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Transfer of Chirality in the [2,3] Sigmatropic Rearrangement of Allylic Alcohols to β,γ-Unsaturated Amides. Preparation of Optically Active Nine- and Fourteen-Carbon Saturated Isoprenoid Synthons

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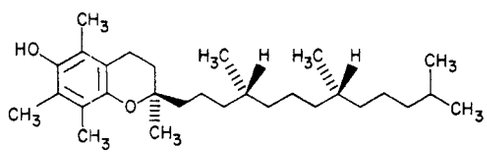
Received May 23, 1977

Reaction of optically active (*R,Z*)-allylic alcohols **8** and **16**, respectively, with *N,N*-dimethylformamide dimethyl acetal proceeded stereoselectively, via a [2,3] sigmatropic rearrangement, to give optically active (2*R,E*)-β,γ-unsaturated amides **9** and **17**, with nearly 100% chiral transmission. The (*S,E*)-allylic alcohols **13** and **21**, however, afforded mixtures of (2*R,E*)- and (2*S,Z*)-β,γ-unsaturated amides, from which the nearly optically pure (2*R,E*) isomer could be isolated by chromatography. The optically active amides **9** and **17** were transformed, respectively, into 2(*R*),6-dimethylheptan-1-ol (**2**) and 2(*R*),6(*R*),10-trimethylundecan-1-ol (**4**), which are important intermediates in vitamin E synthesis.

The optically active aliphatic side-chain synthons **2**–**5** are important intermediates in the synthesis of (2*R*,4′*R*,8′-*R*)-α-tocopherol[1] (**1**, vitamin E). The 14- and 15-carbon units **4**[2] and **5**,[3] respectively, were first prepared by degradation of natural phytol. Recently, the preparation of optically active synthons **2** (9-carbon unit) and **4** (14-carbon unit) from (*S*)-(+)-β-hydroxyisobutyric acid (**6**) was reported.[4] Since the homologous units **3** and **5** had been synthesized starting from isovaleraldehyde (**7**) via stereoselective Claisen rearrangements[5] of optically active allylic alcohols, we were also interested in the possibility of preparing the lower homologues **2** and **4** from **7**, using a related approach involving [2,3] sigmatropic shifts.



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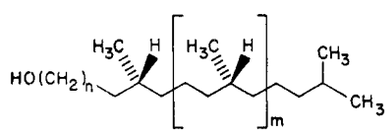
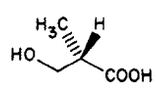


	m	n
2	0	0
3	0	1
4	1	0
5	1	1



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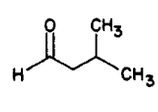


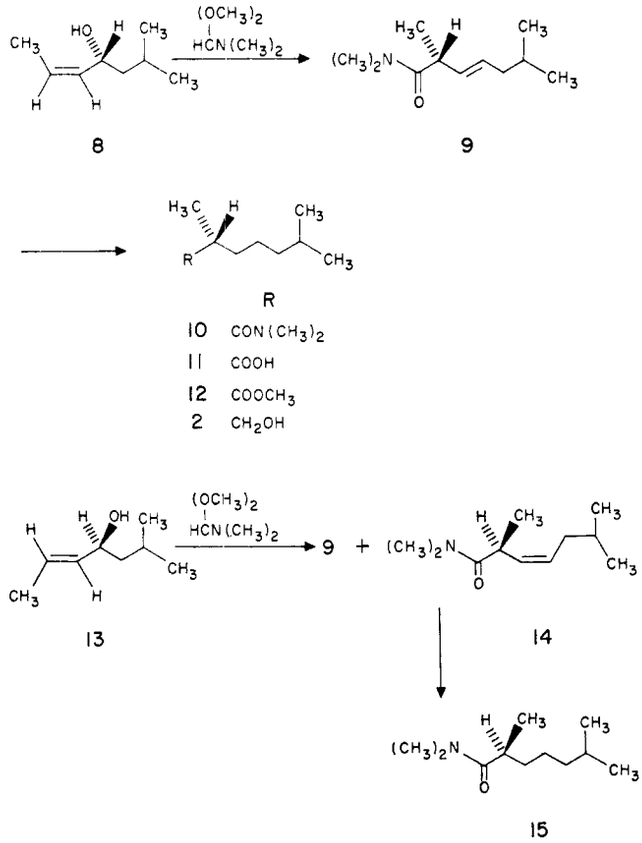
7

The transmission of chirality in a [2,3] sigmatropic process was observed in the conversion of sulfenates to sulfoxides,[6] and later in the Wittig[7] and allylic amine oxide[8] rearrangements. Although the conversion of an allylic halide to a carboxylic acid via a [2,3] sigmatropic process had been recorded,[9] the transmission of chirality associated with a new carbon–carbon bond formation by such a process was noted only in the Wittig rearrangement.[7] Büchi and co-workers[10] recently discovered that allylic alcohols could be transformed into homologous β,γ-unsaturated amides via a [2,3] sigmatropic process, by heating with *N,N*-dimethylformamide acetals. These findings, together with our earlier observations[5] that several variants of the Claisen rearrangement proceeded with essentially 100% chiral transmission, led to the expectation that optically active allylic alcohols should give enantiomerically enriched β,γ-unsaturated amides by the Büchi process. In this report, we wish to present the results of a thorough investigation into the extent of chiral transmission in this one carbon homologation process. The application of this [2,3] sigmatropic rearrangement to the synthesis of optically active saturated isoprenoid synthons **2** and **4** will also be described.

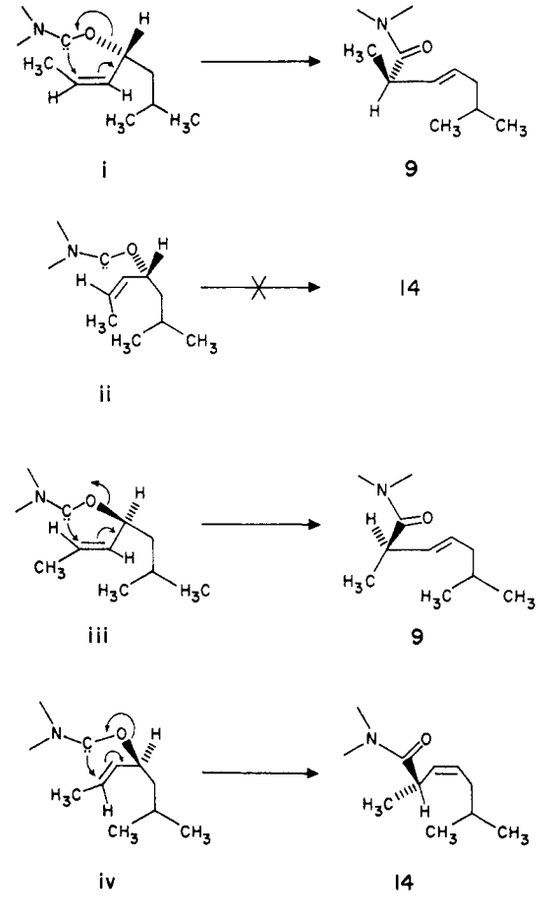
Results

Reaction of the (*R,Z*)-allylic alcohol **8** (96.5% *R*, 3.5% *S*; prepared from isovaleraldehyde as reported earlier[5]) with *N,N*-dimethylformamide dimethyl acetal[10] in refluxing xylene for 93 h gave, in 49% yield, the optically active β,γ-unsaturated amide **9**. (Scheme I). ^{1}H NMR studies on this compound using tris(3-(heptafluoropropylhydroxymethyl)-*d*-camphorato)-europium(III) [Eu(hfc)$_3$] revealed the presence of two pairs

Scheme I



Scheme II



of doublets arising from the C(2) methyl moiety, centered at δ 2.67 and 3.04 ppm, in a ratio of approximately 96:4 respectively.[11] The newly formed double bond was shown to be *E* by its IR absorption at 975 cm^{-1} and a coupling constant of 15 Hz for the olefinic protons in the NMR spectrum. Furthermore, GC analysis of **9** showed only one component. Therefore, the conversion of (*R*,*Z*)-allylic alcohol **8** to the (*E*)-unsaturated amide **9** had proceeded with complete stereoselectivity.

The absolute configuration of the newly created asymmetric center in **9** was determined as follows. Hydrogenation of **9** using palladium catalyst gave the saturated amide **10**, $[\alpha]^{25}_D$ −27.1° ($CHCl_3$), showing an enantiomeric ratio of approximately 96:4 by ^1H NMR studies as described above. The amide **10** was hydrolyzed in concentrated HCl to give the acid **11**, which on treatment with diazomethane afforded the known methyl ester **12**, $[\alpha]^{25}_D$ −20.1° ($CHCl_3$)[12,13] having an enantiomeric composition of 92% *R* and 8% *S* by NMR analysis. Therefore, racemization[14] had occurred to some extent during acidic hydrolysis of amide **10**. The methyl ester **12** was further reduced with lithium aluminum hydride to the known 9-carbon optically active (*R*)-alcohol **2**.[4] Thus, the *R* absolute configuration of unsaturated amide **9** was fully established.

We reported previously[5] that both optically active (*Z*)- and (*E*)-allylic alcohols underwent Claisen rearrangements with nearly 100% chiral transmission. Therefore, the (*S*,*E*)-allylic alcohol **13** (97.8% *S*, 2.2% *R*)[5] was subjected to investigation also. Treatment of **13** with *N*,*N*,-dimethylformamide dimethyl acetal afforded, however, a mixture of β,γ-unsaturated amides (*E*)-**9** (87% by GC) and (*Z*)-**14** (13%). NMR analysis of this mixture using a chiral shifts reagent as described above revealed approximately 87% *R* and 13% *S*. The nearly pure (*E*)-**9** (98.4% *E*, 1.6% *Z*) could be isolated by column chromatography on silica gel and was shown by NMR to be 98 ± 2% *R*. Further purification of a mixture of **9** and **14** by thick-layer chromatography on silica gel gave a substance consisting of 80.4% (*Z*)-isomer **14** and 19.5% (*E*)-isomer **9**. Hydrogenation of this material afforded the saturated amide **15**, $[\alpha]^{25}_D$ +15.3° ($CHCl_3$), having an enantiomeric composition of approximately 80% *S* and 20% *R* by NMR analysis. Therefore, the *S*,*Z* configuration of unsaturated amide **14** was rigorously established. Since nearly enantiomeric pure (*R*,*E*)-**9** was isolated, the conversion of (*S*,*E*)-allylic alcohol **13** to the (*E*) unsaturated amide **9** could also be considered to proceed with complete chiral transmission.

Büchi[10] suggested that the reaction proceeded via a carbene intermediate, which underwent a concerted [2,3] sigmatropic process to give β,γ-unsaturated amide. Our experimental results indicate that the carbene intermediates derived from allylic alcohols (*R*,*Z*)-**8** and (*S*,*E*)-**13** are best represented by i and iii, respectively (Scheme II), which rearrange through a five-membered cyclic transition state and via a doubly suprafacial [2,3] sigmatropic process,[7,8] to give the optically active unsaturated amide (*R*,*E*)-**9**. The alternate rotational intermediates ii and iv (derived from **8** and **13**, respectively), which would lead to *Z* products, are not favorable because of the presence of severe nonbonded interactions, particularly in ii, involving the methyl and isopropyl moieties. This explains why the allylic alcohol (*R*,*Z*)-**8** rearranges stereoselectively to the (all-*E*)-unsaturated amide **9**, while the (*S*,*E*)-**13** gives mainly (*E*)-**9** and a minor amount of (*Z*)-**14**. The complete transfer of chirality observed in transforming the allylic alcohols **8** and **13** into the unsaturated amide (*R*,*E*)-**9** strongly supports the proposed concerted mechanism.[7,8,10]

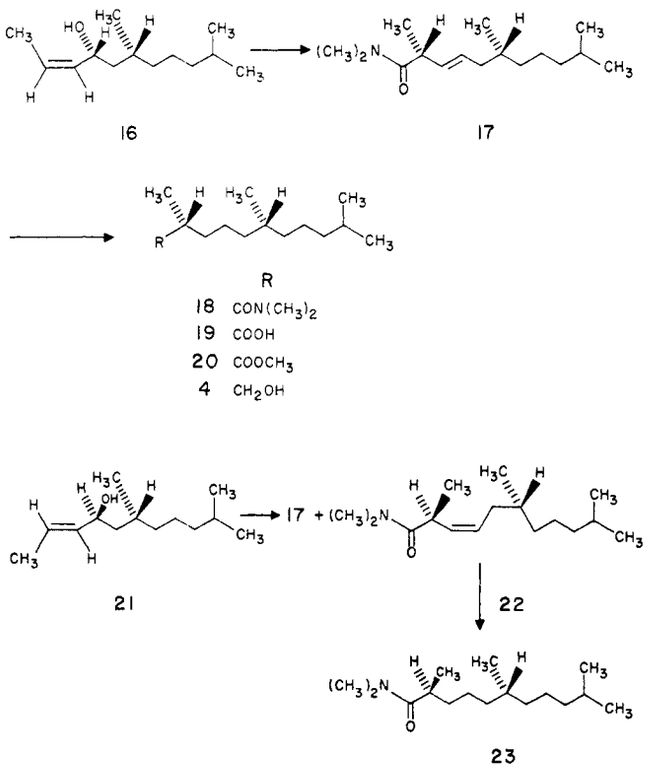
Similarly, reaction of (4*R*,6*R*,*Z*)-allylic alcohol[5] **16** (89.7% 4*R*, 10.3% 4*S*) with *N*,*N*-dimethylformamide dimethyl acetal afforded the 14-carbon, optically active, (2*R*,6*R*,*E*)-unsaturated amide **17** (Scheme III) (86% 2*R* and 14% 2*S*). Hydrogenation of **17** gave the saturated amide **18**, $[\alpha]^{25}_D$ −15.3° ($CHCl_3$). The (4*S*,6*R*,*E*)-allylic alcohol **21** (95% 4*S*, 5% 4*R*) yielded a mixture of (*E*)-**17** (86.5%) and (*Z*)-**22** (13.5%) under

Table I. Summary of Results

Starting alcohol[a]	Product	Run	Compositions % R^c	% S^c	% E^g	% Z^g	$[\alpha]^{25}D^b$	Chemical yield, %	% transfer of chirality
8	9	1	96	4	100	0	−72.7°	49.5	100[d]
		2	96	4	100	0	−75.6°	49	
	10		96	4			−27.1°		
	12		92	8			−20.1°		
13	9 &	1	87	13	87	13.1	−46.4°	76	89[e]
	14	2	87	13	87	13	−47.1°	73	
		3	85	15	86.2	13.8	−38.6°	76	87[e], 100[f]
	10 & 15		85	15			−21.6°		
	12		85	15			−15.9°		
16	17		86	14	100	0	−43.7°	40.5	96[d]
	18		86	14			−15.3°		
	20		86	14			−11.3°		
21	17, 22		82	18	86.5	13.5	−30.5°	66	87[e], ~96[f]

[a] Enantiomeric composition of **8**, 96.5% *R*, 3.5% *S*; for **13**, 97.8% *S*, 2.2% *R*; for **16**, 89.7% 4*R*, 10.3% 4*S*; for **21**, 95% 4*S*, 5% 4*R*.[5] [b] In $CHCl_3$. [c] Determined by NMR (by peak height, limit of accuracy ca. ±2%) using Eu(hfc)$_3$—tris(3-(heptafluoropropylhydroxymethylene)-*d*-camphorato)europium(III). [d] Calculated as % major enantiomer in product/% major enantiomer in starting material × 100. [e] Calculated as % total *R* configuration in the original *E,Z* mixture/% major enantiomer in starting material × 100. [f] Calculated as % major *R* enantiomer in the isolated *E* product/% major enantiomer in starting material × 100. [g] Determined by GC.

Scheme III



the same conditions. The results of these experiments and those with substrates **8** and **13** are summarized in Table I. A sample of the nearly pure unsaturated **17** (95.2% *E*, 4.8% *Z*) was isolated from the mixture by thick-layer chromatography, and was shown by NMR analysis to possess an enantiomeric composition of 92% 2*R* and 8% 2*S* at the new chiral center. Based on the enantiomeric compositions of the starting alcohols **16** and **21**, the [2,3] sigmatropic process leading to the (*E*)-unsaturated amide **17** was again nearly stereospecific (Table I). The minor (*Z*)-isomer **22** was obtained in a purity of 62.6% *Z* and 37.4% *E*. NMR analysis of this material revealed a composition of ~61% 2*S* and 39% 2*R*. Hydrogenation of this mixture gave the saturated amide **23**, $[\alpha]^{25}D$ +4.6°, having an enantiomeric compositon of ~60% 2*S* and ~40% 2*R*. Therefore, the (*Z*)-isomer **22** undoubtedly had the 2*S* absolute configuration. The saturated amide **18** (86% 2*R*, derived from **17**) was hydrolyzed to the acid **19**, and then converted to the methyl ester **20**, having an enantiomeric composition of approximately 86% *R* and 14% *S* at C(2). Reduction of **20** with lithium aluminum hydride afforded the known 14-carbon optically active alcohol (2*R*,6*R*)-**4**,[2,4] to which was assigned the *R* configuration predominantly at C(2) also. The utilization of optically active alcohols **2** and **4** in vitamin E synthesis had been described.[2,4]

In summary, this paper describes the synthesis of optically active 2(*R*),6-dimethylheptan-1-ol (**2**) and 2(*R*),6(*R*),10-trimethylundecan-1-ol (**4**) by the application of stereoselective [2,3] sigmatropic rearrangement. The results clearly show that (1) optically active (*Z*)-allylic alcohols rearrange to the homologous (*E*)-β,γ-unsaturated amides with 96–100% chiral transmission, when heated with *N,N*-dimethylformamide dimethyl acetal; (2) the (*E*)-allylic alcohols yield a mixture of (*E*)- and (*Z*)-unsaturated amides having different absolute configurations. The enantiomerically pure *E* isomer can be isolated from the mixture by chromatography. These findings[15] and results reported by other groups,[6–8] in conjunction with our early report[5] concerning the complete transfer of chirality in various Claisen rearrangements, suggest wide, potential applicability of such sigmatropic processes for the synthesis of optically active substances.

Experimental Section

Unless otherwise noted, the "usual workup" procedure involves dilution of the reaction mixture with water followed by three extractions with the specific solvent. The organic extracts were then combined, washed with water, dried over anhydrous $MgSO_4$, filtered, and concetnrated under water aspirator pressure, at 35–40 °C, on a rotary evaporator. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Varian A-60 and HA-100 spectrometers were used to obtain the ^1H NMR spectra ($CDCl_3$ solution). Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Gas–liquid chromatography was performed using Becker 409 or Hewlett-Packard 5700 instruments with flame-ionization detector.

(*R*)-(−)-(*E*)-2,6-Dimethyl-3-heptenoic Acid *N,N*-Dimethylamide (9). (A) From 8. A mixture of 2.56 g (0.02 mol) of optically active (*R*)-(+)-(*Z*)-6-methyl-2-hepten-4-ol (**8**) [96.5% *R*, 3.5% *S*; $[\alpha]^{25}D$ +21.0° ($CHCl_3$)][5] and 15 g (0.126 mol) of *N,N*-dimethylformamide dimethyl acetal in 40 mL of xylene was refluxed, under continuous removal of methanol for 93 h. The xylene and excess re-

agent were evaporated off at 55 °C/12–20 mm to give 3.12 g of a light-brown-colored oil. This material was chromatographed on 100 g of silica gel. Elution with ether–petroleum ether (1:3) afforded 1.796 g of unsaturated amide **9** (49% yield). A sample (1.47 g) was evaporatively distilled at 80–85 °C/0.10 mm to give 1.42 g of **9** as a colorless liquid: $[\alpha]^{25}_D$ −75.6° (*c* 5.15, $CHCl_3$); IR (neat) 1660 (C=O), 975 cm^{-1} [(*E*)-CH=CH]; NMR δ 5.48 [m, 2, (*E*)-CH=CH], 2.97, 3.05 [2 s, 6, $N(CH_3)_2$], 3.32 (m, 1, CH_3CH), 1.92 (m, 2, CH_2), 1.60 [m, 1, $(CH_3)_2CH$], 1.20 (d, 3, CH_3CH), 0.87 ppm [d, 6, $(CH_3)_2CH$]; a solution of 22 mg of **9** and 55 mg of $Eu(hfc)_3$ in $CDCl_3$ showed signals at δ 2.67 (d, CH_3CH, 96% *R*), 3.04 (d, CH_3CH, 4% *S*), 6.55 ppm (dt, *J* = 15 Hz, $-CH_2CH$=CH); GC (Becker I, 3 m × 4 mm column packed with 10% OV-225 on GCQ 100/120; isothermal at 140 °C; N_2, 30 mL/min;), homogeneous, retention time 52.5 min.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.82; H, 11.72; N, 7.47.

(B) From 13. A mixture of 1.28 g (0.01 mol) of (*S*)-(−)-(*E*)-6-methyl-2-hepten-4-ol (**13**) [97.8% 4*S*, 2.2% 4*R*; $[\alpha]^{25}_D$ −9.88° ($CHCl_3$)][5] and 7.5 g (0.063 mmol) of *N,N*-dimethylformamide dimethyl acetal in 20 mL of xylene was refluxed for 89 h under continuous removal of methanol. It was worked up as before and the crude product was distilled to give 1.39 g (76% yield) of a mixture of the unsaturated amides **9** and **14** as a colorless oil: bp 82–92 °C/0.2 mm; $[\alpha]^{25}_D$ −47.1° (*c* 5.02, $CHCl_3$); GC [Becker I, 3 m × 4 mm column packed with 10% OV-225 on GCQ 100/120, isothermal at 140 °C; N_2 at 30 mL/min]: 87% *E* (retention time 52.8 min), 13% *Z* (retention time 55.2 min); NMR δ 5.45 (m, 2, CH=CH), 3.55 (m, *Z* isomer, CH_3CH, ~13%), 3.30 (m, *E* isomer, CH_3CH, ~87%), 1.18 (d, *E* isomer, CH_3CH, ~87%), 1.15 (d, *Z* isomer, CH_3CH, ~13%), 0.94 [d, *Z* isomer, $(CH_3)_2CH$, ~13%], 0.84 ppm [d, *E* isomer, $(CH_3)_2CH$, ~87%]; 87% *R*, 13% *S* [22 mg of sample and 46 mg of $Eu(hfc)_3$ in $CDCl_3$, δ 2.43 and 2.75 ppm, respectively].

Separation of Isomers. The mixture of **9** and **14** (3.0 g, from another preparation, $[\alpha]^{25}_D$ −38.6°; 86.2% *E*, 13.8% *Z*) was chromatographed on 150 g of silica gel. Elution with CH_2Cl_2–ether (23:2) gave 741 mg of the (*E*)-unsaturated amide **9**, after purification by evaporative distillation at 85–90 °C/0.2–0.3 mm, $[\alpha]^{25}_D$ − 67.9° (*c* 2.82, $CHCl_3$); GC (conditions same as above) 98.4% *E*, 1.6% *Z*; NMR (conditions same as above) 98 ± 2% *R*; IR (neat) 1645 (C=O), 970 cm^{-1} [(*E*)-CH=CH]. The column was further eluted with CH_2Cl_2–ether (22:3) to give 2.0 g of material containing mostly the (*E*)-isomer **9**. Further elution with CH_2Cl_2–ether (4:1) afforded 100 mg of a mixture of **9** and **14**. This material was evaporatively distilled at 85–90 °C/0.2–0.3 mm to give 93 mg of colorless oil: $[\alpha]^{25}_D$ +42.9° (*c* 3.05, $CHCl_3$); GC 51.11% (*E*)-**9**, 48.89% (*Z*)-**14**; GC–MS *m/e* 183 (M^+) for both isomers; NMR (22 mg of sample, 44 mg of $Eu(hfc)_3$ in $CDCl_3$) δ 6.8 (t, *J* = 11 Hz, (*Z*)-CH_3CHCH=CH), 6.62 (dd, *J* = 15.5 Hz, (*E*)-CH_3CHCH=CH), 6.25 (dt, *J* = 15.5 Hz, (*E*)-CH=$CHCH_2$–, ~50%), 5.72 (dt, *J* = 11 Hz, (*Z*)-CH=$CHCH_2$–, ~50%), 2.05 (d, CH_3CH, ~50% *R*), 2.35 ppm (m, CH_3CH, ~50% *S*).

Further purification of the above mixture by thick-layer chromatography on silica gel (ether–methylene chloride 3:7) gave after evaporative distillation at 95–97 °C/0.35 mm 35 mg of (*S*)-(+)-(*Z*)-2,6-dimethyl-3-heptenoic acid *N,N*-dimethylamide (**14**): $[\alpha]^{25}_D$ +121° (dioxane); GC 80.4% (*Z*)-**14**, 19.5% (*E*)-**9**; MS *m/e* 183 (M^+).

(*R*)-(−)-2,6-Dimethylheptanoic Acid *N,N*-Dimethylamide (10). A. A mixture of 1.20 g of unsaturated amide **9** (prepared from **8**) and 120 mg of 5% palladium on charcoal in 50 mL of ethyl acetate was stirred in an atmosphere of hydrogen at 23 °C for 4.0 h. The catalyst was filtered, the filtrate was concentrated in vacuo, and the residue was evaporatively distilled at 82–89 °C/0.15 mm to yield 1.19 g of the saturated amide **10** as a colorless oil: $[\alpha]^{25}_D$ −27.1° (*c* 5.11, $CHCl_3$); 97.8% pure by GC analysis (HP 5700A, 9 ft × 4 mm column packed with OV-101 on 10% GCQ, 80–260 °C at 2 °C/min, N_2 30 mL/min, retention time 49 min); NMR (24 mg of sample, 70 mg of $Eu(hfc)_3$ in $CDCl_3$) δ 4.34 [2 s, $(CH_3)_2N$, 4% *S*], 4.13 [2 s, $(CH_3)_2N$, 96% *R*], 2.48 (d, CH_3CH, 4% *S*), 2.30 ppm (d, CH_3CH, 96% *R*).

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30, H, 12.51; N, 7.56. Found: C, 71.13; H, 12.47; N, 7.66.

B. A mixture of 1.10 g of **9** and **14** ($[\alpha]^{25}_D$ −46.4°, 87% *E*, 13% *Z*, prepared from allylic alcohol **13**) was hydrogenated as described above to give 1.07 g of colorless oil: bp 83 °C/0.13 mm; $[\alpha]^{25}_D$ −21.6° (*c* 5.08, $CHCl_3$); 98% pure by GC analysis; NMR showed 85% *R*, 15% *S*.

(*S*)-(+)-2,6-Dimethylheptanoic Acid *N,N*-Dimethylamide (15). A mixture of 34 mg of **14** (80.4% (*Z*)-**15**, 19.5% (*E*)-**9**) and 30 mg of 5% palladium on carbon in 8 mL of ethyl acetate was stirred in an atmosphere of hydrogen at 23 °C for 17 h. It was worked up as before to give 30 mg of colorless oil, after evaporative distillation at 100–104 °C/0.5 mm, $[\alpha]^{25}_D$ +15.3° (*c* 3.0, $CHCl_3$); MS *m/e* 101 (base peak); NMR revealed ~80% *S*, 20% *R*.

(*R*)-(−)-2,6-Dimethylheptanoic Acid (11). A. A mixture of 538 mg of the saturated amide **10** (prepared from **8** as described above, 96% *R*; $[\alpha]^{25}_D$ −27.1°) and 10 mL of concentrated hydrochloric acid was refluxed with stirring for 20 h. After evaporation of most of the HCl at 45–50 °C/15–20 mm, the oily residue was taken into 10% aqueous NaOH. It was then worked up as usual to give 375 mg of crude acid **11**. Evaporative distillation of this material at 82–86°C/0.15 mm gave 365 mg (81% yield) of pure acid **11** as a colorless oil: $[\alpha]^{25}_D$ −15.6° (*c* 4.92, $CHCl_3$).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.60; H, 11.59.

B. A 462-mg sample of the saturated amide **9** (84.6% *R*, 15.4% *S*, $[\alpha]^{25}_D$ −21.6°, prepared from allylic alcohol **13** as described above) was hydrolyzed as above to give 248 mg of colorless oil: bp 92–95 °C/0.2 mm; $[\alpha]^{25}_D$ −12.8° (*c* 5.04, $CHCl_3$).

(*R*)-(−)-Methyl-2,6-dimethylheptanoate (12). A. A 300-mg sample of the acid **11** ($[\alpha]^{25}_D$ −15.6°, preparation described above from **8**) was dissolved in ether and treated with an excess of ethereal diazomethane. The yellow solution was kept at 23 °C for 17 h. Evaporation of the ether to dryness at 45 °C/20 mm and evaporative distillation of the crude product afforded 260 mg of ester **12**: bp 114–119 °C/45 mm; $[\alpha]^{25}_D$ −20.1° (*c* 1.12, $CHCl_3$); homogeneous on GC analysis. This ester was analyzed by NMR as follows. A 23.5-mg sample was dissolved in 0.45 mL of $CDCl_3$, to which 71.5 mg of $Eu(hfc)_3$ was added. The NMR spectrum (HA 100) revealed two sets of doublets for the C(2) methyl group centered at δ 3.48 and 3.58 ppm in 92% *R* and 8% *S*, respectively. The doublet at δ 3.48 was shown to be the *R* enantiomer by comparison with a sample of **12** derived from natural (*R*)-citronellal.[12]

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.73; H, 11.70. Found: C, 69.86; H, 11.81.

B. A sample of the acid **11** ($[\alpha]^{25}_D$ −12.8°, preparation from **14** described above) was also converted to the methyl ester **12**: $[\alpha]^{25}_D$ −15.9° (*c* 1.42, $CHCl_3$); NMR analysis as described above showed two pairs of doublets centered at δ 3.52 (85% *R*) and 3.62 ppm (15% *S*), respectively.

(*R*)-(+)-2,6-Dimethylheptan-1-ol (2). A mixture of 105 mg of ester **12** ($[\alpha]^{25}_D$ −20.1°, preparation from **8** described above) and 100 mg of lithium aluminum hydride in 15 mL of dry ether was refluxed with stirring for 2.5 h. The reaction mixture was cooled in an ice bath, and the excess of hydride was destroyed by carefully adding water and followed by 20 mL of cold aqueous 2 N H_2SO_4. It was worked up with ether in the usual manner and evaporative distillation of the crude product gave 65 mg of alcohol **2** as a colorless oil: bp 130 °C/30 mm; $[\alpha]^{25}_D$ +9.2° (*c* 1.10, benzene) [lit.[4] $[\alpha]^{25}_D$ +10.1° (benzene)].

(2*R*,6*R*)-(−)-(*E*)-2,6,10,*N,N*-Pentamethylundec-3-enamide (17). (A) From (4*R*,6*R*)-(+)-(*Z*)-6,10-Dimethylundec-2-en-4-ol (16). A mixture of 1.54 g (7.77 mmol) of (*Z*)-allylic alcohol **16** (89.7% 4*R*, 10.3% 4*S*, preparation reported previously[5]) and 7.0 g (58.8 mmol) of *N,N*-dimethylformamide dimethyl acetal in 15 mL of xylene was refluxed at 124–126 °C for 93 h under continuous removal of methanol. The xylene was evaporated off at reduced pressure and the crude amide (2.20 g) was chromatographed on 40 g of silica gel. Elution with ether–petroleum ether (1:4) gave 0.815 g of product, which was evaporatively distilled at 116–119 °C/0.15 mm to give 0.8 g (40.5% yield) of the unsaturated amide **17** as a colorless oil: $[\alpha]^{25}_D$ −43.7° (*c* 5.00, $CHCl_3$); GC (Becker I, 9 ft × 4 mm column packed with OV-225 on 10% GCQ 100/120, isothermal at 165 °C, N_2 30 mL/min) 97.1% pure (retention time 145 min), no *Z* isomer detected; IR (neat) 1650 (C=O), 968 cm^{-1} [(*E*)-CH=CH]; NMR δ 0.85 [d, 6, $(CH_3)_2CH$], 0.82 (d, 3, CH_3CH), 1.18 (d, 3, CH_3CHCO), 2.92, 3.00, [2s, 6, $(CH_3)_2N$], 3.31 (m, 1, CH_3CHCO), 5.43 ppm (m, 2, CH=CH); on addition of 82 mg of $Eu(hfc)_3$ to 21 mg of the sample, the C(2) methyl group appeared as two pairs of doublets centered at δ 4.42 (86% 2*R*) and 5.19 ppm (14% 2*S*), respectively.

Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 75.90; H, 12.59; N, 5.48.

(B) From (4*S*, 6*R*)-(−)-(*E*)-6,10-Dimethylundec-2-en-4-ol (21). A 1.45-g sample of (*E*)-allylic alcohol **21** (95% 4*S*, 5% 4*R*, preparation described previously[5]) was treated with 7.0 g of *N,N*-dimethylformamide dimethyl acetal in the same manner as described above. There was obtained 1.22 g (66% yield) of unsaturated amides **17** and **22**, after chromatographic purification and evaporative distillation at 138–142 °C/0.25 mm, $[\alpha]^{25}_D$ −30.5° (*c* 4.93, $CHCl_3$); GC (conditions same as in part A): 86.5% *E* (retention time 133 min), 13.5% *Z* (retention time 140 min); GC–MS both major and minor peak had *m/e* 253 (M^+), 210, 182, 140 and 72 (base peak); NMR δ 5.48 (m, 2, CH=CH), 3.6 (m, CH_3CHCO, *Z* isomer), 3.29 (m, CH_3CHCO, *E* isomer), 3.00 [2 s, $(CH_3)_2N$], 1.22 (d, CH_3CHCO, *E* isomer), 1.18 (d, CH_3CHCO, *Z* isomer), 0.85 [d, 6, $(CH_3)_2CH$], 0.83 ppm (d, 3, CH_3CH);

82% 2*R*, 18% 2*S* [using Eu(hfc)$_3$ as described in section A].

A 600-mg sample of this mixture was further purified by thick-layer chromatography on silica gel (ether–methylene chloride 3:7) to give 305 mg of the (*E*)-unsaturated amide **17**: bp 130–135 °C/0.35 mm; $[\alpha]^{25}_D$ −46.0° (*c* 4.43, $CHCl_3$); GC (conditions same as in part A) 95.2% *E*, 4.8% *Z*; NMR [22 mg of sample, 84 mg of Eu(hfc)$_3$ in $CDCl_3$] δ 3.40 (d, **CH$_3$**CHCO, 92% 2*R*), 3.87, 3.97 (2d, **CH$_3$**CHCO, ~8% 2*S*), 7.48 ppm (dt, *J* = 15.5 Hz, (*E*)-CH=**CH**CH–); IR (neat) 1640 (C=O), 970 cm^{-1} [(*E*)-CH=CH].

Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 76.04; H, 12.49; N, 5.43.

A 71-mg sample of material enriched in the (*Z*)-unsaturated amide **22** was also obtained from this preparation, bp 139 °C/0.4 mm; $[\alpha]^{25}_D$ +49.7° (*c*, 1.99, $CHCl_3$); GC 37.4% *E*, 62.6% *Z*; NMR (15 mg of sample, 56.5 mg of Eu(hfc)$_3$ in $CDCl_3$) δ 3.34 (d, **CH$_3$**CHCO, 39% 2*R*), 3.80, 3.96 (2d, **CH$_3$**CHO, 61% 2*S*), 6.26 ppm (dt, *J* = 10.5 Hz, (*Z*)-CH=**CH**CH$_2$); IR (neat) 1650 (C=O), 970 [(*E*)-CH=CH], 710 cm^{-1} [(*Z*)-CH=CH]; MS *m/e* 253 (M^+).

(2*R*, 6*R*)-(−)-2,6,10,*N*,*N*-Pentamethylundecanamide (18). A mixture of 636 mg of the unsaturated amide **17** ($[\alpha]^{25}_D$ −43.7°, preparation from **16** as described above) and 75 mg of 5% palladium on carbon in 25 mL of ethyl acetate was stirred in an atmosphere of hydrogen at 23 °C for 4.0 h. It was worked up as usual, and the product was evaporatively distilled at 140 °C/0.5–0.7 mm to give 607 mg of the saturated amide **18** as a colorless oil: $[\alpha]^{25}_D$ −15.3° (*c* 5.23, $CHCl_3$); NMR [21.6 mg of sample, 190 mg of Eu(hfc)$_3$ in $CDCl_3$] δ 3.27 (d, **CH$_3$**CHCO, 86% 2*R*), 3.58 ppm (d, **CH$_3$**CHCO, 14% 2*S*); IR (neat) 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48. Found: C, 74.79; H, 13.11; N, 5.64.

(2*S*,6*R*)-(+)-2,6,10,*N*,*N*-Pentamethylundecanamide (23). A 31-mg sample of the unsaturated amide **22** ($[\alpha]^{25}_D$ +49.7° preparation from **21** described above) was hydrogenated in the same manner as before to give 30 mg of the saturated amide **23**, bp 135 °C/0.3 mm; $[\alpha]^{25}_D$ +4.6° (*c* 1.62, $CHCl_3$); MS *m/e* 255 (M^+), 72 (base peak); NMR 60% (2*S*), 40% (2*R*) (conditions described above).

(2*R*, 6*R*)-(−)-2,6,10-Trimethylundecanoic Acid (19). A mixture of 415 mg of the saturated amide **18** ($[\alpha]^{25}_D$ −15.3°, preparation from (*Z*)-allylic alcohol **16** as described above) and 10 mL of concentrated hydrochloric acid was refluxed with stirring for 24 h. The reaction mixture was worked up in the usual manner, and the crude product was evaporatively distilled at 135 °C/0.15 mm to yield 305 mg (82% yield) of the saturated acid **19**, $[\alpha]^{25}_D$ −8.6° (*c* 4.84, $CHCl_3$).

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.69; H, 12.34.

(−)-Methyl-(2*R*,6*R*)-2,6,10-Trimethylundecanoate (20). A 270-mg sample of the acid **19** ($[\alpha]^{25}_D$ −8.6°) was dissolved in ether and treated with an excess of ethereal solution of diazomethane at 23 °C for 2.0 h. Evaporative distillation of the crude product at 98–101 °C/0.15 mm gave 247 mg of the ester **20** as a colorless oil: $[\alpha]^{25}_D$ −11.3° (*c* 1.11, $CHCl_3$); IR (neat) 1740 cm^{-1} ($COOCH_3$); homogeneous on GC analysis; NMR (20.5 mg of **20**, 59.5 mg of Eu(hfc)$_3$ in $CDCl_3$) δ 3.44 (d, **CH$_3$**CHCOOCH$_3$, 86% 2*R*), 3.54 ppm (d, **CH$_3$**CHCOOCH$_3$, 14% 2*S*).

Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.48. Found: C, 74.26; H, 12.46.

(2*R*,6*R*)-(+)-2,6,10-Trimethylundecan-1-ol (4). A suspension of 172 mg of the ester **20** ($[\alpha]^{25}_D$ −11.3°) and 170 mg of lithium aluminum hydride in 20 mL of dry ether was refluxed with stirring for 2.5 h. The reaction mixture was worked up as described previously. Evaporative distillation of the crude product (155 mg) at 100–102 °C/0.08 mm gave in quantitative yield 152 mg of pure alcohol **4** as a colorless liquid: $[\alpha]^{25}_D$ +6.1° (*c* 2.04, hexane) [lit.[4] $[\alpha]^{25}_D$ +9.4° (*c* 2.04 hexane)]; IR (neat) 3320 cm^{-1} (CH_2OH).

Anal. Calcd for $C_{14}H_{30}O$: C, 78.43; H, 14.11. Found: C, 78.65; H, 14.07.

Acknowledgments. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N.J., for carrying out most of the spectral, microanalytical, and polarimetric determinations in this work. Special thanks are due to Dr. T. Williams and his co-workers in the NMR laboratory for contributions regarding the determination of enantiomeric compositions using chiral shift reagents. The discussion with Professor Büchi was particularly valuable and we would also like to thank him for a preprint of his publication.

Registry No.—**2**, 59983-44-7; **4**, 54154-25-5; **8**, 59983-76-5; **9**, 63702-26-1; **10**, 63702-27-2; **11**, 60148-94-9; **12**, 60148-95-0; **13**, 59983-79-8; **14**, 63702-28-3; **15**, 63702-29-4; **16**, 59991-72-9; **17**, 63713-90-6; **18**, 63702-30-7; **19**, 31653-13-1; **20**, 63702-31-8; **21**, 59983-89-0; **22**, 63702-32-9; **23**, 63702-33-0; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5.

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(11) Racemic **9** (prepared from racemic **8**) displayed two sets of doublets centered at δ 2.66 and 3.00 ppm, respectively, with equal intensity. A mixture (1:1) of racemic **9** and optically active **9** exhibited two doublets centered at δ 2.72 and 3.1 ppm, respectively, in a ratio of ~3:1.

(12) Samples of **11** and **12** prepared from natural (*R*)-(+)-3,7-dimethyl-6-octenal (~87% *R*)[13] had $[\alpha]^{25}_D$ −13.4° (*c* 5, $CHCl_3$) and $[\alpha]^{25}_D$ −16.6° (*c* 1, $CHCl_3$), respectively. We thank Dr. D. Valentine for providing us with these compounds.

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(14) Racemization did not seem to occur on hydrogenation of unsaturated amide **9** using palladium catalyst, in contrast to the results reported[5] on the hydrogenation of unsaturated esters or acids.

(15) To our knowledge, these are believed to be first examples representing the formation of a carbon–carbon single bond with essentially complete chiral transmission via a [2,3] sigmatropic process. For reviews on asymmetric reactions, see the following: (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J. (1971). (b) J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974). (c) D. Seebach and H. O. Kalinowski, *Angew. Chem.*, **88**, 415 (1976).