Conformationally Rigid Acyclic 2,2,6,6-Tetramethyl-3,5-Heptanediol (TMHDiol) Derivative as a New Class of Chiral Auxiliaries

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Abstract: As a new chiral auxiliary, a 2,2,6,6-tetramethyl-3,5-heptanediol (TMHDiol) derivative has been developed. This chiral auxiliary is an acyclic, but strongly conformationally biased, molecule. Conjugate addition of lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) to the enoates having a TMHD auxiliary proceeded with high diasteroselectivities to give β-amino esters in high yields, although the use of conventional auxiliaries such as 8-phenylmenthyl and oxazolidone resulted in low diastereoselectivity. Organocopper conjugate addition to TMHD crotonate, heptanoate, and cinnamate produced high diastereoselectivities, and Diels–Alder reaction of TMHD acrylate with cyclopentadiene in the presence of $TiCl_4$ afforded an endo adduct exclusively with high diasteroselectivity. The addition of LSA proceeded via an s–cis conformation of enoates, but the organocopper addition in the presence of $BF_3{\cdot}OEt_2$ and the Diels–Alder reaction in the presence of $TiCl_4$ proceeded through an s–trans form.

The molecular design of chiral auxiliaries is becoming a subject of keen interest in organic synthesis. In general, molecules **1** containing a chiral auxiliary consist of three units; a shielding part, a reactive part, and a tether which connects a shielding and a reactive part (Scheme I). The conformational rigidity of auxiliaries is essential to produce high asymmetric induction. For that reason, *conformationally fixed cyclic* or *metal-chelated rigid* auxiliaries have commonly been used for asymmetric synthesis (for example, rigid template in Scheme I).[1] The use of acyclic molecules as the tether is not common because of their conformational unpredictability. However, an acyclic template has a potential for adopting an induced fit type conformation because of its flexibility. De Clercq et al. have used simple propane derivatives **2**, having a substituent at the C-2 position, as an open chain template.[2] The introduction of a sterically bulky anchor (A = trityl) afforded significant diastereomeric excess (72–76%) in the Diels–Alder reaction of **2** (Y = Ph, X = $O_2CCH{=}CH_2$) with cyclopentadiene.[2] The *gem*-dialkyl effect, which is the name given to the acceleration of a cyclization due to the substitution of alkyl groups for hydrogen atoms on the carbon chain, might also bring X close to Y (**3**),[3] and actually such an effect has been observed for intramolecular cyclization reactions. More recently, Saito and his co-workers have reported very high asymmetric induction via a strongly conformationally biased acyclic system without the assistance of chelation.[4] We report that the 1,3-di-*tert*-butyl-substituted propane unit acts as a conformatinoally homogeneous template (**4**) without the assistance of chelation. The use of this new template enables us to achieve high asymmetric induction in the Michael additions of lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) to enoates, while the use of an 8-phenylmenthyl or an oxazolidone chiral auxiliary resulted in low diastereoselectivities. Furthermore, organocopper conjugate additions and Diels–Alder reactions of enoates bearing this template produce high diastereoselectivities.

Results and Discussion

Synthesis of *meso*-2,2,6,6,-Tetramethyl-3,5-heptanediol (TMHDiol) (6) and Its Derivatives. We previously reported that *meso*-dimethylglutric hemialdehyde **5** adopts a rigid conformation in solution without any assistance of chelating reagents.[5] It was though that the conformational property of **5** would be between a rigid cyclic and a flexible acyclic molecule, and thus we were interested in utilizing such a tailor-made molecule[6] as a chiral auxiliary. Extension of techniques learned in the study of **5** led us to synthesize *meso*-2,2,6,6-tetramethyl-3,5-heptanediol (**6**) (TMHDiol). As shown in Scheme II, racemic **6** (syn isomer) was prepared in high yield via aldol condensation between pinacolone and pivalaldehyde followed by reduction with Dibal.[7] TMHDiol (**6**) was treated with KH and BzCl to give (±)-**7**, which was converted to α,β-unsaturated esters **8** upon treatment with enoic acid chlorides in the presence of AgCN.[8] The X-ray structural analysis of (racemic) TMHD cinnamate (**8d**) is shown in Figure 1. It is clearly demonstrated that one side of the double bond, C6–C7, is shielded effectively by the phenyl group of the benzoate ester, and the enoate moiety adopts an s-cis conformation.

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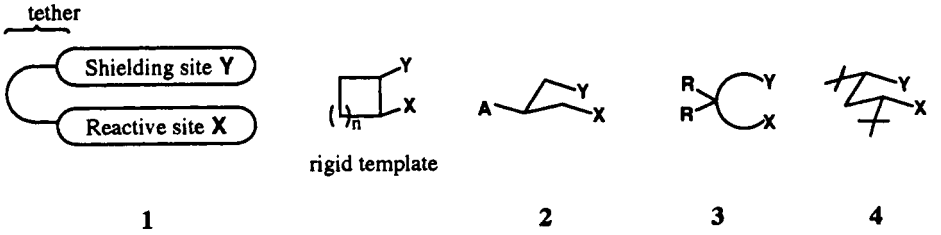
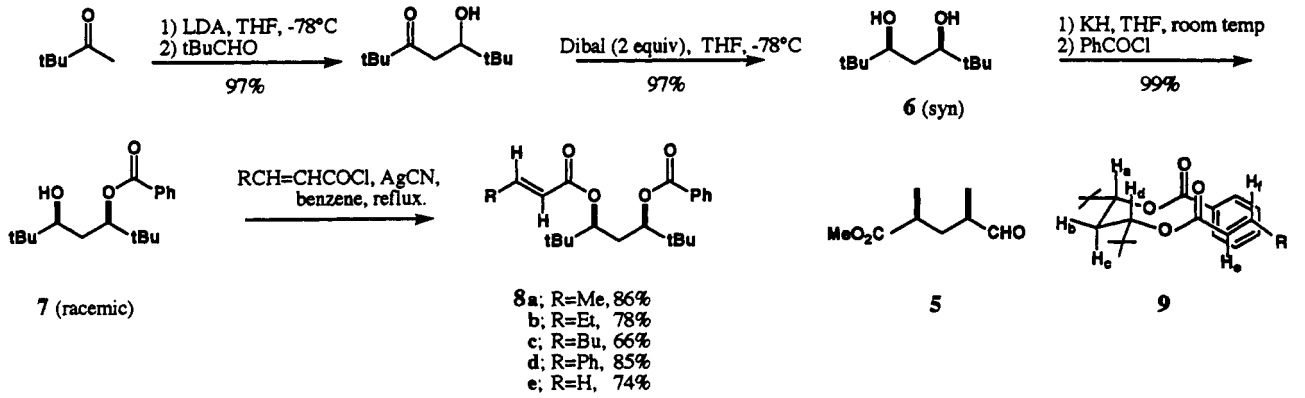
Scheme I. Chiral Auxiliaries with Acyclic Tether[a]



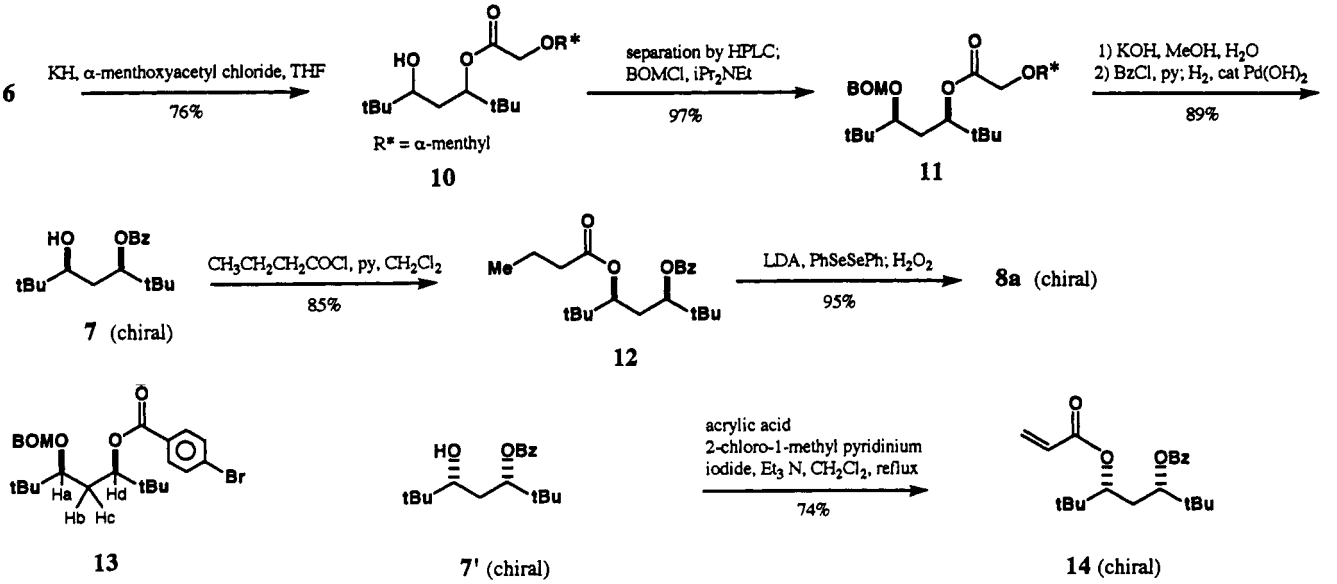
1 2 3 4

[a]An auxiliary consists of a tether and a shielding site.

Scheme II. Synthesis of Enoates Bearing a Racemic TMHD Auxiliary



Scheme III. Synthesis of Enoates Having a Chiral TMHD Auxiliary



The effective shielding of the double bond of **8a** by the phenyl ring was also confirmed in solution. The ^{1}H NMR spectrum of **8a** in $CDCl_3$ showed the following coupling constants and chemical shifts (see **9**); $J_{ac} = J_{cd} = 8.5$ Hz, $J_{ab} = J_{bd} = 2.5$ Hz, δ H_e 5.55 ppm and δ H_f 6.58 ppm, protons of R(Me) δ 1.60 ppm. The olefinic and methyl protons are significantly shielded by the aromatic ring, since the chemical shifts of H_e and H_f move upfield by ca. 0.4 ppm in comparison with the chemical shift of ordinary olefinic protons. It is clear that **8** is a conformationally rigid acyclic molecule.

The synthesis of enantiomers of **7** and **8a** is shown in Scheme III. TMHDiol (**6**) was converted to a mixture of diastereomers of **10** upon treatment with α-menthoxyacetyl chloride, which was separated by HPLC. Treatment of one of the diastereomers with (benzyloxy)methyl chloride (BOMCl) gave **11**. Removal of the α-menthoxyacetyl group upon treatment with KOH, benzoyl protection of the free alcohol, and removal of the BOM group produced chiral **7** in good yield; $[\alpha]^{23}_D$ 30.27° (*c* 0.094, C_6H_6). An enantiomer **7'** was prepared similarly from the other diastereomer of **10**; $[\alpha]^{23}_D$ −30.42° (*c* = 0.093, C_6H_6). The absolute configuration of chiral **7** was determined unambiguously by X-ray analysis of the bromophenyl derivative **13**, which was prepared from **11** using *p*-bromobenzoyl chloride instead of benzoyl chloride (Figure 2). Now both enantiomers were in hand. However, the reaction of crotonyl chloride with chiral **7** in the presence of AgCN resulted in racemization. The racemization presumably took place in the following way: the AgCN method produced HCN, which equilibrated the benzoyl group via migration between the two oxygens of chiral **7**. Accordingly, esterification under acidic conditions should be avoided. We chose a two-step synthesis for this particular case. Treatment of chiral **7** with butyryl chloride in pyridine–CH_2Cl_2 gave **12** without racemization in 85% yield. The phenylselenylation of **12** using LDA–PhSeSePh followed by deselenylation with H_2O_2 produced

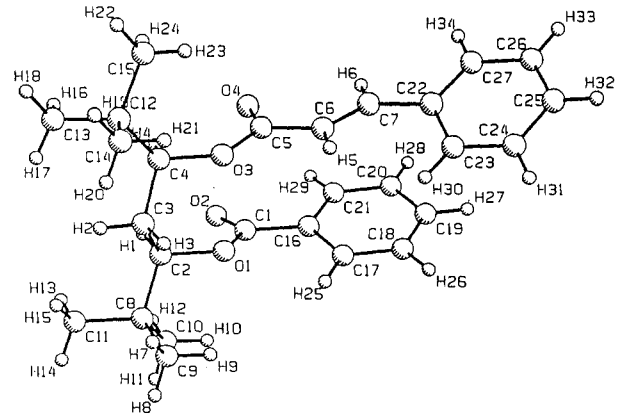


Figure 1. ORTEP diagram for **8d**.

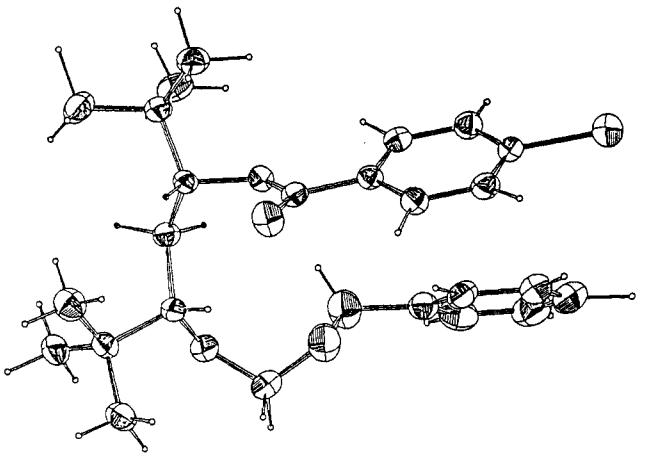


Figure 2. ORTEP diagram for **13**.

chiral **8a** in 95% yield. The RCOCl–pyridine method for the esterification of **7** was not applicable to crotonyl chloride bearing allylic hydrogens, presumably because the γ-hydrogen would be abstracted by the base; in fact, cinnamoyl chloride having no allylic hydrogens was able to be used as RCOCl and its direct esterification was accomplished. The acrylate derivative **14** was synthesized by the esterification of **7′** (chiral) with acrylic acid using 2-chloro-1-methylpyridinium iodide–Et_3N.[9] The optical purity of chiral **8a** and **14** was checked by examination of their ^1H NMR spectra in the presence of $Eu(hfc)_2$, which established that no racemization took place during the esterification steps.

Conjugate Addition of Lithium *N*-Benzyl-*N*-(trimethylsilyl)-amide (LSA). Recently, we have reported that LSA is an excellent nucleophile which adds only in a 1,4-manner to enoates such as crotonates without being accompanied by 1,2-addition or hydrogen abstraction at the γ-position.[10] The resulting β-amino esters[13] are important for the synthesis of biologically active natural products, including β-lactams. Especially, asymmetric conjugate addition of metal amides to enoates is needed for chiral synthesis of β-lactam antibiotics.[10e,11] Accordingly, we examined the conjugate addition of LSA to the enoates **15** and **16** having conventional auxiliaries. The addition of LSA to both enoates proceeded regioselectively in a 1,4-manner to give the corresponding β-amino esters in high yields, but the diastereoselectivities were not high: 70% de was obtained from **15**[12] and 40% de from **16**. Then, the conjugate addition of LSA to racemic TMHD enoates (**8a,b,d**) was studied, and the results are summarized in Table I. Very high diastereoselectivity was obtained in all cases (entries 1–4). As expected from the X-ray structural analysis of **8d** and from the ^1H NMR spectrum of **8a**, the aromatic ring blocks the back face of the double bond when in the s–cis conformation (see **9**), and therefore the nucleophile is forced to attack from the front side. In order to confirm this mechanism and determine the stereochemistry of **17** (the major product), the conjugate addition of LSA to chiral **8a** was carried out. The resulting β-amino esters were converted to amino alcohol **19** upon treatment with $LiAlH_4$: $[\alpha]^{27}_D$ + 59.4° (*c* 0.092, EtOH). The absolute configuration (*S*) of **19** was determined by comparing its $[\alpha]_D$ value with that of authentic (3*S*)-3-(benzylamino)butanol, $[\alpha]^{rt}_D$ + 31.5° (*c* 1.8, $CHCl_3$), for ca. 45% ee.[13] It is known that the conjugate addition of LSA to methyl crotonate proceeds via the s-cis conformation.[10b] The observed results imply that the addition proceeds through a six-membered transition state **20** in which lithium coordinates to the oxygen of the enoate carbonyl group, in accord with the previous X-ray and spectral data supporting an s-cis conformation. When HMPA was added to THF, the chemical yield of β-amino esters **17** and **18** decreased significantly (entry 4) but the diastereoselectivity did not change significantly. The addition of 23% HMPA[14] stopped the conjugate

Table I. Conjugate Addition of LSA to **8** (Racemic)[a]

entry	8 (R)	solvent	yield, % (recovery of 8)	diastereomer ratio 17:18
1	**8a** (Me)	THF	95	95:5
2	**8b** (Et)	THF	67 (21)	95:5
3	**8d** (Ph)	THF	75 (20)	93:7
4	**8d** (Ph)	THF–13% HMPA	30 (49)	92:8

[a] The reaction of LSA (0.42 mmol) with **8** (0.41 mmol) was carried out at −78 °C. The diastereomer ratio was determined by ^1H NMR spectra.

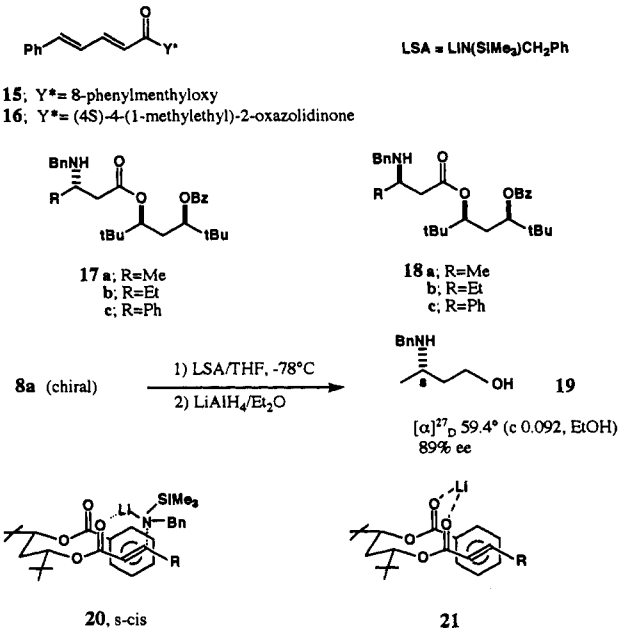


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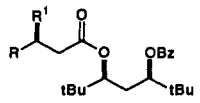
Table II. Conjugate Addition of Organocoppers to **8** (Racemic)[a]

entry	8 (R)	R^1CuLn	yield, % (recovery of 8)	diastereomer ratio 22:23
				22a:23a
1	**8a** (Me)	$PhCu\cdot BF_3$	29 (55)	94:6
2	**8a** (Me)	$Ph_2CuLi\cdot BF_3$	79	75:25
3	**8a** (Me)	$Ph_2CuLi\cdot 2BF_3$	73 (27)	96:4
				22b:23b
4	**8a** (Me)	$BuCu\cdot BF_3$	68	100:0
5	**8a** (Me)	$Bu_2CuLi\cdot BF_3$	55	89:11
6	**8a** (Me)	$Bu_2CuLi\cdot 2BF_3$	73	95:5
7	**8c** (Bu)	$MeCu\cdot BF_3$	23 (68)	11:89
8	**8c** (Bu)	$Me_2CuLi\cdot 2BF_3$	70 (10)	8:92
				22c:23c
9	**8c** (Bu)	$Ph_2CuLi\cdot BF_3$	68	75:25
10	**8c** (Bu)	$Ph_2CuLi\cdot 2BF_3$	71	90:10
11	**8d** (Ph)	$BuCu\cdot BF_3$	77	7:93
12	**8d** (Ph)	$Bu_2CuLi\cdot BF_3$	84	11:89
13	**8d** (Ph)	$Bu_2CuLi\cdot 2BF_3$	63	7:93

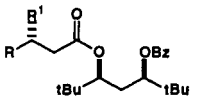
[a] Normally, to an ether solution of 2 equiv of R^1CuLn was added 1 equiv of **8** at −78 °C. The isomer ratio was determined by ^1H NMR (entries 1–3, 9–13) or HPLC (entries 4–8).

addition completely. Perhaps HMPA prevents the chelation of lithium to the carbonyl oxygen because of its strong coordinating ability to lithium, and thus the yield diminishes to 30% by adding 13% HMPA. The uniform diasteroselectivity in the presence of HMPA clearly suggests that lithium does not operate to hold the orientation of two carbonyl groups in such as way as shown in **21**; a strong conformational preference of the TMHD tether and two ester groups brings the π-electron systems close.

Conjugate Additions of Organocopper Reagents. Since the addition of the nitrogen nucleophile proceeded with high diastereoselectivity, we next examined the conjugate addition of organocopper reagents to **8** (racemic). The results are summarized in Table II. Very high diastereoselectivity was accomplished

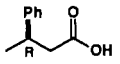


22 a; R=Me, R^1=Ph
b; R=Me, R^1=Bu
c; R=Bu, R^1=Ph

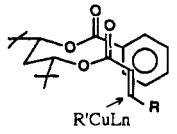


23 a; R=Me, R^1=Ph
b; R=Me, R^1=Bu
c; R=Bu, R^1=Ph

8a (chiral) → 1) $Ph_2CuLi\cdot 2BF_3$ 2) KOH/H_2O-MeOH



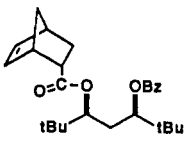
24 $[\alpha]^{27}_D$ −45.8° (c 0.77, C6H6)



25 s-trans

by using organocopper·BF_3 reagents.[15] The use of TMSCl instead of BF_3OEt_2 resulted in low conversion and low diastereoselectivity.[15] It should be noticed that the use of $R_2CuLi\cdot 2BF_3\cdot OEt_2$ enhanced the diastereoselectivity in comparison with the conjugate addition via $R_2CuLi\cdot BF_3\cdot OEt_2$ (entry 3 vs 2, 6 vs 5, 10 vs 9, 13 vs 12), and chemical yields in some cases were also enhanced with this reagent. In order to determine the stereochemistry of **22** (major products in entries 1–6, 9, and 10) and to elucidate the conformation of **8** in the transition state, the conjugate addition of phenylcopper reagent to chiral **8a** was carried out. The conjugate adducts were treated with KOH in H_2O–MeOH to afford **24**; $[\alpha]^{27}_D$ −45.8° (*c* 0.77, C_6H_6). Comparison of this $[\alpha]_D$ value with that of authentic (3*R*)-3-phenylbutyric acid, $[\alpha]^{25}_D$ −56.8° (*c* 9, C_6H_6),[16] led to the assignment of the *R* configuration. Accordingly, the copper reagent attacks the double bond of the s-trans enoate from the front face (see **25**). It is known that the conjugate addition of RCu in the presence of $BF_3\cdot OEt_2$ proceeds via s-trans conformation,[16] and the present result is in good agreement with this previous conclusion. It should be noted that the conformation of enoate **8a** dramatically changes from s-cis (**9**, Figure 1, and **20**) to s-trans (**25**) in the presence of $BF_3\cdot OEt_2$.[17]

Diels–Alder Reactions with Cyclopentadiene. To make clear the usefulness of the TMHD auxiliary, we next carried out Diels–Alder reactions of racemic **8e** with cyclopentadiene in CH_2Cl_2–hexane at −78 °C. When a catalytic amount of $TiCl_4$ (0.5 equiv) was used, the diastereomer ratio of the endo adducts (**26**:**27**) was 91:9 and the chemical yield was 96%. The use of 1 equiv of $TiCl_4$



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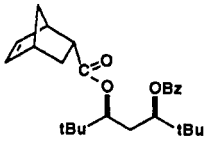

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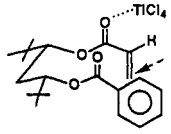
14 (chiral) → 1) 0.5 equiv $TiCl_4$ 2) 3) $LiAlH_4$

28 $[\alpha]^{23}_D$ −72.1° (c 0.332, EtOH)



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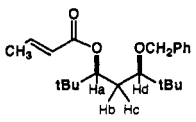

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resulted in polymerization of cyclopentadiene, and the use of 0.1 equiv of $TiCl_4$ afforded an 87:13 mixture of **26** and **27** in 93% yield. The acrylate of (*S*)-ethyl lactate reacts with cyclopentadiene in the presence of 0.5 equiv of $TiCl_4$ to afford a 92:8 mixture of the corresponding endo adducts along with small amounts of the exo adducts.[18] Diphenylmethyl- and 3,3-dimethylbutyl-shielded camphor auxiliaries, which have a conformationally rigid cyclic tether, produce 66–94% de in the Diels–Alder reaction of the acrylates with cyclopentadiene.[1c] We next examined the addition of chiral **14** with cyclopentadiene to elucidate the face selection. The reduction of the adduct with $LiAlH_4$ gave **28**: $[\alpha]^{23}_D$ −72.1° (*c* 0.332, EtOH). Comparison of this $[\alpha]_D$ value with that of the authentic *R* enantiomer (70%

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ee), $[\alpha]^{25}_D$ +67.7° (c = 0.718, EtOH),[19] led to the assignment of the *S* configuration. Accordingly, cyclopentadiene attacks *s-trans*-acrylate from the *re* face of the olefin (**29**). As pointed out previously, the Lewis acid presumably is essential for stabilization of the acrylate s-trans conformation relative to its s-cis form.[1c,20]

Conclusion

The rigid coplanar π-stacking structure of **8** (as shown in **9**, **20**, **25**, and **29**) is due not merely to the presence of two *tert*-butyl groups but also to the presence of two ester groups. As is evident from the X-ray structure of **13** shown in Figure 2, the carbon chain of **13** does not adopt a zigzag structure as in **9**. The coupling constants of **13** also indicate a distorted framework; J_{ac} = 7.0 Hz, J_{ab} = 2.0 Hz, J_{cd} = 11.5 Hz, and J_{bd} = 1.8 Hz. The distorted structure of **30** is also confirmed by the coupling constants; J_{ac} = 2.5 Hz, J_{ab} = 6.5 Hz, J_{bd} = 1.7 Hz, and J_{cd} = 11.0 Hz. These results clearly indicate that when one of the two hydroxy oxygen substituents changes from a carbonyl to an alkyl group, perfect coplanarity of the two substituents at the C-3 and C-5 positions in **6** is lost, resulting in decreased asymmetric induction. In fact, the conjugate addition of $Bu_2CuLi{\cdot}2BF_3$ to **30** produced an 80:20 mixture of diastereomers. The π-stacking effect together with the perfect overlapping of the two ester planes is apparent from the coupling constants of **12**; J_{ac} = 9.0 Hz, J_{ab} = 2.5 Hz, J_{bd} = 3.5 Hz, and J_{cd} = 7.5 Hz. The double bond of the enoates is not a key factor for adopting a zigzag framework; rather, the presence of the two ester groups in addition to the *tert*-butyl groups is essential for producing high asymmetric induction in the above reactions. The chiral auxiliaries first developed by Evans, Oppolzer, and Helmchen for enolate alkylation, aldol reaction, and Diels–Alder cycloaddition were assigned to be chelating.[1] Concurrently, auxiliaries that depended only on conformational effects of cyclic systems were developed (Corey and Ensley,[20] Whitesell[1]). More recently, asymmetric inductions in which the conformational restraints of acyclic substituents attached to cyclic templates dictate the reaction course have been reported.[21] The newly developed TMHD auxiliary is not unique in achieving induction without chelation. It is novel that it is totally acyclic, yet allows a strong preference for the convergent conformation necessary for remote induction. Although further work is needed in order to extend the present acyclic template to an induced fit type chiral auxiliary, TMHDiol derivatives have already provided a synthetically useful level of asymmetric induction, e.g. for the synthesis of β-amino esters.

Experimental Section

5-Hydroxy-2,2,6,6,-tetramethylheptan-3-one. Diisopropylamine (16.8 mL, 0.12 mol) was dissolved in 100 mL of dry THF at 0 °C. To this solution was added dropwise a hexane solution of *n*-BuLi (1.16 M, 68.3 mL). The mixture was stirred for 10 min and then cooled to -78 °C. Pinacolone (12.5 mL, 0.1 mol) was added via a syringe, and stirring was continued for 20 min. To the resulting white suspension was added pivalaldehyde (10.9 mL, 0.1 mol) via a syringe. The mixture was stirred for 2 h at -78 °C and then poured into an aqueous saturated NH_4Cl solution. The usual workup gave 17.6 g of the β-hydroxy ketone as a white solid (97%). Without further purification, the product was used as the starting material of the next transformation: ^{1}H NMR ($CDCl_3$) δ 3.66 (1H, ddd, J = 10.1, 2.0, and 1.7 Hz), 3.17 (1H, d, J = 2.0 Hz), 2.72 (1H, dd, J = 17.1 and 1.7 Hz), 2.43 (1H, dd, J = 17.1 and 10.1 Hz), 1.16 (9H, s) 0.92 (9H, s); IR (KBr) 3475, 2800, 1700, 1460, 1380, 1360, 1320, 1280, 1060, 1000 cm^{-1}.

***meso*-2,2,6,6-Tetramethyl-3,5-heptanediol (6) (TMHDiol).** To a solution of 5-hydroxy-2,2,6,6-tetramethylheptan-3-one (4.66 g, 25 mmol) in THF (100 mL) was added Dibal (1 M in hexane, 55 mL, 55 mmol) at –78 °C, and the solution was stirred for 2 h at this temperature. The reaction mixture was allowed to warm to room temperature and quenched with 2 N aqueous HCl solution. The mixture was extracted twice with ether, and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and with brine. Drying with anhydrous $MgSO_4$ and concentration gave **6** (4.56 g, 97% yield, syn:anti = 95:5) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.45 (2H, dd, J = 2.0 and 13.8 Hz), 2.78 (2H, bs), 1.73 (1H, ddd, J = 2.0, 2.0, and 19.0 Hz), 1.28 (1H, ddd, J = 13.8, 13.8, and 19.0 Hz), 0.91 (18H, s); IR (KBr) 3400, 2900, 1470, 1100, 880 cm^{-1}. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.10; H, 12.66.

5-(Benzoyloxy)-2,2,6,6,-tetramethylheptan3-ol (7). To a suspension of KH (1.2 g, 35 wt %, 10.5 mmol) in 40 mL of dry THF was added under N_2 a solution of TMHDiol (**6**) (1.97 g, 10.5 mmol) dissolved in 20 mL of dry THF. Stirring was continued for 30 min at room temperature, and a THF (7 mL) solution of benzoyl chloride (1.2 mL, 10.3 mmol) was added. The resulting mixture was stirred overnight and quenched with saturated aqueous NH_4Cl solution. The usual workup gave 3.9 g of crude product. Purification with column chromatography (100 g, SiO_2, hexane:AcOEt = 50:1 as an eluant) afforded 3.04 g of **7** (99% yield): ^{1}H NMR ($CDCl_3$) δ 8.10–8.02 (2H, m), 7.62–7.40 (3H, m), 4.92 (1H, dd, J = 4.2 and 5.9 Hz), 3.38 (1H, dd, J = 1.5 and 10.0 Hz), 2.11 (1H, ddd, J = 15.5, 4.2, and 1.5 Hz), 1.48 (1H, ddd, J = 15.5, 10.0, and 5.9 Hz), 1.02 (9H, s), 0.90 (9H, s); IR (KBr) 3460, 2940, 2860, 1680, 1590, cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.86; H, 9.56.

3-(Benzoyloxy)-2,2,6,6-tetramethyl-5-heptyl Crotonate (8a). To a solution of **7** (806 mg, 2.76 mmol) dissolved in dry benzene (10 mL) kept under N_2 were added AgCN (402 mg, 3.0 mmol) and crotonyl chloride (0.30 mL, 3.0 mmol). The mixture was refluxed for 2 h and then cooled to room temperature. The resulting mixture was filtrated and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure and purification with column chromatography (60 g, SiO_2, hexane:EtOAc = 30:1 as an eluant) gave 857 mg of **8a** (86%): ^{1}H NMR ($CDCl_3$) δ 8.04–7.96 (2H, m), 7.56–7.36 (3H, m), 6.58 (1H, dq, J = 15.8 and 6.8 Hz), 5.55 (1H, dq, J = 15.8 and 1.4 Hz), 5.06 (1H, dd, J = 2.5 and 8.5 Hz), 4.95 (1H, dd, J = 2.5 and 8.5 Hz), 2.07 (1H, ddd, J = 15.0, 2.5, and 2.5 Hz), 1.78 (1H, ddd, J = 15.0, and 8.5 Hz), 1.60 (3H, dd, J = 1.4 and 6.8 Hz), 0.98 (9H, s), 0.90 (9H, s); IR (KBr) 3090, 3060, 3030, 2960, 2870, 1720, 1665, 1600, 1580, 1480, 1450 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.13; H, 8.93.

3-(Benzoyloxy)-2,2,6,6,-tetramethyl-5-heptyl 2-Pentenoate (8b). A procedure similar to that described for **8a** was employed: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.40–7.96 (2H, m), 7.56–7.36 (3H, m), 6.66 (1H, dt, J = 15.0 and 6.0 Hz), 5.52 (1H, dt, J = 15.0 and 1.5 Hz), 5.08 (1H, dd, J = 8.0 and 2.5 Hz), 4.96 (1H, dd, J = 8.9 and 2.5 Hz), 2.08 (1H, ddd, J = 15.3, 2.5, and 2.5 Hz), 1.96 (2H, m), 1.79 (1H, ddd, J = 15.3, 8.9, and 8.0 Hz), 0.97 (9H, s), 0.91 (9H, s), 0.89 (3H, t, J = 7.3 Hz); IR (CCl_4) 2950, 2875, 1710, 1650, 1360, 1340, 1265, 1170, 1105, 1040 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.26; H, 9.22. Found: C, 73.48; H, 8.97.

3-(Benzoyloxy)-2,2,6,6,-tetramethyl-5-heptyl 2-Heptenoate (8c). A procedure similar to that described for **8a** was employed: ^{1}H NMR ($CDCl_3$) δ 8.04–7.96 (2H, m), 7.60–7.30 (3H, m), 6.63

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(1H, dq, J = 15.3 and 6.3 Hz), 5.53 (1H, dq, J = 15.3 and 1.5 Hz), 5.07 (1H, dd, J = 2.9 and 8.5 Hz), 4.95 (1H, dd, J = 2.5 and 9.0 Hz), 2.08 (1H, ddd, J = 2.5, 2.9, and 15.1 Hz), 2.00–1.86 (2H, m), 1.78 (1H, ddd, J = 8.5, 9.0, and 15.1 Hz), 1.30–1.22 (2H, m), 1.0–0.80 (5H, m), 0.97 (9H, s), 0.91 (9H, s); IR (KBr) 2960, 2930, 2870, 1720, 1650, 1270, 1165, 1110 cm^{-1}. Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.64; H, 9.50.

3-(Benzoyloxy)-2,2,6,6-tetramethyl-5-heptyl Cinnamate (8d). A procedure similar to that described for **8a** was employed: ^1H NMR ($CDCl_3$) δ 7.95 (2H, m), 7.28 (1H, d, J = 15.8 Hz), 7.40–7.20 (8H, m), 6.13 (1H, d, J = 15.8 Hz), 5.11 (1H, dd, J = 8.2 and 2.5 Hz), 5.03 (1H, dd, J = 9.1 and 2.5 Hz), 2.11 (1H, ddd, J = 15.0, 2.5, and 2.5 Hz), 1.85 (1H, ddd, J = 15.0, 9.1, and 8.2 Hz), 0.99 (9H, s), 0.94 (9H, s); IR (KBr) 3060, 2960, 2870, 1730, 1635, 1600, 1570, 1480, 1470, 1445, 1260, 1160 cm^{-1}. Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.75; H, 8.11. Found: C, 76.72; H, 8.11.

3-(Benzoyloxy)-2,2,6,6,-tetramethyl-5-heptyl Acrylate (8e). To a stirred solution of **7** (575 mg, 2.1 mmol) in 4 mL of CH_2Cl_2 were added tributylamine (1.2 mL, 4.8 mmol) and acrylic acid (151 mg, 2.1 mmol). To this solution was added 2-chloro-1-methylpyridinium iodide (720 mg, 2.4 mmol). After refluxing for 2 h, removal of the solvent under reduced pressure and purification with column chromatography (40 g, SiO_2, hexane: EtOAc = 20:1 as an eluant) gave 535 mg of **8e** (74%): ^1H NMR (270 MHz, $CDCl_3$) δ 8.04–7.35 (5H, m), 6.09 (1H, dd, J = 17.5 and 1.5 Hz), 5.87 (1H, dd, J = 17.5 and 10.5 Hz), 5.54 (1H, dd, J = 10.5 and 1.5 Hz), 5.06 (1H, dd, J = 8.4 and 3.5 Hz), 4.97 (1H, dd, J = 8.8 and 2.7 Hz), 2.12 (1H, ddd, J = 15.0, 3.5, and 2.7 Hz), 1.78 (1H, ddd, J = 15.0, 8.8, and 8.4 Hz), 0.98 (9H, s), 0.91 (9H, s); IR (neat) 2950, 1720, 1470, 1400, 1360, 1280, 1180 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.45; H, 8.93.

(3*S*,5*R*)-5-(α-Menthoxyacetoxy)-2,2,6,6-tetramethylheptan-3-ol (10). To a suspension of KH (721 mg, 35 wt %) in dry THF (20 mL) was added under N_2 a solution of THMDiol (**6**) (1.14 g, 6 mmol) dissolved in dry THF (20 mL). Stirring was continued for 40 min at room temperature. A solution of α-methoxyacetyl chloride (1.43 g, 6.2 mmol) in dry THF (15 mL) was added. The reaction mixture was stirred overnight and then quenched with saturated aqueous NH_4Cl solution. The usual workup followed by purification with column chromatography (100 g, SiO_2, hexane: EtOAc = 30:1 as an eluant) gave 1.73 g of **10** (76% yield) as an oil. Two diastereomers were separated by HPLC (D-SIL-5–06 of YMC, hexane:EtOAc = 10:1, flow = 5 mL/min, t_R = 25.4 and 28.163 min). **(10′) (3*R*,5*S*)-5-(α-Menthoxyacetoxy)-2,2,6,6-tetramethylheptan-3-ol (10′)** (t_R = 25.4 min): ^1H NMR ($CDCl_3$) δ 4.81 (1H, dd, J = 4.5 and 7.5 Hz), 4.12 (2H, ABq, J = 16.0 Hz, $\Delta\nu$ = 16.0 Hz), 3.30 (1H, dd, J = 9.5 and 1.0 Hz), 3.16 (1H, ddd, J = 10.0, 10.0, and 3.9 Hz), 2.29 (1H, m), 2.12–2.0 (1H, m), 2.0–1.9 (1H, m), 1.70–1.58 (2H, m), 1.46–1.22 (4H, m), 1.72 (1H, bs), 0.92 (9H, s), 0.90 (3H, d, J =6.5 Hz), 0.89 (3H, d, J = 6.5 Hz), 0.79 (3H, d, J = 6.5 Hz), 0.96–0.85 (2H, m); IR (neat) 3500, 2950, 2870, 1760, 1480, 1460, 1370, 1270, 1200, 1100 cm^{-1}. Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.53. Found: C, 72.00; H, 11.68. **10** (t_R = 28.163 min): ^1H NMR ($CDCl_3$) δ 4.81 (1H, dd, J = 7.5 and 4.5 Hz), 4.12 (2H, ABq, J = 15.5 Hz, $\Delta\nu$ = 27.0 Hz), 3.30 (1H, bd, J = 9.5 Hz), 3.15 (1H, ddd, J = 10.5, 10.5, and 3.7 Hz), 2.30 (1H, m), 2.06 (1H, m), 1.94 (1H, m), 1.70–1.56 (2H, m), 1.46–1.42 (4H, m), 0.92 (9H, s), 0.87 (9H, s), 0.89 (6H, d, J = 6.0 Hz), 0.78 (3H, d, J–6.5 Hz), 0.95–0.85 (2H, m); IR (neat) 3500, 2950, 2870, 1760, 1480, 1460, 1365, 1270, 1200, 1120 cm^{-1}. Anal. Calcd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.53. Found: C, 71.90; H, 11.50.

(3*R*,5*S*)-5-[(Benzyloxy)methoxy]-3-(α-menthoxyacetoxy)-2,2,6,6-tetramethylheptane (11). To a solution of the alcohol **10** (751 mg, 1.95 mmol) in CH_2Cl_2 (8 mL) were added 0.85 mL of diisopropylethylamine (4.9 mmol) and 0.54 mL of benzyl chloromethyl ether (3.9 mmol). The mixture was refluxed for 2 h and then cooled to room temperature. Ether was added, and the organic layer was washed twice with aqueous 1 N HCl solution, twice with saturated aqueous $NaHCO_3$ solution, and with brine. The usual workup and purification with column chromatography (SiO_2, 40 g, hexane:EtOAc = 50:1 as an eluant) gave 957 mg of **11** as a colorless oil (97% yield): ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, m), 4.85 (1H, dd, J = 12.0 and 1.9 Hz). 4.71 (2H, ABq, J = 6.9 Hz, $\Delta\nu$ = 44 Hz), 4.61 (2H, ABq, J = 11.8 Hz, $\Delta\nu$ = 21.0 Hz), 4.08 (2H, ABq, J = 16.2 Hz, $\Delta\nu$ = 16.2 Hz), 3.20 (1H, dd, J = 7.0 and 1.5 Hz), 3.04 (1H, ddd, J = 10.5, 10.5, and 4.0 Hz), 2.31 (1H, m), 2.06 (1H, ddd, J = 15.0, 7.0, and 1.9 Hz), 1.96 (1H, m), 0.95 (9H, s), 0.91 (9H, s), 0.87 (3H, d, J = 6.5 Hz), 0.86 (3H, d, J = 6.5 Hz), 0.74 (3H, d, J = 6.9 Hz), 1.80–0.90 (10H, m); IR (neat) 2960, 2875, 1750, 1720, 1450, 1360, 1280, 1120, 1040, 1020 cm^{-1}. Anal. Calcd for $C_{31}H_{52}O_5$: C, 73.77; H, 10.38. Found: C, 73.76; H, 10.12. The same procedure as above was used for the synthesis of **11′** from **10′**: ^1H NMR ($CDCl_3$) δ 7.40–7.20 (5H, m), 4.84 (1H, dd, J = 11.7 and 1.9 Hz), 4.71 (2H, ABq, J = 7.5 Hz, $\Delta\nu$ = 45.0 Hz), 4.61 (2H, ABq, J = 12.0 Hz, $\Delta\nu$ = 28.0 Hz), 4.08 (2H, ABq, J = 16.0 Hz, $\Delta\nu$ = 61.0 Hz), 3.20 (1H, dd, J = 6.9 and 1.5 Hz), 3.01 (1H, ddd, J = 10.5, 10.5, 4.2 Hz), 2.27 (1H, m), 2.05 (1H, ddd, J = 15.2, 6.9, and 1.9 Hz), 1.96 (1H, m), 0.95 (9H, s), 0.91 (9H, s), 0.88 (3H, d, J = 6.5 Hz), 0.87 (3H, d, J = 6.5 Hz), 0.74 (3H, d, J = 6.8 Hz), 1.70–0.80 (10H, m); IR (neat) 2960, 2875, 1750, 1720, 1450, 1360, 1280, 1120, 1050, 1020 cm^{-1}. Anal. Calcd for $C_{31}H_{52}O_5$: C, 73.77; H, 10.38. Found: C, 73.76; H, 10.29.

(3*R*,5*S*)-5-{(Benzyloxy)methoxy)]-2,2,6,6,-tetramethylheptan-3-ol (11-1). To a solution of **11** (957 mg, 1.89 mmol) in 90% MeOH–H_2O (10 mL) was added KOH (1.134 g, 20 mmol). The mixture was refluxed for 2 h and then diluted with ether. The organic layer was washed twice with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product with column chromatography (40 g of Merck SiO_2, hexane:AcOEt = 30:1 as an eluant) gave 570 mg of the desired product (95% yield): ^1H NMR ($CDCl_3$) δ 7.40–7.25 (5H, m), 4.89 (2H, ABq, J = 6.5 Hz, $\Delta\nu$ = 20.5 Hz), 4.68 (2H, ABq, J = 12.0 Hz, $\Delta\nu$ = 21.0 Hz), 3.38 (1H, dd, J = 6.5 and 4.0 Hz), 3.30 (1H, dd, J = 10.2 and 1.8 Hz), 1.90 (1H, ddd, J = 15.0, 4.0, and 1.8 Hz), 1.41 (1H, ddd, J = 15.0, 10.2, and 6.5 Hz), 0.91 (9H, s), 0.88 (9H, s), 0.88 (9H, s); IR (neat) 3500, 2975, 2880, 1480, 1390, 1360, 1160, 1040, 1020 cm^{-1}.

(3*R*,5*S*)-3-(Benzoyloxy)-5-{(benzyloxy)methoxy)]-2,2,6,6-tetramethylheptane (11-2). To a solution of the alcohol **11-1** (421 mg, 1.36 mmol) in pyridine (4 mL) was added at room temperature 0.32 mL of benzoyl chloride (2.7 mmol). Stirring was continued overnight. The usual workup gave 750 mg of yellow oil. Purification with column chromatography (50 g, SiO_2, hexane:EtOAc = 50:1 as an eluant) afforded 544 mg of **11-2** (97% yield): ^1H NMR ($CDCl_3$) δ 8.00–7.93 (2H, m), 7.50–7.40 (1H, m), 7.36–7.26 (2H, m), 7.20–7.10 (3H, m), 7.02–6.96 (2H, m), 4.95 (2H, dd, J = 1.9 and 11.0 Hz), 4.60 (2H, ABq, J = 6.5 Hz, $\Delta\nu$ = 43.3 Hz), 4.40 (2H, ABq, J = 12.1 Hz, $\Delta\nu$ = 33.4 Hz), 3.22 (1H, dd, J = 7.0 and 1.9 Hz), 2.09 (1H, ddd, J = 15.6, 7.0, and 1.9 Hz), 1.68 (1H, ddd, J = 15.6, 11.0, and 1.9 Hz), 0.92 (9H, s), 0.91 (9H, s); IR (KBr) 2950, 2890, 2870, 1700, 1595, 1560, 1470, 1445, 1360, 1270, 1155, 1100, 1050, 1040 cm^{-1}. Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.74; h, 8.71.

(3*S*,5*R*)-5-(Benzoyloxy)-2,2,6,6-tetramethylheptan-3-ol [(7 (Chiral)]. To a solution of the BOM ether **11–2** (718 mg, 1.74 mmol) in 4 mL of EtOH was added 72 mg of $Pd(OH)_2$. Hydrogen was introduced into the flask, and the mixture was stirred overnight at room temperature. Purification of the crude product with

column chromatography (20 g of SiO_2, hexane:AcOEt = 30:1 as an eluant) gave 493 mg of **7** (chiral) as a colorless oil (97% yield): $[\alpha]^{23}_D$ 30.27 (*c* 0.094, C_6H_6). **7′** (chiral): $[\alpha]^{23}_D$ −30.42 (*c* 0.093, C_6H_6).

(3*R*,5*S*)-3-(Benzoyloxy)-5-(butanoyloxy)-2,2,6,6-tetramethylheptane (12). To a solution of **7** (chiral) (445 mg, 1.52 mmol) dissolved in 6 mL of CH_2Cl_2 were added at 0 °C pyridine (0.5 mL) and butyryl chloride (0.24 mL, 2.3 mmol). Stirring was continued overnight at room temperature. The usual workup and purification with column chromatography (50 g SiO_2, hexane:EtOAc = 50:1 as an eluant) gave 470 mg of **12** (85% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.10–8.00 (2H, m), 7.60–7.30 (3H, m), 5.02 (1H, dd, *J* = 7.5 and 3.5 Hz), 4.91 (1H, dd, *J* = 9.0 and 2.5 Hz), 2.09 (1H, ddd, *J* = 15.2, 3.5, and 2.5 Hz), 2.07 (2H, t, *J* = 7.2 Hz), 1.71 (1H, ddd, *J* = 15.2, 9.0, and 7.5 Hz), 1.55–1.30 (2H, m), 0.98 (9H, s), 0.89 (9H, s), 0.81 (3H, t, J = 7.5 Hz); IR (neat) 2960, 2870, 1760, 1730, 1560, 1270, 1170 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.99; H, 9.54.

(3*R*,5*S*)-3-(Benzoyloxy)-2,2,6,6-tetramethyl-5-heptyl Crotonate[8a (Chiral)]. To a THF (4 mL) solution of diisopropylamine (0.21 mL, 1.5 mmol), cooled at 0 °C, was added BuLi-hexane solution (0.74 mL × 1.62 M, 1.2 mmol). The mixture was stirred for 10 min and then cooled to −78 °C. A THF (4 mL) solution of the ester **12** (370 mg, 1.0 mmol) was added. The reaction mixture was stirred for 10 min at −78 °C. To the reaction mixture was added 350 mg of PhSeSePh (1.1 mmol) in THF (4 mL). The resulting mixture was allowed to warm to room temperature and quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted twice with ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and 550 mg of crude product was obtained. This crude product was used for further purification. To the crude product dissolved in 3 mL of AcOEt–THF (2:1) at 0 °C were added 250 mg of $NaHCO_3$ and 0.4 mL of 30% H_2O_2. The mixture was stirred overnight at room temperature. The resulting mixture was diluted with ether and washed twice with a saturated aqueous solution of $Na_2S_2O_3$ and of $NaHCO_3$ and with brine. The usual workup and purification with silica gel column chromatography (SiO_2, 30 g, hexane:AcOEt = 30:1) gave 349 mg of the desired product (95%).

(3*S,5*R**)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3*S**)-3-(Benzylamino)butanoate (17a).** To a solution of *N*-(trimethylsilyl)benzylamine (0.1 mL, 0.5 mmol) in THF (5 mL) at 0 °C was slowly added *n*-BuLi (0.27 mL, 1.56 M in hexane, 0.42 mmol). After stirring for 20 min, the solution was cooled to −78 °C. To this solution was added a solution of TMHD crotonate **8a** (169 mg, 0.41 mmol) in THF (3 mL). After stirring for an additional 10 min, the reaction was quenched with 2 mL of MeOH. An aqueous saturated solution of $NaHCO_3$ was added to the solution, and the mixture was extracted twice with ether. Removal of the solvent under reduced pressure and purification with column chromatography (15 g, SiO_2, hexane:EtOAc = 5:1 as an eluant) gave 135 mg of **17a** (96%). The diastereoisomer ratio was determined by ^{1}H NMR: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.60–8.10 (2H, m), 7.58–7.36 (3H, m), 7.32–7.22 (5H, m), 5.02 (1H, dd, *J* = 7.3 and 3.5 Hz), 4.91 (1H, dd, *J* = 9.0 and 2.8 Hz), 3.67 (2H, ABq, *J* = 12.8 Hz, Δν = 21.0 Hz), 2.91 (1H, m), 2.31 (1H, dd, *J* = 16.0 and 7.2 Hz), 2.18 (1H, dd, *J* = 16.0 and 5.0 Hz), 2.10 (1H, ddd, *J* = 15.0, 3.5, and 2.8 Hz), 1.71 (1H, ddd, *J* = 15.0, 9.0, and 7.3 Hz), 0.99 (3H, d, *J* = 6.5 Hz), 0.98 (9H, s), 0.88 (9H, s); IR (neat). Anal. Calcd for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found: C, 74.25; H, 8.67; N, 3.00.

(3*S,5*R**)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3*S**)-3-(Benzylamino)pentanoate (17b).** A procedure similar to that described for **17a** was employed: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.80–8.00 (2H, m), 7.57–7.37 (3H, m), 7.32–7.20 (5H, m), 5.02 (1H, dd, *J* = 7.5 and 3.8 Hz), 4.92 (1H, dd, *J* = 8.8 and 2.5 Hz), 3.66 (2H, s), 2.77 (1H, m), 2.27 (2H, d, *J* = 6.0 Hz), 2.11 (1H, ddd, *J* = 15.2, 3.8, and 2.5 Hz), 1.70 (1H, ddd, *J* = 15.2, 8.8, and 7.5 Hz), 1.50–1.30 (2H, m), 0.98 (9H, s), 0.89 (9H, s), 0.81 (3H, t, *J* = 7.2 Hz); IR (neat) 3350, 2980, 2880, 1720, 1450, 1360, 1270, 1160 cm^{-1}. Anal. Calcd for $C_{30}H_{43}NO_4$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.43; H, 8.97; N, 2.95.

(3*S,5*R**)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3*S**)-3-(Benzylamino)hydrocinnamate (17c).** A procedure similar to that described for **17a** was employed: ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.02–7.98 (2H, m), 7.53–7.18 (13H, m), 5.01 (1H, dd, *J* = 7.5 and 3.5 Hz), 4.91 (1H, dd, *J* = 9.0 and 2.5 Hz), 3.99 (1H, dd, *J* = 9.5 and 4.0 Hz), 3.48 (2H, ABq, *J* = 12.5 Hz, Δν = 13.0 Hz), 2.55 (1H, dd, *J* = 16.5 and 9.5 Hz), 2.43 (1H, dd, *J* = 16.5 and 4.0 Hz), 2.08 (1H, ddd, *J* = 15.5, 3.5, and 2.5 Hz), 1.66 (1H, ddd, *J* = 15.5, 9.0, and 7.5 Hz), 0.97 (9H, s), 0.85 (9H, s); IR (neat) 3350, 2950, 2980, 1720, 1450, 1370, 1280, 1160 cm^{-1}. Anal. Calcd for $C_{34}H_{43}NO_4$: C, 77.09; H, 8.18; N, 2.64. Found: C, 76.68; H, 7.89; N, 2.49.

Conjugate Addition to 8. The addition of $Bu_2CuLi{\cdot}2BF_3$ to **8a** is representative. In a 30-mL two-necked flask, equipped with a magnetic stirrer and maintained under Ar, were placed 95.6 mg (0.50 mmol) of CuI and 4 mL of dry ether. BuLi in hexane (1.64 M, 1 mmol) was added at −55 °C, and the resulting mixture was stirred for 20 min at this temperature. The mixture was cooled to −78 °C, and 0.13 mL (1.0 mmol) of $BF_3{\cdot}OEt_2$ was added. The mixture was stirred for a while, and then an ether (3 mL) solution of 84.7 mg (0.23 mmol) of **8a** was added. Stirring was continued for 1 h below −50 °C. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted three times with ether. The combined organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave 108 mg of crude product. Purification with column chromatography (10 g, SiO_2, hexane:EtOAc = 50:1 as an eluant) afforded 71.7 mg (74% yield) of the conjugate adducts as an oil. The diastereoisomer ratio was determined by HPLC (YMCR-SIL-5-06); **22b** (t_R = 22.43 min):**23b** (t_R = 23.35 min) = 95:5.

(3*R,5*S**)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3*S**)-3-methylheptanoate (22b):** ^{1}H NMR ($CDCl_3$) δ 8.10–8.0 (2H, m), 7.60–7.36 (3H, m), 5.20 (1H, dd, *J* = 7.4 and 3.8 Hz), 4.90 (1 H, dd, *J* = 8.4 and 3.0 Hz), 2.10 (1 H, ddd, *J* = 14.9, 3.8, and 3.0 Hz), 2.10 (1 H, dd, *J* = 15.2 and 5.5 Hz), 1.89 (1 H, dd, *J* = 15.2 and 8.5 Hz), 1.68 (1 H, ddd, *J* = 14.9, 8.4, and 7.4 Hz), 0.98 (9H, s), 0.90 (9H, s), 0.81 (3H, d, *J* = 6.5 Hz), 1.40–0.80 (10H, m); IR (neat) 3060, 3030, 2960, 2880, 1720, 1580, 1465, 1395, 1365, 1275, 1240, 1190, 1160, 1130, 1050, 1000 cm^{-1}. Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.56; H, 10.17. ^{1}H NMR ($CDCl_3$) of a minor isomer, **23b**: 8.10–8.00 (2H, m), 7.60–7.36 (3H, m), 5.02 (1H, dd, *J* = 7.2 and 3.9 Hz), 4.89 (1H, dd, *J* = 8.9 and 3.0 Hz), 2.12 (1H, dd, *J* = 15.1 and 6.0 Hz), 2.12 (1H, ddd, *J* = 15.0, 3.9, and 3.0 Hz), 1.93 (1H, dd, *J* = 15.1 and 7.5 Hz), 1.69 (1H, ddd, *J* = 15.0, 8.9, and 7.2 Hz), 0.98 (9H, s), 0.91 (9H, s), 0.82 (3H, d, *J* = 6.7 Hz), 1.40–0.80 (9H, m).

(3*S,5*R**)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3*R**)-3-phenylbutanoate (22a):** ^{1}H NMR ($CDCl_3$) δ 8.04–7.98 (2H, m), 7.60–6.98 (8H, m), 4.98 (1H, dd, *J* = 7.5 and 3.7 Hz), 4.87 (1H, dd, *J* = 8.8 and 2.9 Hz), 3.07 (1H, qdd, *J* = 6.7, 8.8, and 6.0 Hz), 2.52 (1H, dd, *J* = 16.0 and 6.0 Hz), 2.37 (1H, dd, *J* = 16.0 and 8.8 Hz), 2.07 (1H, ddd, *J* = 15.5, 3.7, and 2.9 Hz), 1.63 (1H, ddd, *J* = 15.5, 8.8, and 7.5 Hz), 1.16 (3H, d, *J* = 6.7 Hz), 0.96 (9H, s), 0.83 (9H, s); IR (neat) 2960, 2870, 1720, 1600, 1580, 1470, 1450, 1365, 1270, 1160, 1110, 1050, 1020, 990 cm^{-1}. Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.80; H, 8.76. A minor isomer, **23a**, could not be isolated in a pure form, but was obtained as a mixture with **22a** and identified by the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 8.08–7.98 (2H, m), 7.60–698 (8H, m), 4.98 (1H, dd, *J* = 7.5 and 3.7 Hz), 4.82

(1H, dd, J = 8.9 and 2.5 Hz), 3.07 (1H, qdd, J = 7.5, 7.5, and 6.7 Hz), 2.47 (1H, dd, J = 15.5 and 7.5 Hz), 2.37 (1H, dd, J = 15.5 and 7.5 Hz), 2.07 (1H, ddd, J = 15.5, 8.9, and 7.5 Hz), 1.62 (1H, ddd, J = 15.5, 3.7 and 2.5 Hz), 1.18 (3H, d, J = 6.7 Hz), 0.97 (9H, s), 0.74 (9H, s).

(3S*,5R*)-5-(Benzoyloxy)-2,2,6,6-tetramethyl-3-heptyl (3R*)-3-phenylheptanoate (22c): ^{1}H NMR ($CDCl_3$) δ 8.08–7.98 (2H, m), 7.60–7.96 (8H, m), 4.97 (1H, dd, J = 7.5 and 3.9 Hz), 4.76 (1H, dd, J = 8.9 and 2.9 Hz), 2.90 (1H, m), 2.45 (1H, dd, J = 15.5 and 6.5 Hz), 2.38 (1H, dd, J = 15.5 and 8.5 Hz), 2.03 (1H, ddd, J = 15.6, 3.9, and 2.9 Hz), 1.8–0.8 (10H, m), 0.95 (9H, s), 0.67 (9H, s); IR (neat) 2950, 2860, 1740, 1600, 1560, 1450, 1370, 1260, 1160 cm^{-1}. Anal. Calcd. for $_{31}H_{44}O_4$: C, 77.46; H, 9.23. Found: C, 77.40 H, 9.33. A minor isomer, **23c** could not be isolated in a pure form, but was obtained as a mixture with **22c**: ^{1}H NMR ($CDCl_3$) δ 8.07–7.97 (2H, m), 7.60–7.06 (8H, m), 4.95 (1H, dd, J = 7.9 and 3.8 Hz), 4.83 (1H, dd, J = 8.7 and 3.1 Hz), 2.89 (1H, m), 2.52–2.38 (2H, m), 2.04 (1H, ddd, J = 15.1, 3.8, and 3.1 Hz), 1.8–0.8 (10H, m), 0.94 (9H, s), 0.76 (9H, s).

Diels–Alder Reaction between TMHD Acrylate and Cyclopentadiene in the Presence of 0.5 equiv of $TiCl_4$. To a stirred solution of TMHD acrylate (119 mg, 0.34 mmol) in 4 mL of CH_2Cl_2–hexane (1:1) was added $TiCl_4$ (0.17 mL, 1 M in CH_2Cl_2, 0.17 mmol) at –78 °C. After stirring for 10 min at this temperature, a solution of cyclopentadiene (0.5 mL) in CH_2Cl_2 was added to this yellow solution. The reaction mixture was allowed to warm to –30 °C and was stirred overnight at this temperature. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$, and the mixture was extracted twice with ether. The organic phase was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification with column chromatography (10 g, SiO_2, hexane:EtOAc = 50:1 as an eluant) gave 135 mg of a desired product (96%). The diastereoisomer ratio was determined by HPLC (YMC R-SIL-5-06; hexane:AcOEt = 20:1, flow rate = 0.5 mL/min).

(3R*,5S*)-3-(Benzoyloxy)-2,2,6,6-tetramethyl-5-heptyl (1S*,2S*,4R*)-5-norbornene-2-carboxylate (26) (t_R = 19.8 min): ^{1}H NMR 270 MHz, $CDCl_3$) δ 8.08–8.00 (2H, m), 7.60–7.35 (3H, m), 6.12 (1H, dd, J = 5.5 and 3.5 Hz), 5.78 (1H, dd, J = 5.8 and 2.9 Hz), 5.00 (1H, dd, J = 7.5 and 3.5 Hz), 4.83 (1H, dd, J = 9.0 and 2.5 Hz), 3.03 (1H, m), 2.77 (1H, m), 2.74 (1H, ddd, J = 9.0, 3.5, and 3.5 Hz), 2.09 (1H, ddd, J = 15.5, 3.5, and 2.5 Hz), 1.71 (1H, ddd, J = 15.5, 9.0, and 7.5 Hz), 1.56 (1H, ddd, J = 11.5, 9.0, and 3.5 Hz), 1.31 (1H, ddd, J = 8.0, 4.5, and 1.5 Hz), 1.19 (1H, ddd, J = 11.5, 4.5, and 2.5 Hz), 1.11 (1H, bd, J = 8.0 Hz), 0.97 (9H, s), 0.91 (9H, s); IR (CCl_4) 2950, 2860, 1720, 1360, 1265, 1160, 1105 cm^{-1}. Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.33; H, 9.05.

(3R*,5S*)-3-(Benzoyloxy)-2,2,6,6-tetramethyl-5-heptyl (1R*,2R*,4S*)-5-norbornene-2-carboxylate (27) (t_R = 21.6 min): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.09–8.02 (2H, m), 7.59–7.39 (3H, m), 6.03 (1H, dd, J = 5.5 and 3.0 Hz), 5.98 (1H, dd, J = 5.5 and 2.5 Hz), 5.00 (1H, dd, J = 7.5 and 4.0 Hz), 4.82 (1H, dd, J = 8.5 and 3.0 Hz), 3.05 (1H, m), 2.80 (1H, ddd, J = 9.5, 4.0, and 3.0 Hz), 1.80–1.58 (2H, m), 1.38–1.08 (3H, m), 0.98 (9H, s), 0.85 (9H, s).

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Supplementary Material Available: Listing of crystal data, positional parameters, bond distances, and bond angles for **8d** and **13** (19 pages). Ordering information is given on any current masthead page.