Synthesis of *(R)*- and *(S)*-10-Methyl-1-dodecyl Acetate, Sex Pheromone Components of the Smaller Tea Tortrix Moth (*Adoxophyes sp.*), from Chiral Synthons Prepared *via* Asymmetric Synthesis

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10-Methyl-1-dodecyl acetate (*1*) is an important minor component of the female sex pheromone of the smaller tea tortrix moth (*Adoxophyes sp.*) (Fig. 1).[1,2] The (*R*)-enantiomer was determined to be slightly more active than the (*S*)-enantiomer.[3] A recent field evaluation suggests that there is an optimum *(R)/(S)*-ratio of 95/5 for trapping of males.[4] Investigations like these obviously require access to both enantiomers in very high optical and chemical purities.

Mori reported the first synthesis of both optically active forms of *1* using *(R)*-(+)-citronellol as starting material.[5] Two alternative approaches were then presented by Sonnet.[6,7,8] Starting from 10-undecenoic acid, both lead to *(R)-1* and *(S)-1* in e.e's above 80 %. The key step in one of these syntheses involves an asymmetric alkylation of a chiral amide enolate to create a new chiral center.[7] The resulting diastereomeric mixture is then separated by HPLC to give mainly one diastereomer which is used in subsequent steps. The other route proceeds *via* classical resolution of diastereomeric amides followed by a five step sequence leading to *(R)*- and *(S)-1* (>99 % e.e.).[8]

We have recently developed a method for the preparation of chiral 2-alkylalkanoic acids,[9] and have now used this method to prepare the enantiomerically pure 2-methylbutanoic acids *2*, which were reduced to the corresponding alcohols *(R)-3* and *(S)-3*. Starting from these alcohols, both enantiomers of 10-methyl-1-dodecyl acetate (*1*) were prepared in reasonable overall yields and very high optical purities in three steps (Fig. 2).

Thus *(R)*-2-methyl-1-butanol [*(R)-3*] was obtained by lithium aluminium hydride reduction of *(R)-2* (>98 % e.e). This reduction proceeded with little or no racemisation as judged by the NMR of the ester obtained from *(R)-3* and (+)-α-methoxy-α-phenylacetic acid chloride [(+)-MTPA−Cl] (*cf.* Experimental). *(R)-3* was then converted to its methylsulfonate ester[11] [*(R)-4*], which in a lithium chlorocuprate catalysed reaction[12,13] was coupled with the Grignard reagent *6* prepared from the tetrahydropyranyl ether of 8-bromo-1-octanol[14] to give, after hydrolysis, *(R)-5*. Acetylation with acetic anhydride/pyridine furnished *(R)*-10-methyl-1-dodecyl acetate *(R-1)* (>98 % e.e). *(S)-1* was synthesized in the same way from alcohol *S-3*.

(R)-2-Methylbutanoic acid [*(R)-2*] was obtained almost optically pure employing our alkylation procedure (Fig. 3).[9] The major *(R,S)*-diastereomer of *8* was conveniently separated from *(S,S)-8* by flash chromatography and then hydrolysed furnishing *(R)-2*

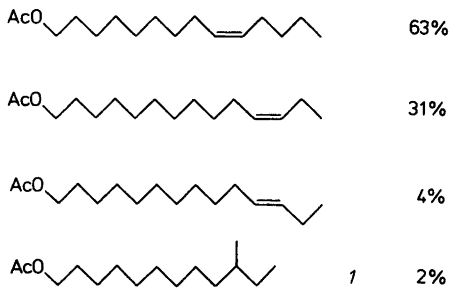

Fig. 1. Four component sex pheromone of the smaller tea tortrix moth.[1]

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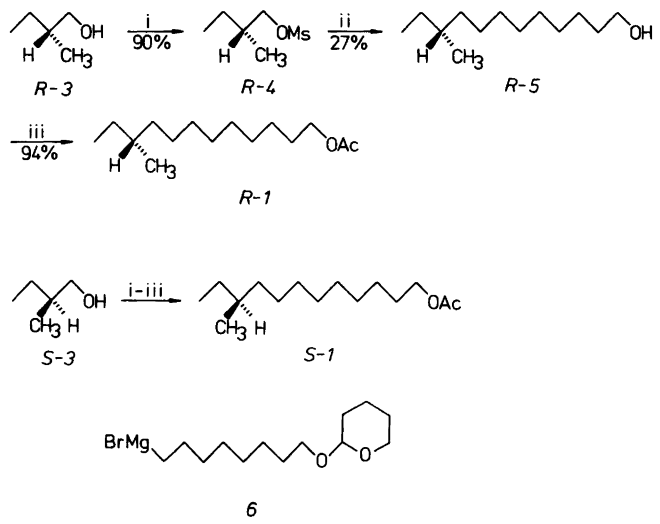

Fig. 2. Conditions. (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, (ii) 1. Li_2CuCl_4 (0.1 M, THF) 0.05 eq., 0 °C, 2. Compound *6* (2.0 eq.), −5 °C, 3. 25 °C, 17 h., 4. $H_3O^+-H_2O$, 5. MeOH–TsOH. (iii) Ac_2O, pyridine.

(>98 % e.e.). Similarly, *(S)-2* was obtained by alkylation of the butanoyl analogue of *7* with methyl iodide giving *(S,S)-8* (75 % d.e.) and hydrolysis of this amide. However, since *(S)-3* (>98 % e.e.) is commercially available this material was used to synthesize *(S)-1*.

Lithium chlorocuprate catalysed coupling reactions have been employed successfully in several synthetic applications giving moderate to high yields[15–20] but despite several attempts to raise the yield in the coupling of mesylate *4* with the Grignard reagent *6* we were unable to isolate more than 27 % yield of the alcohol *5*. Other substrates with steric requirements similar to those of the mesylate *4* have given comparable results in this reaction.[21] Exchange of the mesylate for the corresponding tosylate gave at best *ca.* 20 % yield. An attempt to use a cuprate mediated reaction[22] of 2-methylbutylmagnesium bromide with 8-bromo-1-(2-tetrahydropyranyloxy)-octane (*6*) gave only a 10–15 % yield.

Our route to the enantiomers of *1* starting from highly pure enantiomers of the alcohols (*R*)- and *(S)-3* has the advantage of being short since only two isolated intermediate products are involved.

Experimental. GLC analyses were performed on a Pye Unicam Series 204 instrument using a 25 m fused silica capillary column coated with Carbowax 20M, i.d. 0.2 mm. Air bath temperatures registered in a Büchi GKR-50 Kugelrohr oven are given instead of boiling points unless otherwise stated.

Chromatographic separation of diastereomers of α,α-dimethyl-1-(2-methyl-1-oxobutyl)-2-pyrrolidinemethanol, 8. Amide *8*[9] [5.13 g, GLC purity >99 %, (*R,S*)/(*S,S*) diastereomer

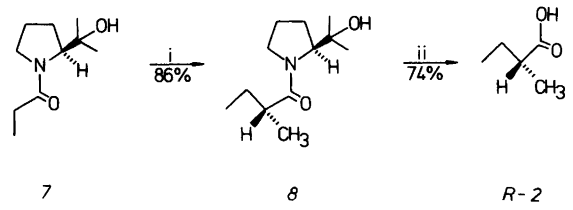

Fig. 3. Conditions. (i) 1. LDA (2.25 eq.), THF, 0 °C, 2. C_2H_5I, 0 °C, 3. NH_4Cl (aq,sat,), (ii) 3 M HCl (aq)–dioxane, 1:1, 42 h, 90–95 °C.

ratio=92/8] was flash chromatographed on silica gel. Gradient elution with light petroleum (40–60 °C) – EtOAc first furnished the (*R,S*) diastereomer. Fractions containing mixtures of diastereomers were concentrated and rechromatographed. After five runs 3.73 g essentially pure (*R,S*) diastereomer, >99 % d.e. (GLC), together with 1.23 g of a (*R,S*)/(*S,S*) diastereomer mixture in a ratio of 74/26 were obtained (GLC conditions for compound *8*: carrier gas He, 1.2 kg/cm^2, 155 °C, retention times: (*R,S*) 797 s, (*S,S*) 842 s).

(R)-2-Methyl-1-butanoic acid [(R)-2]. Hydrolysis[9] of *(R,S)-8* (>99 % d.e., 3.24 g) afforded acid *(R)-2* (1.15 g, 74 %), air bath 100–105 °C/15mmHg, $[\alpha]_D^{26}$ −18.9° (neat) [Lit.[23] $[\alpha]_D^{25}$5 −18.8° (neat)], GLC purity 99 %.

(R)-2-Methyl-1-butanol [(R)-3]. Acid *(R)-2* (1.01 g, 9.9 mmol) was dissolved in ether (18 ml) and added (15 min) to a suspension of lithium aluminium hydride (0.68 g, 17.8 mmol) in dry ether (18 ml) under N_2. The reaction mixture was stirred for 5 h followed by addition of 50 ml of aqueous acid (1 M H_2SO_4/H_2O : 1/10). Extractive work up yielded alcohol *(R)-3* (0.727 g, 83 %). The optical purity of *(R)-3* was determined by the formation of an ester upon reaction with (+)-MTPA–Cl. NMR (200 MHz): δ 0.90 [3H, t, $-CH_2-CH_3$], 0.91 [3H, d, $>CH-CH_3$], 1.09–1.48 (2H, 12 line m, $C-CH_2-C$), 1.77 [1H, m, $>CH-CH_3$], 3.55 (3H, s, $-OCH_3$), 4.08 [1H, dd, $-C(H)H-O$], 4.25 [1H, dd, $-C(H)H-O$], 7.37–7.54 (5H, m, C_6H_5). The 4 line signals centered at δ 4.08 and 4.25 arise from the diastereotopic protons H_A and H_B on carbon 1 of the *(R)*-2-methylbutyl moiety [$-C^2(CH_3)H-C^1H_AH_B-$OMTPA]. In the corresponding ester of (+)-MTPA–Cl with *(S)-3* these protons have coinciding chemical shifts giving a clean doublet at δ 4.17 (J=6.1 Hz). The ratio of the integral of the sum of the two doublets of doublets from the *(R)*-form to that of the single doublet from the *(S)*-form was >99/1. Thus *(R)-3* was assigned an e.e. of >98 %.

(R)-2-Methyl-1-butyl mesylate [(R)-4]. Alcohol *(R)-3* (0.72 g, 8.2 mmol) was dissolved in CH_2Cl_2 (35 ml) containing triethylamine (1.20 g, 11.9 mmol) and cooled to −5 °C under N_2. Methane sulfonyl chloride (0.68 ml, 1.1 eq.) was then added *via* syringe (10 min, −5–0 °C) and stirring was continued (0 °C, 2 h). The reaction mixture was poured onto ice-water (15 ml) and the organic phase was separated, washed successively with 1 M HCl (aq.) $NaHCO_3$ (aq., sat.), NaCl (aq., sat.) and dried ($MgSO_4$). Concentration *in vacuo* and distillation furnished *(R)-4* (1.12 g, 83 %), b.p. 108 °C/0.12 mmHg, $[\alpha]_D^{25}$ −2.63° (neat), GLC purity >99 %. [*(S)-4* was synthesized in the same way from *(S)-3* in 90 % yield $[\alpha]_D^{23}$ +2.64° (neat), GLC purity 98 %]. NMR (200 MHz): δ 0.93 [3H, t, $-CH_2-CH_3$], 0.98 [3H, d, $>CH-CH_3$], 1.24 [1H, m, $-C(H)H-CH_3$], 1.49 [1H, m, $-C(H)H-CH_3$], 1.80 [1H, m, $>CH-CH_3$], 3.01 (3H, s, $-SO_2CH_3$), 4.07 (2H, m, $-CH_2-O$).

(R)-10-Methyl-1-dodecanol [(R)-5]. Freshly distilled bromide *6* (0.59 g, 2.0 mmol) dissolved in THF (1.5 ml) was added to Mg (51 mg, 2.1 mmol) in THF (1.5 ml) at 40 °C under N_2. At reflux temperature the reaction was then initiated by addition of a drop of dibromoethane and the reaction mixture was refluxed (90 min), cooled to 30 °C and diluted with THF (1.5 ml). The Grignard reagent was added *via* syringe to a cold solution (−5–0 °C) containing mesylate *(R)-4* (0.17 g, 1.0 mmol) in THF (1.5 ml) and 0.5 ml of a 0.1 M Li_2CuCl_4-solution (THF). After completion of this addition (15 min) the mixture was stirred for 3 hours at −5–0 °C and then allowed to reach room temperature overnight (17 h). The solution was poured onto ice-water and pH was adjusted to 4–5. The combined ethereal extracts of this mixture were washed successively with H_2O, $NaHCO_3$ (aq., sat.) and NaCl (aq., sat.). Drying ($MgSO_4$) and concentration *in vacuo* gave an oil which was dissolved in MeOH (10 ml) containing a catalytic amount of TsOH and stirred. This mixture was partitioned between H_2O and ether. The aqueous phase was extracted with ether and the organic phases were combined and washed with $NaHCO_3$ (aq., sat.) and NaCl (aq., sat.) Drying ($MgSO_4$), concentration and purification by flash column chromatography gave an oil which was distilled to yield *(R)-5* (54 mg, 27 %), air bath 125–135 °C/0.25 mmHg, GLC purity >99 %. NMR (200 MHz): δ 0.85 [3H, t, $-CH_2-CH_3$], 0.87 [3H, d, $>CH-CH_3$], 1.00–1.45 (18H, bs, $C-CH_2-C$), 1.45–1.80 [2H, m, $>CH-CH_3$, O*H*], 3.64 (2H, t, $-CH_2-O$).

(R)-10-Methyl-1-dodecyl acetate [(R)-1]. Alcohol *(R)-5* (51 mg, 0.26 mmol) was stirred (24h, r.t.) with acetic anhydride (1 ml) in dry pyridine (5 ml) poured onto ice-water followed by extractive work-up. Distillation gave *(R)-1* (59 mg, 94 %), air bath 120–125 °C/0.05 mmHg, $[\alpha]_D^{23}$ −5.84° (c 2.21, $CHCl_3$) [Lit.[8] $[\alpha]_D^{24}$ −5.57° (c 21.8, $CHCl_3$)], GLC purity >99 %

(140 °C, He 1,2 kg/cm^2, r.t. 408 s). IR (film): 2950 (s), 2890 (m), 1740 (s), 1465 (m), 1360 (m), 1235 (s), 1040 (m), 970 (w), 715 (w) cm^{-1}. MS [IP 70 eV; *m/e* (% rel. int.)]: 182 (0.2 [M−AcOH]), 153 (12.4), 125 (7.6), 111 (9.2), 97 (46.3), 83 (57.2), 70 (59.1), 61 (35.6), 55 (70.8), 43 (100). NMR (200 MHz): δ 0.85 [6H, d+t, >CH−C*H*$_3$, −CH$_2$−C*H*$_3$], 1.00−1.45 (18H, bs, C−C*H*$_2$−C), 1.55−1.75 [1H, m, >C*H*−CH$_3$], 2.05 (3H, s, COC*H*$_3$), 4.05 (2H, t, −C*H*$_2$O).

(S)-10-Methyl-1-dodecyl acetate [(S)-1]. This acetate was prepared from alcohol *(S)-5* in the same manner as described above for the enantiomer. $[\alpha]_D^{20}$ +5.92° (c 2.13, $CHCl_3$) [Lit.[8] $[\alpha]_D^{24}$ +5.60° (c 21.8, $CHCl_3$)]. GLC purity >99 %. All spectral data (NMR, IR, MS) were in agreement with those given for *(R)-1*.

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