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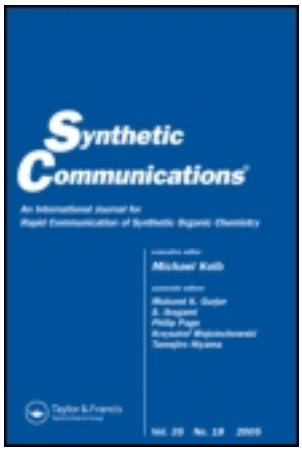

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SYNTHESIS OF THE FOUR POSSIBLE STEREOISOMERS OF N-2′-METHYLBUTYL-2-METHYLBUTYLAMIDE, THE SEX PHEROMONE OF THE LONGHORN BEETLE MIGDOLUS FRYANUS WESTWOOD

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SYNTHETIC COMMUNICATIONS, 31(23), 3685–3698 (2001)

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SYNTHESIS OF THE FOUR POSSIBLE STEREOISOMERS OF *N*-2′-METHYLBUTYL-2-METHYLBUTYLAMIDE, THE SEX PHEROMONE OF THE LONGHORN BEETLE *MIGDOLUS FRYANUS* WESTWOOD

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ABSTRACT

The four stereoisomers of *N*-2′-methylbutyl-2-methylbutylamide, the sex pheromone of the longhorn beetle *Migdolus fryanus*, an economically important pest of sugarcane in South America, were synthesized. The key intermediate

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2-methylbutan-1-ol is commercially available only in its (*S*)-(−)-form. The (*R*)-(+)-enantiomer was obtained optically pure from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate in five steps.

The longhorn beetle *Migdolus fryanus* is an economically important pest of sugarcane in South America. The major problem in control of this pest by use of traditional pesticides is that the insect spends most of its lifetime in the subsoil.[1] In this context, the use of pheromones, an environmentally friendly control, has a potential application. Della Lucia and co-workers[2] have described that males of the sugarcane borer are attracted to females by means of a sex pheromone. In São Paulo State, Brazil, mating usually occurs during a few days between October and March. Based on these results, Leal and co-workers[3] have isolated and identified the female sex pheromone from volatile extracts of the insect.

Although two female-specific compounds, namely, *N*-2′-methylbutyl-2-methylbutylamide (**1**) and *N*-formyl L-isoleucine methyl ester, were identified, field tests with synthetic chemicals revealed that only the amide was active and that the amino acid derivative neither increased or decreased trap catches by the amide. This is the first known long-range female-released sex pheromone for the family Cerambycidae and the first identification of an amide as a sex pheromone.

In order to establish the correct structure of the natural pheromone, several amides were synthesized by the reaction of appropriate commercially available anhydrides or acid chlorides with amines. Those compounds were compared with the natural product by gas chromatography-mass spectroscopy (GC-MS) and chiral gas chromatography.[3] Partial separation of the stereoisomers was achieved on a CP-Cyclodextrin column. Separation of the diastereoisomers (2′*S*,2*S*)-**1** and (2′*S*,2*R*)-**1** was almost baseline, however, there was no resolution of the diastereoisomers (2′*S*,2*S*)-**1** and (2′*R*,2*S*)-**1**, probably because the stereocenter is separated from the functional group (N) by a methylene group. The natural product gave a single peak, which had the same retention time and co-eluted with the diastereoisomeric mixture (2′*S*,2*R*/*S*)-**1**. Based on biosynthesis reasoning, the absolute configuration of the natural product has been suggested by Leal as *N*-(2′*S*)-methylbutyl-(2*S*)-methylabutylamide (**1**), although the stereochemistry at C-2 remains to be analytically determined.

Thus, the synthesis of all of the four possible stereoisomers of *N*-2′-methylbutyl-2-methylbutylamide (**1**) is necessary to establish the absolute configuration of the naturally occurring pheromone and also to clarify the relationship between absolute configuration and the bioactivity of the chiral pheromone.[4]

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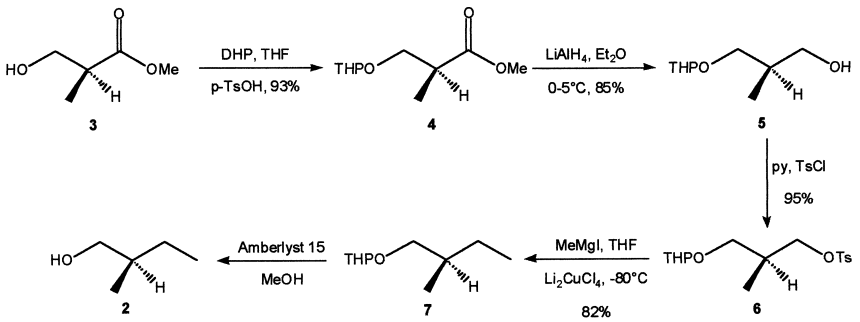
The synthetic pathway to prepare the four stereoisomers of amide (**1**) is based on a common intermediate, the 2-methylbutan-1-ol (**2**), which is commercially available only in its (*S*)-(−)-form. Few procedures are described in the literature for the preparation of the chiral synthon (*R*)-(+)-2-methylbutan-1-ol, which can be used in the synthesis of a series of chiral methyl-branched pheromones.[5] Bestmann et al.[6] have performed the separation of diastereomeric phenylglycinolamides of 2-methylbutyric acid by MPLC obtaining the pure enantiomers of the acid, which were then reduced by $LiALH_4$ to the corresponding alcohols (*R*)- and (*S*)-**2**. Geresh et al.[5] have prepared (*R*)-**2** in 82% enantiomeric excess (e.e.) by a chemoenzymatic synthesis, in which the key step is a reduction catalyzed by baker's yeast. Guoqiang et al.[7] have synthesized the (*R*)-2-methylbutyric acid in 84% e.e. *via* asymmetric alkylation of a prolinol amide derivative.

In this study, enantiomeric pure (*R*)-2-methylbutan-1-ol was prepared from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate using the methodology developed by Mori (Scheme 1).[8] Protection of the hydroxyl group of **3** with dihydropyran furnished the tetrahydropyran (THP) derivative **4**, in 93% yield, which was reduced by $LiAlH_4$ in 85% yield. Alcohol **5** was converted into its corresponding tosylate **6**, in 95% yield, which was then coupled with Li_2CuCl_4 as catalyst[9] to a methyl magnesium iodide affording **7** in 82% yield. When we tried to carry out this coupling in a large scale (up to 24 mmol), by-products from nucleophilic substitution and elimination reactions were observed. This problem was solved by dilution and controlling very carefully the reaction temperature at −80°C. Removal of the protective group from **7** was performed either by use *p*-TsOH or Amberlyst® 15 in methanol as catalysts.[10] However, due to its high volatility, alcohol (*R*)-**2** was always obtained with traces of methanol, preventing the evaluation of its enantiomeric purity by measuring its specific rotation.



Scheme 1.

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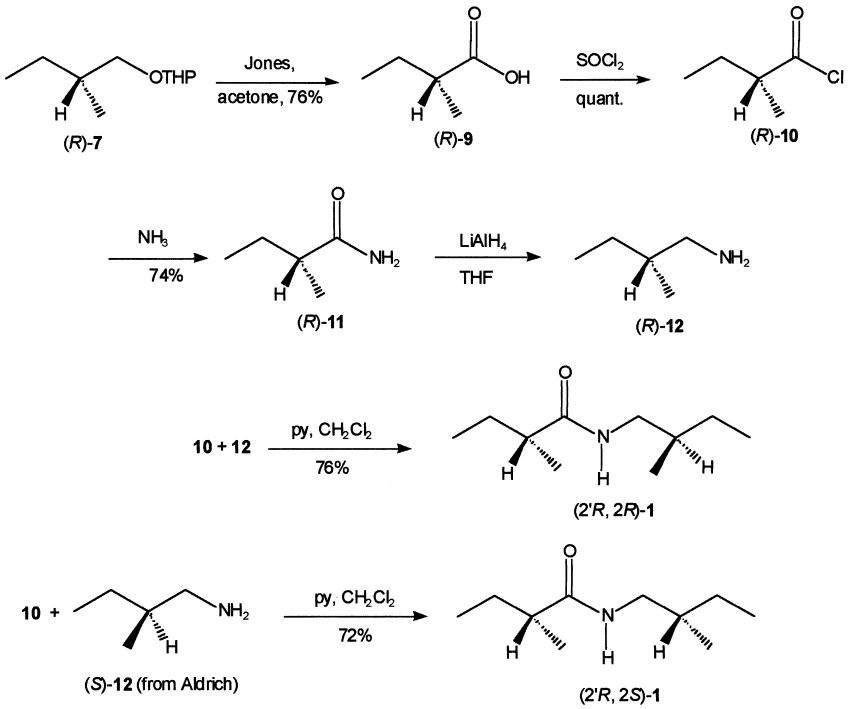
The enantiomeric excess of the synthetic alcohol (*R*)-**2** was measured by ^{1}H-NMR spectroscopy analysis of its corresponding (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic ester (**8**)[11] in comparison with the esters prepared from the racemic- and commercial (*S*)-**2**. While Mosher ester (2′*R*/*S*,2*R*)-**8** showed a multiplet between 4.04 and 4.30 ppm corresponding to the hydrogens at C-2′, (2′*S*,2*R*)-**8** showed a doublet at 4.16 ppm and (2′*R*,2*R*)-**8** two double doublets at 4.09 and 4.24 ppm respectively.

Having prepared (*R*)-2-methylbutan-1-ol (**2**) in high enantiomeric excess (>99%), the synthesis of the four stereoisomers of *N*-2′-methylbutyl-2-methylbutylamide (**1**) could then be carried out. Our synthetic strategy is described in Schemes 2 and 3.

Acid (*R*)-**9** was then prepared directly from (*R*)-**7** by Jones oxidation in 76% yield. The enantiomeric purity (>99% ee) was determined by reducing acid (*R*)-**9** with BH_3.DMS to afford (*R*)-**2**, which was then converted into the corresponding MTPA ester (2′*R*,2*R*)-**8** and analyzed by ^{1}H-NMR spectroscopy. (*R*)-**9** was converted into their corresponding acyl chloride **10** with



Scheme 2.

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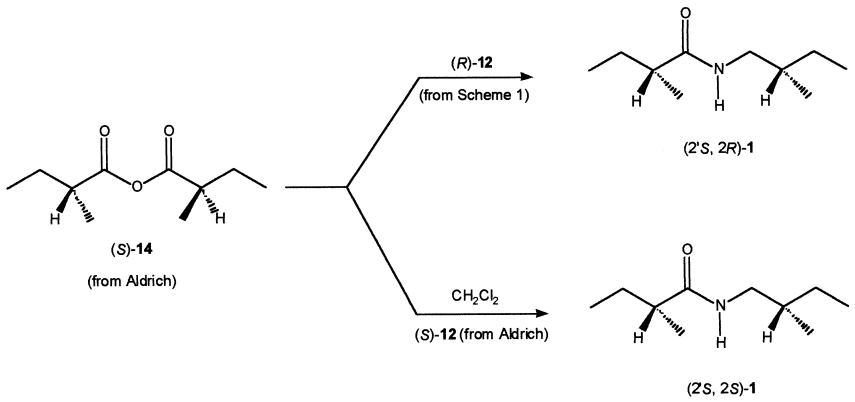

Scheme 3.

thionyl chloride in quantitative yield. Treatment of **10** with ammonium hydroxide (28% NH_3 in water) afforded amide **11** in 74% yield. Compound **11** was reduced using $LiAlH_4$ in THF yielding the amine **12**, which was not isolated due to its high volatility. Finally, a solution of amine **12** in THF was added to a solution of acyl chloride **10** and pyridine in methylene chloride to afford amide **1** in 72–76% yield over two steps (Scheme 2).

The enantiomeric purity of amine **12** was investigated by ^{1}H- and ^{19}F-NMR analysis of their corresponding MTPA amides **13**. Although separation of the signal corresponding to the α-nitrogen methylene in the ^{1}H-NMR was not baseline, it was possible to estimate an enantiomeric excess of at least 65% for amine **12**. No separation was observed for the CF_3 group in the ^{19}F-NMR spectrum. Attempts to analyze these MTPA amides by chiral GC and chiral HPLC also failed. According to this result, an epimerization has occurred during the preparation of amine **12**, probably under the reaction conditions used for the formation of amide **11** from acyl chloride **10**. Further studies in order to determine how the epimerization process occurs are in progress.

The stereoisomers (2′*S*, 2*S*)-**1** and (2′*S*, 2*R*)-**1** were obtained from (*S*)-(+)-2-methylbutyric anhydride (**14**) (98% ee, commercial available from Aldrich) and (*S*)- and (*R*)-**12** respectively, in dichloromethane (Scheme 3).

In order to verify the enantiomeric purity of the final product the four stereoisomers of amide **1** were analyzed by GC using several chiral columns, however, no resolution was obtained. Four different chiral polysaccharide phases in HPLC were also investigated without success.

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The optical rotation obtained for (2′*S*,2*S*)-**1** was $[\alpha]_D^{20} = +27.83$ ($c = 3.18$, diethyl ether) and we assumed that its enantiomeric excess is $>99.5\%$ because it was synthesized from commercial available reagents (*S*)-**12** and (*S*)-**13**. By analogy, the ee of amide (2′*R*,2*R*)-**1** would be $>80\%$.

In conclusion, a simple synthetic route for all four possible stereoisomers of *N*-2′-methylbutyl-2-methylbutylamide (**1**), the sex pheromone of the longhorn beetle *Migdolus fryanus*, has been achieved using as key intermediate the 2-methylbutan-1-ol (**2**). While the chiral synthon (*S*)-**2** is commercially available, the (*R*)-enantiomer was obtained with high e.e ($>99\%$) from the commercial available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**3**). Since no chiroptical data of the natural pheromone are available, we have to rely on the careful comparison of pheromone activity of the four stereoisomers of **1** in order to deduce the absolute configuration of the natural product. The biological study is in progress and will be published elsewhere in due course.

EXPERIMENTAL

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co. Reagents and solvents were purified when necessary according to the usual procedures described in the literature. The IR spectra refer to films and were measured on a Bomen M102 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-200 (200 and 50 MHz respectively) and ARX-400 (400 and 100 MHz respectively). ^{19}F-NMR spectra were recorded on a Brucker ARX-400 (376.5 MHz). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Mass Spectra were recorded on a Shimadzu GCMS-QP5000. Analytical thin-layer chromatography was performed on a 0.25 μm film of silica gel containing fluorescent indicator UV_{254} supported on an aluminum sheet (Sigma–Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh, E. Merck). Gas chromatography was performed in a Shimadzu GC-17A with H_2 as carrier and using a DB-5 column. Elemental analyses were performed on a Fisons EA 1108 CHNS-O.

Methyl (*S*)-(+)-3-(tetrahydro-2-pyranyloxy)-2-methylpropionate (4)

In a 250 mL flask equipped with a magnetic stir bar and rubber septum was added methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**3**) (Aldrich, 99%

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ee/GLC) (14.0 mL; 127 mmol) in dry diethyl ether (127 mL), followed by dihydropyran (DHP) (13.88 mL; 152.4 mmol) and *p*-toluenesulfonic acid (0.25 g; 12.7 mmol). The reaction mixture was stirred for 12 h at RT and then washed with saturated $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by distillation (75°C at 0.5 mmHg) to give 23.8 g (93% yield) of the desired ester **4** as a colorless oil: purity > 98%. $[\alpha]_D^{25}$:+16.3 ($c = 3.9$, diethyl ether). IR (ν_{max}, film cm^{-1}): 2944, 2874, 1741, 1457, 1439, 1354, 1201, 1125, 1075, 1034, 969, 903, 870, 815. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [1.18 (d, J = 2.74 Hz) and 1.20 (d, J = 2.74 Hz), 3H]; 1.48–1.82 (m, 6H); 2.78 (sext, J = 6.9 Hz, 1H); 3.41–3.61 (m, 2H); [3.69 (s) and 3.70 (s), 3H]; 3.74–3.93 (m, 2H); [4.59 (t, J = 3.36 Hz) and 4.62 (t, J = 3.36 Hz], 1H]. ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.83; (18.94 and 19.16); 25.27; (30.32 and 30.43); (39.86 and 40.03); 51.44; (61.59 and 62.69); (68.85 and 69.18); (98.26 and 98.85); (175.10 and 175.17). MS (rel intensity) *m*/*z* 50 (1.8); 51 (2.0); 53 (6.0); 54 (6.9); 55 (47.7); 56 (41.5); 57 (38.5); 58 (4.2); 59 (60.1); 60 (2.1); 61 (1.7); 67 (17.3); 68 (1.8); 69 (29.2); 70 (1.9); 71 (1.8); 73 (10.6); 74 (1.5); 83 (6.8); 84 (18.4); 85 (100); 86 (7.0); 87 (8.7); 88 (10.0); 100 (4.5); 101 (60.3); 102 (5.1); 115 (14.4); 129 (3.2); 147 (1.3). Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.32; H, 9.06.

(*R*)-(+)-2-Methyl-3-(tetrahydro-2-pyranyloxy)-propan-1-ol (5) (as a diastereomeric mixture)

To a stirred solution of $LiAlH_4$ (3.29 g; 86.4 mmol) in diethyl ether (220 mL) was added a solution of ester **4** (21.94 g; 108 mmol) in diethyl ether (110 mL) at 0–5°C. After stirring for 12 h at rt, the mixture was cooled and water (3.3 mL) was added followed by 15% aqueous NaOH (3.3 mL) and water (9.9 mL). The resulting mixture was filtered through celite using diethyl ether (150 mL) as eluent. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Distillation afforded (bp = 98°C, 0.5 mmHg) 15.94 g (85% yield) of the alcohol **5** as a colorless oil: purity > 99%. $[\alpha]_D$:+1.2 ($c = 1.471$, diethyl ether). IR (ν_{max}, film cm^{-1}): 3441; 2942; 1455; 1353; 1201; 1122; 1030; 975. ^{1}H-NMR (400 MHz, $CDCl_3$); δ [0.91 (d, J = 3.85 Hz) and 0.93 (d, J = 3.85 Hz), 3H]; 1.51–2.03 (m, 7H); 3.26 (bs, 1H); [3.34 (dd, J = 6.9, 9.52 Hz) and 3.42 (dd, J = 6.9, 9.52 Hz), 1H]; 3.48–3.59 (m, 3H); [3.67 (dd, J = 6.9, 9.52 Hz) and 3.77 (dd, J = 6.9, 9.52 Hz), 1H]; 3.87 (oct, J = 3.85, 1H); 4.58 (t, J = 4.32 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (13.36 and 13.48); 19.36; 25.09; 30.33; (35.33 and 35.56); 62.20; (66.16 and 66.22); 71.17; (98.82 and 98.02). MS (rel intensity) *m*/*z* 50 (2.9); 51 (3.3); 53 (8.2); 54 (11.1); 55 (98.7); 56 (67.5); 57 (42.2); 58 (2.9); 59 (2.9);

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67 (15.8); 68 (1.4); 69 (3.4); 70 (1.5); 71 (3.0); 72 (7.9); 73 (17.0); 74 (3.2); 77 (1.7); 83 (7.8); 84 (24.2); 85 (100); 86 (5.6); 101 (26.6); 102 (1.8); 103 (1.5); 115 (1.5); 144.2 (0.8). Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.03; H, 10.52.

(*R*)-(+)-2-Methyl-3-(tetrahydro-2-pyranyloxy)-propyl-*p*-toluenesulfonate (6) (as a diastereomeric mixture)

A solution of **5** (15.0 g; 86.21 mmol) in anhydrous pyridine (110 mL) was cooled to 0–5°C and then *p*-toluenesulfonyl chloride (21.87 g; 115 mmol) wad added. The mixture was maintained at this temperature for 12 h. The reaction was quenched with ice-water (30mL) and the aqueous layer was extracted with ether (3 × 20 mL). The combined ether extracts were washed with 10% aqueous $CuSO_4$ (3 × 10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL), then dried over anhydrous Na_2SO_4. Solvent removal followed by Baeckström's chromatography, using a gradient of hexane and ethyl acetate as eluent, yielded 26 g of **6** (92%), as a colorless oil: purity >99%. $[\alpha]_D$:+6.8 ($c = 7.01$, diethyl ether). IR (ν_{max}, film cm^{-1}): 2942; 1602; 1364; 1182; 1037; 971; 817, 733. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [0.93 (d, J = 1.98 Hz) and 0.94 (d, J = 1.98 Hz), 3H]; 1.44–1.62 (m, 6H); [1.71–1.73 (m) and 2.05–2.11 (m), 1H]; 2.44 (s, 3H); 3.22 (ddd, J = 4.9, 9.7, 27.5 Hz, 1H), 3.43–3.48 (m, 1H), 3.60 (ddd, J = 5.2, 9.7, 20.3 Hz, 1H); 3.70–3.75 (m, 1H); [3.94 (dd, J = 5.9, 9.3 Hz) and 4.06 (dd, J = 5.9, 9.3 Hz), 1H); 4.01 (m, 1H]; [4.44 (t, J = 3.7) and 4.47 (t, J = 3.7 Hz), 1H]; 7.34 (d, J = 8.1 Hz, 2H); 7.79 (d, J = 8.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ (13.49 and 13.57); (19.19 and 19.32); 21.50, 25.31; (30.36 and 30.60); (33.43 and 33.57); 35.46; (61.89 and 62.09); 63.54; (67.92 and 68.35); (72.14 and 72.17); (98.54 and 98.05), 127.81; 129.75; 133.21; 144.61. MS (rel intensity) *m*/*z* 50 (5.2); 51 (7.1); 52 (2.5); 53 (10.9); 54 (15.6); 55 (100); 56 (34.6); 57.1 (30.2); 58.2 (2.0); 59 (1.5); 63 (3.2); 65 (13.9); 67 (10.1); 69 (7.5); 71 (7.3); 72 (10.4); 73 (4.2); 77 (2.0); 83 (12.7); 84 (32.6); 85 (56.6); 86 (3.2); 89 (3.2); 91 (33.2); 92 (6.1); 101.2 (27.6); 107.1 (2.3); 108 (2.3); 155 (17.0); 156 (4.9); 172 (4.5); 173 (14.5); 227 (1.4). Anal. Calcd. for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.37; S, 9.76. Found: C, 58.56; H, 7.61; S, 9.68.

(*R*)-(−)-2-Methyl-1-(tetrahydro-2-pyranyloxy)-butan-1-ol (7) (as a diastereomeric mixture)

To a mixture of magnesium turnings (1.46 g; 61.0 mmol) in anhydrous diethyl ether (64 mL) was added methyl iodide (3.8 mL; 61.0 mmol). After

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disappearance of the metal, this solution was transferred *via* a cannula to a solution containing tosylate **6** (4.00 g; 12 mmol) in anhydrous THF (120 mL) at −80°C under nitrogen. Then a 0.10 M solution of lithium tetrachlorocuprate in THF (2.29 mL) was added. The mixture was allowed to warm to room temperature and stirred for 12 h and then it was washed with saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with ether (3 × 20 mL), then the combined organic layers were washed with H_2O (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography, using a gradient from 0 to 40% v/v of ethyl acetate in hexane, to give 1.72 g (82% yield) of the desired product **7** as a colorless oil: purity > 99%. $[\alpha]_D$: −3.04 ($c = 2.07$, ethyl ether). IR (ν_{max}, film cm^{-1}): 2951; 2874; 1461; 1376; 1351; 1129; 1031. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [0.90 (t, J = 6.8 Hz) and 0.92 (d, 6.6 Hz), 3H]; 1.14 (oct, J = 7.35 Hz, 1H), 1.42–1.83 (m, 8H); [3.15 (dd, J = 6.0, 9.4 Hz) and 3.24 (dd, J = 6.0, 9.4 Hz), 1H]; 3.60 (dd, J = 6.4, 9.4 Hz, 1H); 3.47–3.53 (m, 1H); 3.86 (ddd, J = 3.6, 7.6, 11.2 Hz, 1H], 4.56 (t, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (11.27 and 11.34); (16.53 and 16.67); (19.51 and 19.55); 25.49; (26.23 and 26.29); 30.68; 34.97; (62.05 and 62.12); (72.70 and 72.81); (98.77 and 98.97). MS (rel intensity) *m*/*z* 50 (1.3); 51 (1.8); 53 (5.1); 54 (15.6); 55 (35.3); 56 (55.9); 57 (28.4); 58 (2.3); 59 (1.0); 67 (12.8); 69 (1.7); 70 (11.4); 71 (30.7); 72 (1.7); 74 (1.9); 83 (2.7); 84 (7.4); 85 (100); 86 (5.9); 101 (8.8); 114 (1.2); 115 (10.2); 142 (0.9). Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.69; H, 11.76.

(*R*)-(+)-2-Methylbutan-1-ol (2)

Amberlyst® 15 (0.697 g) was added to a solution of **7** (4 g; 23.25 mmol) in methanol (46.5 mL). The mixture was stirred at 45°C for 40 min, then the resin was filtered and the solution was concentrated by fractionated distillation at 1 atm. GC analysis of the crude product showed 100% conversion to the desired alcohol (*R*)-**2** which contained traces of methanol. The IR and NMR spectra were identical with those of commercial (*S*)-**2**.

General Procedure for the Preparation of the Mosher Esters 8

To a solution of 2-methylbutan-1-ol (0.0035 g, 0.040 mmol) in anhydrous CH_2Cl_2 (300 μL) were added anhydrous pyridine (10 μL) and (*S*)-(+)-MTPA chloride (0.0025 g, 0.010 mmol) at −20°C. After stirring

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for 4 h, the reaction was quenched with water (2 mL) and extracted with ethyl ether (3 × 3 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product **8** was obtained (0.0028 g, 92% yield) after purification by flash column chromatography.

(2′*R*/*S*)-2′-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(2′*R*/S,2*R*)-8]: colorless oil: purity >97%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.85–0.93 (m, 6H); 1.20–1.39 (m, 2H); 1.76 (oct, J = 6.7 Hz, 1H); 3.55 (s, 3H); {[4.09 (dd, J = 6.1, 10.7 Hz) and 4.24 (dd, J = 6.1, 10.7 Hz)] and 4.16 (d, J = 6.1 Hz), 2H}; 7.38–7.53 (m, 5H). ^{19}F-NMR (376.5 MHz, $CDCl_3$), δ −72.42 (s); −72.02 (s).

(2′*S*)-2′-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(2′*S*,2*R*)-8]: colorless oil: purity >96%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 3H); 0.91 (d, J = 6.7 Hz, 3H); 1.13–1.25 (m, 1H); 1.34–1.44 (m, 1H); 1.78 (oct, J = 6.7 Hz , 1H); 3.55 (s, 3H); 4.16 (d, J = 6.1 Hz, 2H); 7.38–7.53 (m, 5H). ^{19}F-NMR (376.5 MHz, $CDCl_3$), δ −72.42 (s).

(2′*R*)-2′-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(2′*R*,2*R*)-8]: colorless oil: purity >96%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 3H); 0.91 (d, J = 6.7 Hz, 3H); 1.14–1.26 (m, 1H); 1.33–1.46 (m, 1H); 1.78 (oct, J = 6.7 Hz, 1H); 3.55 (s, 3H); 4.09 (d, J = 6.1 Hz, 1H); 4.24 (dd, J = 6.1, 10.7 Hz, 1H); 7.38–7.53 (m, 5H). ^{19}F-NMR (376.5 MHz, $CDCl_3$), δ −72.02 (s).

(*R*)-(−)-2-Methylbutyric acid [(*R*)-9]

To a solution of CrO_3 (2.80 g; 0.028 mol) in water (4 mL), sulfuric acid (2.44 mL) was added dropwise at 0°C. Acetone (75 mL) was then added, followed by a dropwise addition of **7** (6.88 g; 0.04 mol). The mixture was stirred for 1h then a saturated solution of sodium bisulfide was added until the solution became green. The solvent was then evaporated under vacuum and the crude product was extracted with ethyl ether (4 × 20 mL). The combined organic layers was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The desired acid (*R*)-**9** was obtained in 75% yield (3.06 g) without further purification. IR (ν_{max}, film cm^{-1}): 3445; 2983; 1710; 1462; 1262, 1253, 942. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.95 (t, J = 7.60 Hz, 3H); 1.17(d, J = 7.20 Hz, 3H); 1.50 (dquint, J = 15.20, 7.20 Hz, 1H); 1.69 (dquint, J = 15.20, 7.20 Hz, 1H); 2.39 (sext, J = 7.20 Hz, 1H); 11.05 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ 11.57, 16.68, 26.59, 41.01, 183.64.

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(*R*)-2-Methylbutyryl chloride (10)

In a flask adapted with a condenser containing **9** (1 g; 9.8 mmoles) was added $SOCl_2$ (1.73 mL; 14.7 mmoles). The resulting mixture was stirred under reflux for 4 h, then benzene (10 mL) was added. The solvent was distilled at 60°C, followed by the desired acyl chloride **10** (1.67 g), at 80°C, as a colorless oil: purity >99%. IR (ν_{max}, film) cm^{-1}: 2967; 2361; 1793; 1460; 919.

(*R*)-2-Methylbutylamide (11)

To a 28% solution of ammonium hydroxide (0.25 mL) was added **10** (0.10 g, 0.83 mmol) dropwise at 0–5°C. A white solid appeared instantaneously. The mixture was diluted in ethyl acetate (10 mL) and water (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The desired amide **11** was obtained in 74% yield (0.062 g) without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.94 (t, J = 7.40 Hz, 3H); 1.18 (d, J = 7.00 Hz, 3H); 1.36–1.83 (m, 2H); 2.19 (sext, J = 7.20 Hz, 1H); 5.60 (bs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ 11.67, 17.27, 27.13, 42.30, 179.63.

(*R*)-(+)-2-Methylbutylamine (12)

To a stirred solution of $LiAlH_4$ (0.023 g; 0.60 mmol) in anhydrous THF (5 mL) was added a solution of amide **11** (0.051 g; 0.51 mmol) in THF (0.5 mL) at 0–5°C. After stirring for 6h at rt, the mixture was cooled and water (0.02 mL) was added followed by 10% aqueous NaOH (0.02 mL) and water (0.069 mL) again. The resulting mixture was filtered through celite with THF (3 mL) as eluent. The solution containing amine **12** was employed in the next step without concentration or purification. Colorless oil: purity >98%. IR (ν_{max}, film) cm^{-1}: 3423; 2920; 2363; 1958; 1598; 1463; 886. ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 0.87 (t, J = 6.8 Hz, 3H); 0.88(d, J = 7.6 Hz, 3H); 1.07–1.19 (m, 2H); 1.27 (5, 2H); 1.30–1.45 (m, 2H); (2.47 (dd, J = 12.8, 6.8 Hz) and 2.61 (dd, J = 12.8, 5.6 Hz), 1H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 11.24, 16.87, 25.52, 37.88; 47.97.

General Procedure for the Preparation of the Mosher Amides 13

To a solution of 2-methylbutylamine **12** (0.0035 g, 0.040 mmol) in anhydrous CH_2Cl_2 (300 μL) anhydrous pyridine (10 μL) and (*S*)-(+)-MTPA chloride (0.0025 g, 0.010 mmol) at −20°C were added. After stirring

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for 4 h, the reaction was quenched with water (2 mL) and extracted with ethyl ether (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product **13** was obtained (0.0028 g, 92% yield) after purification by flash column chromatography.

***N*-(2′*R*/*S*)-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetamide [(2′*R*/*S*,2*R*)-13]:** colorless oil: purity >97%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.9 (t, J = 7.4 Hz, 3H); 0.89 (d, J = 7.7 Hz, 3H); 1.10–1.46 (m, 2H); 1.60 (oct, J = 6.2 Hz, 1H); (3.11 (ddd, J = 6.10, 7.23, 13.35 Hz, 1H); 3.31 (ddd, J = 6.10, 7.23, 13.35 Hz, 1H)); 3.23 (ddd, J = 5.9, 7.0, 12.8 Hz, 2H); 3.42 (s, 3H); 6.82 (bs, 1H); 7.40 (t, J = 3.8 Hz, 3H); 7.52 (t, J = 3.9 Hz, 2H).

***N*-(2′*S*)-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetamide [(2′*S*,2*R*)-13]:** colorless oil: purity >98%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.9 (t, J = 7.4 Hz, 3H); 0.89 (d, J = 7.7 Hz, 3H); 1.10–1.42 (m, 2H); 1.63 (oct, J = 6.2 Hz, 1H); 3.11 (ddd, J = 6.10, 7.23, 13.35 Hz, 1H); 3.31 (ddd, J = 6.10, 7.23, 13.35 Hz, 1H), 3.42 (s, 3H); 6.82 (bs, 1H); 7.40 (t, J = 3.8 Hz, 3H); 7.52 (t, J = 3.9 Hz, 2H).

***N*-(2′*R*)-Methylbutyl (2*R*)-α-methoxy-α-(trifluoromethyl)phenylacetamide [(2′*R*,2*R*)-13]:** colorless oil: purity >97%. ^{1}H-NMR (400 MHz, $CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 3H); 0.91 (d, J = 6.7 Hz, 3H); 1.15–1.39 (m, 2H); 1.78 (oct, J = 6.7 Hz, 1H); 3.23 (ddd, J = 5.9, 7.0, 12.8 Hz, 2H); 3.42 (s, 3H); 7.40 (t, J = 3.8 Hz, 3H); 7.52 (t, J = 3.9 Hz, 2H).

General Procedure for the Preparation of the Amides (2′*S*,2*S*) and (2′*S*,2*R*)-1

To a solution of CH_2Cl_2 (0.5 mL) and (*S*)-(+)-2-methylbutyric anhydride (**14**) (98% ee from Aldrich) (0.10 mL, 0.5 mmol), was added (*R*)-**12** or (*S*)-(−)-2-methylbutylamine (99% ee, from Aldrich) (0.059 mL, 0.5 mmol). The mixture was stirred at RT for 2 h and then diluted with ethyl ether (10 mL). The organic layer was washed with water (3×3 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography with 5% ethyl acetate in hexane as eluent affording the desired amide (2′*S*,2*S*) and (2′*S*,2*R*)-**1** (0.085 g) in quantitative yield.

(+)-*N*-(2′*S*)-Methylbutyl-(2*S*)-methylbutylamide [(2′*S*,2*S*)-1] (1.48 g, 76% yield). Colorless oil: purity >99%. $[\alpha]_D^{20} = +27.83$ (*c* = 3.18, diethyl ether). IR (ν_{max}, film) cm^{-1}: 3302; 2953; 2372; 1957; 1648; 1550; 1461; 1234. ^{1}H-NMR (400 MHz-$CDCl_3$) δ: 0.88 (t, J = 6.8 Hz, 9H), 1.1 (d, J = 6.8Hz, 3H), 1.23–1.30 (m, 1H), 1.34–1.39 (m, 2H), 1.49–1.57 (m, 1H), 1.59–1.72 (m, 1H), 2.06 (sext, J = 6.8 Hz, 1H), 3.04–3.11 (m, 1H), 3.12–3.20

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(m, 1H), 5.4 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 176.6, 44.8, 43.2, 34.8, 27.2, 26.9, 17.5, 17.0, 11.8, 11.2. MS (rel intensity): *m*/*z* 50 (0.5); 51 (0.9); 53 (3.3); 54 (2.5); 55 (17.4); 56 (10.7); 57 (100); 58 (24.3); 59 (1.7); 67.2 (0.6); 68 (0.8); 69 (3.2); 70 (4.5); 71 (11.6); 72 (5.6); 73 (3.5); 74 (6.1); 84 (1.9); 85 (40.5); 86 (22); 87 (7.9); 100 (6.3); 102 (1.8); 114 (7.8); 115 (5.4); 116 (0.9); 142 (3.7); 143 (6.0); 156 (3.4); 171 (M^+, 2.1). Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.91; H, 12.39; N, 8.23.

(+)-*N*-(2′*S*)-Methylbutyl-(2*R*)-methylbutylamide [(2′*S*,2*R*)-1] (1.48 g, 76% yield). Colorless oil: purity >99%. $[\alpha]_D^{20}$:+17.23 (*c* = 3.36, diethyl ether). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 9H), 1.09 (d, J = 6.8 Hz, 3H), 1.19–1.25 (m, 1H), 1.30–1.44 (m, 2H), 1.46–1.55 (m, 1H), 1.56–1.67 (m, 1H), 2.06 (sext, J = 6.8 Hz, 1H), 2.96–3.02 (m, 1H), 3.15–3.22 (m, 1H), 5.6 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 176.5, 44.8, 43.3, 34.9, 27.3, 26.9, 17.6, 17.0, 11.9, 11.2.

General Procedure for the Preparation of the Amides (2′*R*,2*S*) and (2′*R*,2*R*)-1

To a solution of amine (*S*)-**12** (from Aldrich) or (*R*)-**12** in THF, were added pyridine (1 eq.) and acyl chloride **10** (1.04 eq.). The mixture was stirred for 30 min at rt, then 10% aqueous NaOH (5mL) was added. The organic layer was separated and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography with 5% ethyl acetate in hexane as eluent gave the desired amide **1**.

(−)-N-(2′*R*)-Methylbutyl-(2*S*)-methylbutylamide [(2′*R*,2*S*)-**1**] (50 mg, 72% yield). colorless oil: purity >98%. $[\alpha]_D^{20}$: −21.68 (*c*=3.18, diethyl ether). The IR and NMR spectra were identical with those of (2′*S*,2*R*)-**1**.

(−)-N-(2′*R*)-Methylbutyl-(2*R*)-methylbutylamide [(2′*R*,2*R*)-**1**] (50 mg, 72% yield). Colorless oil: purity >99%. $[\alpha]_D^{20}$: −22.26 (*c*=3.14, diethyl ether). The IR and NMR spectra were identical with those of (2′*S*,2*S*)-**1**.

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