylation, cross-metathesis, and enantioselective 1,4-addition, allows for the preparation of both of the diastereomers in enantiopure form with judicious

(29) Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *J. Med. Chem.* **2002**, *45*, 2289–2293.

(30) The dimer **18** could not be separated from **17**. It could be separated from the product of the following conjugate addition, however. Pure **17** could be obtained via cross-metathesis with methyl acrylate followed by transesterification. For this route and the separate synthesis and characterization of **18**, see the Supporting Information.

(31) Despite selective syntheses of both enantiomers of lasiol, the absolute configuration of the natural compound has not been established.

(32) Certain reaction conditions, such as extended reaction times or the use of Pd/C as the catalyst, led to the formation of a complex mixture of products, probably due to partial trans-acetalization. For precedents, see: (a) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901–7904. (b) Börjesson, L.; Csöregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989–2999.

(33) (a) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261–264. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299.

choice of the ligands in the copper catalyzed reactions. The *anti*-diastereomer of the products was formed more easily than the *syn*-product in most cases, but on many occasions it was possible to form either diastereomer in high diastereoselectivity and excellent enantioselectivity.

The protocol's utility was demonstrated through the total syntheses of the ant pheromones (−)-lasiol and (+)-faranal in six and nine steps, respectively, from an achiral precursor. The products were obtained with excellent diastereomeric and enantiomeric purity and high overall yields. This makes these approaches the shortest, highest yielding, and most selective catalytic asymmetric total syntheses of these pheromones reported so far and very competitive with existing methods that employ the chiral pool, chiral auxiliaries, or other methods based on stoichiometric chiral reagents.

Experimental Section

(−)-(*S*,*E*)-Methyl 4-Phenylpent-2-enoate (5a).[4c] In a Schlenk tube equipped with septum and stirring bar were dissolved CuBr·SMe_2 (15.0 μmol, 3.08 mg) and ligand **L2** (18.0 μmol, 12.4 mg) in CH_2Cl_2 (3.0 mL), and the mixture was stirred under argon at rt for 10 min. The mixture was cooled to −75 °C, and MeMgBr (3.0 M solution in Et_2O, 1.73 mmol, 0.575 mL) was added dropwise. Following this, cinnamyl bromide (296 mg, 1.50 mmol) was added dropwise over 15 min via a syringe pump. Once the addition was complete, the resulting mixture was stirred at − 75 °C for 4 h. The reaction was quenched by addition of MeOH (0.5 mL), and the mixture was allowed to reach rt. Aqueous NH_4Cl solution (1 M, 2 mL) was added to the mixture. The organic layer was separated, and the resulting aqueous layer was extracted with Et_2O (0.5 mL, 3×). The combined organic layers were dried and concentrated to a yellow oil, which was dissolved in CH_2Cl_2 (3 mL) in a dry Schlenk tube under argon. Methyl acrylate (645 mg, 7.5 mmol) and Hoveyda−Grubbs second-generation catalyst (18 mg, 0.03 mmol) were added sequentially producing a light green solution which was stirred for 36 h at rt. The mixture was then concentrated in vacuo to a dark brown oil. Purification of this residue by silica gel chromatography (SiO_2, 2:98 to 5:95 Et_2O/pentane) afforded **5a** as a colorless oil: 66% yield; $[\alpha]_D = -20$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.29−7.25 (m, 2H), 7.21−7.14 (m, 3H), 7.07 (dd, J = 15.7 and 6.7 Hz, 1H), 5.77 (dd, J = 15.7 and 1.5 Hz, 1H), 3.67 (s, 3H), 3.61−3.54 (m, 1H), 1.38 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 167.1, 152.9, 143.2, 128.6, 127.3, 126.7, 119.6, 51.4, 42.0, 20.1; MS (EI) *m*/*z* 190 (M^+, 40), 159 (18), 131 (100), 91 (22), 51 (13); HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0995.

(+)-(*S*)-3-phenyl-1-butene (2a).[4c] To a stirred solution of CuBr·SMe_2 (15 μmol, 3.1 mg) and ligand **L2** (18 μmol, 12.4 mg) in dry CH_2Cl_2 (2 mL), at −75 °C, under a N_2 atmosphere, was added MeMgBr (1.73 mmol, 3.0 M solution in Et_2O) dropwise via syringe. A solution of cinnamyl bromide (1.50 mmol, 296 mg) in CH_2Cl_2 (0.6 mL) was then added dropwise, and the reaction mixture was stirred overnight at −75 °C. After 16 h, MeOH (1 mL) was added, and the reaction was allowed to reach rt. Aqueous NH_4Cl (2 mL) was added, and the biphasic system was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 2 mL). Combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. Flash chromatography (silica gel, pentane) afforded a mixture of S_N2' (**2**) and S_N2 (**3**) products. Combined yield: 91%; **2**/**3** ratio = 98:2; ee >99.5%; $[\alpha]_D = +7.4$ (*c* 1.0, $CHCl_3$) [lit.[4c] $[\alpha]_D = +5.4$ (*c* 1.2, $CHCl_3$)]; R_f = 0.80 (pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 7.0 Hz, 3H), 3.45−3.52 (m, 1H), 5.02−5.08 (m, 2H), 6.02 (ddd, J = 16.8, 10.2 and 6.6 Hz, 1H), 7.17−7.36 (m, 5H); MS (EI) *m*/*z* 132 (M^+, 27), 117 (100), 91 (25). Enantiomeric excess was determined by chiral GC ^{34}analysis, CP-Chiralsil-Dex-CB (25 m × 0.25 mm), initial temperature 75 °C, isothermic, retention times (min): 13.9 (*R*) and 14.3 (*S*). Retention time **3a**: 26.7 min.

(−)-(*S*,*E*)-5-Phenylhex-3-en-2-one (5b). A solution of terminal olefin **2a** (0.50 mmol) in dry CH_2Cl_2 (2.0 mL) was stirred under a N_2 atmosphere at rt. Methyl vinyl ketone **4b** (2.5 mmol) was added via syringe in one portion, followed by Hoveyda−Grubbs second-generation catalyst (2 mol %, 6.3 mg). The mixture was stirred overnight. After completion of the reaction (20 h), the solvent was evaporated, and the crude mixture was subjected to flash chromatography (silica gel, pentane−pentane/ethyl acetate 99.5:0.5, v/v) affording product **5b**: 90% yield; >99.5% ee, $[\alpha]_D = -20.6$ (*c* 1.0, $CHCl_3$); R_f = 0.50 (pentane/EtOAc, 9:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3H), 2.24 (s, 3H), 3.62−3.65 (m, 1H), 6.07 (dd, J = 16.0 and 1.2 Hz, 1H), 6.92 (dd, J = 16.0 and 6.8 Hz, 1H), 7.17−7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 27.2, 42.5, 127.1, 127.6, 129.0, 129.9, 143.5, 151.9, 199.2; MS (EI) *m*/*z* 174 (M^+, 56), 131 (100), 91 (30); HRMS calcd for $C_{12}H_{14}O$ 174.1045, found 174.1043. Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OB-H, heptane/*i*-PrOH, 98/2, v/v). Retention times (min): 36.8 (*R*) and 40.9 (*S*).

(−)-*S*-Ethyl (*S*,*E*)-4-Phenylpent-2-enethioate (5c). A solution of terminal olefin **2a** (0.50 mmol) in dry CH_2Cl_2 (2.0 mL) was stirred under a N_2 atmosphere at rt. Ethyl thioacrylate (**4c**) (1.0 mmol, 116 μL) was added via syringe in one portion, followed by Hoveyda−Grubbs second-generation catalyst (5 mol %, 16.0 mg). After 8 h, another portion of Hoveyda−Grubbs second-generation catalyst (5 mol %, 16.0 mg) was added. Upon complete conversion of **2a** (40 h), the solvent was evaporated, and the crude mixture was subjected to flash chromatography (silica gel, pentane−pentane/ethyl acetate 99.5:0.5, v/v) affording the product **5c**: 83% yield; 97% ee; $[\alpha]_D = -7.0$ (c 1.0, $CHCl_3$); R_f = 0.48 (pentane/Et_2O, 95:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.43 (d, J = 7.6 Hz, 3H), 2.93 (q, J = 7.2 Hz, 2H), 3.56−3.62 (m, 1H), 6.07 (dd, J = 15.6 and 1.6 Hz, 1H), 7.03 (dd, J = 15.6 and 6.8 Hz, 1H), 7.20−7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 20.2, 23.1, 42.0, 126.8, 127.4, 128.7, 143.1, 148.4, 190.2; MS (EI) *m*/*z* 220 (M^+, 24), 159 (100), 115 (37); HRMS calcd for $C_{13}H_{16}OS$ 220.0922, found 220.0921. Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD-H, heptane/*i*-PrOH, 99.5:0.5, v/v). Retention times (min): 18.5 (*S*) and 21.2 (*R*).

(+)-(3*S*,4*S*)-Methyl 3-Ethyl-4-phenylpentanoate (*anti*-7a).[4c] In a Schlenk tube were dissolved CuBr·SMe_2 (8.0 μmol, 1.62 mg) and ligand (*R*,*S*)-**L3** (9.4 μmol, 5.60 mg) in CH_2Cl_2 (1.5 mL), and the mixture was stirred under argon at rt for 10 min. The mixture was cooled to −75 °C, and EtMgBr (3.0 M in Et_2O, 0.78 mmol) was added dropwise. After the mixture was stirred for 5 min at that temperature, a solution of **5a** (30 mg, 0.16 mmol) in CH_2Cl_2 (0.25 mL) was added dropwise over 10 min. After the mixture was stirred at −75 °C for 22 h, MeOH (0.25 mL) and aq NH_4Cl (1 M, 2 mL) were added sequentially, and the mixture was warmed to rt. After extraction with Et_2O (0.5 mL, 3 ×), the combined organic layers were dried and concentrated to a yellow oil which was purified by flash chromatography (SiO_2, 2:99 Et_2O/pentane) to yield *anti*-**7a** as a colorless oil: 81% yield; 98% de, >99.5% ee (major diastereomer); $[\alpha]_D = +25$ (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 7.26−7.12 (m, 5H), 3.57 (s, 3H), 2.82−2.73 (m, 1H), 2.30−2.15 (m, 2H), 2.08−1.97 (m, 1H), 1.38−1.27 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H), 1.14−1.06 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 174.1, 145.6, 128.2, 127.7, 126.0, 51.4, 42.8, 41.4, 35.3, 24.4, 17.1, 11.1; MS (EI) *m*/*z* 220 (M^+, 20), 189 (11), 146 (43), 105 (100) 57 (21); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1457. Diastereoselectivity was determined using a Chiraldex G-TA column (30 m × 0.25 mm), 100 °C isothermic, retention times (min): 59.6 (minor: 3*R*,4*S* and 3*S*,4*R*) and 62.4 (major, 3*S*,4*S*). Alternatively, the diastereoselectivity was determined by ^{1}H NMR spectroscopy, by integration of the signals at 3.5 ppm corresponding to the methyl ester group. Enantiomeric excess was determined using a Chiraldex

(34) (a) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; Díaz, P. *Synlett* **2006**, 837–840. (b) Ibarra, C. A.; Arias, S.; Fernández, M. J.; Sinisterra, J. V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 503–508. (c) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214–4223.

B-PM column (30 m−0.25 mm), 85 °C isothermic. Retention times (min): 240.5 (3*S*,4*S*), 245.5 (3*R*,4*R*).

(+)-(3*R*,4*S*)-Methyl 3-Ethyl-4-phenylpentanoate (*syn*-7a).[4c] As for *anti*-**7a**, but using (*S*,*R*)-**L3** instead of (*R*,*S*)-**L3**: 84% yield; 92% de, >99.5% ee (major diastereomer); $[\alpha]_D = +6$ (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.24−7.20 (m, 2H), 7.14−7.11 (m, 3H), 3.53 (s, 3H), 2.71−2.67 (m, 1H), 2.16−2.01 (m, 3H), 1.44−1.29 (m, 2H), 1.19 (d, $J = 7.2$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR δ 174.0, 145.6, 128.2, 127.8, 126.1, 51.3, 42.5, 41.8, 36.3, 23.1, 18.2, 10.4; MS (EI) *m*/*z* 220 (M^+, 18), 189 (12), 146 (58), 105 (100); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1462. Diastereoselectivity was determined using a Chiraldex G-TA column (30 m × 0.25 mm), 100 °C, retention times (min): 59.6 (major: 3*R*,4*S*), 62.4 (minor: 3*S*,4*S*) and 63.3 (minor: 3*R*,4*R*). Alternatively, the de was determined by ^{1}H NMR spectroscopy by integration of the signals at 3.57 and 3.53 ppm corresponding to the methyl ester groups. Enantiomeric excess was determined using a CP Chiralsil Dex CB column (25m × 0.25 mm), initial $T = 70$ °C, gradient: 3 °C/min to 110 °C, 110 °C isothermic, retention times (min): 78.5 (3*S*,4*R*), 80.3 (3*R*,4*S*).

(+)-(4*S*,5*S*)-4-Methyl-5-phenylhexan-2-one (*anti*-8a). In a Schlenk tube, (*R*,*S*)-**L1** (7.5 μmol, 5.54 mg) was dissolved in *t*-BuOMe (1.0 mL) and stirred under a N_2-atmosphere at rt for 10 min. The mixture was cooled to −75 °C, and MeMgBr (0.15 mmol, 3.0 M solution in Et_2O) was added dropwise. After the mixture was stirred for 5 min at that temperature, a solution of **5b** (0.11 mmol, 20 mg) in dry *t*-BuOMe (0.5 mL) was added dropwise over 10 min. After 16 h, methanol (0.5 mL) was added, and the mixture was allowed to reach rt. Aqueous NH_4Cl (2 mL) was added, and the biphasic system was stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 3 mL). Combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. Flash chromatography (silica gel, pentane−pentane/Et_2O, 99.5:0.5, v/v) afforded a mixure of *syn*-**8a** and *anti*-**8a**: 73% yield, 96% de, >99.5% ee (major diastereomer); $[\alpha]_D = +12.5$ (*c* 1.0, $CHCl_3$); $R_f = 0.52$ (pentane/EtOAc, 9:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, $J = 6.3$ Hz, 3H) 1.27 (d, $J = 6.9$ Hz, 3H), 2.13 (s, 3H), 2.09−2.34 (m, 2H), 2.47−2.53 (m, 1H), 2.60−2.70 (m, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 18.1, 30.5, 35.2, 44.5, 48.2, 126.0, 127.9, 128.1, 145.1, 208.9; MS (EI) *m*/*z* 190 (M^+, 8), 132 (100), 105 (86); HRMS calcd for $C_{13}H_{18}O$ 190.1358, found 190.1352. Diastereoisomeric ratio and enantiomeric excess were determined by chiral GC analysis, CP Chiralsil Dex CB (25 m × 0.25 mm), initial temperature 75 °C, gradient: 3 °C/min; retention times (min): 26.4 (*syn*) and 25.8 (4*S*,5*S*), 26.1 (4*R*,5*R*). Alternatively, the dr was determined by ^{1}H NMR spectroscopy by comparison of $COCH_3$ signal (2.13 ppm for *anti*, 2.00 ppm for *syn*).

(+)-(4*R*,5*S*)-4-Methyl-5-phenylhexan-2-one (*syn*-8a). The same procedure as for *anti*-**8a** but using (*S*,*R*)-**L1** instead of (*R*,*S*)-**L1**. Reaction time: 18 h. The reaction afforded a mixture of *syn* and *anti* isomers: 46% yield, 72% de, 66% ee (major diastereomer); $[\alpha]_D = +4.7$ (*c* 0.3, $CHCl_3$, 84% ee, 92% de);[35] $R_f = 0.58$ (pentane/EtOAc, 9:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 6.9$ Hz, 3H), 2.00 (s, 3H), 2.09−2.34 (m, 3H), 2.45−2.58 (m, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4, 18.5, 30.4, 35.5, 45.1, 49.4, 126.1, 127.6, 128.3, 146.2, 209.0; MS (EI) *m*/*z* 190 (M^+, 8), 149 (35), 132 (100), 105 (75); HRMS calcd for $C_{13}H_{18}O$ 190.1358, found 190.1349. Diastereoisomeric ratio was determined by chiral GC analysis, CP Chiralsil Dex CB (25 m × 0.25 mm), initial temperature 75 °C, gradient: 3 °C/min; retention times (min): 26.4 (*syn*) and 25.8 (4*S*,5*S*), 26.1 (4*R*,5*R*). Alternatively, the dr was determined by ^{1}H NMR spectroscopy, by the comparison of $COCH_3$ signal (2.13 ppm for *anti*, 2.00 ppm for *syn*). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ-H, heptane/*i*-PrOH, 99/1, v/v, 40 °C). Retention times (min): 20.8 (4*S*,5*R*) and 22.4 (4*R*,5*S*).

(+)-*S*-Ethyl (3*S*,4*S*)-3-Methyl-4-phenylpentanethioate (*anti*-9a). In a Schlenk tube CuI (3.3 μmol, 0.63 mg) and (*R*)-**L4** (3.6 μmol, 2.46 mg) were dissolved in CH_2Cl_2 (0.5 mL) and stirred under a N_2 atmosphere at rt for 50 min. The solvent was evaporated, and the residue was dissolved in *t*-BuOMe (1.2 mL). The mixture was cooled to −75 °C, and MeMgBr (3.0 M in Et_2O, 0.44 mmol) was added dropwise. After the mixture was stirred for 5 min at that temperature, a solution of **5c** (0.11 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise over 10 min. After the mixture was stirred at −75 °C for 18 h, MeOH (0.25 mL) and NH_4Cl (1 M, 2 mL) were added sequentially, and the mixture was warmed to rt. After extraction with Et_2O (0.5 mL, 3×), the combined organic layers were dried and concentrated to a yellow oil, which was subjected to flash chromatography (silica gel, pentane/Et_2O 99.75:0.25, v/v) to afford *syn*-**9a** and *anti*-**9a**: 96% yield, 99% de, 99% ee (major diastereomer); $[\alpha]_D = +31.4$ (*c* 0.35, $CHCl_3$); $R_f = 0.50$ (pentane/Et_2O 95:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, $J = 6.8$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H), 2.24−2.36 (m, 2H), 2.62−2.68 (m, 2H), 2.87 (q, $J = 7.6$ Hz, 2H), 7.15−7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 17.2, 18.5, 23.3, 37.0, 44.5, 48.8, 126.1, 127.8, 128.1, 144.8, 199.3; MS (EI) *m*/*z* 236 (M^+, 12), 175 (100), 132 (35), 105 (66), 91 (30); HRMS calcd for $C_{14}H_{20}OS$ 236.1235, found 236.1244. Diastereoisomeric ratio was determined by chiral GC analysis, Chiralsil G-TA (25 m × 0.25 mm), initial temperature 75 °C, gradient: 3 °C/min; retention times (min): 30.0 (*syn*) and 30.6 (*anti*). Alternatively, the dr was determined by ^{1}H NMR spectroscopy, by the comparison of $PhCHCH_3$ signal (doublet, 0.80 ppm for *anti*, 0.95 ppm for *syn*). Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H, heptane/*i*-PrOH, 99/1, v/v, 40 °C). Retention times (min): 12.3 (3*S*,4*S*) and 13.5 (3*R*,4*R*).

(+)-*S*-Ethyl (3*R*,4*S*)-3-Methyl-4-phenylpentanethioate (*syn*-9a). The same procedure as for *anti*-**9a** however using (*S*)-**L4** instead of (*R*)-**L4**. The reaction afforded a mixture of *syn* and *anti* isomers: 82% yield; 90% de, >99.5% ee (major diastereomer); $[\alpha]_D = +23.0$ (*c* 1.0, $CHCl_3$); $R_f = 0.50$ (pentane/Et_2O 95:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, $J = 6.8$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.25 (d, $J = 6.4$ Hz, 3H), 2.16−2.33 (m, 2H), 2.44−2.62 (m, 2H), 2.83 (q, $J = 7.6$ Hz, 2H), 7.16−7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 16.6, 18.0, 23.2, 37.3, 44.7, 49.6, 126.2, 127.6, 128.3, 145.7, 199.4; MS (EI) *m*/*z* 236 (M^+, 12), 175 (100), 132 (43), 105 (64), 91 (34); HRMS calcd for $C_{14}H_{20}OS$ 236.1235, found 236.1247. Diastereoisomeric ratio was determined with by GC analysis, Chiralsil G-TA (25 m × 0.25 mm), initial temperature 75 °C, gradient: 3 °C/min; retention times (min): 30.0 (*syn*) and 30.6 (*anti*). Alternatively, the dr was determined by ^{1}H NMR spectroscopy, by the comparison of $PhCHCH_3$ signal (doublet, 0.80 ppm for *anti*, 0.95 ppm for *syn*). Enantiomeric excess was determined on a derivative of *syn*-**9a**, the tertiary alcohol (4*R*,5*S*)-2,4-dimethyl-5-phenylhexan-2-ol: To a cooled (0 °C) solution of a sample of *syn*-**9a** in Et_2O was added MeMgBr (ca. 5 equiv), the reaction was heated at reflux for 2 h, quenched with satd aqueous NH_4Cl and extracted with Et_2O. GC analysis was performed on a crude sample of the tertiary alcohol: CP Chiralsil Dex CB column (25 m × 0.25 mm), initial $T = 70$ °C, gradient: 3 °C/min to 150 °C, 150 °C isothermic. Retention times (min): 30.1 (4*S*,5*R*), 30.4 (4*R*,5*S*).

(−)-*S*-Ethyl (*E*,4*S*)-(2)-5-(Benzyloxy)-4-methyl-2-pentenethioate (17).[36] In a dry Schlenk tube, under a N_2 atmosphere, Hoveyda−Grubbs second-generation catalyst (50 μmol, 31.3 mg) was added to a solution of *S*-ethyl thioacrylate **4c** (2.0 mmol, 229 μL) and **16** (1.0 mmol, 176 mg) in CH_2Cl_2 (2.5 mL). The resulting green solution was heated for 6 h at reflux temperature. The mixture was allowed to cool, a second portion of the catalyst was added

(35) Optical rotation measured of the product of a reaction with reaction time 3 h, which had lower conversion and yield.

(36) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709–710.

(50 μmol, 31.3 mg), and the mixture was heated for another 18 h at reflux temperature. The mixture was then concentrated in vacuo and purified by flash chromatography (SiO_2, 5:95 Et_2O/pentane, R_f = 0.5), which afforded an inseparable mixture of **17** and the side product **18** (236 mg, ratio **17**:**18** = 20:1, 83% corrected yield **17**) as a colorless oil: 94% ee; $[\alpha]_D = -17.6$ (*c* 1.9, $CHCl_3$); ^{1}H NMR δ 7.37−7.26 (m, 5H), 6.88 (dd, *J* = 7.0 and 15.7 Hz, 1H), 6.14 (dd, *J* = 1.4 and 15.7 Hz, 1H), 4.52 (s, 2H), 3.44−3.37 (m, 2H), 2.95 (q, *J* = 7.4 Hz, 2H), 2.69−2.61 (m, 1H), 1.28 (t, *J* = 7.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 190.1, 146.9, 138.1, 128.3, 128.2, 127.6, 127.5, 73.7, 73.1, 36.7, 23.1, 16.0, 14.8; MS (EI) *m*/*z* 264 (M^+, 0.2), 235 (2), 203 (4), 174 (11), 145 (9), 117 (12), 92 (8), 91 (100), 83 (6), 82 (14), 65 (6); HRMS calcd for $C_{15}H_{20}SO_2$ 264.1187, found 264.1184. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H (98% heptane/*i*-PrOH), 40 °C. Retention times (min): 20.7 (*S*-enantiomer) and 26.3 (*R*-enantiomer).

(+)-*S*-Ethyl (3*S*,4*S*)-5-(Benzyloxy)-3,4-dimethylpentanethioate (*anti*-12). A dry Schlenk tube equipped with septum and stirring bar was charged with CuI (42 μmol, 8.0 mg), (*R*)-Tol-BINAP (46 μmol, 31.2 mg), and *t*-BuOMe (11.0 mL) and stirred under a N_2 atmosphere at rt until a yellow color appeared. The mixture was cooled to −70 °C, methyl Grignard reagent (5.6 mmol, 3 M solution in Et_2O, 1.85 mL) was added dropwise, and the mixture was stirred for 10 min. Unsaturated thioester **17** (contaminated with **18**) (1.39 mmol, 94 wt %, 391 mg) was added dropwise as a solution in 3.5 mL of CH_2Cl_2 at that temperature. The resulting mixture was stirred at −70 °C for 16 h. The reaction was quenched by addition of MeOH (2 mL) and satd aqueous NH_4Cl solution (10 mL), and the mixture was removed from the cooling bath and allowed to reach rt. Subsequently, enough H_2O to dissolve all salts and 15 mL of Et_2O were added, the organic layer was separated, and the resulting aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a yellow oil, which was purified by flash chromatography (SiO_2, 5:95 Et_2O/pentane, R_f = 0.35), affording *anti*-**12** as a colorless oil (352 mg): 91% yield; 98:2 dr, >99.5% ee (major diastereomer); $[\alpha]_D = +5.1$ (*c* 2.4, $CHCl_3$); ^{1}H NMR δ 7.35−7.26 (m, 5H), 4.50 (s, 2H), 3.39 (dd, *J* = 6.5 and 9.3 Hz, 1H), 3.29 (dd, *J* = 6.4 and 9.3 Hz, 1H), 2.88 (q, *J* = 7.4 Hz, 2H), 2.62 (dd, *J* = 4.3 and 14.4 Hz, 1H), 2.35 (dd, *J* = 9.7 and 14.4 Hz, 1H), 2.28−2.18 (m, 1H), 1.87−1.76 (m, 1H), 1.25 (t, *J* = 7.4 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 199.6, 138.6, 128.3, 127.5, 127.4, 73.2, 73.0, 47.8, 37.8, 32.9, 23.3, 16.8, 14.8, 13.9; MS (EI) *m*/*z* 280 (M^+, 0.3), 219 (14), 92 (9), 91 (100); HRMS calcd for $C_{16}H_{24}SO_2$ 280.1497, found 280.1498. Enantiomeric excess and diastereomeric ratio were determined by chiral HPLC analysis, Chiralcel OB-H (99.7% heptane/*i*-PrOH), 40 °C. Retention times (min): 25.4 (3*R*,4*S*), 29.0 (3*S*,4*S* [major]), 33.5 (3*R*,4*R*) and 38.1 (3*S*,4*R*).

(+)-(3*S*,4*S*)-5-(Benzyloxy)-3,4-dimethylpentanal (19). Thioester *anti*-**12** (0.36 mmol, 101 mg) was dissolved in CH_2Cl_2 (3.5 mL) under a N_2 atmosphere in a dry Schlenk tube equipped with stirring bar and septum. The solution was cooled to −55 °C, and a solution of diisobutylaluminum hydride (0.55 mmol, 1.0 M in CH_2Cl_2, 0.55 mL) was added dropwise. After the mixture was stirred at −55 °C for 2 h, a satd aqueous solution of Rochelle salt (5 mL) was added and the resulting mixture was stirred vigorously at rt for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10:90 Et_2O/pentane, R_f = 0.35), which afforded **19** as a colorless oil (76 mg): 96% yield; $[\alpha]_D = +14.7$ (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 9.72 (dd, *J* = 1.6 and 2.9 Hz, 1H), 7.37−7.26 (m, 5H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.36 (dd, *J* = 7.0 and 9.3 Hz, 1H), 3.32 (dd, *J* = 6.0 and 9.4 Hz, 1H), 2.46 (ddd, *J* = 1.4, 4.3 and 15.9 Hz, 1H), 2.35−2.25 (m, 1H), 2.17 (ddd, *J* = 2.9, 9.2 and 15.8 Hz, 1H), 1.89−1.78 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 203.0, 138.4, 128.3, 127.5, 127.5, 73.1, 73.0, 47.3, 37.8, 29.5, 17.6, 13.5; MS (EI) *m*/*z* 220 (M^+, 5), 177 (6), 129 (7), 113 (22), 111 (6), 108 (27), 107 (32), 96 (7), 95 (6), 92 (35), 91 (100), 83 (12), 81 (11), 79 (6), 77 (7), 71 (20), 70 (8), 69 (15), 65 (13); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1455.

(+)-Benzyl (2*S*,3*S*)-2,3,6-Trimethyl-5-heptenyl Ether (20). In a dry Schlenk tube equipped with septum and stirring bar was suspended isopropyltriphenylphosphonium iodide (1.33 mmol, 577 mg) in THF (8.5 mL) under a N_2 atmosphere and the mixture cooled to 0 °C. A solution of *n*-BuLi (1.33 mmol, 1.6 M in hexanes, 0.83 mL) was added dropwise, and the mixture was stirred at 0 °C for 15 min. The resulting red mixture was cooled to −78 °C and stirred for 15 min at this temperature, after which time a solution of aldehyde **19** (0.43 mmol, 94.9 mg) in THF (4.5 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 60 min and then at 0 °C for 1.5 h, and then a satd aqueous solution of NH_4Cl (1 mL) was added. The mixture was diluted with EtOAc (20 mL) and washed with a satd aqueous solution of NH_4Cl (2 × 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1:99 Et_2O/pentane, R_f = 0.55), which afforded **20** as a colorless oil (95 mg): 90% yield; $[\alpha]_D = +8.4$ (*c* 2.1, $CHCl_3$); ^{1}H NMR δ 7.36−7.25 (m, 5H), 5.12 (t, *J* = 7.2 Hz, 1H), 4.50 (s, 2H), 3.46 (dd, *J* = 5.7 and 9.1 Hz, 1H), 3.29 (dd, *J* = 7.3 and 9.1 Hz, 1H), 2.06−1.99 (m, 1H), 1.86−1.74 (m, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.63−1.54 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 138.8, 131.8, 128.3, 127.5, 127.4, 123.8, 73.8, 73.0, 37.8, 35.8, 31.5, 25.8, 17.8, 16.9, 14.4; MS (EI) *m*/*z* 247 (7), 246 (M^+, 38), 175 (14), 155 (9), 138 (8), 137 (42), 97 (23), 96 (11), 95 (20), 92 (12), 91 (100), 83 (10), 81 (17), 71 (6), 70 (6), 69 (53), 65 (7), 57 (10), 55 (16); HRMS calcd for $C_{17}H_{26}O$ 246.1984, found 246.1979.

(−)-Lasiol [(2*S*,3*S*)-2,3,6-Trimethyl-5-hepten-1-ol] (10).[19−22] Liquid NH_3 was condensed in a dry Schlenk flask under a N_2 atmosphere at −78 °C. A second dry Schlenk flask under N_2 was equipped with septum and stirring bar, charged with pieces of Li (5.8 mmol, 40 mg) and THF (3.0 mL), and cooled to −78 °C. The flasks were connected via cannula, and the flask with NH_3 was removed from the cooling bath allowing the NH_3 (ca. 10 mL) to distill into the second flask. After the dark blue solution was stirred at −78 °C for 30 min, a solution of **20** (0.34 mmol, 84.3 mg) in THF (2.0 mL) was added dropwise. After 20 min, solid NH_4Cl (1.5 g) was added carefully, and the NH_3 was allowed to evaporate using a waterbath at rt. A satd aqueous solution of NaCl (10 mL) was added, followed by just enough H_2O to dissolve all of the salts. The organic layer was separated, and the resulting water layer was extracted with Et_2O (3×, 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20:80 Et_2O/pentane, R_f = 0.4) to afford (−)-lasiol **10** as a colorless liquid (52 mg): 99% yield; $[\alpha]_D = -10.2$ (*c* 1.9, *n*-hexane) [lit.[22c] $[\alpha]_D = -12.1$ (*c* 0.995, *n*-hexane)]; ^{1}H NMR δ 5.12 (br t, *J* = 7.2 Hz, 1H), 3.65 (dd, *J* = 5.4 and 10.6 Hz, 1H), 3.46 (dd, *J* = 7.1 and 10.6 Hz, 1H), 2.00−2.07 (m, 1H), 1.84−1.51 (m, 10H, containing two singlets of each 3H: 1.70 and 1.60 ppm), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR δ 132.0, 123.5, 66.0, 40.2, 35.4, 31.3, 25.8, 17.7, 16.9, 13.7; spectroscopic data were in good agreement with those reported in literature;[19] MS (EI) *m*/*z* 156 (M^+, 38), 139 (7), 138 (10), 137 (9), 125 (6), 123 (33), 109 (19), 97 (21), 96 (34), 95 (25), 86 (6), 85 (32), 83 (13), 82 (24), 81 (21), 71 (16), 70 (55), 69 (100), 68 (12), 67 (16), 59 (10), 58 (7), 57 (19), 56 (17), 55 (46), 53 (11); HRMS calcd for $C_{10}H_{20}O$ 156.1514, found 156.1519.

(+)-2-((2*S*,3*S*)-4-(Benzyloxy)-2,3-dimethylbutyl)-1,3-dioxolane (21). A catalytic amount of *p*-TsOH·H_2O (0.26 mmol, 50 mg) was added to a stirred suspension of aldehyde **19** (4.7 mmol, 1.04 g), ethylene glycol (30 mmol, 1.5 mL), and 5.0 g of $MgSO_4$ in 60 mL of benzene. The mixture was heated at reflux temperature for 14 h,

after which it was diluted with 50 mL of Et_2O and filtered. The filtrate was washed with satd aq $NaHCO_3$ (40 mL) and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10:90 Et_2O/pentane, $R_f = 0.25$) to afford **21** as a colorless oil (1.19 g): 95% yield; $[\alpha]_D = +3.0$ (*c* 5.2, $CHCl_3$); ^1H NMR δ 7.36−7.25 (m, 5H), 4.89 (dd, $J = 4.4$ and 5.9 Hz, 1H), 4.49 (s, 2H), 3.99−3.91 (m, 2H), 3.89−8.80 (m, 2H), 3.42 (dd, $J = 6.0$ and 9.2 Hz, 1H), 3.27 (dd, $J = 7.0$ and 9.2 Hz, 1H), 1.90−1.76 (m, 2H), 1.69 (ddd, $J = 3.8$, 5.9 and 13.8 Hz, 1H), 1.47 (ddd, $J = 4.4$, 9.8 and 14.0 Hz, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 138.7, 128.2, 127.4, 127.3, 104.1, 73.4, 72.9, 64.7, 64.5, 38.3, 36.9, 31.0, 17.1, 13.6; MS (EI) *m*/*z* 264 (M^+, 0.8), 173 (6), 157 (10), 115 (11), 113 (14), 107 (7), 97 (6), 96 (6), 92 (7), 91 (54), 73 (100), 65 (6); HRMS calcd for $C_{16}H_{24}O_3$ 264.1726, found 264.1735.

(−)-(2*S*,3*S*)-4-(1,3-Dioxolan-2-yl)-2,3-dimethylbutan-1-ol (22). A suspension of benzyl ether **21** (0.3 mmol, 79 mg) and $Pd(OH)_2$/C (15 μmol, 60 wt % (moist), dry: 20 wt % $Pd(OH)_2$, 26 mg) in EtOAc (3.0 mL) was stirred vigorously at rt under a H_2 atmosphere for 30 min. Celite was added, and the suspension was filtered over Celite. The filtercake was washed with EtOAc, and the combined filtrates were concentrated. The residue was purified by flash chromatography (SiO_2, 20:80 to 100:0 Et_2O/pentane gradient, R_f (70:30) = 0.35), to afford **22** as a colorless oil (52 mg): 99% yield; $[\alpha]_D = -20.3$ (*c* 2.4, $CHCl_3$); ^1H NMR δ 4.86 (dd, $J = 3.6$ and 6.2 Hz, 1H), 3.97−3.88 (m, 2H), 3.86−3.78 (m, 2H), 3.49 (dd, $J = 7.4$ and 11.0 Hz, 1H), 3.39 (dd, $J = 6.5$ and 11.0 Hz, 1H), 2.38 (br s, 1H), 1.89−1.79 (m, 1H), 1.69−1.59 (m, 2H), 1.45−1.38 (m, 1H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.79 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 103.9, 65.1, 64.5, 64.4, 40.2, 35.7, 29.5, 17.7, 12.2; MS (EI) *m*/*z* 173 ($[M - H]^+$, 4), 115 (8), 113 (7), 102 (10), 88 (13), 85 (5), 74 (12), 73 (100), 71 (8), 69 (7), 55 (8); MS (CI) *m*/*z* 193 (11), 192 ($[M + NH_4]^+$, 100), 175 ($[M + H]^+$, 6), 147 (12), 131 (6), 130 (62), 113 (16); HRMS calcd for $[M - H]^+$ $C_9H_{17}O_3$ 173.1178, found 173.1185.

(+)-2-((2*S*,3*S*)-4-Iodo-2,3-dimethylbutyl)-1,3-dioxolane (14). To a stirred solution of alcohol **22** (0.27 mmol, 46 mg), PPh_3 (0.4 mmol, 105 mg), and imidazole (0.5 mmol, 34 mg) in benzene (2.0 mL) and DMF (0.1 mL) was added I_2 (0.45 mmol, 114 mg) in one portion. The resulting mixture was stirred at rt for 45 min, after which it was poured into 5 mL of satd aq $Na_2S_2O_3$ solution and extracted with Et_2O (5 mL, 2×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 5:95 Et_2O/pentane, $R_f = 0.25$) to afford **14** as a colorless oil (69 mg): 91% yield; $[\alpha]_D = +1.3$ (*c* 3.2, $CHCl_3$); ^1H NMR δ 4.89 (dd, $J = 4.3$ and 5.8 Hz, 1H), 4.00−3.92 (m, 2H), 3.89−3.81 (m, 2H), 3.27 (dd, $J = 4.7$ and 9.7 Hz, 1H), 3.10 (dd, $J = 7.9$ and 9.7 Hz, 1H), 1.85−1.76 (m, 1H), 1.68 (ddd, $J = 3.8$, 5.7 and 13.7 Hz, 1H), 1.64−1.56 (m, 1H), 1.48 (ddd, $J = 4.3$, 9.6 and 13.9 Hz, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR δ 103.6, 64.7, 64.5, 40.5, 36.5, 33.5, 17.1, 17.1, 14.2; MS (EI) *m*/*z* 283 (7), 157, (8), 95 (7), 73 (100); MS (CI) *m*/*z* 302 ($[M + NH_4]^+$, 17), 69 (100); HRMS calcd for $[M - H]^+$ $C_9H_{16}O_2I$ 283.0195, found 283.0248.

(−)-2-((2*S*,3*R*,5*E*,9*Z*)-2,3,6,10-Tetramethyldodeca-5,9-dienyl)-1,3-dioxolane (23). A dry Schlenk tube equipped with septum and stirring bar was charged with alkyl iodide **14** (232 μmol, 66 mg) and Et_2O (1.2 mL) under a N_2 atmosphere and cooled to −78 °C. *t*-BuLi (0.51 mmol, 1.9 M solution in pentane, 0.27 mL) was added dropwise via syringe, and the solution was stirred at −78 °C for 20 min. A solution of dried $ZnBr_2$ (0.29 mmol, 65 mg) in THF (0.7 mL) was added dropwise via syringe, and the resulting mixture was allowed to warm to 0 °C in 1 h. At 0 °C, a solution of (1*E*,5*Z*)-1-iodo-2,6-dimethylocta-1,5-diene **13** (0.35 mmol, 92 mg) and $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (11.6 μmol, 9.5 mg) in a mixture of THF/DMF (0.8 mL, 1:1) was added via syringe, and the resulting green suspension was stirred at rt for 16 h. H_2O (5 mL) was added to the mixture, which was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1:99−2:98 Et_2O/pentane gradient, R_f (1:99) = 0.1), affording **23** as a colorless oil (48 mg): 71% yield; $[\alpha]_D = -3.8$ (*c* 0.9, $CHCl_3$); ^1H NMR δ 5.12 (br t, $J = 6.7$ Hz, 1H), 5.06 (br t, $J = 6.5$ Hz, 1H), 4.88 (dd, $J = 4.4$ and 5.8 Hz, 1H), 4.00−3.91 (m, 2H), 3.89−3.80 (m, 2H), 2.10−1.95 (m, 7H), 1.83−1.75 (m, 1H), 1.74−1.67 (m, 2H), 1.66 (dd, $J = 1.2$ and 2.4 Hz, 3H), 1.58 (s, 3H), 1.40−1.42 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H), 0.93 (d, $J = 6.1$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 136.9, 135.3, 123.9, 123.7, 104.3, 64.7, 64.5, 40.1, 38.8, 37.1, 33.5, 31.3, 26.2, 24.7, 22.8, 16.8, 16.0, 15.9, 12.8; MS (EI) *m*/*z* 294 (M^+, 4), 149 (6), 123 (7), 121 (5), 115 (7), 114 (6), 113 (100), 107 (16), 95 (15), 93 (6), 83 (21), 81 (16), 73 (66), 69 (10), 67 (10), 55 (44); HRMS calcd for $C_{19}H_{34}O_2$ 294.2559, found 294.2550.

(+)-Faranal [(3*S*,4*R*,6*E*,10*Z*)-3,4,7,11-Tetramethyl-trideca-6,10-dienal] (11).[23−28] In a Schlenk flask under a N_2 atmosphere was dissolved dioxolane **23** (63 μmol, 18.5 mg) in a mixture of THF and water (24 mL, 5:1). *p*-TsOH·H_2O (1.26 mmol, 240 mg) was added, and the solution was heated at reflux temperature for 1 h. The mixture was poured into satd aqueous $NaHCO_3$ (20 mL) and extracted with 40 mL of Et_2O. The organic layer was subsequently washed with satd aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2:98 Et_2O/pentane, $R_f = 0.2$), affording **11** as a colorless oil (9.7 mg): 62% yield; $[\alpha]_D = +19.2$ (*c* 1.0, $CHCl_3$) [lit.[28] $[\alpha]_D = +17.4$ (*c* 4.12, $CHCl_3$); lit.[27b] $[\alpha]_D = +17.5$ (*c* 0.52, *n*-hexane)]; ^1H NMR δ 9.74 (dd, $J = 1.7$ and 2.6 Hz, 1H), 5.11 (br t, $J = 6.7$ Hz, 1H), 5.05 (br t, $J = 6.6$ Hz, 1H), 2.47−2.41 (m, 1H), 2.21−1.95 (m, 9H), 1.87−1.78 (m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.52−1.42 (m, 1H), 0.96 (t, $J = 7.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR δ 203.3, 137.1, 135.9, 123.8, 123.0, 47.4, 40.1, 38.4, 32.0, 31.8, 26.2, 24.7, 22.8, 17.5, 16.1, 15.9, 12.8; spectroscopic data were in good agreement with those reported in literature.[28] MS (EI) *m*/*z* 250 (M^+, 6), 203 (5), 194 (7), 193 (44), 177 (5), 175 (12), 149 (9), 138 (6), 137 (23), 136 (6), 124 (5), 123 (29), 122 (7), 121 (9), 111 (8), 109 (13), 107 (17), 99 (6), 97 (9), 96 (7), 95 (20), 93 (9), 84 (8), 83 (100), 82 (23), 81 (27), 79 (6), 69 (20), 68 (7), 67 (17), 57 (5), 55 (87), 53 (7); HRMS calcd for $C_{17}H_{30}O$ 250.2297, found 250.2307.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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