Asymmetric synthesis towards (3*Z*,6*R*)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate, a component of the California red scale pheromone

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MARK WHITTAKER, COLIN R. MCARTHUR, and CLIFFORD C. LEZNOFF. Can. J. Chem. **63**, 2844 (1985).

The key chiral synthons, (*R*)-3-isopropenyl-6-heptenoic acid and (*R*)-3-isopropenyl-6-heptenal, needed for the synthesis of (3*Z*,6*R*)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate, a component of the sex pheromone of the California red scale, *Aonidiella aurantii*, have been prepared by asymmetric synthesis. The chiral acid was synthesized in 86% ee by an asymmetric 1,4-addition of isopropenylmagnesium bromide to the *l*-ephedrine amide derived from (*E*)-2,6-heptadienoic acid, followed by base hydrolysis. Acid hydrolysis gave the chiral 3-(3-buten-1-yl)-4,4-dimethylbutyrolactone. The chiral aldehyde was prepared in greater than 99% ee by an asymmetric 1,4-addition of isopropenylmagnesium bromide to the imine derived from (*S*)-(+)-*tert*-butyl 2-amino-3,3-dimethylbutyrate and (*E*)-2,6-heptadienal. The 1,4-addition reactions of *n*-butyllithium or isopropenyllithium to (4*S*,5*S*)-(+)-2-[1-(*E*-1,5-hexadienyl)]-4-methoxymethyl-5-phenyl-2-oxazoline gave the addition products, and sequential mild hydrolysis and reduction of these adducts yielded chiral 3-*n*-butyl-6-hepten-1-ol for the former adduct but a mixture of products was obtained from the latter adduct.

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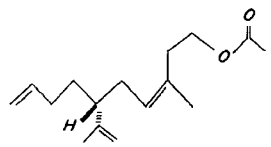
Utilisant une synthèse asymétrique, on a préparé les synthons chiraux clés, acide isopropényl-3(*R*) heptène-6 oïque et isopropényl-3(*R*) heptène-6 al, nécessaires à la synthèse de l'acétate du méthyl-3(*Z*) isopropényl-6(*R*) décadiène-3,9 yle-1, une composante de la phérémone sexuelle de l'écaille rouge de la Californie *Aonidiella aurantii*. On a préparé l'acide chiral avec un ee de 86% en faisant appel à une addition asymétrique-1,4 du bromure d'isopropénylmagnésium sur l'amide de la *l*-éphédrine provenant de l'acide heptadiène-2,6(*E*) oïque, suivie d'une hydrolyse basique. L'hydrolyse acide permet d'accéder à la (butène-3 yl-1)-3 diméthyl-4,4 butyrolactone chirale. On a préparé l'aldéhyde chiral avec un ee supérieur à 99% en procédant à une addition-1,4 asymétrique du bromure d'isopénylmagnésium sur l'imide obtenu par réaction du (+)-amino-2(*S*) diméthyl-3,3 butyrate de *tert*-butyle et de l'heptadiène-2,6(*E*) al. Les réactions d'additions-1,4 du *n*-butyllithium ou de l'isopropényllithium sur la (+)-[(hexadiène-1,5(*E*) yl)-1]-2 méthoxyméthyl-4(*S*) phényl-5(*S*) oxazoline-2 conduisent aux produits d'addition et une hydrolyse douce subséquente suivie d'une réduction de ces adduits conduit au *n*-butyl-3 heptène-6 ol-1 chiral lorsqu'on part du premier adduit; toutefois, le second adduit ne conduit qu'à un mélange de produits.

[Traduit par le journal]

The sex pheromones of the California red scale, *Aonidiella aurantii* (Maskell), an insect which is a severe pest of citrus in California, Australia, and the Mediterranean countries, were identified as a mixture of (3*Z*,6*R*)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate (**1**) and (3*S*,6*R*)-3-methyl-6-isopropenyl-9-decen-1-yl acetate (**2**) (1–4). Each of these compounds exhibits equal independent ability to attract the male insects (4).



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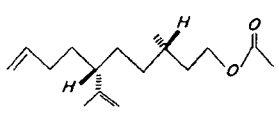

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Our related interests in the synthesis of insect sex attractants on insoluble polymer supports (5) and the use of solid phases in asymmetric syntheses (6) have naturally led us to consider the possibilities of asymmetric synthesis of chiral sex pheromones on solid phases. Our attention focussed on compound **1** containing a single chiral centre. Component **1** was first synthesized from (*S*)-(+)-carvone in 2.6% overall yield (2). A racemic mixture of **1** and its enantiomer was subsequently synthesized in 32% (7) and 27% (8) yields, respectively. Two other preparations of **1** have been reported recently, starting from (*S*)-(+)-carvone (9). Thus, all syntheses of **1** (2, 9) started from the same naturally occurring chiral precursor. Our desire to prepare compound **1** using polymer-bound chiral auxillaries *via asymmetric synthesis* led us to examine satisfactory methods for the asymmetric synthesis of **1** in solution as a necessary prerequisite step.

A key chiral intermediate used in the synthesis of **1** was (*R*)-3-isopropenyl-6-heptenal (**3**), previously obtained by lengthy conversion of the natural product (*S*)-(+)-carvone (2, 9*a*). Compound **3** could potentially be made much more readily by asymmetric 1,4-additions to at least three different possible α,β-unsaturated functionalized precursors, and we can designate these routes as the ephedrine, the aldimine, and the oxazoline routes.

The ephedrine route

It has been shown that chiral α,β-unsaturated amides, prepared from (1*R*,2*S*)-(−)-α-(1-methylaminoethyl)benzyl alcohol (*l*-ephedrine) in 1,4-addition reactions with Grignard reagents, can give, after acid hydrolysis, chiral β-substituted carboxylic acids in greater than 95% enantiomeric excess (ee) (10). This initial report (10), however, used only simple aliphatic amides and Grignard reagents and it remained to be seen if this attractive asymmetric synthesis could be applied to the synthesis of a more complex β-substituted aldehyde such as **3**. The chiral α,β-unsaturated amide necessary for this synthesis is *N*-(*E*-2,6-heptadienoyl)-*l*-ephedrine (**4**) and is prepared as shown in Scheme 1.

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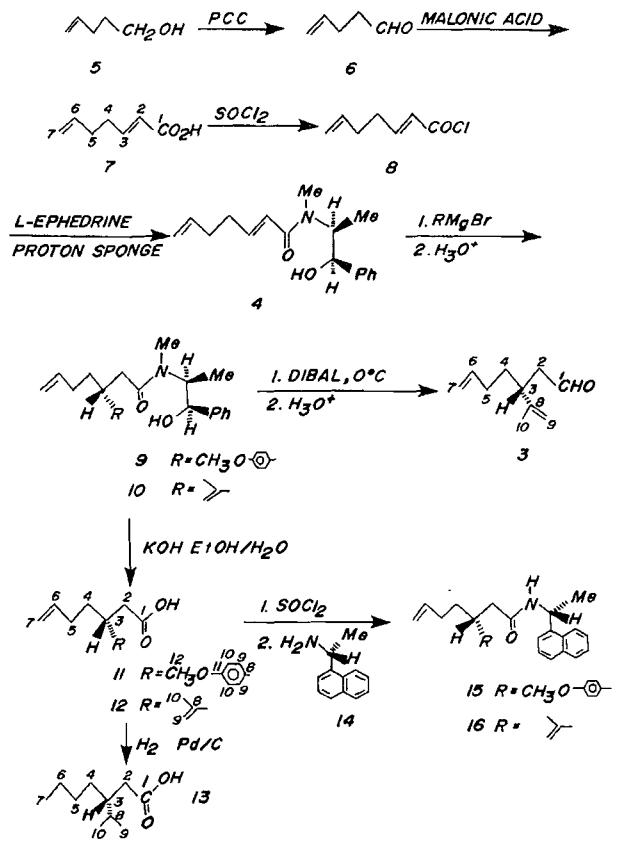
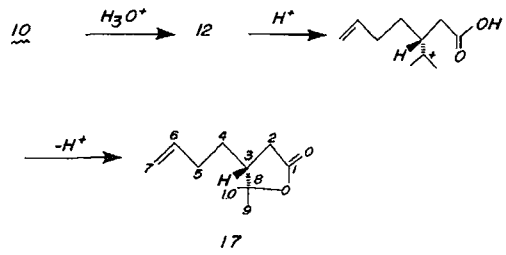


SCHEME 1

Oxidation of 4-penten-1-ol (**5**) with pyridinium chlorochromate (PCC) in methylene chloride (11) gave the volatile 4-pentenal (**6**) (12, 13) in 55% yield. Treatment of **6** with malonic acid in pyridine and pyrrolidine at 20°C overnight followed by refluxing for 5 h gives a 70–80% yield of (*E*)-2,6-heptadienoic acid (**7**) (13), contaminated by some of the *Z* isomer as shown by ^{13}C nmr. The mixture of (*E*) and (*Z*)-**7** was treated with thionyl chloride to give pure (*E*)-2,6-heptadienoyl chloride (**8**) in high yield with concomitant conversion of the minor (*Z*)-**7** isomer to the (*E*)-**7** isomer (14). Compound **8** was converted to the desired **4** by treatment with *l*-ephedrine in the presence of proton sponge (10). To test the usefulness of 1,4-addition reactions to adduct **4**, *p*-methoxyphenylmagnesium bromide in tetrahydrofuran (THF) was caused to react with **4** at 0°C for 24 h to give *N*-(3-*p*-methoxyphenyl-6-heptenoyl)-*l*-ephedrine (**9**) in 59% yield. Similarly, treatment of **4** with isopropenylmagnesium bromide in ether/THF mixtures at 0°C for 48 h gave *N*-(3-isopropenyl-6-heptenoyl)-*l*-ephedrine (**10**) in 51–69% yield. Compounds **9** and **10** were cleaved by base hydrolysis with a 10% potassium hydroxide in ethanol/water mixture to give optically active 3-*p*-methoxyphenyl-6-heptenoic acid (**11**) and 3-isopropenyl-6-heptenoic acid (**12**) in 49–57% and 63–80% yield, respectively. Hydrogenation of **12** gave the known compound (*R*)-3-isopropylheptanoic acid (**13**) (15), thus confirming the absolute configuration of **12** to be *R*, as desired. The absolute configuration of **11** has not been determined in this study, but it is considered likely that it is also *R*, since it possesses a negative optical rotation as has been reported (15) for a structurally related series of (*R*)-3-*o*-methoxyphenylalkanoic acids.



SCHEME 2

Determination of the enantiomeric excess of **12** by hydrogenation to **13** and comparison of the optical rotation with that reported in the literature was not reliable, because of some racemization occurring during the hydrogenation. Attempts to evaluate the enantiomeric excess in which acids **11** and **12** were formed, by hplc separation of the respective diastereomers of amides **9** and **10**, were not successful. Consequently, the method of Bergot *et al.* (16) was adopted. Acids **11** and **12** were converted to their acid chlorides and treated with (*R*)-(+)-1-(1-naphthyl)ethylamine (**14**) to give *N*-[(*R*)-1-(1-naphthyl)-ethyl]-3-*p*-methoxyphenyl-6-heptenamide (**15**) and (*R*)-*N*-[(*R*)-1-(1-naphthyl)ethyl]-3-isopropenyl-6-heptenamide (**16**). The chiral amides **15** and **16** were analysed by hplc (2, 16, 17) and the results indicated that the asymmetric 1,4-addition to **4** gave **9** and **10** having up to 86% ee (Table 1). In order to obtain this extent of asymmetric induction it was necessary to employ, in the 1,4-addition step, a high proportion of ether to THF. However, the use of pure ether was precluded by the instability of isopropenylmagnesium bromide in the absence of THF (18). It was found that the sluggish formation of this Grignard reagent at low THF concentrations could be ameliorated by ultrasonic irradiation (19). Compound **10** can be cleaved (20) with diisobutylaluminium hydride (DIBAL) at 0°C to **3**, albeit in low yield, and hence **3** has now been prepared via asymmetric synthesis.

Simple amides of *l*-ephedrine were cleaved under strong acid conditions (10). Acid hydrolysis of **10** did not give the free acid **12** but rather 3-(3-buten-1-yl)-4,4-dimethylbutyrolactone (**17**) in 75% yield. Compound **17** was optically active but its ee has not yet been determined. The mechanism of formation of **17** from **10** has not been explored but is likely to follow a pathway outlined in Scheme 2.

Although we had succeeded in preparing the key chiral pheromone intermediate **3** by an asymmetric synthesis route, several difficulties were still apparent. Firstly, the ee of **3**, although high, was not as high as **3** prepared via a natural product precursor such as (*S*)-(+)-carvone. Secondly, the direct cleavage of the amide **10** to **3** proceeded in low yield and hence **3** would have to be made via acid **12** which would most likely involve two more steps. Thirdly, the ephedrine route seemed less adaptable to solid phase methods than other possible routes and hence further approaches to the asymmetric synthesis of **3** were sought.

The aldimine route

The 1,4-addition of Grignard reagents to chiral α,β-unsaturated aldimines prepared from α,β-unsaturated aldehydes and chiral *tert*-butyl 2-amino-3,3-dimethylbutyrate (**26**) has been demonstrated (21) to give chiral β-substituted aldehydes in greater than 95% ee. Since the key intermediate (**3**) in the synthesis of **1** is a β-substituted aldehyde, we decided to attempt this method for the preparation of **3**. The original

TABLE 1. Results from asymmetric 1,4-addition reactions and subsequent cleavage

Entry	Substrate	Nucleophile (equivalents)	Solvent	Conditions (temp. (°C)/time (h))	Product after cleavage	Overall yield (%)	Optical rotation ($[\alpha]_D$ (c))[a]	Enantiomeric excess (%)
1	**4**	*p*-$CH_3OC_6H_4MgBr$ (6)	THF	0/14	**11**	25	−11.32° (3.28)	55[b]
2	**4**	*p*-$CH_3OC_6H_4MgBr$ (8)	THF/Et_2O(1:15)	−55/4, then −18/48	**11**	56	−16.90° (5.38)	82
3	**4**	$CH_2(CH_3)CMgBr$ (6)	THF	0/48	**12**	41	−3.13° (2.05)	46[b]
4	**4**	$CH_2(CH_3)CMgBr$ (10)	THF/Et_2O(1:19)	−50/3, then 0/48	**12**	51	−5.28° (13.67)	78[b]
5	**4**	$CH_2(CH_3)CMgBr$ (10)	THF/Et_2O(1:49)	−55/3, then −20/48	**12**	41	−5.85° (18.36)	86
6	**27**	$CH_2(CH_3)CMgBr$ (4)	THF/Et_2O(1:5)	−60/1, then −21/14	**3**	43	−0.47° (7.89)	>99
7	**30**	$CH_3(CH_2)_3Li$ (1.5)	THF	−78/3.5	**34**	40	−1.18° (2.12)	96
8	**30**	$CH_2(CH_3)CLi$ (3)	THF	−78/3	**35**	0	—	—

[a] Optical rotations measured at 21 ± 2°C using $CHCl_3$ as solvent.
[b] Enantiomeric excess determined indirectly by comparison of optical rotation with that of sample of known ee, as determined by hplc separation of diastereomeric amides.

SCHEME 3

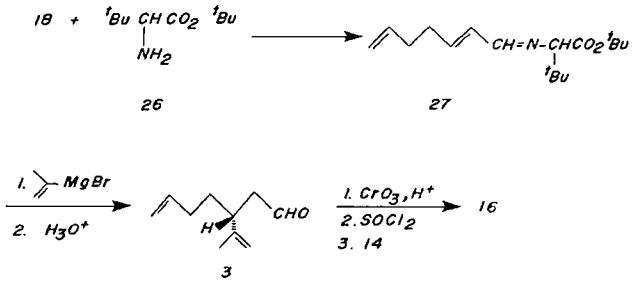
SCHEME 4

publication of this method was restricted to rather simple α,β-unsaturated aldimines, but we considered that this aldimine route would be successful even for more complicated substrates such as (*E*)-2,6-heptadienal (**18**) (Scheme 3).

Treatment of **6** with ethyl malonate (half-ester) in a pyridine/pyrrolidine mixture yielded ethyl 2,6-heptadienoate (**19**) in 79% yield. Reduction of **19** with two equivalents of diisobutylaluminium hydride at −25°C gave a 4:1 mixture of 2,6-heptadien-1-ol (**20**) and 6-hepten-1-ol (**21**) in 82% yield. Oxidation of this mixture by PCC yielded a mixture of 2,6-heptadienal (**18**) and 6-heptenal (**22**) as shown in Scheme 3. Compound **22** was removed from this mixture by washing with aqueous sodium bisulphite, giving pure **18** in 39% yield from **19**.

During the course of this work, Bestmann *et al.* (22) described the synthesis of **18** in 25% yield by the direct reaction of **6** with a stabilized ylide and indeed our own early synthesis by this route also gave **18** in 20% yield. The preparation of **18** according to Scheme 3 was unsatisfactory as a result of poor overall yields, contamination with **22**, and, in addition, the fact that **18** was obtained as a mixture of *E* and *Z* isomers. Many procedures described in the literature exist for the synthesis of α,β-unsaturated aldehydes from a simple aldehyde, but attempts to prepare **18** by various methods (23–25) were either unsuccessful or gave impure **18** in low yield. Finally, treatment of **6** with 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (**23**) according to the procedure of Meyers *et al.* (26) gave the alcohol adduct (**24**). Reduction of **24** with sodium borohydride gave the tetrahydro-1,3-oxazine (**25**), which on mild acid hydrolysis gave **18** in 37% overall yield (Scheme 4).

Treatment of the α,β-unsaturated aldehyde **18** with racemic *tert*-butyl 2-amino-3,3-dimethylbutyrate (**26**) or (*S*)-(+)-**26** at 0°C in benzene overnight gave the crude α,β-unsaturated aldimine **27**. Addition of isopropenylmagnesium bromide in ether/THF (5:1) at −60°C gave, upon mild acid work-up, a



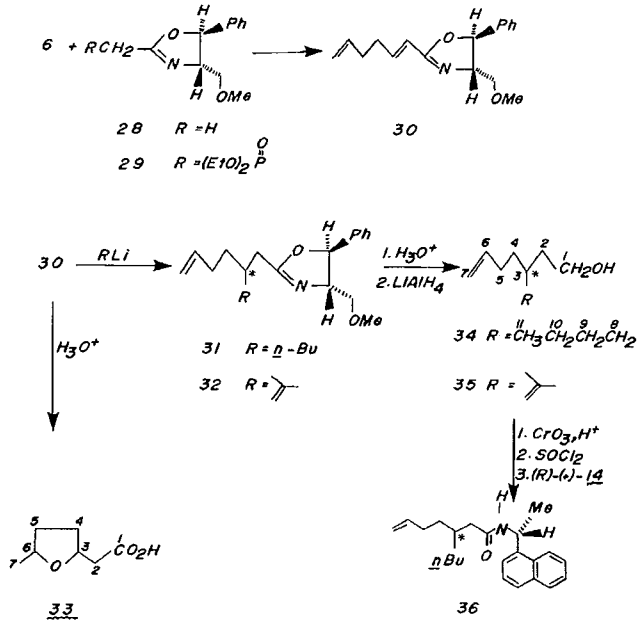
SCHEME 5

racemic mixture of **3** with its enantiomer or optically active **3** in a 43–50% yield. The enantiomeric purity of **3** was determined in a similar manner (2) to that described above for **12**. Thus oxidation of **3** gave **12**, which was converted to its acid chloride and treated with **14** to give **16**. The hplc analysis (2, 16, 17) of **16**, prepared from a racemic mixture of **3** and its enantiomer, resulted in complete resolution of the two equally abundant diastereomers, while **16** prepared from optically active **3** showed only one diastereomer and no trace of the other isomer. Furthermore, **16**, prepared from optically active **3** and (*S*)-(−)-1-(1-naphthyl)ethylamine (the enantiomer of **14**), showed only the other diastereomer by hplc analysis. The absolute configuration of pure **3** was determined to be *R*, by comparison of the hplc retention times of these diastereomeric amides (**16**) with those of **16** prepared from **12** in the ephedrine route described above. Thus, the asymmetric synthesis of **3** has been achieved in >99% ee ((*R*)-configuration), which is as high or higher than that derived from a natural product. In addition, the aldimine route lends itself particularly to development using solid-phase techniques, which would ensure ready recovery of the chiral auxiliary. The one limitation is the rather modest yield in the key coupling step. For this reason we examined even a third method for asymmetric 1,4-addition reactions.

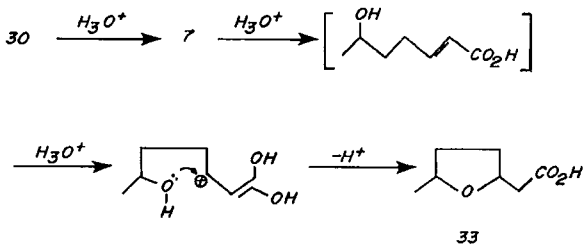
The oxazoline route

It has been reported that nucleophilic additon of organolithium reagents to chiral α,β-unsaturated oxazolines can lead to chiral β-substituted alkanoic acids having >90% ee (15). This strategy can be readily adapted to the synthesis of the key intermediate **3** as shown in Scheme 6. Treatment of **6** with (4*S*,5*S*)-(−)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline (**28**) (15) or (4*S*,5*S*)-(−)-2-(diethylphosphonomethyl)-4-methoxymethyl-5-phenyl-2-oxazoline (**29**) (27) by reported methods gave (4*S*,5*S*)-(+)-2-[1-(*E*-1,5-hexadienyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (**30**) in 26 and 84% yield, respectively. Since the 2-substituted oxazoline **30**, containing two olefinic groups, was more elaborate than the simpler oxazolines previously described, we wished to test the reactivity of **30** with a simple alkyllithium as well as the desired isopropenyllithium. The reaction of oxazoline **30** was thus carried out with either *n*-butyllithium or isopropenyllithium in THF at −78°C to give either (4*S*,5*S*)-2-[1-(3-*n*-butyl-5-hexenyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (**31**) or (4*S*,5*S*)-2-[1-(3-isopropenyl-5-hexenyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (**32**) in 90% and 63% yields, respectively.

The normal strong acid hydrolysis (15) of **31** gave a complex mixture of products, from which the desired 3-*n*-butyl-6-heptenoic acid could not be separated. Consequently the similar hydrolysis of **32** was not attempted. However, this result did lead us to examine the hydrolysis of the precursor α,β-



SCHEME 6



SCHEME 7

unsaturated oxazoline **30**, which we found gave 2-(5-methyltetrahydrofuranyl)acetic acid (**33**) in 62% yield, as did the strong acid treatment of **7**. Although the order and details of the mechanism of the hydrolysis of **30** have not been examined, a likely course of reaction, involving hydrolysis of the oxazoline with concomitant hydration of the terminal olefin, is outlined (Scheme 7). It is probable that hydration of the terminal olefin is also responsible for the mixture of products obtained from the hydrolysis of **31**.

The two-step procedure for the cleavage of oxazolines involving mild acid hydrolysis, followed by reduction with lithium aluminium hydride (28) of **31**, did give predominantly one enantiomer of 3-*n*-butyl-6-hepten-1-ol (**34**) in 44% yield, but an identical cleavage of **32** gave a complex mixture of products from which the desired 3-isopropenyl-6-hepten-1-ol (**35**) could not be isolated. Oxidation of **34** gave 3-*n*-butyl-6-heptenoic acid, which was converted to its acid chloride and treated with **14** to give *N*-[(*R*)-1-(1-naphthyl)ethyl]-3-*n*-butyl-6-heptenamide (**36**). Analysis of this diastereomeric amide by hplc, as described above for **15** and **16**, indicated that **34** had been formed in 96% ee. However, no attempts were made in this study to determine the absolute configuration of the enantiomer, **34**, that was formed.

Although the 1,4-addition of isopropenyllithium to the α,β-unsaturated oxazoline **30** proceeded well to give **32**, sufficiently mild methods of cleavage of **32** to give **3**, **12**, or **35** were not found. Various methods reported to cleave oxazolines

TABLE 2. ^{13}C Chemical shifts of **3**, **7**, **11**–**13**, **17**–**19**, **33**, and **34**

	δ ppm									
Carbon[a]	**3**	**7**[d]	**11**	**12**	**13**	**17**	**18**	**19**[d]	**33**[e]	**34**
1	202.3	172.3	178.6(p)	178.3(p)	180.3(p)	175.6	193.2	166.4	175.8, 175.7(p)	60.6(p)
2	47.4	121.2	41.7(p)	38.9(p)	35.9(p)	34.9	132.6	121.5	40.7, 40.4(p)	36.5(p)[b]
3	40.9	151.2	40.3(n)	42.8(n)	40.6(n)	45.1	157.1	148.1	75.7, 75.0(n)[b]	33.6(n)
4	31.1[b]	31.5[b]	31.3(p)[b]	31.2(p)[b]	30.6(p)[b]	28.2[b]	31.2	31.8[b]	33.3, 32.3(p)[c]	33.1(p)[b]
5	32.2[b]	31.9[b]	35.3(p)[b]	32.0(p)[b]	29.4(p)[b]	32.4[b]	31.2	31.3[b]	74.9, 74.5(n)[b]	32.8(p)[b]
6	138.1	137.0	138.0(n)	138.2(n)	22.9(p)	137.3	136.6	136.9	31.7, 30.9(p)[c]	139.0(n)
7	114.9[c]	115.4	114.8(p)	114.8(p)[c]	14.0(n)	115.7	115.2	115.3	21.1, 20.8(n)	114.0(p)
8	145.5	—	135.3(p)	145.6(p)	29.6(n)	86.7	—	60.0	—	30.7(p)[b]
9	112.7[c]	—	128.3(n)	112.6(p)[c]	19.3(n)[c]	27.4[c]	—	14.0	—	28.5(p)[b]
10	18.6	—	113.8(n)	18.6(n)	18.5(n)[c]	21.9[c]	—	—	—	22.9(p)
11	—	—	158.1(p)	—	—	—	—	—	—	13.9(n)
12	—	—	55.1(n)	—	—	—	—	—	—	—

[a]The numbering of the carbon atoms in the above compounds follows that given for these structures in Schemes 1, 2, 3, and 6 and does not necessarily follow from the names of these compounds. All spectra were recorded, using $CDCl_3$ as solvent, at 300 MHz except for compounds **7** and **18**, whose spectra were recorded at 400 MHz. Inversion–recovery (*J*-modulated spin-echo) spectra were recorded for **11**–**13**, **33**, and **34** (p indicates a positive signal due to C or CH_2, n indicates a negative signal due to CH or CH_3).

[b]These assignments may be interchanged.

[c]These assignments may be interchanged.

[d]Minor signals due to *Z*-isomer are not reported.

[e]*Cis* and *trans* isomers give rise to a duplication of signals.

under mild conditions (29–31) were attempted using **31** as a model. However, either no reaction or low yields of cleavage products were observed. A new procedure for the cleavage of oxazolines has not been attempted (32).

In summary, we have shown that a chiral pheromone intermediate can be prepared in a satisfactory yield having an extremely high ee (Table 1) by asymmetric synthesis, which demonstrates that asymmetric synthesis can compete effectively with the synthesis of chiral molecules from natural products, or through resolution of racemates. The elaboration of the key intermediate **3**, by reaction with a ylide, to the red scale pheromone component **1** has not been attempted in this study, since a procedure for this transformation has been previously reported (2). Although this method lacked stereoselectivity, resulting in a 1:1 mixture of (*E*)- and (*Z*)-**1**, the problem has been overcome by Heath *et al.* (17) in the synthesis of (3*Z*,-6*R*)-3,9-dimethyl-6-isopropenyl-3,9-decadien-1-yl propionate (the white peach scale pheromone) from a similar chiral synthon, (*R*)-6-methyl-3-isopropenyl-6-heptenal.

Experimental

Linde argon was used to maintain inert atmosphere conditions. Solvents required for reactions were dried and distilled before use. All reaction mixtures were stirred with a magnetic stirrer. Grignard reagents were prepared by slow addition of alkenyl or aryl bromide to activated magnesium turnings in an appropriate solvent, and sonication (19) of the reaction flask and contents in a 125-W Branson B220 ultrasonic bath filled with distilled water at 20°C. Most distillations were conducted using a Kugelrohr apparatus (bulb-to-bulb) and, for these, the temperature range of the heater at which the main fraction was collected is reported. Flash chromatography (33) was carried out using 20–45 μm silica gel as supplied by Terochem Laboratories Ltd., Toronto, Ont. High-performance liquid chromatography was conducted on a Spectra Physics SP8000 fitted with an analytical column (6.3 mm × 25 cm) of 10-μm Spherisorb silica gel and a mobile phase of 5–12.5% ethyl acetate in hexane (water saturated) with uv detection (254 nm). Melting points (mp) were determined using a Kofler hot stage melting point apparatus and are uncorrected. Optical rotations were determined using a Perkin–Elmer 141 polarimeter at 21 ± 2°C. Infrared spectra (ir) were recorded on a Pye Unicam SP1000 infrared spectrophotometer as neat films between NaCl discs unless specified otherwise. Nuclear magnetic resonance spectra for protons (^1H nmr) were recorded on a Varian EM360 (60 MHz), Bruker AM300 (300 MHz), or Bruker WH400 (400 MHz) spectrometer and are expressed in ppm (δ values) relative to tetramethylsilane as internal reference in deuteriochloroform. (The splittings of the signals are described as singlets (s), broad singlets (bs), doublets (d), triplets (t), quartets (q), doublet of doublets (dd), doublet of triplets (dt), or multiplets (m).) The ^{13}C nmr spectra were recorded in $CDCl_3$ on a Bruker AM300 (300 MHz) or a Bruker WH400 (400 MHz) and have been assigned using standard correlations (34) (Table 2). Mass spectra (ms) were recorded at 70 eV on a VG Micromass 16F mass spectrometer. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ont., Dr. C. Daessele, Montreal, P.Q., or Canadian Microanalytical Service Ltd., Vancouver, B.C.

4-Pentenal (6)

Following the method of Corey and Suggs (11) 4-penten-1-ol (**5**) (8.51 g, 99 mmol) was oxidized by pyridinium chlorochromate (PCC) (38.4 g, 178 mmol) in methylene chloride (185 mL). Distillation and careful fractionation gave the volatile **6** (4.57 g, 55% yield); bp 102–104°C (lit. (35) bp 103–104°C); liquid; ir ν: 1735 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 9.75 (t, 1H, J = 2 Hz, C*H*O), 6.30–5.50 (m, 1H, =C*H*—), 5.30–4.80 (m, 2H, CH_2=), 2.80–2.00 (m, 4H, CH_2CH_2). 2,4-Dinitrophenylhydrazone derivative; mp 119–120°C (lit. (34) mp 120°C).

2,6-Heptadienoic acid (7)

A mixture of **6** (4.38 g, 52 mmol), malonic acid (6.51 g, 63 mmol), pyridine (10 mL), and pyrrolidine (2 mL) was stirred overnight under argon and subsequently heated at 90°C for 5 h. The reaction mixture was cooled, acidified with 2 *N* hydrochloric acid, and extracted with ether. The combined organic extracts were washed with water and saturated brine, then dried over magnesium sulphate ($MgSO_4$) and concentrated. The residue was distilled (bulb-to-bulb, 1.0 Torr (1 Torr = 133.3 Pa), 74–84°C) to give **7** (5.16 g, 79% yield); liquid; ir ν: 3000 (O—H), 1710 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 12.45 (s, 1H, disappears in D_2O, O*H*), 7.45–6.85 (m, 1H, C*H*=CHCO$_2$H), 6.15–5.50 (m, 2H, CH_2=C*H* and C*H*CO$_2$H), 5.25–4.85 (m, 2H, CH_2=CH), 2.55–2.15 (m, 4H, CH_2CH_2). *Anal.* calcd. for $C_7H_{10}O_2$: C 66.65, H 7.99; found: C 66.66, H 8.26.

(E)-2,6-Heptadienoyl chloride (8)

Freshly distilled thionyl chloride (7 mL) was added dropwise to **7**

(1.443 g, 11.5 mmol) at 0°C with stirring. The mixture was allowed to warm to ambient temperature, and after 1 h it was heated to reflux for 0.5 h before removing excess thionyl chloride by distillation. Distillation (bulb-to-bulb, 0.075 Torr, 60–70°C) of the residue gave **8** (1.570 g, 94% yield); liquid; ir ν: 1765 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 7.60–7.05 (m, 1H, C*H*=CHCOCl), 6.30–5.50 (m, 2H, CH_2=C*H* and C*H*COCl), 5.30–4.85 (m, 2H, CH_2=CH), 2.60–2.20 (m, 4H, CH_2CH_2).

N-*(E-2,6-Heptadienoyl)-l-ephedrine (4)*

Compound **8** (1.494 g, 10.3 mmol) was added in one portion to a stirred mixture of proton sponge (2.20 g, 10.3 mmol) and *l*-ephedrine (1.697 g, 10.3 mmol) in THF (25 mL) at 0°C under argon. The mixture was allowed to warm up to room temperature and then stirred overnight. Cold 1 *N* hydrochloric acid (20 mL) was added and the product extracted with ethyl acetate, dried ($MgSO_4$), and concentrated. Flash chromatography (40% ethyl acetate/hexane) of the residue gave **4** (2.456 g, 88% yield); viscous oil; $[\alpha]_D$ −129.91° (*c* 2.62, $CHCl_3$); ir ν: 3390 (O—H), 1610 (C=O) cm^{-1}; ^1H nmr (400 MHz) δ: 7.32–7.16 (m, 5H, C_6H_5), 6.76 (dt, 0.7H, *J* = 15 Hz, C*H*=CHCON of *E*-amide[2]), 6.37 (dt, 0.3H, *J* = 15 Hz, C*H*=CHCON of *Z*-amide[2]), 6.10 (d, 0.7H, *J* = 15 Hz, C*H*CON of *E*-amide), 5.84 (d, 0.3H, *J* = 15 Hz, C*H*CON of *Z*-amide), 5.80–5.60 (m, 1H, CH_2=C*H*), 5.04–4.86 (m, 2H, CH_2=CH), 4.76 (d, 1H, *J* = 3 Hz, C*H*OH), 4.52–4.49 (m, 0.7H, NC*H*CH_3 of *E*-amide), 4.05–3.99 (m, 0.3H, NC*H*CH_3 of *Z*-amide), 2.77 (s, 0.7H, NCH_3 of *E*-amide), 2.74 (s, 0.7H, NCH_3 of *Z*-amide), 2.26–2.12 (m, 4H, CH_2CH_2), 2.06 (bs, 1H, O*H*), 1.27 (d, 0.3H, *J* = 7 Hz, NCHCH_3 of *Z*-amide), 1.10 (d, 0.7H, *J* = 7 Hz, NCHCH_3 of *E*-amide); ms *m/z*: 274 (M^+ + 1, 0.3), 255 (3), 166 (81), 109 (53), 81 (35), 79 (17), 58 (100), 55 (16). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.32, H 8.39, N 5.08.

N-*(3-p-Methoxyphenyl-6-heptenoyl)-l-ephedrine (9)*

To a stirred solution of the Grignard reagent, prepared from *p*-methoxyphenyl bromide (2.75 mL, 22 mmol) and magnesium (0.53 g, 22 mmol) in THF (20 mL), was added dropwise a solution of **4** (0.990 g, 3.6 mmol) in THF (5 mL) at 0°C under argon. After 14 h at 0°C a phosphate buffer solution (pH 7, 20 mL) was added and the resulting mixture filtered through Celite. The product was extracted into ethyl acetate, dried ($MgSO_4$), and concentrated. Flash chromatography (40% ethyl acetate/hexane) of the residue gave **9** (0.812 g, 59% yield); viscous oil; ir ν: 3400 (O—H), 1625 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 7.33–7.22 (m, 5H, C_6H_5), 7.01 (AA'XX', 4H, $CH_3OC_6H_4$), 5.84–5.68 (m, 1H, CH_2=C*H*), 4.95–4.89 (m, 2H, CH_2=CH), 4.70 (d, 1H, *J* = 3 Hz, C*H*OH), 4.42–4.29 (m, 1H, NC*H*CH_3), 3.75 (s, 3H, CH_3O), 3.19–3.07 (m, 1H, $CH_3OC_6H_4CH$), 2.90–2.74 (m, 2H, CH_2CON), 2.54 (s, 3H, NCH_3), 2.49–2.44 (bs, 1H, O*H*), 1.89–1.56 (m, 4H, CH_2CH_2), 1.06 (d, 3H, *J* = 7 Hz, CHCH_3); ms *m/z*: 382 (M^+ +1, 3), 275 (32), 274 (86), 175 (65), 134 (35), 121 (100), 79 (29), 58 (99). *Anal.* calcd. for $C_{24}H_{31}NO_3$: C 75.56, H 8.19, N 3.67; found: C 75.54, H 8.19, N 3.70.

N-*(3-Isopropenyl-6-heptenoyl)-l-ephedrine (10)*

In a manner similar to that described above for **9**, **4** was converted, under the conditions listed in Table 1, to **10** (51–69% yield); viscous oil; ir ν: 3480 (O—H), 1660 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 7.35–7.22 (m, 5H, C_6H_5), 5.83–5.73 (m, 1H, CH_2=C*H*), 5.01–4.70 (m, 4H, CH_2=CH and CH_2=C), 4.61–4.42 (m, 1H, NC*H*CH_3), 4.36 (d, 1H, *J* = 3 Hz, C*H*OH), 2.70 (s and smaller s due to *E*- and *Z*-amide isomers, 3H, NCH_3), 2.64–2.55 (m, 1H, C*H*CH_2CON), 2.40–2.19 (m, 2H, CH_2CON), 2.16–1.76 (m, 2H, CH_2=CHCH_2), 1.66 (s and smaller s due to *E*- and *Z*-amide isomers, 3H, $CH_3(CH_2$=)C), 1.55–1.29 (m, 3H, CH_2=CHCH_2CH_2 and O*H*), 1.16 (d, 3H, *J* = 7 Hz, CHCH_3); ms *m/z*: 316 (M^+ + 1, 0.8), 3.15 (M^+, 0.6), 209 (23), 208 (92), 109 (22), 81 (20), 67 (23), 58 (100), 55 (23). *Anal.* calcd. for $C_{20}H_{29}NO_2$: C 76.15, H 9.27, N 4.44; found: C 76.33, H 9.37, N 4.54.

3-p-Methoxyphenyl-6-heptenoic acid (11)

A solution of **9** (0.2401 g, 0.63 mmol) in 10% NaOH (20 mL, 1:1 EtOH/H_2O) was heated at reflux for 78 h. After cooling, the mixture was acidified with 2 *N* HCl, and the product extracted into ether, dried ($MgSO_4$), and concentrated. Distillation (bulb-to-bulb, 0.05 Torr, 120–130°C) gave **11** (0.0619 g, 42% yield); liquid; $[\alpha]_D$ −11.32° (*c* 3.28, $CHCl_3$); ir ν: 3200 (O—H), 1720 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 10.10 (bs, 1H, O*H*), 6.96 (AA'XX', 4H, $CH_3OC_6H_4$), 5.85–5.68 (m, 1H, CH_2=C*H*), 4.97–4.90 (m, 2H, CH_2=CH), 3.78 (s, 3H, CH_3O), 3.10–3.01 (m, 1H, C*H*CH_2CO_2H), 2.60 (t, 2H, *J* = 7 Hz, CH_2CO_2H), 1.95–1.60 (m, 4H, CH_2CH_2); ms *m/z*: 234 (M^+, 48), 192 (49), 179 (93), 175 (89), 137 (99), 134 (26), 121 (100), 91 (20). *Anal.* calcd. for $C_{14}H_{18}O_3$: C 71.77, H 7.74; found: C 71.72, H 7.99.

(R)-3-Isopropenyl-6-heptenoic acid (12)

In a manner similar to that described above for **11**, **10** was converted to **12** (distilled bulb-to-bulb, 0.05 Torr, 95–105°C, 63–80% yield); liquid; $[\alpha]_D$ see Table 1; ir ν: 3150 (O—H), 1730 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 10.60 (bs, 1H, O*H*), 5.89–5.72 (m, 1H, CH_2=C*H*), 5.04–4.78 (m, 4H, CH_2=CH and CH_2=C), 2.69–2.57 (m, 1H, C*H*CH_2CO_2H), 2.41 (d, 2H, *J* = 7.5 Hz, CH_2CO_2H), 2.10–1.93 (m, 2H, CH_2=CHCH_2), 1.67 (s, 3H, CH_3), 1.52–1.45 (m, 2H, CH_2=CHCH_2CH_2); ms *m/z*: 168 (M^+, 4), 108 (63), 93 (38), 81 (52), 69 (100), 67 (46), 55 (67), 43 (50), 41 (90). *Anal.* calcd. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.20, H 9.99.

(R)-3-Isopropylheptanoic acid (13)

Hydrogen was passed over a stirred mixture of **12** (0.0682 g, 0.41 mmol; $[\alpha]_D$ −3.13 (*c* 2.05, $CHCl_3$)) and 10% palladium on charcoal (0.0212 g) in ethanol (15 mL) for 16 h at room temperature. The solution was filtered, the solvent removed, and the resulting oil distilled (bulb-to-bulb, 0.1 Torr, 100–110°C) to give **13** (0.0677 g, 97% yield); liquid; $[\alpha]_D$ −0.45° (*c* 2.23, $CHCl_3$) (lit. (15) $[\alpha]_D$ −0.82° (neat)); ir ν: 3050 (O—H), 1720 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 10.52 (bs, 1H, O*H*), 2.37–2.14 (m, 2H, CH_2CO_2H), 1.84–1.72 (m, 2H, $(CH_3)_2CHCH$), 1.41–1.18 (m, 6H, $CH_3CH_2CH_2CH_2$), 0.98–0.84 (m, 9H, CH_3CH_2 and $(CH_3)_3CH$); ms *m/z*: 173 (M^+ + 1, 2), 129 (42), 113 (78), 112 (69), 72 (56), 70 (71), 69 (100), 60 (40), 57 (99), 56 (54), 55 (64), 43 (68), 41 (76). *Anal.* calcd. for $C_{10}H_{20}O_2$: C 69.72, H 11.70; found: C 69.66, H 11.85.

N-*[(R)-1-(Naphthyl)ethyl]-3-p-methoxyphenyl-6-heptenamide (15)*

To a solution of **11** (0.0677 g, 0.29 mmol; $[\alpha]_D$ −16.90 (*c* 5.38), $CHCl_3$)) in ether (3 mL) containing a catalytic amount of *N,N*-dimethylformamide (5 μL) was added thionyl chloride (63 μL, 0.87 mmol). After stirring for 4 h at room temperature, the mixture was concentrated to remove excess thionyl chloride. Ether (5 mL) was added and the resulting solution cooled to 0°C, whereupon a solution of **14** (0.0744 g, 0.44 mmol) and proton sponge (0.0932 g, 0.44 mmol) in ether (5 mL) was added dropwise. A precipitate formed, and the reaction mixture was allowed to warm to room temperature and was stirred overnight. Ice-cold 1 *N* hydrochloric acid (15 mL) was added and the product extracted into ether, washed with brine, dried ($MgSO_4$), and concentrated to give crude **15** (0.1093 g, 98% yield). Crude **15** was analysed by hplc directly, to avoid fractionation. Separation of the two diastereomers was obtained in 0.8 h by using 10% ethyl acetate in hexane at 1.0 mL/min. The predominant diastereomer, the second to elute, was collected by hplc; ir ν: 3300 (N—H), 1650 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 7.94–7.10 (m, 7H, $C_{10}H_7$), 6.84 (AA'XX', 4H, $CH_3OC_6H_4$), 5.85–5.65 (m, 2H, C*H*NH and CH_2=C*H*), 5.41 (s, 1H, N*H*), 5.96–5.89 (m, 2H, CH_2=CH), 3.75 (s, 3H, CH_3O), 3.14–3.00 (m, 1H, C*H*CH_2CO_2H), 2.24–2.14 (m, 2H, CH_2CON), 1.84–1.60 (m, 4H, CH_2CH_2), 1.54 (d, 3H, CH_3CH).

(R)-N-[(R)-1-(1-Naphthyl)ethyl]-3-isopropenyl-6-heptenamide (16) via route shown in Scheme 1

In a manner similar to that described above for **15**, **12** was converted

[2] The *E*- and *Z*-amide isomers are distinguishable on the nmr time scale (36).

to **16** (78% crude yield) and analysed directly by hplc. Separation of the two diastereomers was achieved in 0.25 h using 12.5% ethyl acetate in hexane at 1.5 mL/min. The (*R,S*)-diastereomer (11 min) eluted prior to the predominant (*R,R*)-diastereomer (13 min); the identity of these diastereomers was confirmed as described below for the aldimine route. A sample of **16** was purified by flash chromatography (25% ethyl acetate/hexane); ir ν: 3320 (N—H), 1650 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 8.12–7.40 (m, 7H, $C_{10}H_7$), 6.02–5.87 (m, 2H, N*H* and C*H*NH), 5.82–5.75 (m, 1H, CH_2=C*H*), 5.11–4.72 (m, 4H, CH_2=CH and CH_2=C), 2.68–2.55 (m, 1H, C*H*CH_2CON), 2.26–2.15 (m, 2H, CH_2CON), 2.07–1.88 (m, 2H, CH_2=CHCH_2), 1.61 (s and d, 6H, CH_3=C and CH_3CH), 1.50–1.33 (m, 2H, CH_2=CHCH_2CH_2).

(R)-3-Isopropenyl-6-heptenal (3) via route shown in Scheme 1

DIBAL (5.2 mL of a 1 *M* solution in hexane, 5.2 mmol) was added dropwise over 1.5 h to a stirred solution of **10** (0.544 g, 1.7 mmol) (Entry 5 in Table 1) in THF (10 mL) at 0°C under argon. After 0.5 h the mixture was quenched by the addition of ice-cold 10% sulphuric acid (30 mL), and then stirred for 1 h. The product was extracted with ether, washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The residue was distilled (bulb-to-bulb, 0.05 Torr, 55–65°C) to give **3** (0.055 g, 21% yield); liquid; $[\alpha]_D$ −0.42° (*c* 2.53, $CHCl_3$); ir ν: 1735 (C=O), 1650 (C=C) cm^{-1}; ^1H nmr (300 MHz) δ: 9.66 (t, 1H, J = 2 Hz, C*H*O), 5.87–5.72 (m, 1H, CH_2=C*H*), 5.04–4.78 (m, 4H, CH_2=CH and CH_2=C), 2.78–2.67 (m, 1H, C*H*CH_2CO_2H), 2.49–2.42 (m, 2H, CH_2CO_2H), 2.07–1.93 (m, 2H, CH_2=CHCH_2), 1.66 (d, 3H, J = 0.9 Hz, CH_3), 1.56–1.42 (m, 2H, CH_2=CHCH_2CH_2); ms *m/z*: 152 (M^+, 0.2), 123 (12), 108 (11), 95 (26), 81 (24), 69 (100), 67 (29), 55 (21), 41 (16). 2,4-Dinitrophenylhydrazone derivative; mp 81–83°C. *Anal.* calcd. for $C_{16}H_{20}N_4O_4$: C 57.82, H 6.07, N 16.86; found: C 57.93, H 6.24, N 16.73.

(R)-3-(3-Buten-1-yl)-4,4-dimethylbutyrolactone (17)

Compound **10** (0.1239 g, 0.39 mmol) (Entry 3 in Table 1) was dissolved in ethanolic hydrochloric acid (5 mL of a solution prepared by the addition of 35% hydrochloric acid (4 mL) and ethanol (50 mL)) and the resulting mixture was refluxed overnight. After cooling, water (10 mL) was added and the product extracted with ether. The combined organic extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was distilled (bulb-to-bulb, 0.35 Torr, 110–120°C) to give **17** (0.0496 g, 75% yield); liquid; $[\alpha]_D$ −24.85° (*c* 0.780, $CHCl_3$); ir ν: 1780 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 5.86–5.70 (m, 1H, CH_2=C*H*), 5.12–5.01 (m, 2H, CH_2=CH), 2.72–2.59 (m, 1H, C*H*CH_2CO_2), 2.37–1.95 (m, 4H, CH_2CO_2 and CH_2=CHCH_2), 1.67–1.53 (m, 2H, CH_2=CHCH_2-CH_2), 1.45 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ms *m/z*: 168 (M^+, 14), 153 (100), 135 (45), 110 (35), 82 (35), 67 (65), 59 (44), 41 (62). *Anal.* calcd. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.20, H 9.59.

Ethyl 2,6-heptadienoate (19)

Following a similar procedure to that described for the preparation of **7**, the monoethyl ester of malonic acid (37) (13.2 g, 100 mmol) was reacted with **6** (6.5 g, 77 mmol) in a mixture of pyridine (8 mL) and pyrrolidine (1.5 mL). Distillation (bulb-to-bulb, 0.05 Torr, 50–55°C) gave **19** (9.42 g, 79% yield); liquid; ir ν: 1735 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 7.50–6.80 (m, 1H, C*H*=CHCO$_2$), 6.10–5.50 (m, 2H, C*H*CO$_2$ and CH_2=C*H*), 5.30–4.80 (m, 2H, CH_2=CH), 4.18 (q, 2H, J = 7 Hz, CH_2CH_3), 2.55–2.15 (m, 4H, CH_2CH_2), 1.24 (t, 3H, J = 7 Hz, CH_3); ms *m/z*: 154 (M^+, 1), 109 (44), 81 (100), 80 (42), 79 (28), 55 (25), 41 (59), 39 (34). *Anal.* calcd. for $C_9H_{14}O_2$: C 70.10, H 9.15; found: C 69.64, H 9.50.

2,6-Heptadienal (18) via route shown in Scheme 3

To a stirred solution of **19** (2.029 g, 13.2 mmol) in hexane (40 mL), at −20°C under argon, was added dropwise DIBAL (26.5 mL of 1 *M* solution in hexane) over 1 h. The reaction mixture after 1 h was allowed to warm to 0°C. Methanol (4 mL) was added, followed by water (1 mL) and sufficient dilute hydrochloric acid to acidify the reaction mixture. The product was extracted with ether, washed with 1 *N* hydrochloric acid, saturated sodium hydrogen carbonate, saturated brine, dried ($MgSO_4$), and concentrated. The residue (1.218 g, 82% yield) was shown by ^1H nmr to be a 4:1 mixture of **20** and **21**; ^1H nmr (60 MHz) δ: 6.35–5.30 (m, 3.3H, C*H*=C*H*CH_2OH, CH_2=C*H* of **20** and CH_2=C*H* of **21**), 5.25–4.85 (m, 2.5H, CH_2=CH of **20** and of **21**), 3.67 (t, 0.5H, J = 5.5 Hz, CH_2OH of **21**), 2.90 (bs, 1.3H, disappears in D_2O, O*H* of **20** and of **21**), 2.40–1.85 (m, 5.5H, CH_2CH_2 of **20** and $CH_2CH_2CH_2CH_2$ of **21**).

The crude mixture of **20** and **21** (1.218 g, 10.8 mmol) was oxidized by PCC (3.00 g, 13.9 mmol) in methylene chloride (35 mL) following the procedure of Corey and Suggs (11). The crude product oil was washed with 0.4 *M* sodium metabisulphite (10 mL), extracted with ether, dried ($MgSO_4$), and concentrated. Distillation (bulb-to-bulb, 16 Torr, 60–71°C (lit. (22) bp 16 Torr, 58–65°C)), gave **18**, contaminated by 3% of **22**, (0.566 g, 39% yield from **19**); liquid; ir ν: 1700 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 9.82 (t, 0.03H, J = 1.5 Hz, C*H*O of **22**), 9.55 (d, 1H, J = 8 Hz, C*H*O), 7.35–6.60 (m, 1H, C*H*=CHCHO), 6.40–5.50 (m, 2H, C*H*CHO and CH_2=C*H*), 5.30–4.85 (m, 2H, CH_2=CH), 2.60–2.10 (m, 4H, CH_2CH_2).

(E)-2,6-Heptadienal (18) via route shown in Scheme 4

Following the general procedure of Meyers *et al.* (26), 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (3.613 g, 25.6 mmol) in THF (25 mL) was lithiated by the dropwise addition of *n*-butyllithium (17.6 mL of a 1.6 *M* solution in hexane, 28.2 mmol) at −78°C under argon over 1 h. After a yellow precipitate had formed, **6** (2.368 g, 28.2 mmol) in THF (5 mL) was added dropwise over 0.5 h. The reaction mixture was allowed to warm slowly to room temperature and worked up as described by Meyers *et al.* (26) to give crude **24** (4.787 g, 83% yield); liquid; ir ν: 3360 (O—H), 1670 (C=N) cm^{-1}. Reduction of crude **24** (3.574 g, 15.9 mmol) by sodium borohydride (0.613 g, 16.1 mmol) at pH 6–8 in the manner described by Meyers *et al.* (26) gave crude **25** (3.543 g, 98% yield); liquid; ir ν: 3350 (O—H) cm^{-1}. Crude **25** (3.543 g, 15.6 mmol) was added dropwise to a boiling aqueous solution (100 mL) of oxalic acid (7 g). The water azeotrope, which distilled off, was collected and the product extracted into ether, dried ($MgSO_4$), and concentrated to give **18** (0.769 g, 44% yield from **24**); liquid; ir ν: 1700 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 9.51 (d, 1H, J = 8 Hz, C*H*O), 6.90–6.81 (m, 1H, C*H*=CHCHO), 6.18–6.09 (m, 1H, CH=C*H*CHO), 5.88–5.74 (m, 1H, CH_2=C*H*), 5.11–5.02 (m, 2H, CH_2=CH), 2.50–2.24 (m, 4H, CH_2CH_2); ms *m/z*: 110 (M^+, 4), 109 (14), 95 (32), 81 (100), 79 (42), 41 (71).

Racemic 3-isopropenyl-6-heptenal (3) via route shown in Scheme 5

Following the general procedure described by Hashimoto *et al.* (21), **18** (0.349 g, 3.17 mmol) was condensed with racemic **26** (0.592 g, 3.16 mmol) in benzene (16 mL) to afford, after work-up, crude **27** (0.838 g, 95% yield); oil; ir ν: 1735 (C=O), 1660 (C=N) cm^{-1}; ^1H nmr (300 MHz) δ: 7.76 (d, 1H, J = 9 Hz, C*H*=N), 6.43–6.15 (m, 2H, C*H*=C*H*CH=N), 5.90–5.72 (m, 1H, CH_2=C*H*), 5.11–4.92 (m, 2H, CH_2=CH), 3.30 (s, 1H, C*H*CO$_2$), 2.39–2.13 (m, 4H, CH_2CH_2), 1.47 (s, 9H, $CO_2C(CH_3)_3$), 0.98 (s, 9H, $CHC(CH_3)_3$). A solution of the total crude **27** in THF (5 mL) was added dropwise to a stirred solution of isopropenylmagnesium bromide, prepared from isopropenyl bromide (1.15 g, 9.5 mmol) and magnesium (0.23 g, 9.5 mmol), in THF (20 mL) at −70°C. After 3 h the reaction mixture was allowed to warm up to −15°C and was kept at this temperature overnight. Hydrolytic work-up, as described by Hashimoto *et al.* (21), followed by flash chromatography (10% ether/hexane) and subsequent distillation (bulb-to-bulb, 0.1 Torr, 65–75°C) gave racemic **3** (0.243 g, 50%), identical to **3** prepared via Scheme 1, as described above.

(R)-3-Isopropenyl-6-heptenal (3) via route shown in Scheme 5

In a manner similar to that described above for racemic **3**, **18** was condensed with chiral **26** and converted, under the conditions reported in Table 1, to **3** (43% yield); $[\alpha]_D$ −0.47° (*c* 7.89, $CHCl_3$).

(R)-N-[(R)-1-(1-Naphthyl)ethyl]-3-isopropenyl-6-heptenamide (16) via route shown in Scheme 5

Following the procedure described by Heath *et al.* (17), **3** (0.0883 g, 0.58 mmol) in acetone (15 mL) was oxidized by Jones reagent (38)

(0.3 mL, 0.8 mmol) to give crude **12** (0.0823 g, 84% yield). This compound was converted, in a manner similar to that described above, to crude **16** (0.0959 g, 52% overall yield) and analysed directly by hplc. At identical retention times to those reported above, the (*R,S*)-diastereomer (11 min) eluted prior to the predominant (*R,R*)-diastereomer (13 min). Under identical hplc conditions, a preparation of **16** from a racemic mixture of **3** and its enantiomer gave two peaks of identical area at 11 and 13 min, whereas for a preparation of **16** from optically active **3** and (*S*)-(−)-**14** the predominant (*S,R*)-diastereomer (11 min) eluted prior to the (*S,S*)-diastereomer (13 min).

*(4S,5S)-(+)-2-[1-(*E*-1,5-Hexadienyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (30)*

Method A

Following the procedure described by Meyers *et al.* (15), **28** (6.00 g, 29.3 mmol) in THF (50 mL) was lithiated at −78°C, and **6** (2.50 g, 29.8 mmol) in THF (4 mL) was added dropwise. After the appropriate work-up the product was treated with trifluoroacetic acid (6 drops) in benzene (150 mL) and the mixture refluxed overnight; a Dean–Stark trap was employed to remove water. The cooled solution was washed with 5% sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated. Flash chromatography (20% ether/hexane) gave **30** (3.30 g, 26% yield); oil; $[\alpha]_D$ 50.31° (*c* 1.60, $CHCl_3$); ir *ν*: 1680 (C=N) cm^{-1}; ^1H nmr (60 MHz) δ: 7.32 (s, 5H, C_6H_5), 7.04–6.51 (m, 1H, C*H*=CHC=N), 6.31–5.52 (m, 2H, CH_2=C*H* and CHC=N), 5.32 (d, 1H, *J* = 7 Hz, OC*H*), 5.24–5.01 (m, 2H, CH_2=CH), 4.32–4.00 (m, 1H, NC*H*), 3.66–3.46 (m, 2H, CH_2O), 3.40 (s, 3H, OCH_3), 2.45–2.12 (m, 4H, CH_2CH_2); ms *m/z*: 271 (M^+, 11), 241 (6), 226 (100), 182 (28), 151 (29), 134 (32), 119 (95), 109 (44), 91 (60), 74 (37), 45 (39).

Method B

Crude **29** (8.056 g, 24.6 mmol), prepared by the method of Ziegler and Gilligan (27), and **6** (2.94 g, 35.0 mmol) were dissolved in THF (25 mL, containing two drops of water) and cooled to −78°C. Potassium *tert*-butoxide (3.4 g, 30.0 mmol) in THF (20 mL) was added slowly and the reaction conducted and worked up in the manner described by Meyers *et al.* (15) to give **30** (5.88 g, 89% yield), identical to **30** prepared by method A, described above.

*(4S,5S)-2-[1-(3-*n*-Butyl-5-hexenyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (31)*

A solution of **30** (2.707 g, 9.99 mmol) in THF (30 mL) was added dropwise over 1 h to *n*-butyllithium (13.8 mL of a 1.6 *M* solution in hexane, 22.1 mmol) in THF (125 mL) at −78°C under argon, and the mixture was stirred for 2.5 h at the same temperature. The reaction was quenched at −78°C by the addition of methanol (3 mL). The reaction mixture was allowed to warm up to ambient temperature, then treated with water (100 mL) and extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude **31** (2.949 g, 90% yield); ir *ν*: 1655 (C=N) cm^{-1}; ^1H nmr (60 MHz) δ: 7.36 (s, 5H, C_6H_5), 6.27–5.52 (m, 1H, CH_2=C*H*), 5.32 (d, 1H, *J* = 7 Hz, OC*H*), 4.31–3.98 (m, 1H, NC*H*), 3.80–3.47 (m, 2H, CH_2O), 3.40 (s, 3H, OCH_3), 2.60–0.75 (m, 16H, aliphatic envelope); ms *m/z*: 321 (M^+, 2), 284 (22), 222 (100), 180 (84), 152 (41), 124 (57), 99 (46), 83 (64), 55 (62), 41 (84).

(4S,5S)-2-[1-(3-Isopropenyl-5-hexenyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (32)

In a manner similar to that described above for **31**, **30** was reacted with isopropenyllithium, prepared from *tert*-butyllithium and isopropenyl bromide (39), to give after flash chromatography (40% ethyl acetate/hexane) **32** (0.680 g, 63% yield); ir *ν*: 1660 (C=N) cm^{-1}; ^1H nmr (60 MHz) δ: 7.33 (s, 5H, C_6H_5), 6.25–5.51 (m, 1H, CH_2=C*H*), 5.30 (d, 1H, *J* = 7 Hz, OC*H*), 5.22–4.78 (m, 4H, CH_2=CH and CH_2=C), 4.32–3.95 (m, 1H, NC*H*), 3.75–3.50 (m, 2H, CH_2O), 3.43 (s, 3H, OCH_3), 2.70–1.05 (m, 10H, aliphatic envelope); ms *m/z*: 313 (M^+, 1), 224 (18), 193 (13), 165 (13), 136 (15), 109 (24), 74 (100), 55 (22), 43 (26).

2-(5-Methyltetrahydrofuranyl)acetic acid (33)

A solution of **30** or **7** (1.73–2.57 mmol) in 4 *N* sulphuric acid (10–15 mL) was refluxed for 4 h. The reaction mixture was allowed to cool, and then was extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), concentrated, and distilled (bulb-to-bulb, 1.20 Torr, 125–135°C) to give **33** (62% yield from either **30** or **7**); liquid n_D^{23} 1.4532 (lit. (40) n_D^{25} 1.4520); ir *ν*: 3100 (O—H), 1720 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 10.31 (s, 1H, O*H*), 4.65–3.75 (m, 2H, C*H*OC*H*), 2.55 (dt, 2H, *J* = 2 and 7 Hz, CH_2CO_2), 2.40–1.35 (m, 4H, CH_2CH_2), 1.23 (dd, 3H, *J* = 1.5 and 6 Hz, CH_3); ms *m/z*: 144 (M^+, 5), 111 (30), 102 (100), 85 (87), 84 (38), 56 (82), 55 (92), 43 (89), 41 (89). *Anal.* calcd. for $C_7H_{12}O_3$: C 58.32, H 8.39; found: C 58.32, H 8.32.

*3-*n*-Butyl-6-hepten-1-ol (34)*

A solution of crude **31** (0.416 g, 1.26 mmol) in 3% ethanolic hydrochloric acid (10 mL) was refluxed overnight. After cooling, the mixture was concentrated, water (10 mL) was added, and the resulting solution was neutralized and then extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated. The resulting viscous oil was dissolved in THF (7 mL), lithium aluminum hydride (0.15 g, 3.90 mmol) added, and the reaction mixture stirred overnight at ambient temperature. The reaction mixture was cooled to 0°C and the excess hydride destroyed by the slow addition of methanol (1 mL), followed by water (10 mL). The product was extracted into ether, washed with brine, dried ($MgSO_4$), concentrated, and distilled (bulb-to-bulb, 0.1 Torr, 66–77°C) to give **34** (0.094 g, 44% yield); liquid; $[\alpha]_D$ −1.18° (*c* 2.12, $CHCl_3$); ir *ν*: 3475 (O—H) cm^{-1}; ^1H nmr (300 MHz) δ: 5.81–5.66 (m, 1H, CH_2=C*H*), 4.98–4.83 (m, 2H, CH_2=CH), 3.54 (t, 2H, *J* = 7 Hz, CH_2OH), 3.11 (bs, 1H, O*H*), 2.06–1.92 (m, 2H, CH_2=CHCH_2), 1.50–0.75 (m, 14H, aliphatic envelope); ms *m/z*: 137 (M^+ − CH_3 and H_2O, 0.5), 124 (M^+ − CH_2=CH_2 and H_2O, 5), 123 (13), 113 (11), 110 (10), 109 (6), 95 (47), 81 (30), 69 (53), 67 (34), 55 (100), 43 (30), 41 (60). Compound **34** was oxidized by PCC to 3-*n*-butyl-6-heptenal (81% yield); ir *ν*: 1740 (C=O) cm^{-1}; ms *m/z*: 168 (M^+, 0.2), 150 (2). 2,4-Dinitrophenylhydrazone derivative; mp 65–67°C. *Anal.* calcd. for $C_{17}H_{24}N_4O_4$: C 58.61, H 6.94, N 16.08; found: C 58.42, H 6.87, N 15.80.

N-*[(*R*)-1-(Naphthyl)ethyl]-3-*n*-butyl-6-heptenamide (36)*

Jones reagent (38) (1.18 mL, 2.26 mmol) was used to oxidize **34** (0.1285 g, 0.76 mmol), in a manner similar to that described above for **3**, to give after distillation (bulb-to-bulb, 1.5 Torr, 130–140°C) 3-*n*-butyl-6-heptenoic acid (0.0605 g, 44% yield); ir *ν*: 3105 (O—H), 1720 (C=O) cm^{-1}; ^1H nmr (60 MHz) δ: 11.00 (bs, 1H, O*H*), 6.10–5.43 (m, 1H, CH_2=C*H*), 5.17–4.74 (m, 2H, CH_2=CH), 2.34 (d, 2H, *J* = 6 Hz, CH_2CO_2), 2.28–0.80 (m, 14H, aliphatic envelope). Following a procedure similar to that described above for **16**, 3-*n*-butyl-6-heptenoic acid was converted to crude **36** (0.1021 g, 92% yield) and analysed directly by hplc. Separation of the two diastereomers was achieved in 0.75 h using 5% ethyl acetate in hexane at 1.0 mL/min. The predominant diastereomer eluted first. A sample of **36** was purified by flash chromatography (20% ethyl acetate/hexane); ir *ν*: 3320 (N—H), 1640 (C=O) cm^{-1}; ^1H nmr (300 MHz) δ: 8.13–7.38 (m, 7H, $C_{10}H_7$), 5.98–5.86 (m, 2H, N*H* and C*H*NH), 5.78–5.62 (m, 1H, CH_2=C*H*), 4.97–4.86 (m, 2H, CH_2=CH), 2.14–1.85 (m, 5H, CH_2=CHCH_2CH_2C*H*CH_2), 1.63 (d, 3H, *J* = 6 Hz, CHCH_3), 1.39–1.16 (m, 8H, $(CH_2)_3CH_3$ and CH_2=CHCH_2CH_2), 0.86 (t, 3H, *J* = 6.5 Hz, CH_2CH_3); ms *m/z*: 337 (M^+, 15), 213 (29), 170 (19), 156 (38), 155 (100), 153 (17), 55 (19).

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