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Efficient Remote Axial-to-Central Chirality Transfer in Enantioselective SmI_2-Mediated Reductive Coupling of Aldehydes with Crotonates of Atropisomeric 1-Naphthamides

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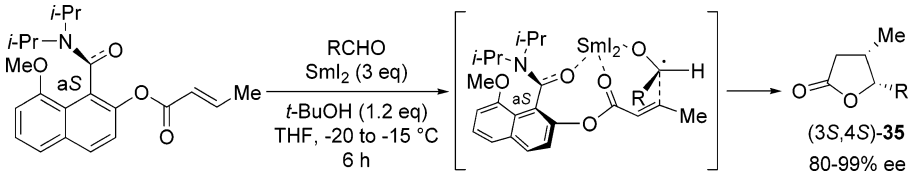

Control of enantioselectivity by remote amide conformation has been studied in SmI_2-mediated reductive coupling of aldehydes with the crotonates possessing different 2-substituted 8-methoxy-1-naphthamides. The enantiomers of atropisomeric 8-methoxy-1-naphthamides were prepared through a chemical resolution process, and their absolute stereochemistry was determined by X-ray crystal structural analysis. It was found that the linkage between crotonate and the C2 position of 8-methoxy-1-naphthamides remarkably influenced the efficiency of remote chirality transfer originated from the amide conformation. Among the four crotonates examined, the one derived from 2-hydroxy-8-methoxy-1-naphthamide reacted with pentanal to afford the highest ee of >99% for the *cis*-γ-butyrolactone and in 90% combined yield with a cis/trans ratio of 90:10. We developed a new procedure for attaching the chiral crotonate via the C8 oxygen to a Rink amide resin under mild conditions and obtained the same level of highly remote axial-to-central chirality transfer in the solid-phase reaction.

Introduction

Chirality transfer or asymmetric induction from chiral catalysts or chiral auxiliaries is the basis for asymmetric synthesis of enantiomerically enriched chiral molecules. The efficiency of the chirality transfer is largely dependent on how tight the interaction is between the chirality source and the reacting site. A short distance is normally considered being favorable for highly efficient chirality transfer or asymmetric induction.[1] It is of interest to study stereocontrol among remote sites.[2,3] One recent example reported by Clayden and co-workers illustrated the state of art in achieving remote stereocontrol in two sites separated by more than 20 bond lengths or a linear distance of >2.5 nm.[3] The system in the work of Clayden and co-workers features chiral relay of rotationally restricted tertiary amides through the space,[3,4] and the axially chiral amide unit is then used to induce stereogenic center(s) in reactions taking place at close proximity, which are normally separated by two bond lengths.[3−5] However, in a system such as the propionates *rac*-**1** (Chart 1), where the α-carbon of the ester is four bond lengths away from the ipso position of the amide subunit, Clayden and co-workers reported poor stereocontrol in aldol reactions, giving 31:69 (for X = H) and 59:41 (for X = $SiMe_3$) mixtures of anti/syn aldols, respectively.[6] It seems that the amide conformation of **1** could not efficiently communicate with the enolate reaction site, although a successful example exists for a similar reaction on the basis of the Fuji et al. binol derivative which gave anti-

(1) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(2) (a) Magnus, N.; Magnus, P. *Tetrahedron Lett.* **1997**, *38*, 3491−3494. (b) Linnane, P.; Magnus, N.; Magnus, P. *Nature* **1997**, *385*, 799−801.

(3) Clayden, J.; Lund, A.; Vallverdu, L.; Helliwell, M. *Nature* **2004**, *431*, 966−971.

(4) (a) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949−951. (b) Clayden, J. *Synlett* **1998**, 810−816. (c) Clayden, J. *Chem. Commun.* **2004**, 127−135.

(5) Selected examples of asymmetric induction using enantio-enriched atropisomeric amides, see: (a) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967−968. (b) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295−1304. (c) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 2634−2540. (d) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279−3283. (e) Clayden, J.; Lund, A.; Youssef, L. H. *Org. Lett.* **2001**, *3*, 4133−4136.

(6) Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232−3249.

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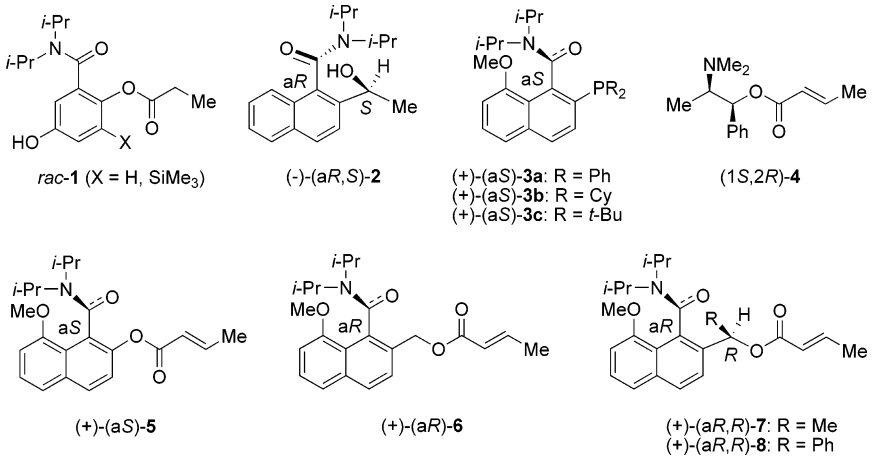
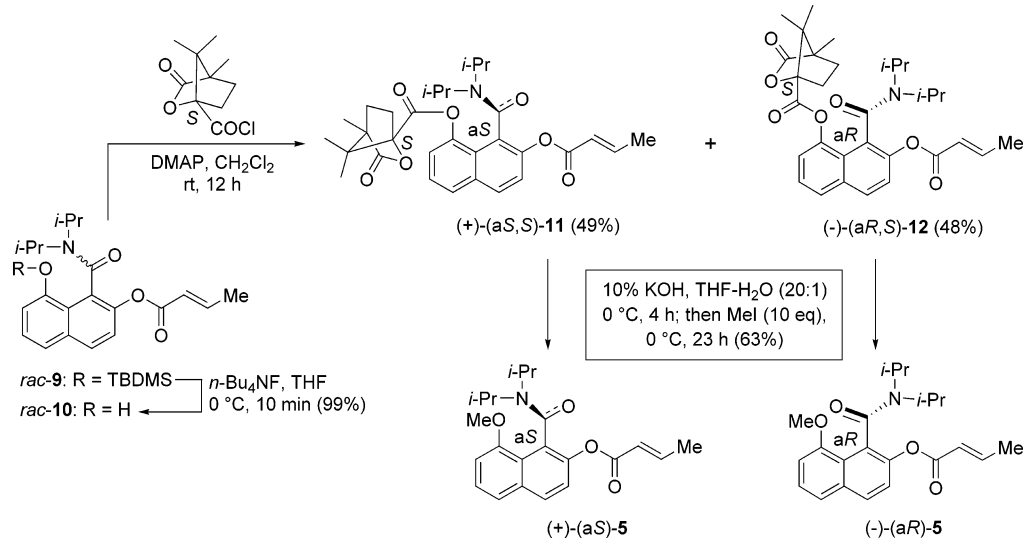
CHART 1. Structures of Conformationally Restricted Benzamides, 1-Naphthamides, and Chiral Crotonates



SCHEME 1. Synthesis of Chiral Crotonates of 2-Hydroxy-8-methoxy-1-naphthamide



selective aldols.[7] In our previous studies on asymmetric reactions and catalysis using enantiomerically pure atropisomeric 1-naphthamides, we have reported highly diastereoselective desymmetrization of *meso*-anhydrides with (−)-(a*R*,*S*)-**2**,[8] Pd-catalyzed asymmetric allylic alkylation with the atropisomeric amide-derived phosphine (A^2phos) (+)-(a*S*)-**3a**,[9a] asymmetric Heck reaction with A^2phos (+)-(a*S*)-**3c**,[9b] and asymmetric Suzuki−Miyaura coupling with A^2phos (+)-(a*S*)-**3b**.[9c] We report here our results on SmI_2-mediated reductive coupling of aldehydes with the chiral crotonates **5**−**8** (Chart 1),[10] possessing atropisomeric 8-methoxy-1-naphthamide scaffolds. By comparison with the reactions of (1*S*,2*R*)-**4**, derived from *N*-methylephedrine,[11] we planned to determine the structural elements essential for highly efficient axial-to-central chirality transfer from the amide moiety to remote centers separated at least by five bond lengths.

Results and Discussion

Synthesis and Stereochemistry Determination of Chiral Crotonates 5−8. In our previous study, we obtained (+)-(a*S*)-**5** in 94.3% ee via kinetic resolution under asymmetric dihydroxylation conditions by using $(DHQD)_2$−PHAL [1,4-bis(9-*O*-dihydroquinidine)phthalazine] as the chiral ligand.[10,12] The absolute stereochemistry of (+)-(a*S*)-**5** was established by correlation to a compound whose absolute stereochemistry was determined by X-ray crystallographic analysis.[10] To prepare enantiomerically pure crotonate **5**, we turned our attention to the chemical resolution approach as shown in Scheme 1. Starting from the known 8-silyloxy compound *rac*-**9**,[10] the 8-hydroxy-

(7) Ahn, M.; Tanaka, K.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 185−192.

(8) Dai, W.-M.; Yeung, K. K. Y.; Chow, C. W.; Williams, I. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1603−1613.

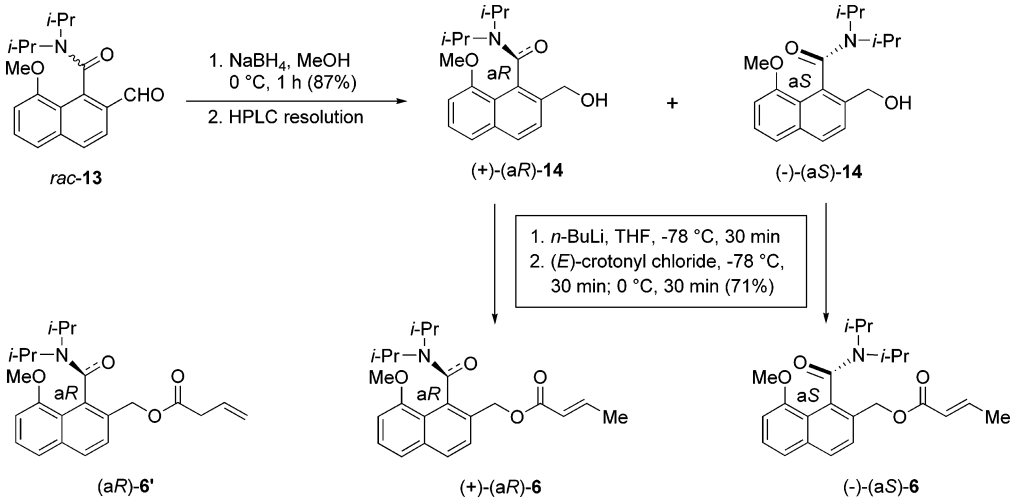
(9) (a) Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y.; Williams, I. D. *Org. Lett.* **2002**, *4*, 1615−1618. (b) Dai, W.-M.; Yeung, K. K. Y.; Wang, Y. *Tetrahedron* **2004**, *60*, 4425−4430. (c) Zhang, Y. Ph.D. Thesis, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China, 2005.

(10) The chiral crotonate (+)-(a*S*)-**5** was prepared previously by kinetic resolution via asymmetric dihydroxylation, see: Dai, W.-M.; Zhang, Y.; Zhang, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 525−535.

(11) (a) Fukuzawa, S.; Seki, K.; Tastuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483. For a review on sequencing reactions with SmI_2, see: (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. For a recent study on the role of proton donors in SmI_2-mediated ketone reduction, see: (c) Chopade, P. R.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44−45.

(12) VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864−7865.

SCHEME 2. Synthesis of Chiral Crotonates of 2-Hydroxymethyl-8-methoxy-1-naphthamide



1-naphthamide *rac*-**10** was obtained in 99% yield after desilylation with *n*-Bu_4NF in THF. Esterification of *rac*-**10** with (*S*)-camphanic chloride in the presence of DMAP in CH_2Cl_2 afforded a pair of diastereomers (+)-(a*S*,*S*)-**11** (49%) and (−)-(a*R*,*S*)-**12** (48%), which were separated by column chromatography on silica gel. The stereochemistries of (+)-(a*S*,*S*)-**11** and (−)-(a*R*,*S*)-**12** were assigned after conversion to the known 8-methoxy derivatives (+)-(a*S*)-**5** and (−)-(a*R*)-**5**, respectively. Because we observed slow racemization of axially chiral 8-hydroxy-1-naphthamide (a*S*)-**10** (not shown) at room temperature after removal of the camphanyl group from (+)-(a*S*)-**11**, we applied a one-pot transformation of (+)-(a*S*,*S*)-**11** and (−)-(a*R*,*S*)-**12** to (+)-(a*S*)-**5** and (−)-(a*R*)-**5** (Scheme 1) in an overall yield of 63%, without isolation of 8-hydroxy-1-naphthamide (a*S*)-**10** and (a*R*)-**10**.

Our preparation of (+)-(a*R*)-**6** and (−)-(a*S*)-**6** was straightforward, starting from the known racemic aldehyde *rac*-**13**[5d,6] (Scheme 2). Clayden and co-workers used a dynamic resolution by using a chiral diamine to obtain (−)-(a*R*)-**13** in 99% ee and in 56% yield from *rac*-**13** through a three-step operation.[5d,6] We obtained both enantiomeric alcohols (+)-(a*R*)-**14** and (−)-(a*S*)-**14** from the reduction of *rac*-**13**, followed by the semipreparative HPLC separation of the racemic alcohol over a chiral stationary phase (Chiralpak AD). The absolute stereochemistry of (−)-(a*S*)-**14** was assigned by oxidation to the known aldehyde (−)-(a*R*)-**13** with a change in priority of the substituents.[5d,6] In the reactions of (+)-(a*R*)-**14** with (*E*)-crotonyl chloride in the presence of Et_3N as the base, we found a byproduct (a*R*)-**6′** (60%), featured with a monosubstituted olefin moiety in the ^1H NMR spectrum, which suggests a 3-butenoate unit. Use of *n*-BuLi as the base could suppress the byproduct to afford the desired crotonate (+)-(a*R*)-**6** or (−)-(a*S*)-**6** in 71% yield.

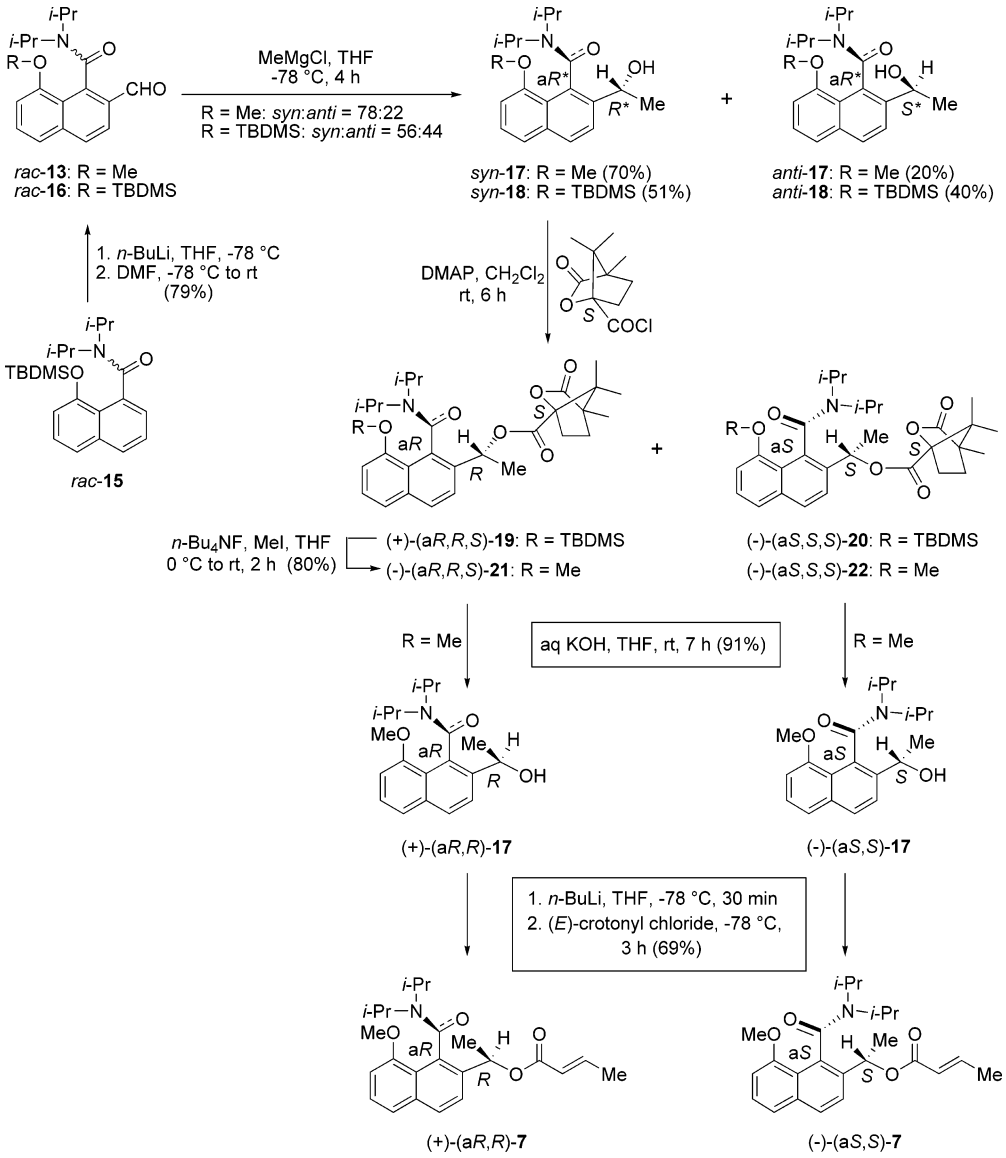
Initially, we planned to use racemic 8-methoxy-1-naphthamide *syn*-**17** for the synthesis of the chiral crotonates (+)-(a*R*,*R*)-**7** and (−)-(a*S*,*S*)-**7** (Scheme 3). The addition of MeMgCl with *rac*-**13** gave a mixture of two diastereomers whose ratio is 78:22 (syn/anti)[13] in favor of the syn isomer.[14] Unfortunately, the diastereomeric camphanic esters of (−)-(a*R*,*R*,*S*)-**21** and (−)-(a*S*,*S*,*S*)-**22** formed from *syn*-**17** could not be separated on a silica gel column. Then, we adopted the chemical resolution of 8-silyloxy analogue *syn*-**18**. Starting from the known amide *rac*-**15**,[9a,10] the aldehyde *rac*-**16** was prepared in 79% yield via the amide-directed ortho lithiation, followed by quenching with DMF. The addition of MeMgCl with *rac*-**16** gave a 56:44 mixture of *syn*-**18** and *anti*-**18** in 91% combined yield. It is interesting to note the diminished atroposelectivity due to the bulky 8-silyloxy group in *rac*-**16** as compared to that of the 8-methoxy analogue *rac*-**13**. We secured the relative stereochemistry of *anti*-**18** by X-ray crystal structural analysis, and the structural drawing is given in Figure S1 of the Supporting Information. Condensation of *syn*-**18** with (*S*)-camphanic chloride in the presence of DMAP in CH_2Cl_2 afforded the pure diastereomers (+)-(a*R*,*R*,*S*)-**19** and (−)-(a*S*,*S*,*S*)-**20** after separation by column chromatography on silica gel. To eliminate the possibility of racemization after desilylation, we developed a one-pot conversion of (+)-(a*R*,*R*,*S*)-**19** and (−)-(a*S*,*S*,*S*)-**20** into the corresponding 8-methoxy derivatives (−)-(a*R*,*R*,*S*)-**21** and (−)-(a*S*,*S*,*S*)-**22**, respectively, via a high-yielding in situ desilylation and methylation process (*n*-Bu_4NF, MeI, THF; Scheme 3). The absolute stereochemistry of (−)-(a*S*,*S*,*S*)-**22** was established again by X-ray crystallographic analysis as illustrated in Figure S2 of the Supporting Information. It in turn confirmed the stereochemistry assignment of the diastereomer (−)-(a*R*,*R*,*S*)-**21**. Finally, removal of the camphanyl group in the esters (−)-(a*R*,*R*,*S*)-**21** and (−)-(a*S*,*S*,*S*)-**22** formed the enantiomerically pure (+)-(a*R*,*R*)-**17** and (−)-(a*S*,*S*)-**17**, which were converted into the chiral crotonates (+)-(a*R*,*R*)-**7** and (−)-(a*S*,*S*)-**7**, respectively, after deprotonation with *n*-BuLi and a reaction with (*E*)-crotonyl chloride.

By following a similar approach as described above, we synthesized the chiral crotonates (+)-(a*R*,*R*)-**8** and (−)-(a*S*,*S*)-**8**, as depicted in Scheme 4. The addition of PhMgCl with *rac*-**13** provided *syn*-**23** as the single isomer in 96% yield. The increased atroposelectivity with PhMgCl is in agreement with the early observation in a similar reaction of the aldehyde lacking the 8-methoxy group.[14] Ester bond formation between racemic *syn*-**23** and (*S*)-camphanic chloride was carried out in

(13) The syn and anti isomers are defined as follows. With an orthogonal orientation of the naphthalene ring and amide moiety in 1-naphthamides, the syn and anti isomers may be viewed by placing the small group (H) of the C2 tetrahedral substituent on the naphthalene plane and pointing toward the C1 amide moiety. Thus, the syn isomer has the amide carbonyl oxygen atom on the same side with the oxygen atom (or functional group) of the tetrahedral substituent.

(14) (a) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577−5580. (b) Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363−1378.

SCHEME 3. Synthesis of Chiral Crotonates of 2-(1′-Hydroxyethyl)-8-methoxy-1-naphthamide



CH_2Cl_2 in the presence of DMAP to afford pure diastereomers (+)-(a*R*,*R*,*S*)-**24** and (−)-(a*S*,*S*,*S*)-**25** after column chromatographic separation over silica gel. The absolute stereochemistry of (−)-(a*S*,*S*,*S*)-**25** was deduced by X-ray crystal structural analysis and the structural drawing is given in Figure S3 of the Supporting Information. Alkaline hydrolysis of (+)-(a*R*,*R*,*S*)-**24** and (−)-(a*S*,*S*,*S*)-**25** gave the enantiomeric alcohols (+)-(a*R*,*R*)-**23** and (−)-(a*S*,*S*)-**23** in 89% yields. The latter were treated with *n*-BuLi and (*E*)-crotonyl chloride to furnish the chiral crotonates (+)-(a*R*,*R*)-**8** and (−)-(a*S*,*S*)-**8**, respectively, in 70% yield.

SmI_2-Mediated Reductive Coupling of Aldehydes with Chiral Crotonates. In 1997, Fukuzawa and co-workers first reported the SmI_2-mediated reductive coupling of aldehydes with chiral acrylates and crotonates derived from *N*-methylephedrine to form chiral γ-butyrolactones in high enantioselectivity.[11a] Recently, Lin and co-workers reported the synthesis of chiral γ-butyrolactones from the SmI_2-mediated reductive coupling of ketones with both achiral and chiral acrylates in the presence of a chiral proton donor.[15] We performed the SmI_2-mediated reductive coupling of aldehydes with our chiral crotonates **5**−**8** prepared above for investigating remote axial-to-central chirality transfer. The results are summarized in Table 1. Reactions of both (−)-(a*R*)-**5** and (+)-(a*S*)-**5** with pentanal gave the γ-butyrolactone **36a** in 90% yield with 90:10 cis/trans isomer ratio (Table 1, entries 1 and 2). The enantioselectivities for both *cis*- and *trans*-**36a** are >99 and ≥95%, respectively. However, the same reactions using chiral crotonates **6**−**8** afforded lower yields of **36a** and lower enantiomer excess in the range of 14−63% for the cis isomer (Table 1, entries 6, 8, and 10), although the cis/trans isomer ratios remained high (83:17−95:5). A similar efficiency in chirality transfer was observed in the reactions of 2,2,2-trimethylacetaldehyde with the chiral crotonates **5**−**7** (entries 4, 7, and 9), while the *cis*-γ-butyrolactone **36c** was obtained in 96% ee from the reaction of (+)-(a*S*)-**5**. We carried out the SmI_2-mediated reductive coupling of isobutyraldehyde and cyclohexanecarboxaldehyde with (+)-(a*S*)-**5** and (−)-(a*R*)-**5**

(15) (a) Xu, M.-H.; Lin, G.-Q.; Xia, L.-J. *Chin. J. Chem.* **1998**, *16*, 561−564. (b) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229−2232. (c) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773−3776. (d) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3952−3962. (e) Wang, W.; Zhong, Y.-W.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 4613−4616. (f) Huang, L.-L.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2005**, *70*, 529−532.

SCHEME 4. Synthesis of Chiral Crotonates of 2-(1′-Hydroxybenzyl)-8-methoxy-1-naphthamide

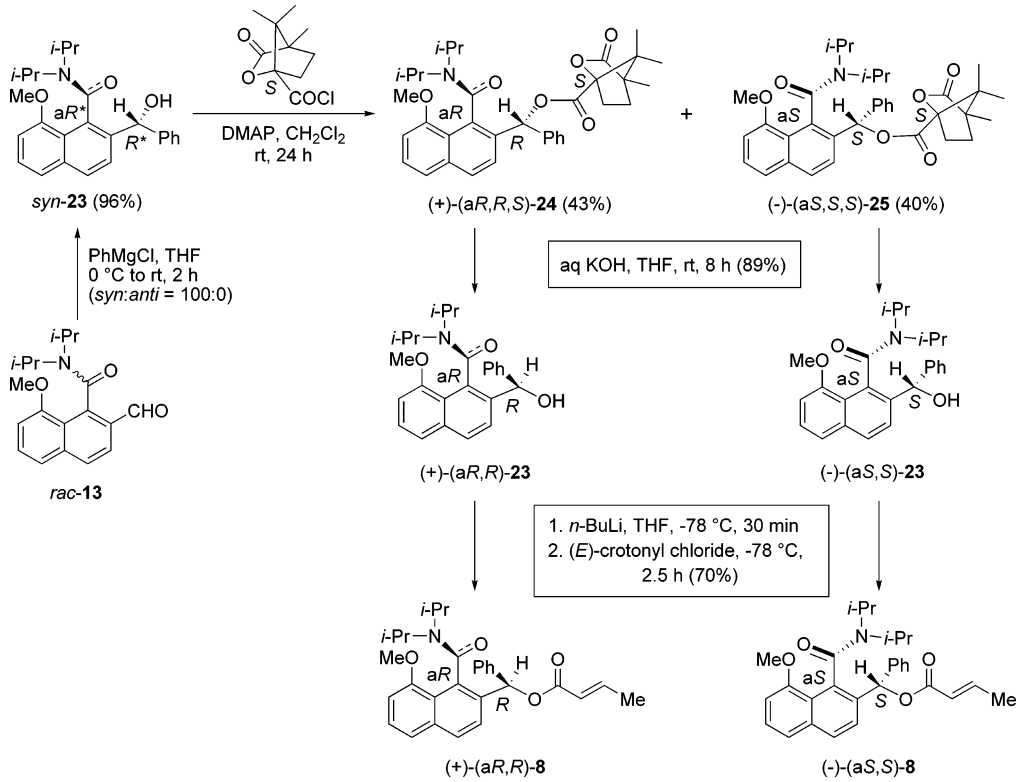
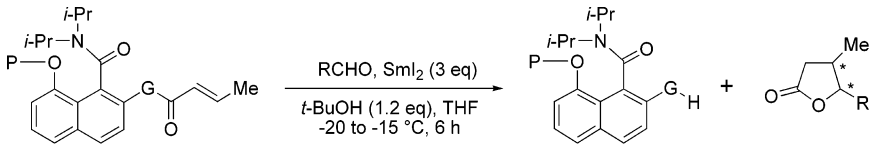


TABLE 1. SmI_2-Mediated Reductive Coupling of Aldehydes with Chiral Crotonates



I: P = Me, resin II: P = Me, resin 36

entry	I	RCHO	yield[a] (%)	cis/trans[b]	ee[c] (%, cis; trans)	cis $[\alpha]^{23}_D$;[e] config.
1	(−)-(a*R*)-**5**	*n*-BuCHO	**36a**: 90	90:10	>99; 96	+80.8; (3*R*,4*R*)
2	(+)-(a*S*)-**5**	*n*-BuCHO	**36a**: 90	90:10	>99; 95	
3	(+)-(a*S*)-**5**	*i*-PrCHO	**36b**: 81	91:9	>99; 75	
4	(+)-(a*S*)-**5**	*t*-BuCHO	**36c**: 85	72:28	96; 61	
5	(−)-(a*R*)-**5**	CyCHO	**36d**: 87	88:12	80[d]	+46.5
6	(−)-(a*S*)-**6**	*n*-BuCHO	**36a**: 55	95:5	32; 46	(3*R*,4*R*)
7	(−)-(a*S*)-**6**	*t*-BuCHO	**36c**: 67	100:0	5	
8	(+)-(a*R*,*R*)-**7**	*n*-BuCHO	**36a**: 48	84:16	63; 76	(3*S*,4*S*)
9	(+)-(a*R*,*R*)-**7**	*t*-BuCHO	**36c**: 45	84:16	36; >95	
10	(−)-(a*S*,*S*)-**8**	*n*-BuCHO	**36a**: 40	83:17	14; 83	(3*R*,4*R*)
11	(a*S*)-**35**	*t*-BuCHO	**36c**: 58	71:29	94; 89	
12	(a*R*)-**35**	CyCHO	**36d**: 66	89:11	88[d]	+50.9

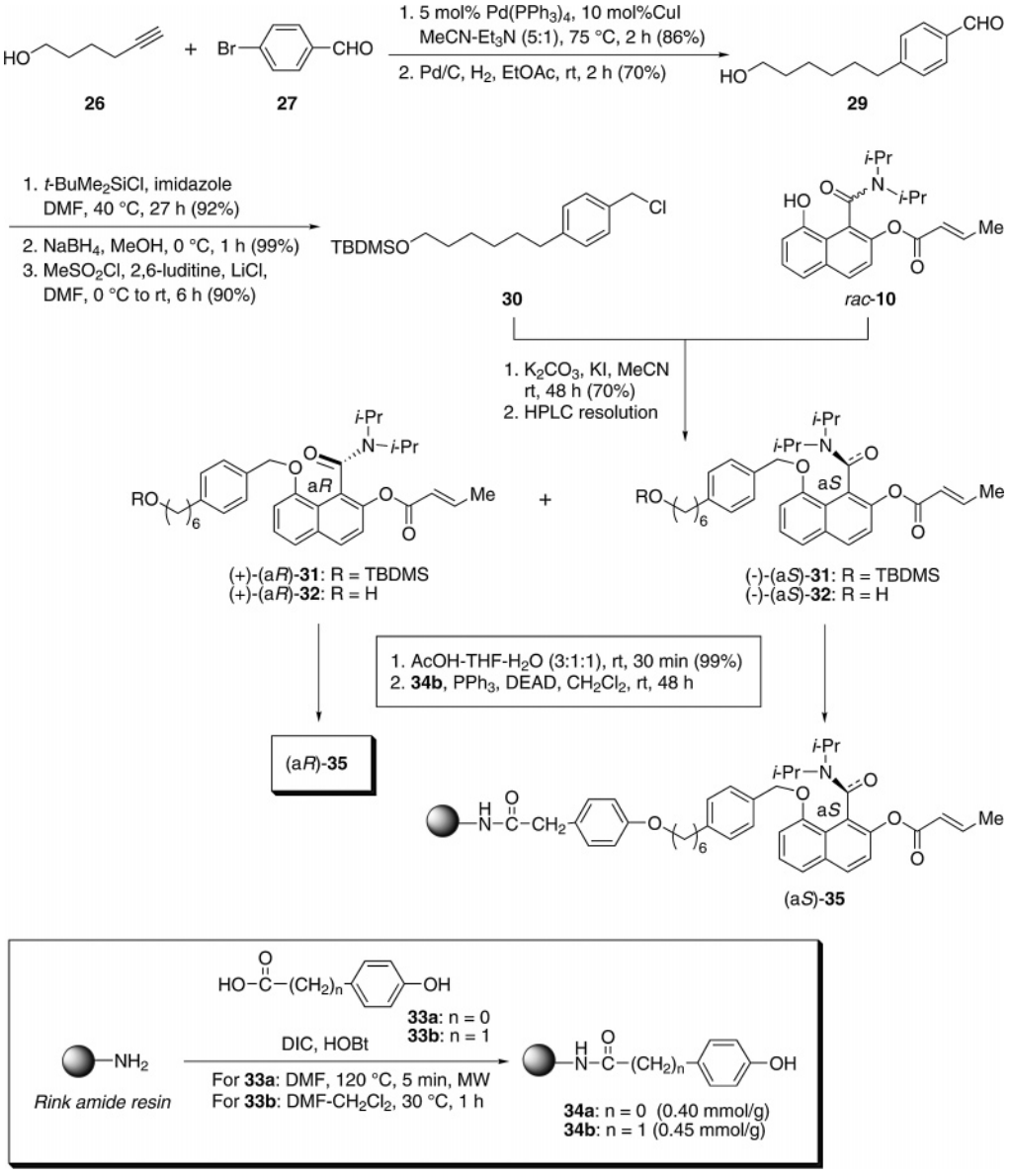
[a] Isolated yield of both isomers. [b] The isomer ratio was determined by the ^{1}H NMR of the crude product mixture. [c] The ee values were determined by GC analysis of the purified product mixture over a chiral stationary phase. The conditions are as follows: column, Cyclosil B (30 m × 0.25 mm i.d. and 0.25 μm film); oven temperature, starting at 120 °C for 2 min and increasing to 220 °C at 0.2−2.5 °C/min; carrier, He at 19 cm/sec; sample injection, 1.5 μL of a sample solution in CH_2Cl_2 (10 mg/mL). [d] The enantiomers of **36d** could not be separated by GC. The ee value was estimated by optical rotation data. [e] Measured in MeOH (c = 0.20−0.65). Reported values in ref 11a for (3*R*,4*R*)-**36a**, +73.8 (94% ee); for (3*S*,4*S*)-**36a**, −74.3 (96% ee); for (+)-**36d**, +55.7 (96% ee); and for (−)-**36d**, −56.8 (97% ee).

to furnish the γ-butyrolactones **36b** and **36d** in 81 and 87% yields and in 91:9 and 88:12 ratios for the cis and trans isomers (Table 1, entries 3 and 5). The enantioselectivity is >99% and 80% for cis-**36b** and cis-**36d**, respectively. The results clearly indicate that the bridging group "G" [−O−, −CH_2O−, −CH(Me)O−, or −CH(Ph)O−] in the substrates **I** significantly influences the efficiency of remote axial-to-central chirality transfer.

Solid-Phase Synthesis. In 2003, Procter and co-workers reported an elegant "asymmetric catch−release" approach to γ-butyrolactones[16,17] by engineering the Fukuzawa et al. *N*-methylephedrinyl acrylate and crotonate[11] onto a solid support. The ephedrine unit serves as a "chiral linker",[18] which is a tether to bridge the resin and the substrate and acts as a chiral auxiliary for inducing chirality during the solid-phase asymmetric transformation. For the reactions of aliphatic aldehydes with the

(16) (a) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402−1403. (b) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476−2482.

SCHEME 5. Synthesis of Resin-Bound Chiral Crotonates of 2-Hydroxy-8-methoxy-1-naphthamide

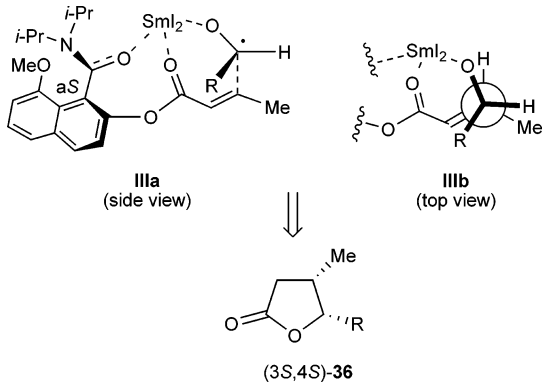


ephedrine-modified resin-bound crotonate in the presence of SmI_2 at −15 °C, the *cis*-γ-butyrolactones **36a**−**d** were obtained in 50−66% yields and in 91−93% ee.[16] We envisioned that the axially chiral crotonate (+)-(a*S*)-**5** and its antipodal may be attached to a resin through the C8 oxygen to produce a new type of resin-bound chiral auxiliary, where the 2,8-dioxygenated *N*,*N*-diisopropyl-1-naphthamide unit functions as an "atropisomeric chiral linker". As a proof-of-concept study, we designed the chiral crotonate (a*R*)-**35** and (a*S*)-**35** bound to the Rink amide resin (Scheme 5). To cope with the acid- and base-sensitive nature of the crotonate, we developed a strategy for attachment of the linker via an aryl ether bond with the resin-bound phenols **34**. We obtained the tailor-made benzyl chloride **30** in good overall yield through a five-step sequence. Coupling the 1-alkyne **26** with 4-bromobenzaldehyde (**27**) in the presence of Pd(0) and Cu(I), followed by hydrogenation of the alkyne, gave the hydroxy aldehyde **29**. The hydroxy group in **29** was protected as the silyl ether, and the aldehyde was reduced by $NaBH_4$ to form the benzyl alcohol. The latter was treated with $MeSO_2Cl$ and 2,6-lutidine in the presence of LiCl to afford directly the benzyl chloride **30**. The reaction of *rac*-**10** at the C8 −OH with **30** in the presence of KI and K_2CO_3 furnished racemic **31**, which was then resolved by semipreparative HPLC over a chiral stationary phase (Chiralpak AD) to give (+)-(a*R*)-**31** and (−)-(a*S*)-**31**. The silyl group in (−)-(a*S*)-**31** was removed under mild acidic conditions to afford the alcohol (−)-(a*S*)-**32** in 99% yield. We initially prepared the resin-bound phenol **34a** from Rink amide resin and 4-hydroxybenzoic acid (**33a**) in DMF, at 120 °C for 5 min under controlled microwave heating.[19] However, coupling of **34a** with the alcohol (+)-(a*R*)-**32** failed at room temperature for 48 h by using PPh_3 and DEAD. We considered

(17) For a pseudoephedrine linker, see: (a) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Lett.* **2002**, *4*, 4583−4585. (b) Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790−801.

(18) For a recent review on polymer-supported chiral auxiliaries in asymmetric synthesis, see: (a) Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387−399. Also see some recent examples of using chiral linkers: (b) Gais, H.-J.; Babu, G. S.; Günter, M.; Das, P. *Eur. J. Org. Chem.* **2004**, 1464−1473. (c) Gaertner, P.; Schuster, C.; Knollmueller, M. *Lett. Org. Chem.* **2004**, *1*, 249−253. (d) Schuster, C.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3211−3223.

CHART 2. Proposed Orientation of Substrates for the Observed Axial-to-Central Chirality Transfer



that the phenol **34a** might be deactivated by the conjugated amide moiety at C4. We synthesized the resin-bound phenol **34b** from 4-hydroxyphenylacetic acid (**33b**) in DMF−CH_2Cl_2 at 30 °C for 1 h. The latter was successfully coupled with (−)-(a*S*)-**32** to give the resin-bound chiral crotonate (a*S*)-**35**. The enantiomer (a*R*)-**35** was prepared similarly from (+)-(a*R*)-**32** and **34b**. We were delighted to find that the SmI_2-mediated reductive coupling of 2,2,2-trimethylacetaldehyde with (a*S*)-**35** gave the γ-butyrolactone **36c** in 58% yield with a 71:29 ratio of cis and trans isomers (Table 1, entry 11). The enantioselectivity is 94 and 89% ee, respectively, for *cis*-**36c** and *trans*-**36c**. Under similar reaction conditions, the resin-bound chiral crotonate (a*R*)-**35** reacted with cyclohexanecarboxaldehyde to give **36d** in 66% yield and with an 89:11 ratio of cis and trans isomers (Table 1, entry 12). The enantioselectivity for *cis*-**36d** is 88% ee, which is slightly higher than the 80% ee obtained in the solution reaction of (−)-(a*R*)-**5** (Table 1, entry 5).

Proposed Mechanism of Chirality Transfer. We propose a chelation-control model **III** as illustrated in Chart 2 for the reaction of (+)-(a*S*)-**5** with aldehydes, leading to the formation of (3*S*,4*S*)-**36** as the major products. Chelation of both carbonyl oxygen atoms of the atropisomeric naphthamide unit and the crotonate moiety within the substrate forms an eight-membered ring complex, which seems to play a key role for the remote axial-to-central chirality transfer as depicted in **IIIa**. The ketyl radical generated from the reduction of aldehydes can coordinate with the Sm(III) cation only from the same side of the amide unit as a result of the unique cage-like complex. Both *s*-cis[20] and *s*-trans[16b] conformations of the crotonate moiety were proposed in the reaction mechanisms; we use the *s*-cis conformation in **III** with the ketyl radical approaching the β carbon of the crotonate from the *si*-face. After careful examination of molecular models, only a nearly eclipsed arrangement is possible for the reactants, as shown in **IIIb**. This model predicts the formation of (3*S*,4*S*)-**36** from (+)-(a*S*)-**5**, being consistent with the experimental results. The other possible model built on the *s*-trans conformation of the crotonate is found in Chart S1 of the Supporting Information. It is energetically less favored and leads to the formation of the antipodal product. In the cases of the chiral crotonates **6**−**8**, the nine-membered ring of the Sm(III) complexes similar to **IIIa** would be formed but to a much smaller degree of preference as a result of the unfavorable ring strain. Therefore, the addition reaction of the ketyl radical with the crotonates might occur through the species without complexation of the atropisomeric naphthamide carbonyl oxygen, resulting in a remarkably diminished efficiency in remote chirality transfer. These results are consistent with the importance of chelation observed by Fukuzawa and co-workers,[11a] because only the racemic product was obtained from the reaction of **4** in the presence of HMPA.

Conclusion

We have examined the structural elements in four chiral crotonates for efficient remote axial-to-central chirality transfer in the SmI_2-mediated enantioselective reductive coupling of aldehydes to form chiral γ-butyrolactones. For accessing to both enantiomers of the chiral crotonates, we used a chemical resolution method in the synthesis, and the stereochemistry of the compounds was carefully established with the help of X-ray crystal structural analysis. We found that the linkage between crotonate and the C2 position of atropisomeric 8-methoxy-1-naphthamides plays a determinant role in the enantioselective reactions. The best substrate for high axial-to-central chirality transfer is the crotonate of atropisomeric 2-hydroxy-8-methoxy-1-naphthamide, affording >96% ee for the *cis*-γ-butyrolactones **36a**−**c**, formed from pentanal, isobutyraldehyde, and 2,2,2-trimethylacetaldehyde, except for 80% ee for the *cis*-γ-butyrolactone **36d**, obtained from the reaction of cyclohexanecarboxaldehyde. A similar level of efficiency in remote axial-to-central chirality transfer has been demonstrated on solid-phase reactions with the resin-bound version of the atropisomeric crotonate. A mechanism was proposed for the remote chiral transfer, featuring a cage-like complex with coordinations to Sm(III) through both amide and ester carbonyl oxygen atoms of the crotonate, along with the ketyl radical generated from the reduction of aldehydes. Our results demonstrate that a remote axial-to-central chirality transfer can be achieved at the remote centers separated at least by five bond lengths.

Experimental Section

General Procedure A. Preparation of Esters of (−)-(1*S*)-Camphanic Acid. (+)-(a*S*,1′*S*,4′*R*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]-heptanecarbonyloxy}-1-naphthamide, (+)-(a*S*,*S*)-11, and (−)-(a*R*,1′*S*,4′*R*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]heptanecarbonyloxy}-1-naphthamide, (−)-(a*R*,*S*)-12. To a solution of *N*,*N*-diisopropyl-2-[2′-(*E*)-butenoyl]-8-hydroxy-1-naphthamide *rac*-**10** (178.0 mg, 0.50 mmol) and DMAP (183.0 mg, 1.50 mmol) in dry CH_2Cl_2 (2 mL) under a nitrogen atmosphere was added a solution of (1*S*)-(−)-camphanic chloride (217.0 mg, 1.00 mmol) in dry CH_2Cl_2 (3 mL), followed by stirring at room temperature for 12 h. The reaction mixture was filtered though a plug of Celite and silica gel by rinsing with EtOAc. The filtrate was concentrated under reduced pressure to give a solid diastereomeric mixture that was separated by flash column chromatography (silica gel, 3% EtOAc−CH_2Cl_2) to give (+)-(a*S*,*S*)-**11** (131.0 mg, 49%, dr > 99.5:0.5 by HPLC) and (−)-(a*R*,*S*)-**12** (130.0 mg, 48%, dr > 99.5:0.5 by HPLC). HPLC conditions are as follows: Chiralpak AD column eluted with 95:5 ratio of hexane−2-propanol at 1.0 mL/min and by UV detection at 254 nm.

(+)-(a*S*,*S*)-**11**: a white solid; mp 88−89 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ +85.6 (*c* 1.22, $CHCl_3$); R_f = 0.30 (9% EtOAc−CH_2Cl_2); IR ($CHCl_3$) 2973, 1790, 1739, 1635, 1312, 1211, 1151, 1094, 1033

(19) (a) Olivos, H. J.; Alluri, P. G.; Reddy, M. M.; Salony, D.; Kodadek, T. *Org. Lett.* **2002**, *4*, 4057−4059. For microwave-assisted solid-phase organic synthesis (MASPOS), see: (b) Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919−2922.

(20) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373−376.

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.28−7.18 (m, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 4.31−4.15 (m, 1H), 3.47−3.33 (m, 1H), 2.60−2.40 (m, 1H), 2.39−2.25 (m, 1H), 1.95 (d, J = 6.9 Hz, 3H), 1.84−1.72 (m, 2H), 1.54 (d, J = 6.9 Hz, 3H), 1.49 (d, J = 6.6 Hz, 3H), 1.28−1.12 (m, 9H), 1.09 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 168.7, 166.4, 164.8, 148.8, 147.5, 146.3, 133.6, 129.9, 127.9, 126.2, 124.9, 124.2, 123.4, 122.1, 121.1, 91.0, 55.6, 54.7, 51.4, 46.9, 33.6, 29.8, 23.4, 22.8, 21.5 (× 2), 19.1, 18.0 (× 2), 10.4; MS (+ESI) m/z 536 (M + H$^+$, 100). Anal. Calcd for $C_{31}H_{37}NO_7$: C, 69.51; H, 6.96; N, 2.62. Found: C, 68.94; H, 6.91; N, 2.51.

(−)-(a*R*,*S*)-**12**: a white solid; mp 95−96 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ −90.0 (*c* 0.74, $CHCl_3$); R_f = 0.40 (9% EtOAc−CH_2Cl_2); IR ($CHCl_3$) 2972, 1790, 1760, 1739, 1635, 1312, 1211, 1150, 1096, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.28−7.18 (m, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.01 (dd, J = 15.6, 2.1 Hz, 1H), 4.12−3.96 (m, 1H), 3.41−3.26 (m, 1H), 2.67−2.45 (m, 2H), 1.95 (dd, J = 7.2, 1.5 Hz, 3H), 1.79−1.66 (m, 2H), 1.59 (d, J = 6.6 Hz, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.19−1.07 (m, 12H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 168.3, 166.8, 164.8, 148.7, 146.8, 146.3, 133.5, 130.0, 127.9, 126.2, 124.9, 124.0, 123.4, 122.1, 121.4, 91.3, 56.7, 55.7, 51.5, 47.0, 31.5, 29.9, 23.6, 22.5, 21.3, 21.2, 19.0, 17.6, 17.5, 10.6; MS (+ESI) m/z 536 (M + H$^+$, 100).

General Procedure B. Preparation of Crotonates by Using *n*-BuLi as the Base. (−)-(a*S*)-*N*,*N*-Diisopropyl-2-[(2′-(*E*)-butenoyloxy)methyl]-8-methoxy-1-naphthamide, (−)-(a*S*)-6. To a flame dried flask with a stirring bar was added a solution of the alcohol (−)-(a*S*)-**14** (64.0 mg, 0.2 mmol) in THF (10 mL) under a nitrogen atmosphere. To the resultant solution, cooled in a dry ice−acetone bath (−78 °C), was added *n*-butyllithium (2.5 M in hexane, 80 μL, 0.2 mmol) dropwise, followed by stirring at −78 °C for 30 min. Crotonyl chloride (24 μL, 0.24 mmol) was added to the mixture, followed by stirring at −78 °C for 30 min and then at 0 °C for 30 min. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 5% EtOAc−hexane) to afford (−)-(a*S*)-**6** (54.0 mg, 71%) as a white solid; mp 121−122 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ −108.5 (*c* 0.95, $CHCl_3$); R_f = 0.38 (33% EtOAc−hexane); IR ($CHCl_3$) 2972, 1720, 1631, 1438, 1316, 1261, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.44−7.37 (m, 2H), 7.04 (dq, J = 15.6, 7.2 Hz, 1H), 6.87 (dd, J = 6.6, 1.8 Hz, 1H), 5.91 (dq, J = 15.6, 1.6 Hz, 1H), 5.39 and 5.34 (ABq, J = 12.9 Hz, 2H), 3.93 (s, 3H), 3.60−3.42 (m, 2H), 1.89 (dd, J = 7.2, 1.8 Hz, 3H), 1.70 (d, J = 6.6 Hz, 3H), 1.67 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.8, 156.2, 145.8, 135.3, 130.5, 128.8, 127.3, 127.2, 123.0, 123.0, 121.9, 121.5, 106.9, 63.8, 56.0, 51.6, 46.6, 21.3, 21.2, 21.1, 20.4, 18.8; MS (+ESI) m/z 384 (M + H$^+$, 100). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.97; H, 7.76; N, 3.62.

General Procedure C. Addition of Grignard Reagents with Aldehydes. (a*R,*R**)- and (a*R**,*S**)-*N*,*N*-Diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-(1′-hydroxyethyl)-1-naphthamide, *syn*-18 and *anti*-18.** To a solution of *rac*-**16** (931.0 mg, 2.25 mmol) in THF (16 mL), cooled in a dry ice−acetone bath (−78 °C), was added MeMgCl (2.25 mL, 6.75 mmol), followed by stirring at −78 °C for 4 h. The reaction was quenched with NH_4Cl (16 mL) and then extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 15% EtOAc−hexane) to afford *syn*-**18** (493.0 mg, 51%) and *anti*-**18** (387.0 mg, 40%).

syn-**18**: a white solid; mp 73−74 °C (CH_2Cl_2−hexane); R_f = 0.50 (33% EtOAc−hexane); IR ($CHCl_3$) 3391, 2963, 2932, 1614, 1256, 1102 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 5.11 (q, J = 6.9 Hz, 1H), 3.75 (septet, J = 6.6 Hz, 1H), 3.10 (septet, J = 6.6 Hz, 1H), 3.10−2.75 (br s, 1H), 1.69 (d, J = 6.9 Hz, 3H), 1.63 (d, J = 6.3 Hz, 3H), 1.61 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.97 (s, 9H), 0.81 (d, J = 6.6 Hz, 3H), 0.45 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 152.8, 140.6, 134.9, 131.5, 129.5, 126.5, 124.6, 124.1, 122.4, 116.8, 65.6, 51.3, 47.0, 27.9 (× 3), 23.1, 21.2, 21.1 (× 2), 21.0, 20.2, −1.55, −3.05; MS (+CI) m/z 430 (M + H$^+$, 3), 412 (M$^+$ − OH, 25), 372 (M$^+$ − *t*-Bu, 100).

anti-**18**: a white solid; mp 189−190 °C (CH_2Cl_2−hexane); R_f = 0.40 (33% EtOAc−hexane); IR ($CHCl_3$) 3414, 2962, 2931, 1616, 1600, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 5.21 (q, J = 6.3 Hz, 1H), 3.77 (septet, J = 6.6 Hz, 1H), 3.14 (septet, J = 6.6 Hz, 1H), 1.95 (br s, 1H), 1.68 (d, J = 6.9 Hz, 3H), 1.62 (d, J = 6.0 Hz, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 7.5 Hz, 3H), 0.99 (s, 9H), 0.90 (d, J = 6.3 Hz, 3H), 0.46 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 153.0, 140.5, 135.1, 130.3, 129.5, 126.3, 124.3, 124.0, 122.3, 116.7, 68.1, 51.1, 46.6, 28.0 (× 3), 26.9, 23.3, 21.4, 21.2, 21.1, 20.4, −1.52, −3.00; MS (+CI) m/z 430 (M + H$^+$, 3), 412 (M$^+$ − OH, 12), 372 (M$^+$ − *t*-Bu, 100). Anal. Calcd for $C_{25}H_{39}NO_3Si$: C, 69.88; H, 9.15; N, 3.26. Found: C, 69.85; H, 9.12; N, 3.16. The relative stereochemistry of *anti*-**18** was confirmed by X-ray crystal structural analysis, as depicted in Figure S1 (see Supporting Information).

General Procedure D. One-Pot Conversion of 8-Silyl Ether to 8-Methyl Ether. (−)-(a*R*,1′*R*,1″*S*,4″*R*)-*N*,*N*-Diisopropyl-8-methoxy-2-{1′-{4″,7″,7″-trimethyl-3″-oxo-2″-oxabicyclo[2.2.1]-heptanecarbonyloxy}ethyl}-1-naphthamide, (−)-(a*R*,*R*,*S*)-21. To a solution of (+)-(a*R*,*R*,*S*)-**19** (48.0 mg, 0.08 mmol) in THF (2 mL), cooled in an ice−water bath (0 °C), was added *n*-Bu_4NF (80 μL, 0.02 mmol) and MeI (50 μL, 0.80 mmol), followed by stirring at 0 °C for 2 h. The reaction mixture was filtered through a plug of Celite and silica gel. The filtrate was concentrated under reduced pressure to give a solid crude product, which was purified by flash column chromatography (silica gel, 5% EtOAc−CH_2Cl_2) to afford (−)-(a*R*,*R*,*S*)-**21** (32.6 mg, 80%) as a white solid; mp 210−211 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ −12.6 (*c* 1.0, $CHCl_3$); R_f = 0.38 (17% EtOAc−CH_2Cl_2); IR ($CHCl_3$) 2974, 1789, 1749, 1728, 1632, 1308, 1262, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.46−7.38 (m, 2H), 6.90−6.81 (m, 1H), 6.37 (q, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.64−3.44 (m, 2H), 2.41 (ddd, J = 13.8, 10.5, 4.2 Hz, 1H), 2.01 (ddd, J = 13.5, 9.3, 4.5 Hz, 1H), 1.90−1.67 (m, 2H), 1.73 (d, J = 6.6 Hz, 3H), 1.70 (d, J = 6.6 Hz, 3H), 1.69 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.04 (s, 3H), 1.01 (d, J = 7.2 Hz, 3H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 169.5, 166.8, 156.3, 135.7, 133.2, 133.1, 129.2, 127.5, 125.3, 121.6, 121.4, 106.7, 91.8, 70.8, 55.8, 55.5, 54.9, 51.3, 46.8, 31.1, 29.6, 21.7, 21.6, 21.5, 21.1, 20.4, 17.5, 17.3, 10.5; MS (+ESI) m/z 509 (M$^+$, 14), 312 (M$^+$ − camphanyloxy, 90), 212 (100). Anal. Calcd for $C_{30}H_{39}NO_6$: C, 70.70; H, 7.71; N, 2.75. Found: C, 70.50; H, 7.75; N, 2.65.

General Procedure E. Hydrolysis of Esters of (1*S*)-Campanic Acid. (+)-(a*R*,*R*)-*N*,*N*-Diisopropyl-8-methoxy-2-(1′-hydroxyethyl)-1-naphthamide, (+)-(a*R*,*R*)-17. To a solution of (−)-(a*R*,*R*,*S*)-**21** (94.0 mg, 0.18 mmol) in THF (10 mL), cooled in an ice−water bath (0 °C), was added a solution of KOH (258.0 mg, 4.60 mmol) in H_2O (1 mL), followed by stirring at room temperature for 7 h. The reaction was quenched with NH_4Cl (10 mL) and then extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 10% EtOAc−CH_2Cl_2) to afford (+)-(a*R*,*R*)-**17** (55.3 mg, 91%) as a white solid; $[\alpha]^{20}_D$ +116.3 (*c* 0.72, $CHCl_3$). Other physical and spectroscopic data are identical to those of *syn*-**17**.

(−)-(a*R*)- and (+)-(a*S*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-methoxy-1-naphthamide, (−)-(a*R*)-5 and (+)-(a*S*)-5. To a solution of (−)-(a*R*,*S*)-**12** (27.0 mg, 0.05 mmol) in THF−H_2O (20:1, 2 mL), cooled in an ice−water bath (0 °C), was added 10% aqueous KOH (56 μL), followed by stirring at 0 °C for 4 h. Then MeI (34 μL, 0.5 mmol) was added to the mixture, followed by stirring at 0 °C for 23 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 3% EtOAc−CH_2Cl_2) to afford the known (−)-(a*R*)-**5** (12.0 mg, 63%). The enantiomer (+)-(a*S*)-**5** was similarly prepared from (+)-(a*S*,*S*)-**11**. The physical and spectroscopic data of (+)-(a*S*)-**5** and (−)-(a*R*)-**5** are identical to those reported before.[10]

***N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-hydroxy-1-naphthamide, *rac*-10.** To a solution of the known *rac*-**9**[10] (469.0 mg, 1.0 mmol) in THF (10 mL), cooled in an ice−water bath (0 °C), and under a nitrogen atmosphere was added TBAF (1.0 M in THF containing 5% H_2O, 1 mL, 1.0 mmol), followed by stirring at 0 °C for 10 min. The reaction mixture was filtered through a plug of Celite and silica gel. The filtrate was concentrated under reduced pressure to give a solid crude product that was purified by flash column chromatography (silica gel, 30% EtOAc−hexane) to afford *rac*-**10** (353.0 mg, 99%) as a colorless gum; R_f = 0.31 (50% EtOAc−hexane); IR ($CHCl_3$) 3056, 2978, 1738, 1608, 1436, 1212, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (br, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.31−7.17 (m, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 6.79 (t, *J* = 8.4 Hz, 1H), 6.55 (t, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 6.06 (dd, *J* = 15.6, 1.8 Hz, 1H), 3.61−3.43 (m, 2 H), 1.98 (d, *J* = 7.2 Hz, 3H), 1.64 (d, *J* = 6.9 Hz, 3H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.2, 152.8, 147.8, 144.3, 133.2, 129.4, 126.4, 124.7, 122.8, 122.3, 121.5, 119.5, 113.7, 52.2, 46.8, 21.5, 21.2, 20.1 (× 2), 19.0; MS (+CI) *m*/*z* 356 (M + H^+, 100); HRMS (+ESI) calcd for $C_{21}H_{25}NO_4Na$ (M + Na^+), 378.1681; found, 378.1675.

(−)-(a*S*)- and (+)-(a*R*)-*N*,*N*-Diisopropyl-2-hydroxymethyl-8-methoxy-1-naphthamide, (−)-(a*S*)-14 and (+)-(a*R*)-14. To a solution of *rac*-**13** (313.0 mg, 1.0 mmol) in MeOH (5 mL), cooled in an ice−water bath (0 °C), was added $NaBH_4$ (76.0 mg, 2.0 mmol), followed by stirring at 0 °C for 1 h. The reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 30% EtOAc−CH_2Cl_2) to afford *rac*-**14** (274.0 mg, 87%) as a white solid. Semipreparative HPLC separation of *rac*-**14** over a Chiralpak AD column (eluted with a 90:10 ratio of hexane−2-propanol at 0.5 mL/min and by UV detection at 254 nm) gave enantiomerically pure (−)-(a*S*)-**14** and (+)-(a*R*)-**14**.

(−)-(a*S*)-**14**: a white solid; mp 185−186 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ −125.6 (*c* 1.02, $CHCl_3$); R_f = 0.28 (50% EtOAc−hexane); IR ($CHCl_3$) 3382, 2973, 1608, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.43−7.39 (m, 2H), 6.86 (dd, *J* = 7.2, 1.85 Hz, 1H), 4.88 and 4.48 (ABq, *J* = 12.3 Hz, 2H), 3.92 (s, 3H), 3.80−3.70 (br s, 1H), 3.58 (septet, *J* = 6.6 Hz, 1H), 3.41 (septet, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 6.9 Hz, 6H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 155.9, 136.0, 135.1, 132.0, 129.4, 128.7, 127.0, 121.9, 121.6, 106.6, 64.1, 56.0, 51.8, 47.0, 21.2, 21.1, 21.0, 20.1; MS (+ESI) *m*/*z* 316 (M + H^+, 75), 298 (M^+ − OH, 100). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.56; H, 7.98; N, 4.37.

(+)-(a*R*)-**14**: a white solid; mp 185−186 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ +125.6 (*c* 0.93, $CHCl_3$); R_f = 0.28 (50% EtOAc−hexane). Other spectroscopic data are identical to those of (−)-(a*S*)-**14**.

The stereochemical assignment of (−)-(a*S*)-**14** was confirmed by PCC oxidation in dry CH_2Cl_2 to the known (−)-(a*R*)-**13**.[5d,6] HPLC retention times for (−)-(a*R*)-**13** and (+)-(a*S*)-**13** are 83.4 and 59.4 min, respectively, over a Chiralpak AD column eluted with 95:5 ratio of hexane−2-propanol at 1.0 mL/min and by UV detection at 262 nm.

***N*,*N*-Diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-formyl-1-naphthamide, *rac*-16.** To a flame-dried flask with a stirring bar was added a solution of the known *rac*-**15**[9a,10] (386.0 mg, 1.0 mmol) in THF (10 mL) under a nitrogen atmosphere. To the resultant solution, cooled in a dry ice−acetone bath (−78 °C), was added *n*-butyllithium (1.3 M in hexane, 3.85 mL, 5.0 mmol) dropwise, followed by stirring at −78 °C for 30 min. Anhydrous DMF (0.54 mL, 7.0 mmol) in THF (1 mL) was added to the mixture, and the resultant mixture was warmed to room temperature followed by stirring for 1 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid residue, which was purified by flash column chromatography (silica gel, 5% EtOAc−hexane) to afford *rac*-**16** (327.0 mg, 79%) as a white solid; mp 128−129 °C (CH_2Cl_2−hexane); R_f = 0.28 (9% EtOAc−hexane); IR ($CHCl_3$) 2963, 1692, 1638, 1310, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.49−7.45 (m, 2H), 7.05 (dd, *J* = 6.6, 3.3 Hz, 1H), 3.80 (septet, *J* = 6.9 Hz, 1H), 3.02 (septet, *J* = 6.9 Hz, 1H), 1.71 (d, *J* = 6.9 Hz, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.50 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 167.4, 153.7, 139.9, 137.7, 130.1, 129.0, 128.9, 123.3, 122.4, 121.9, 116.7, 50.8, 46.6, 27.2 (× 3), 22.6, 20.6, 20.5, 20.4, 19.6, −2.33, −3.68; MS (+CI) *m*/*z* 414 (M + H^+, 22), 356 (M^+ − *t*-Bu, 100). Anal. Calcd for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.53; N, 3.39. Found: C, 70.05; H, 8.54; N, 3.44.

4-(6′-Hydroxyhexyn-1-yl)benzaldhyde, 28. To a suspension of 4-bromobenzaldhyde (**27**, 1.850 g, 10.0 mmol), $Pd(PPh_3)_4$ (578.0 mg, 0.5 mmol), and CuI (191.0 mg, 1.0 mmol) in degassed CH_3CN (15 mL) and Et_3N (3 mL) was added 1-hexyn-6-ol (**26**, 1.32 mL, 12.0 mmol) under a nitrogen atmosphere. The resultant mixture was stirred at 75 °C for 2 h. The reaction mixture was filtered through a short plug of silica gel with rinsing by EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 10% EtOAc−CH_2Cl_2) to give the alkynyl aldehyde (1.740 g, 86%) as a colorless oil; R_f = 0.50 (17% EtOAc−CH_2Cl_2); IR ($CHCl_3$) 3388, 2939, 2230, 1699, 1602, 1208, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.97 (d, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 3.78−3.70 (m, 2H), 2.57−2.47 (m, 2H), 1.84−1.66 (m, 4H) (OH is not found); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 135.5, 132.7 (× 2), 131.0, 130.1 (× 2), 95.2, 81.0, 63.1, 32.7, 25.5, 20.0; MS (+CI) *m*/*z* 203 (M + H^+, 55), 84 (100); HRMS (+ESI) calcd for $C_{13}H_{15}O_2$ (M + H^+), 203.1072; found, 203.1073.

4-(6′-Hydroxyhexyl)benzaldhyde, 29. A suspension of **28** (202.0 mg, 1.0 mmol) and Pd/C (10%, 10.0 mg) in EtOAc (5 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 h. The reaction mixture was filtered through a short plug of silica gel with rinsing by EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 10% EtOAc−CH_2Cl_2) to give **29** (144.0 mg, 70%) as a colorless oil; R_f = 0.50 (25% acetone−hexane); IR ($CHCl_3$) 3375, 2932, 2857, 1697, 1606, 1214, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.74−1.52 (m, 5H), 1.48−1.32 (m,

4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 150.8, 135.0, 130.5 (× 2), 129.6 (× 2), 63.6, 36.9, 33.4, 31.8, 29.8, 26.3; MS (+CI) *m*/*z* 207 (M + H$^+$, 85), 91 (100); HRMS (+ESI) calcd for $C_{13}H_{18}O_2$Na (M + Na$^+$), 229.1204; found, 229.1195.

4-{6′-[(*tert*-Butyldimethylsilyl)oxy]hexyl}benzaldhyde. To a solution of **29** (1.046 g, 5.1 mmol) and imidazole (863.0 mg, 12.8 mmol) in dry DMF (2 mL) was added *tert*-butyldimethylsilyl chloride (917.0 mg, 6.1 mmol), followed by stirring at 40 °C for 27 h. The reaction was quenched by saturated $NaHCO_3$ (10 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc−hexane) to give the silyl ether (1.491 g, 92%) as a colorless oil; R_f = 0.50 (9% EtOAc−hexane); IR ($CHCl_3$) 2930, 2857, 1703, 1606, 1255, 1100, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.72−1.60 (m, 2H), 1.58−1.46 (m, 2H), 1.42−1.32 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 150.9, 135.0, 130.5 (× 2), 129.7 (× 2), 63.9, 36.9, 33.5, 31.8, 29.8, 26.8 (× 3), 26.4, 19.2, −4.4 (× 2); MS (+CI) *m*/*z* 321 (M + H$^+$, 40), 263 (100); HRMS (+ESI) calcd for $C_{19}H_{32}O_2$SiNa (M + Na$^+$), 343.2069; found, 343.2070.

4-{6′-[(*tert*-Butyldimethylsilyl)oxy]hexyl}benzyl Alcohol. To a solution of 4-{6′-[(*tert*-butyldimethylsilyl)oxy]hexyl}benzaldhyde (758.0 mg, 2.4 mmol) in MeOH (10 mL), cooled in an ice−water bath (0 °C), was added $NaBH_4$ (179.0 mg, 4.8 mmol), followed by stirring for 1 h at the same temperature. The reaction was quenched by saturated NH_4Cl (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc−hexane) to give the benzyl alcohol (180.0 mg, 99%) as a colorless oil; R_f = 0.43 (20% EtOAc−hexane); IR ($CHCl_3$) 3342, 2930, 2857, 1463, 1255, 1102, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 4.58 (s, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.81 (br s, 1H), 1.62−1.52 (m, 2H), 1.50−1.40 (m, 2H), 1.38−1.22 (m, 4H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.7, 129.2 (× 2), 127.7 (× 2), 65.9, 64.0, 36.3, 33.5, 32.3, 29.8, 26.7 (× 3), 26.4, 19.2, −4.4 (× 2); MS (+CI) *m*/*z* 323 (M + H$^+$, 4), 191 (100); HRMS (+ESI) calcd for $C_{19}H_{34}O_2$SiNa (M + Na$^+$), 345.2226; found, 345.2216.

4-{6′-[(*tert*-Butyldimethylsilyl)oxy]hexyl}benzyl Chloride, 30. To a suspension of 4-{6′-[(*tert*-butyldimethylsilyl)oxy]hexyl}benzyl alcohol (323.0 mg, 1.0 mmol), 2,6-lutidine (0.47 mL, 4 mmol), and LiCl (170.0 mg, 4.0 mmol) in DMF (5 mL), cooled in an ice−water bath (0 °C), was added dropwise $MeSO_2Cl$ (0.23 mL, 3.0 mmol). After stirring for 2 h at 0 °C, the reaction was allowed to warm to room temperature, followed by stirring for another 4 h. The reaction mixture was diluted with H_2O and extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3% EtOAc−hexane) to give **30** (307.0 mg, 90%) as a colorless oil; R_f = 0.55 (9% EtOAc−hexane); IR ($CHCl_3$) 2930, 2857, 1255, 1101, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.59 (s, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 1.69−1.59 (m, 2H), 1.57−1.47 (m, 2H), 1.41−1.33 (m, 4H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 135.3, 129.4 (× 2), 129.1 (× 2), 63.9, 47.1, 36.4, 33.5, 32.1, 29.8, 26.8 (× 3), 26.4, 19.1, −4.4 (× 2); MS (+CI) *m*/*z* 285 (M$^+$ + 2−*t*-Bu, 46), 283 (M$^+$ − *t*-Bu, 18), 249 (100); HRMS (+ESI) calcd for $C_{19}H_{33}$ClOSi (M + H$^+$), 341.2067; found, 341.2070 (M + H$^+$, 100%), 342.2100 (M + 2, 25%), and 343.2041 (M + 2 + H$^+$, 39%).

(+)-(*aR*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-{4′-[6”-((*tert*-butyldimethylsilyl)oxy)hexyl]-benzyloxy}-1-naphthamide, (+)-(a*R*)-31. To a solution of *rac*-**10** (288.0 mg, 0.81 mmol), anhydrous K_2CO_3 (276.0 mg, 2.00 mmol), and KI (17.0 mg, 0.10 mmol) in dry CH_3CN (2 mL) under a nitrogen atmosphere was added a solution of **30** (340.0 mg, 1.00 mmol) in dry CH_3CN (1 mL), followed by stirring at room temperature for 48 h. The reaction mixture was filtered off though a plug of Celite and silica gel with rinsing by EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 8% EtOAc−hexane) to give *rac*-**31** (374.0 mg, 70%) as a colorless gum.

The enantiomerically pure isomers were obtained by HPLC separation over a chiral stationary phase (Chiralpak AD). The HPLC separation was done by using a 10:90 mixture of *i*-PrOH−hexane at a flow rate of 0.5 mL/min and with UV detection at 254 nm. Retention times are 34.0 min for (+)-(a*R*)-**31** and 62.5 min for (−)-(a*S*)-**31**. (+)-(a*R*)-**31**: a colorless gum; $[\alpha]^{20}_D$ +160.9 (*c* 0.9, $CHCl_3$); R_f = 0.32 (20% EtOAc−hexane); IR ($CHCl_3$) 2930, 2857, 1739, 1638, 1461, 1315, 1212, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.0 Hz, 1H), 7.38−7.11 (m, 6H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 5.98 (d, *J* = 15.3 Hz, 1H), 5.25 (s, 2H), 3.71−3.58 (m, 1H), 3.54 (t, *J* = 6.6 Hz, 2H), 3.50−3.37 (m, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.90 (d, *J* = 6.9 Hz, 3H), 1.60−1.39 (m, 10H), 1.36−1.22 (m, 4H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.85 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 165.0, 154.7, 148.0, 145.1, 142.8, 134.7, 133.8, 129.3, 129.1 (× 2), 127.6 (× 2), 126.5, 125.7, 123.3, 122.8, 122.3, 121.5, 109.2, 70.9, 63.9, 51.5, 46.4, 36.3, 33.5, 32.1, 29.8, 26.7 (× 3), 26.4, 21.3, 21.3, 21.1, 20.9, 19.1, 19.0, −4.5 (× 2); MS (+ESl) *m*/*z* 660 (M + H$^+$, 100); HRMS (+ESI) calcd for $C_{40}H_{57}NO_5$SiNa (M + Na$^+$), 682.3904; found, 682.3872 (M + Na$^+$).

(−)-(a*S*)-**31**: a colorless gum; $[\alpha]^{20}_D$ −152.3 (*c* 1.0, $CHCl_3$). Other physical and spectroscopic data are identical to those of (+)-(a*R*)-**31**.

(+)-(*aR*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-[4′-(6”-hydroxyhexyl)benzyloxy]-1-naphthamide, (+)-(*aR*)-32. A solution of (+)-(*aR*)-**31** (66.0 mg, 0.10 mmol) in a mixture of AcOH (1.5 mL), THF (0.5 mL), and H_2O (0.5 mL) was stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc−hexane) to give (+)-(*aR*)-**32** (54.0 mg, 99%) as a colorless gum; $[\alpha]^{20}_D$ +195.7 (*c* 0.6, $CHCl_3$); R_f = 0.30 (33% EtOAc−hexane); IR ($CHCl_3$) 3394, 2931, 2857, 1738, 1623, 1461, 1317, 1212, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.3 Hz, 1H), 7.40−7.17 (m, 6H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.31 (s, 2H), 3.76−3.64 (m, 1H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.56−3.44 (m, 1H), 2.57 (t, *J* = 8.1 Hz, 2H), 1.97 (dd, *J* = 0.9, 7.2 Hz, 3H), 1.70−1.47 (m, 5H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.51 (d, *J* = 6.6 Hz, 3H), 1.40−1.30 (m, 4H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 165.1, 154.7, 148.1, 145.1, 142.7, 134.8, 133.8, 129.3, 129.2 (× 2), 127.6 (× 2), 126.5, 125.6, 123.3, 122.9, 122.3, 121.6, 109.2, 70.9, 63.6, 51.5, 46.4, 36.3, 33.4, 32.1, 29.8, 26.3, 21.4, 21.3, 21.2, 20.9, 19.0; MS (+Cl) *m*/*z* 546 (M + H$^+$, 100); HRMS (+ESI) calcd for $C_{34}H_{43}NO_5$Na (M + Na$^+$), 568.3039; found, 568.3027.

(a*S*)-(−)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-[4′-(6”-hydroxyhexyl)benzyloxy]-1-naphthamide, (a*S*)-(−)-32. (a*S*)-(−)-**32** was prepared in the same manner as described above for the (a*R*)-(+)-enantiomer as a colorless gum; $[\alpha]^{20}_D$ −166.2 (*c* 1.0, $CHCl_3$). Other physical and spectroscopic data are identical to those of (+)-(a*R*)-**32**.

Preparation of the Resin-Bound Phenol, 34b. Rink amide resin (0.7 mmol/g) was treated with a solution of 20% piperidine in DMF for 1 h at room temperature and then washed with DMF and CH_2Cl_2. The washing procedure was repeated five times, and the resin was dried overnight in vacuo. 4-Hydroxyphenylacetic acid (**33b**; 5.0 equiv) was coupled to the above pretreated resin by using DIC

(5.0 equiv) and HOBt (5.5 equiv) in DMF−CH_2Cl_2 (1:1) at room temperature for 1 h, followed by washing with DMF and CH_2Cl_2 (repeated five times). The resin-bound phenol was dried overnight in vacuo. A resin-free sample of the attached phenol (as 4-hydroxyphenyl acetamide) was obtained after cleavage from the resin by treating with 20% CF_3CO_2H in CH_2Cl_2. The loading of the resin-bound phenol **34b** is estimated to be 0.45 mmol/g by the increased weight. 4-Hydroxyphenyl acetamide: ^{1}H NMR (300 MHz, CD_3OD) δ 7.00 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.1 Hz, 2H), 3.30 (s, 2H).

Preparation of the Resin-Bound Phenol, 34a. As a result of the low reactivity of 4-hydroxybenzoic acid (**33a**), its coupling with Rink amide resin was carried out under microwave heating conditions. The resin and other reactants were charged into a 10 mL pressurized vial containing a magnetic stirrer, and the vial was sealed with a cap containing a silicon septum. The loaded vial was then placed into the cavity of a technical microwave reactor (Emrys creator from Personal Chemistry AB, Uppsala, Sweden) and heated at 120 °C for 5 min to give the resin-bound phenol **34a** with a loading of 0.40 mmol/g after the workup described for **34b**. However, **34a** did not couple with (+)-(*aR*)-**32** in the presence of PPh_3 and DEAD in CH_2Cl_2 at room temperature for 48 h.

Preparation of the Resin-Bound Chiral Crotonate, (a*R*)-35. To a mixture of the resin-bound phenol **34b** (1.0 equiv), Ph_3P (3.3 equiv), and diethyl azodicarboxylate (DEAD; 3.3 equiv) in CH_2Cl_2 (1 mL) was added a solution of (+)-(*aR*)-**32** (3.0 equiv) in CH_2Cl_2 (1 mL) under a nitrogen atmosphere. The resultant mixture was shaken at room temperature for 48 h, and then the resin was collected by filtration and washed with DMF and CH_2Cl_2 (repeated five times). After drying overnight in vacuo, the resin-bound chiral crotonate (a*R*)-**35** was obtained, and the loading (0.45 mmol/g) was estimated by the increased weight of the resin. A resin-free sample of the attached chiral crotonate was obtained after cleavage from the resin. The mass data show an ion at *m*/*z* 679 ($M + H^+$, 100), being consisted with the expected structure. The excess (+)-(*aR*)-**32** was recovered from the reaction mixture by flash column chromatography.

The resin-bound chiral crotonate, (a*S*)-**35**, was prepared from (−)-(*aS*)-**32** in the same manner as described above for (a*R*)-**35**.

General procedure F. SmI_2-Mediated Reductive Coupling of Aldehydes with Chiral Crotonates. To a solution of a chiral crotonate (1.2 equiv), an aldehyde (0.2 mmol, 1.0 equiv), and *t*-BuOH (1.2 equiv) in THF (1 mL), cooled at −20 °C under a nitrogen atmosphere, was added a freshly prepared SmI_2 (3 equiv) solution in THF. The resultant mixture was stirred at −20 to −15 °C for 6 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5% EtOAc−hexane) to give the γ-butyrolactones **36**. The ratio of cis and trans isomers was estimated by ^{1}H NMR spectra, and the enantiomeric excess was determined by GC over a chiral stationary phase. The GC analysis was carried out with a Cyclosil B column (30 m × 0.25 mm i.d., 0.25 μm film) with the oven temperature starting at 120 °C for 2 min and then increasing from 120 to 220 °C at 0.2−2.5 °C/min. The carrier is He at 19 cm/sec with FID detection at 230 °C. A volume of 1.5 μL of a CH_2Cl_2 solution of the sample (10 mg/mL) was prepared and injected for analysis. The results are listed in Table 1, entries 1−10.

General Procedure G. Solid-Phase SmI_2-Mediated Reductive Coupling of Aldehydes with Resin-Bound Chiral Crotonates. A suspension of the resin-bound crotonate (a*R*)-(**35**) (0.2 mmol, 1.0 equiv) in THF (1 mL) under a nitrogen atmosphere was gently stirred for 30 min prior to the addition of an aldehyde (72 μL, 3.0 equiv) and *t*-BuOH (57 μL, 3.0 equiv). The resultant suspension was then allowed to stir for another 1 h at room temperature before being cooled to −15 °C. A precooled solution of freshly prepared SmI_2 (9 equiv) in THF (1 mL) was then added, and the resultant mixture was allowed to stir at −15 °C for 3 h. The reaction was then allowed to warm to room temperature over a period of 6 h. The resin was separated by filtration and washed repeatedly with THF. The combined filtrate was then washed with saturated brine. The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc−hexane) to give **36d** (24.0 mg, 66%) as an 89:11 mixture of cis and trans isomers. A pure sample of *cis*-(+)-**36d** was obtained by repeated flash column chromatographic purification. Optical rotation of the pure *cis*-(+)-**36d** is $[\alpha]^{20}_D$ +50.9 (*c* 0.32 MeOH, 88% ee); lit.[11a] $[\alpha]^{20}_D$ +55.7 (*c* 1.0 MeOH, 95% ee). The results are listed in Table 1, entries 11 and 12.

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Supporting Information Available: General methods and compound characterization, Chart S1, copies of ^{1}H and ^{13}C NMR charts, GC analysis charts, Figures S1−S3, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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