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Assignment of Absolute Stereochemistry to an Insect Pheromone by Chiral Amplification

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Abstract—Chiral amplification, a new strategy for determining the absolute configuration of difficultly available natural secondary alcohols or analogous amines, is described. Using this technique, the *R* configuration can be assigned to both components of the male sex pheromone emitted by the longhorn beetle, *Anaglyptus subfasciatus*. The application of this approach to fourteen alcohols and four amines illustrates its scope and limitations. Copyright © 1996 Elsevier Science Ltd

Introduction

One of the challenges in characterizing a chiral, biologically active natural product is the determination of its absolute stereochemistry. This problem can be especially acute in the case of an insect pheromone, since individual insects may typically produce only nanogram to microgram quantities of important semiochemicals.[1] On this scale, the standard tools for stereochemical investigation, including polarimetry, CD spectroscopy NMR spectroscopy, and X-ray crystallography, have little or nothing to say. The classical approach to determining the absolute stereochemistry of a chiral pheromone has been the synthesis of all possible isomers in high optical purity, followed by both spectroscopic and chromatographic comparisons and bioassay.[1,2] We would like to describe a simple strategy, for which we suggest the term 'chiral amplification', for the solution of this elementary configurational problem. This strategy should be broadly applicable in instances where (1) the natural product has a functional group in a chiral environment and (2) the racemic form of the natural product is readily accessible.

Results and Discussion

The elucidation of absolute configuration in the case of a secondary alcohol, as illustrated in Figure 1, consists of a straightforward protocol, the first step of which is the partial conversion of the racemic alcohol into an unequal mixture of two diastereomeric derivatives, by treatment with less than 1 equivalent of one enantiomer of an appropriate chiral derivatizing reagent. (*R*)-(−)-α-Methoxyl-α-trifluoromethylphenylacetyl chloride [(*R*)-MTPA chloride], which yields (*S*)-MTPA esters as a consequence of the *R*/*S* conventions, is especially useful for this purpose, for reasons made clear below. If there is even a small difference in the rates at which the individual components of the racemic alcohol react with the chiral reagent, as a result of the diastereomeric transition states through which the reactions proceed, incomplete derivatization will give rise to two diastereomeric (*S*)-MTPA derivatives in unequal amounts. The preparation of a mixture containing unequal amounts of the two (*S*)-MTPA derivatives (still stereochemically undefined) is a key step for the success of this strategy. The ratio of the two (*S*)-MTPA esters should then be measurable by ^{1}H NMR spectroscopy as well as by gas chromatographic or HPLC techniques.

In the next step the absolute configuration of each of the two (*S*)-MTPA esters in the above-described mixture is determined. As indicated in Figure 1, the configurations of the alcohol moieties of the two (*S*)-MTPA derivatives should be assignable on the basis of the well-established Mosher method, by considering the differences in ^{1}H NMR chemical shifts to be anticipated for the most favorable conformation of each of the (*S*)-MTPA esters.[3] The ^{1}H NMR data for each component can be obtained from the diastereomeric mixture without the necessity of any preparative separation, since a consideration of relative peak intensities should serve to show which resonances are attributable to the major component and which to the minor one. Based on the conformational model proposed by Kakisawa et al.,[4] the carbinyl proton, ester carbonyl group and trifluoromethyl groups of MTPA esters are coplanar in their preferred conformation. The proton signals of the two R_1 groups (Fig. 1) in the diastereomeric (*S*)-MTPA esters should show different chemical shifts as a consequence of their residence in different magnetic surroundings. Thus, the proton signals of the R_1 group in the stereoisomer represented at the top of Figure 1 should show an upfield chemical shift relative to those of the R_1 group in the isomer represented below, because of the strong diamagnetic shielding effect of the benzene ring. Similarly, the proton signals of the R_2 group in the ester represented by the lower formula should appear upfield of the

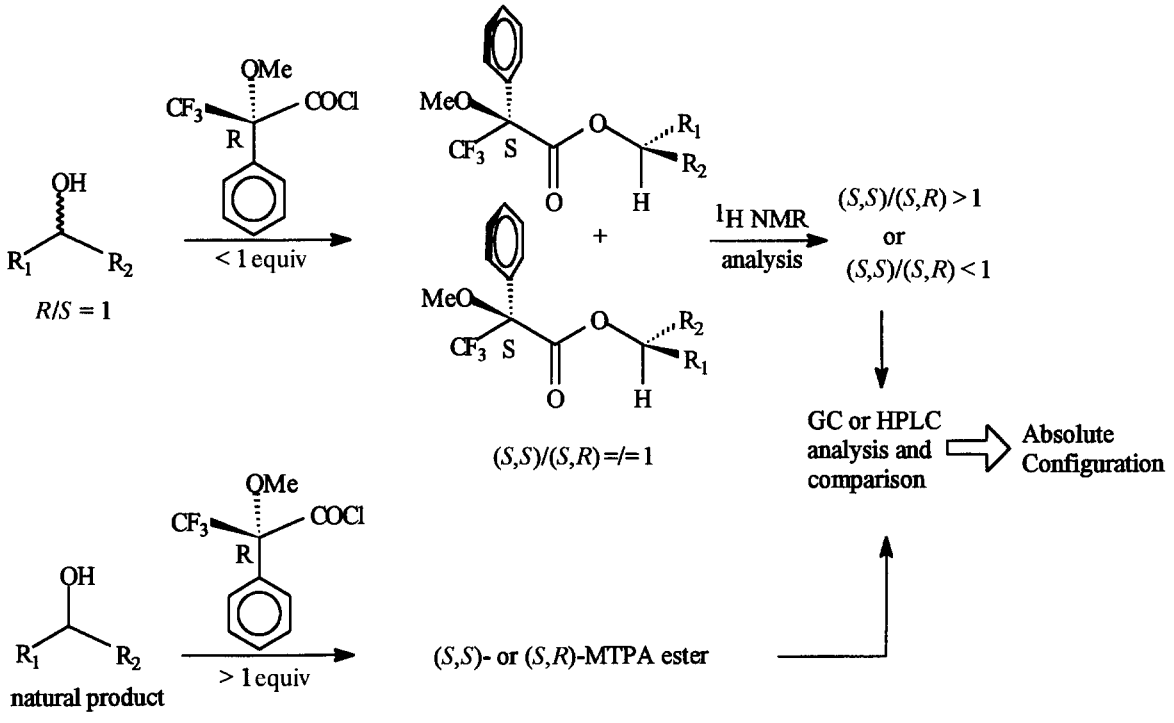


Figure 1. Application of chiral amplification to secondary alcohols.

corresponding group in its partner. On the basis of the ^{1}H NMR spectral data, therefore, the two MTPA esters can be assigned relative configurations; since we know that we are considering (*S*)-MTPA esters, the absolute configuration of each alcohol moiety is immediately apparent.

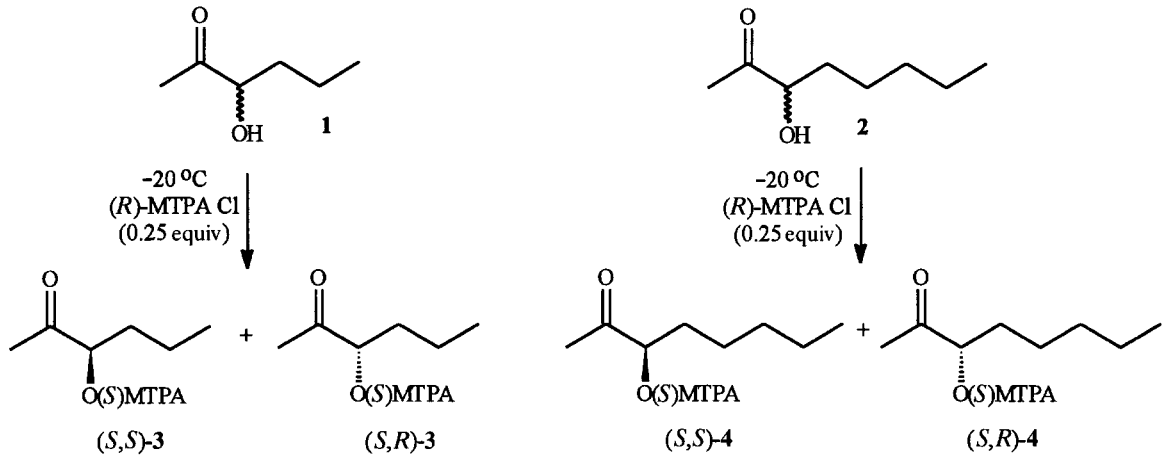
The third step in this process requires an analytical separation of the diastereomeric esters of defined stereochemistry by chromatographic means. The diastereomeric excess observed in the ester ^{1}H NMR spectrum should also be apparent from GC or HPLC analysis. Even a 5% diastereomeric excess should suffice to indicate which chromatographic peak corresponds to which configuration.

As a final step, the natural product itself is derivatized with the same chiral reagent [(*R*)-MTPA chloride] used to derivatize the racemic mixture. A direct chromatographic comparison of the resulting single (*S*)-MTPA ester with the mixture of stereochemically characterized reference compounds leads directly to a configurational assignment for the natural product itself.

We suggest the term *chiral amplification* for this procedure, since it relies on 'amplifying' the information gained simply from chromatography of a small amount (perhaps only a few nanograms) of a derivatized, optically active natural product. By coupling this information with that gained by a ^{1}H NMR spectrometric and chromatographic analysis of a much larger sample, derived from racemic, synthetic material, the absolute configuration of the original natural product can be inferred. It is important to note that this protocol can be carried out without having to perform either a complete resolution or an enantiospecific synthesis, without requiring either a large quantity or even a completely pure sample of the natural product, without a bioassay and without resorting to chiral chromatographic columns.

We applied this procedure for the first time to the case of two simple coleopteran pheromone components, whose structures and stereochemistry we have recently described.[5] The pheromone components are those emitted by males of the longhorn beetle species *Anaglyptus subfasciatus* (Coleoptera: Cerambycide), which we characterized as (*R*)-3-hydroxy-2-hexanone [(*R*)-**1**] and (*R*)-3-hydroxy-2-octanone [(*R*)-**2**], in a 7:1 ratio. The structures were confirmed by the synthesis of the racemic ketols, and the stereochemistry of these ketols was unambiguously established by stereospecific syntheses. However, we were able to assign both ketols the *R* configuration beforehand, using chiral amplification, as described below.

A diastereomeric mixture of (*S*)-MTPA esters, (*S*,*S*)-**3** and (*S*,*R*)-**3**, was prepared from a racemic sample of **1** by allowing (±)-**1** to react with 0.25 equivalent of (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride at −20 °C, producing a 1.1:1 ratio of products (determined by GC analysis) (Scheme 1). The greater diastereomeric excess (ca. 1.3:1) shown in Figures 2 and 4, obtained by column chromatography on silica gel, provided enhanced clarity of the subsequent ^{1}H NMR and GC analyses. The absolute configurations of the resulting (*S*)-MTPA esters were determined from their ^{1}H NMR spectra, based on the chemical shift differences predicted from the conformations shown in Figure 1. Consideration of these models suggested that



Scheme 1. Kinetically controlled acylations of racemic 3-hydroxy-2-hexanone (**1**) and 3-hydroxy-2-octanone (**2**).

(*S*,*S*)-**3** would show its terminal methyl triplet (δ 0.87) upfield relative to the corresponding triplet (δ 0.94) in (*S*,*R*)-**3**, while the singlet methyl resonance (δ 2.22) of the alcohol moiety in the (*S*,*S*)-**3** should be found downfield of the corresponding resonance (δ 2.12) in the (*S*,*R*)-**3** (Fig. 2). Based on these chemical shift differences, the enriched isomer was assigned the (*S*,*S*)-configuration, and the remaining isomer the (*S*,*R*)-configuration. This stereochemical information could then be related to the gas chromatograms of these esters, as shown in Figure 4, leading to the conclusion that the larger peak with the shorter GC retention time (18.85 min) must be the (*S*,*S*)-**3**, while the smaller, late-eluting peak (18.97 min) must be the (*S*,*R*)-**3**. Similarly, the other two (*S*)-MTPA esters, (*S*,*S*)-**4** and (*S*,*R*)-**4**, were prepared (Scheme 1) and identified as indicated in Figures 3 and 4. The enriched (*S*,*S*)-**4** showed a shorter retention time (20.82 min), while its partner (*S*,*R*)-**4** had a longer retention time (20.94 min). Derivatization of the insect pheromone extract containing natural 3-hydroxy-2-hexanone and 3-hydroxy-2-octanone with (*R*)-MTPA chloride gave the corresponding two (*S*)-MTPA esters. Since these (*S*)-MTPA esters correspond exactly in GC retention times to the synthetic (*S*,*R*)-**3** and (*S*,*R*)-**4**, the identification of the natural ketols as the (*R*)-**1** and (*R*)-**2** was complete. These assignments were then confirmed by enantioselective syntheses of both the (*R*)- and (*S*)-isomers of **1** and **2**, followed by comparison of their chromatographic properties with those of the natural products on a chiral GC column.[5]

To examine the possible generality of this particular version of chiral amplification, we have studied the

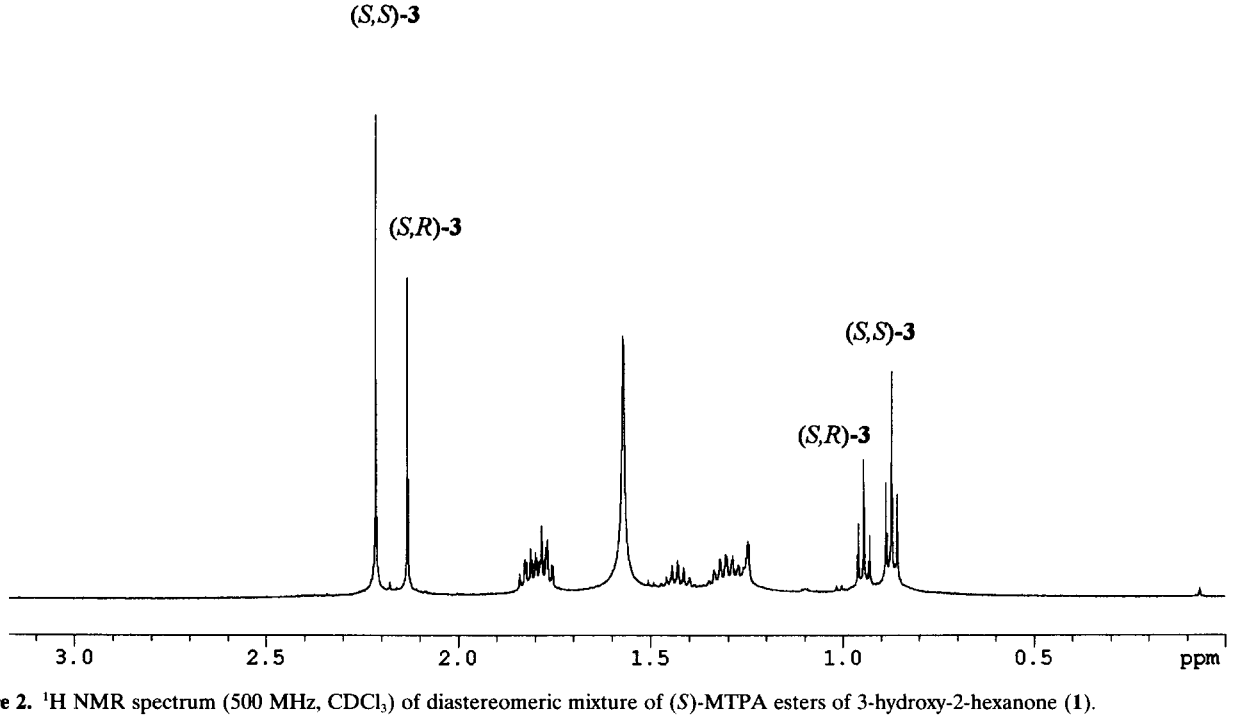


Figure 2. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of diastereomeric mixture of (*S*)-MTPA esters of 3-hydroxy-2-hexanone (**1**).

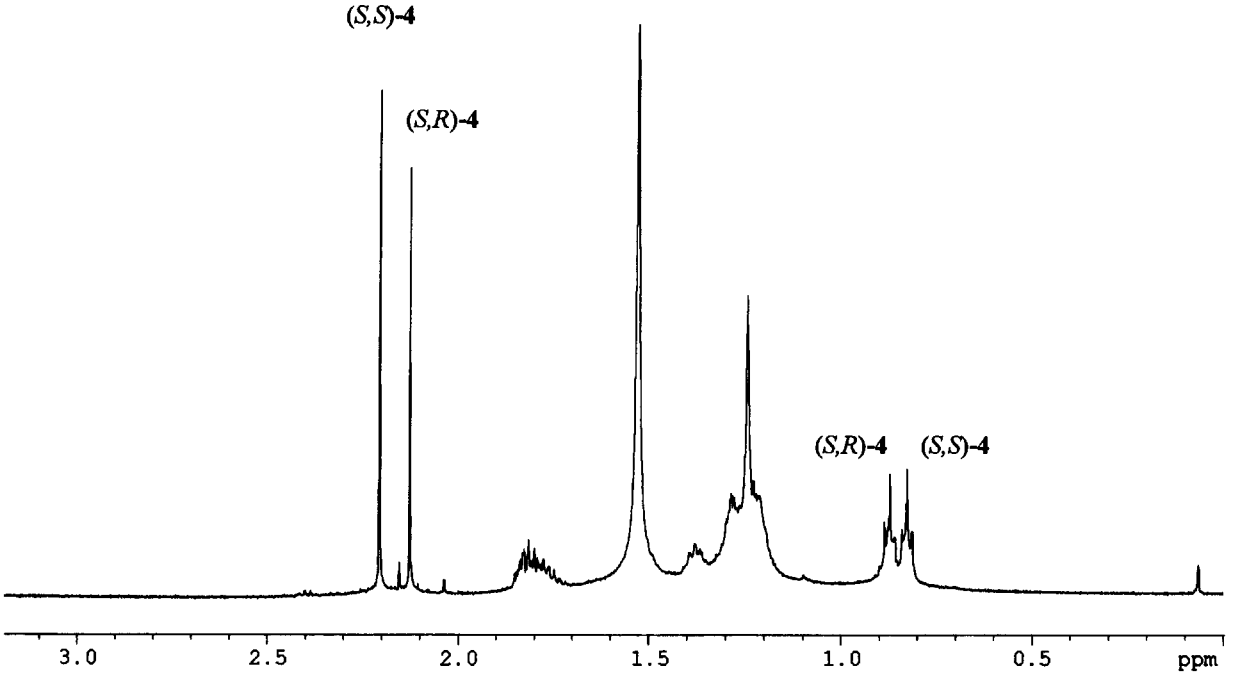


Figure 3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of diastereomeric mixture of (*S*)-MTPA esters of 3-hydroxy-2-hexanone (**2**).

behavior of a total of 14 racemic secondary alcohols. The GC retention times, the ratios of diastereomeric esters obtained directly under kinetic control and the selected ^{1}H NMR data used for configurational assignments are summarized in Table 1. In most cases the kinetically controlled derivatization of the racemic alcohols, under our 'standard' conditions [1.0 equiv of a racemic alcohol, 0.25 equiv of (*R*)-MTPA chloride, pyridine/CH_2Cl_2, −20 °C, 12 h] gave the desired esters with satisfactory diastereomeric excesses. In two cases (entries 6 and 7), the diastereomeric (*S*)-MTPA esters were not resolved under the unoptimized separation conditions used in this study. For cases such as these, it would be necessary to find better separation conditions (for example, by changing the temperature program or column) before the method could be used. Another difficulty is evident in two cases (entries 7 and 10) in which the diastereomeric (*S*)-MTPA esters were resolved chromatographically, but were found to be formed in equal amounts. This difficulty might be

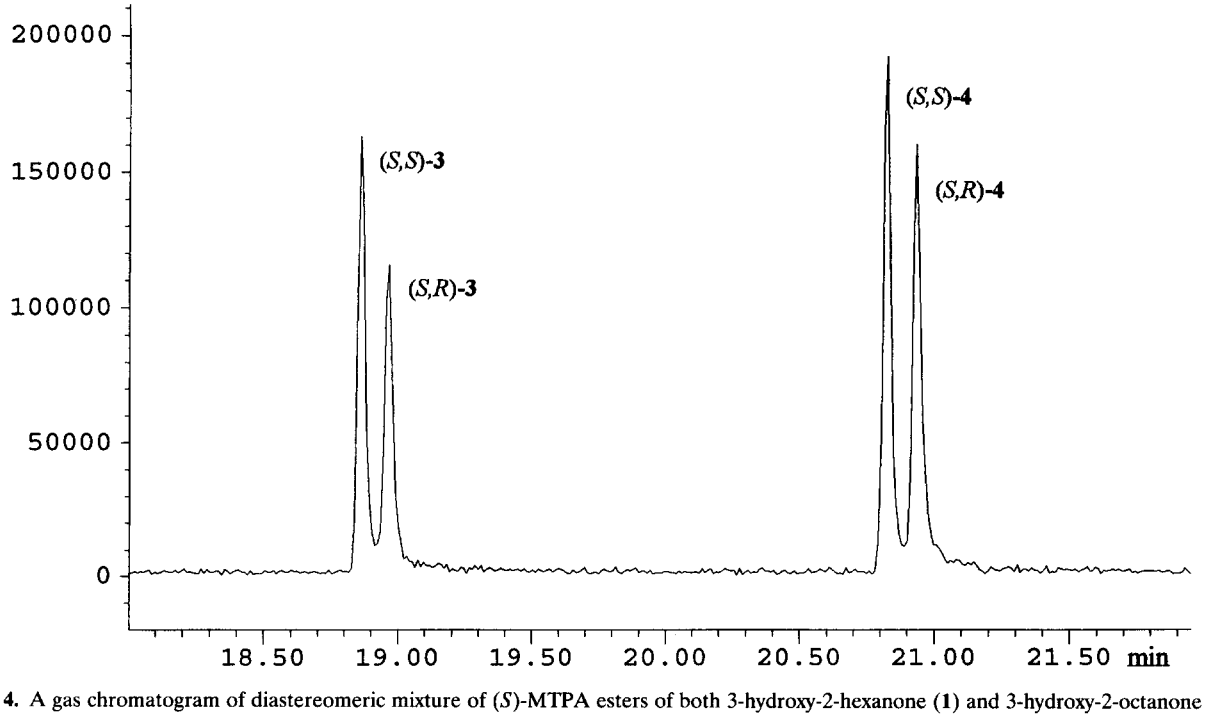
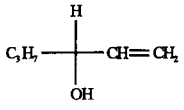
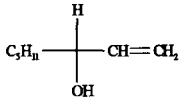
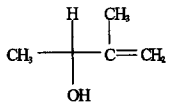
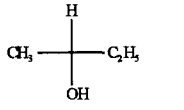
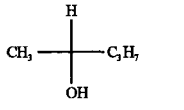
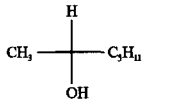
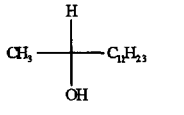
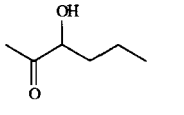
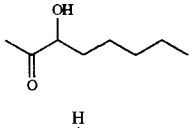
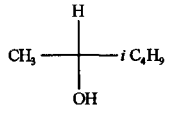
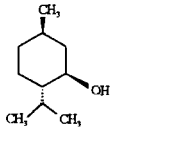
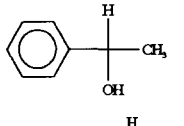
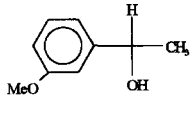
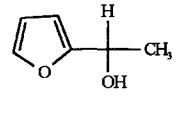


Figure 4. A gas chromatogram of diastereomeric mixture of (*S*)-MTPA esters of both 3-hydroxy-2-hexanone (**1**) and 3-hydroxy-2-octanone (**2**).

Table 1. Kinetically controlled acylation of racemic alcohols and related configurational assignments

No.	Racemic alcohol structures	^{1}H NMR data used for the identification of diastereomers of (*S*)-MTPA esters	(*S,S*)/(*S,R*)	Retention times (min)
1		(*S,S*): 5.82 (ddd, J=17.1, 10.5, 7.0 Hz, CH), 5.35 (ddd, J=17.1, 1.2, 1.3 Hz, CH), 5.23 (ddd, J=10.5, 1.2, 0.9 Hz, CH) (*S,R*): 5.72 (ddd, J=17.1, 10.5, 7.0 Hz, CH), 5.24 (ddd, J=17.1, 1.2, 1.3 Hz, CH), 5.18 (ddd, J=10.5, 1.2, 0.9 Hz, CH)	1.38/1	(*S,S*):16.63 (*S,S*):16.73
2		(*S,S*): 5.80 (ddd, J=14.1, 10.5, 7.0 Hz, CH), 5.34 (ddd, J=17.1, 1.2, 1.3 Hz, CH), 5.23 (ddd, J=10.5, 1.2, 0.9 Hz, CH) (*S,R*): 5.70 (ddd, J=14.1, 10.5, 7.0 Hz, CH), 5.24 (ddd, J=17.1, 1.2, 1.3 Hz, CH), 5.18 (ddd, J=10.5, 1.2, 0.9 Hz, CH)	1.51/1	(*S,S*):18.87 (*S,R*):18.95
3		(*S,S*): 5.25 (d, J=0.6 Hz, CH), 4.90 (dq, J=0.6, 0.6 Hz, CH), 1.73 (d, J=0.6 Hz, CH_3), 1.34 (d, J=6.5 Hz, CH_3). (*S,R*): 4.91 (d, J=0.6 Hz, CH), 4.85 (dq, J=0.6, 0.6 Hz, CH), 1.62 (d, J=0.6 Hz, CH_3), 1.41 (d, J=6.5 Hz, CH_3)	1.42/1	(*S,S*):15.82 (*S,R*):15.87
4		(*S,S*): 0.91 (t, J=7.6 Hz, CH_3), 1.23 (d, J=6.1 Hz, CH_3) (*S,R*): 0.81 (t, J=7.6 Hz, CH_3), 1.31 (d, J=6.1 Hz, CH_3)	1.67/1	(*S,S*):15.03 (*S,R*):15.06
5		(*S,S*): 0.90 (t, J=7.6 Hz, CH_3), 1.23 (d, J=6.1 Hz, CH_3) (*S,R*): 0.83 (t, J=7.6 Hz, CH_3), 1.31 (d, J=6.1 Hz, CH_3)	1.35/1	(*S,S*):16.09 (*S,R*):16.17
6		(*S,S*): 1.23 (d, J=6.1 Hz, CH_3) (*S,R*): 1.31 (d, J=6.1 Hz, CH_3)	1.07/1	(*S,S*):18.09 (*S,R*):18.09
7		(*S,S*): 1.24 (d, J=6.1 Hz, CH_3) (*S,R*): 1.31 (d, J=6.1 Hz, CH_3)	1.00/1	(*S,S*):24.15 (*S,R*):24.15
8		(*S,S*): 0.87 (t, J=7.3 Hz, CH_3), 2.22 (s, CH_3) (*R,S*): 0.94 (t, J=7.3 Hz, CH_3), 2.12 (s, CH_3)	1.10/1	(*S,S*):18.85 (*R,S*):18.97
9		(*S,S*): 0.83 (t, J=7.3 Hz, CH_3), 2.20 (s, CH_3) (*S,R*): 0.87 (t, J=7.3 Hz, CH_3), 2.12 (s, CH_3)	1.11/1	(*S,S*):20.82 (*S,R*):20.94
10		(*S,S*): 1.24 (d, J=6.1 Hz, CH_3), 0.89 (d, J= 6.5 Hz, CH_3), 0.82 (d, J=6.7 Hz, CH_3) (*S,R*): 1.32 (d, J= 6.1 Hz, CH_3), 0.87 (d, J=6.5 Hz, CH_3), 0.80 (d, J=6.7 Hz, CH_3)	1.00/1	16.41 16.50
11		(*S,R*): 0.65 (d, J=7.0 Hz, CH_3), 0.72 (d, J=7.0 Hz, CH_3), 0.91 (d, J=6.4 Hz, CH_3) (*S,S*): 0.75 (d, J=7.0 Hz, CH_3), 0.84 (d, J=7.0 Hz, CH_3), 0.89 (d, J=6.7 Hz, CH_3)	1.12/1	(*S,R*):20:89 (*S,R*):20.93
12		(*S,S*): 1.57 (d, J=6.7 Hz, CH_3) (*S,R*): 1.64 (d, J=6.7 Hz, CH_3)	1.44/1	(*S,S*):19.68 (*S,R*):19.76
13		(*S,S*): 1.57 (d, J=6.7 Hz, CH_3) (*S,R*): 1.64 (d, J=6.7 Hz, CH_3)	1.60/1	(*S,S*):21.88 (*S,R*):22.00
14		(*S,S*): 1.62 (d, J=6.7 Hz, CH_3) (*S,R*): 1.69 (d, J=6.7 Hz, CH_3)	1.21/1	(*S,S*):17.87 (*S,R*):17.95

overcome by using other chiral derivatizing reagents, such as *O*-methylmandelic acid chloride, which have been previously used for the determination of secondary alcohol stereochemistry.[6] Flash chromatography of a 1:1 mixture of two diastereomeric (*S*)-MTPA esters, as already described for the case of **3**, provides an alternative strategy for obtaining some fractions with a significant diastereomeric excess.

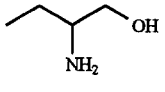
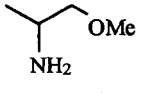
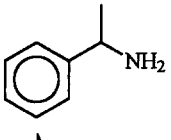
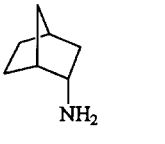
It may be worth noting in passing that for all alcohols studied, the *S*-enantiomers acylated at a rate faster than or equal to that of the *R*-isomers when (*R*)-MTPA chloride was used for derivatization, resulting in the $(S,S)/(S,R) \geq 1$. Another interesting observation for all but one of the alcohols studied (entry 11, Table 1) is that the (*S,S*)-MTPA esters had a retention time shorter than or equal to that of corresponding (*S,R*)-MTPA esters under the particular GC conditions used in the study. These correlations might be useful for a tentative indication of (*S*)-MTPA ester configurations when ^{1}H NMR data are not definitive.

To explore the possibility of extending this methodology to chiral amines, we investigated four amines with the results summarized in Table 2. Since amines acylate more quickly than alcohols under the same reaction conditions, the differential derivatization was not so successful as it had been in the case of alcohols. However, useful differences in amounts of two diastereomeric amides were achieved by flash column chromatography over silica gel. Subsequent ^{1}H NMR measurements and GC analyses of diastereomeric excess in these amides led to the assignment of their stereochemistry.[3]

There are, in fact, a number of variants of this overall procedure that may also prove useful. The alcohols and amines represented in Table 1 and 2 are relatively small, simple molecules. For larger molecules, the MTPA derivatives might not be volatile enough for GC analysis. In this case, replacement of GC by HPLC should be a useful option. Alternatively, the diastereomeric MTPA derivatives of known configurations could be hydrolyzed to the corresponding alcohols or amines. The diastereomeric excess (de) should then give rise to a corresponding enantiomeric excess (ee). A direct chromatographic comparison of the underivatized natural product with an unequal mixture of enantiomers of known configurations would then lead to an assignment of the absolute stereochemistry of the natural product using a chiral GC analysis. It is worth noting that it should not be necessary to have the racemate in the case of compounds with several chiral centers. A pair of epimeric diastereomers at an OH- or NH_2- bearing carbon should lead to the establishment of absolute stereochemistry at this particular center using chiral amplification, independent of the presence of other asymmetric centers. There are many instances in which a natural pheromone is not enantiomerically pure.[7] In this case, the chiral amplification method gives not only absolute configurations but also the ratio of the two enantiomers. In the case of a natural product which is available in sufficient quantities for ^{1}H NMR measurements, the synthetic racemate is no longer required. Complete acylation of the natural product with an unequal mixture of (*S*)-(+)- and (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chlorides should yield a corresponding mixture of (*R*) and (*S*)-MTPA derivatives with a diastereomeric excess identical to that of the enantiomeric excess of the acylating reagents. Analysis of the ^{1}H NMR spectrum of the mixture of diastereomeric derivatives would permit the assignment of absolute configuration to the natural product without having to resort to any chromatographic separation.

Based on these considerations, it is apparent that the chiral amplification methodology, although not univers-

Table 2. Kinetically controlled acylation of racemic amines and related configurational assignments

No.	Racemic amine structures	^{1}H NMR data used for the identification of diastereomers of (*S*)-MTPA amides	(*S,S*)/(*S,R*) (initial)	(*S,S*)/(*S,R*)[a]	Retention times (min)
1		(*S,R*): 0.95 (*t*, J=6.8 Hz, CH_3). (*S,S*): 0.83 (*t*, J=6.8 Hz, CH_3).	0.98/1	1.09/1	(*S,R*):26.23 (*S,S*):26.57
2		(*S,R*): 1.24 (d, J=6.8 Hz, CH_3), 3.05 (s, CH_3). (*S,S*): 1.18 (d, J=6.8 Hz, CH_3), 3.35 (s, CH_3).	0.96/1	1.50/1	(*S,R*):17.69 (*S,S*):17.79
3		(*S,R*): 1.54 (d, J=7.3 Hz, CH_3). (*S,S*): 1.51 (d, J=7.3 Hz, CH_3).	0.98/1	1.71/1	(*S,R*):21.50 (*S,S*):21.85
4		(*S,R*): 0.79 (ddd, J=16.1, 4.4, 2.9 Hz, CH**H**), 2.46 (br, CH). (*S,S*): 0.74 (ddd, J=16.1, 4.4, 2.9 Hz, CH**H**), 2.52 (br, CH).	1.05/1	1.63/1	(*S,R*):21.16 (*S,S*):21.35

[a]The reported ratios were obtained by collecting the later fractions from flash chromatographic separations over silica gel.

ally applicable, should prove useful at least for assigning absolute configurations to difficultly available, optically active natural secondary alcohols and amines.

Experimental

General analytical procedures

^{1}H NMR spectra were recorded on a Varian XL 400 instrument unless noted otherwise. Chemical shifts are reported in ppm relative to the residual $CHCl_3$ peak in solvent $CDCl_3$ at 7.26 ppm. GC analyses were performed on an HP 5890 gas chromatograph equipped with an FID detector and a Hewlett Packard 3396A integrator. The data in Tables 1 and 2 were obtained using a 30 m × 0.25 mm fused-silica column coated with DB-5 (oven temperature was held at 40 °C for 4 min, increased to 200 °C at a rate of 10 °C/min, and held at 200 °C for 20 min). Flash column chromatography was performed over silica gel (60 μm, EM Science, Gibbstown, New Jersey) with ether/hexane as eluent.

General synthetic procedure for (*S*)-MTPA esters

To a methylene chloride (300 μL) solution of an alcohol (40 μmol) was injected 10 μL of dry pyridine. After the solution was cooled to −20 °C, (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (10 μmol) was injected. After 12 h at −20 °C, the reaction mixture was quenched with water (100 μL) and extracted with ether (3 × 3 mL). The combined extract was dried over Na_2SO_4 and subjected to GC analysis on a DB-1 capillary column in order to obtain the ratios of diastereomeric esters. To isolate these esters the extract was concentrated and the residue was subjected to flash chromatography on a pipette column filled with silica gel using ether:hexane (1:20) as eluent. All fractions (0.5 mL/each) containing products were combined and concentrated to give the desired (*S*)-MTPA esters which were further used for ^{1}H NMR and GC analyses.

Preparation of (*S*)-MTPA esters of *Anaglyptus subfascitus* sex pheromone components

Male beetles were placed in a collection system as previously described.[8] The airborne volatiles containing sex pheromone components 3-hydroxy-2-hexanone (**1**) and 3-hydroxy-2-octanone (**2**) were trapped on Super Q (Alltech Associates) and extracted with hexane. The procedure used for the preparation of (*S*)-MTPA esters was identical to that described above, except that an excess amount of (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride and a catalytic amount of 4-dimethylaminopyridine were used.

General synthetic procedure for (*S*)-MTPA amides

The procedure was identical to that described above for the preparation of (*S*)-MTPA esters, except that a more polar eluent (ether:hexane/1:10 to 1:1) was used for chromatographic separation. Each fraction (0.5 mL) containing products was examined by GC analysis to determine the diastereomeric ratio of the two amides. The later fractions, enriched in the more-polar amide, were combined and subjected to ^{1}H NMR and GC analyses.

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