Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 89–96

TETRAHEDRON:
ASYMMETRY

Chemoenzymatic synthesis of (*R*)-(+)-2-methylbutan-1-ol, a chiral synthon for the preparation of optically active pheromones

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Received 19 October 1997; accepted 26 November 1997

Abstract

Optically active (*R*)-(+)-2-methylbutan-1-ol (which is not commercially available) was prepared by a chemoenzymatic synthesis, in which the key step involved a reduction catalyzed by baker's yeast. The synthon was used in the synthesis of (*R*)-10-methyldodecan-1-yl acetate, the chiral methyl-branched pheromone of *Adoxophyes* sp.

1. Introduction

Optically active starting materials are required in the synthesis of biologically active materials such as chiral pheromones, compounds for which the stereochemistry generally dictates the behavioral response of the insect. Until recently, natural products, such as amino acids, sugars or terpenoid structures, were used as the starting materials in the synthesis of chiral pheromones. When the desired stereoisomer was not available, alternative routes had to be developed. For example, (*S*)-(−)-2-methylbutan-1-ol was used as the starting material in the synthesis of (*S*)-Z-(+)-14-methyl-8-hexadecen-1-ol (the intermediate in the synthesis of the antipode of trogodermal).[1,2] The (*R*)-Z- stereoisomer could not be prepared by the same route, because natural (*R*)-(+)-2-methylbutan-1-ol was not available.[3] However, another route, in which (*R*)-(+)-citronellol was used as the starting material, was elaborated.[4] Recently another strategy was undertaken for the synthesis of the chiral synthon, (*R*)-(+)-2-methylbutan-1-ol: reduction of the enantiomerically pure 2-alkylalkanoic acid obtained by chemical resolution of a mixture of diastereomeric amides.[5] This example is by no means unique: other cases are listed in the literature.[6]

Incorporation of biocatalysis into modern organic synthesis for the asymmetric synthesis and kinetic resolution of chiral compounds is already widely practised.[7–9] Optically active α-alkyl substituted alcohols, such as 2-methylbutan-1-ol, can be used as synthons in the synthesis of a series of chiral

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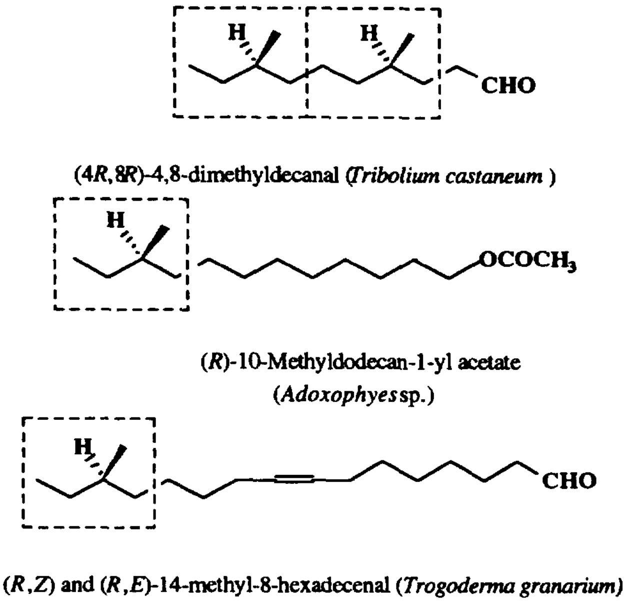
PII: S0957-4166(97)00613-7

methyl-branched pheromones (Scheme 1). In this study, (*R*)-2-methylbutan-1-ol was prepared by an asymmetric synthesis comprising a combination of chemical methods and baker's yeast reduction. The synthon was then further used in the synthesis of (*R*)-10-methyldodecan-1-yl acetate — the component of the pheromone of *Adoxophyes* sp.



(4*R*,8*R*)-4,8-dimethyldecanal (*Tribolium castaneum*)

(*R*)-10-Methyldodecan-1-yl acetate (*Adoxophyes* sp.)

(*R*,*Z*) and (*R*,*E*)-14-methyl-8-hexadecenal (*Trogoderma granarium*)

Scheme 1.

2. Results and discussion

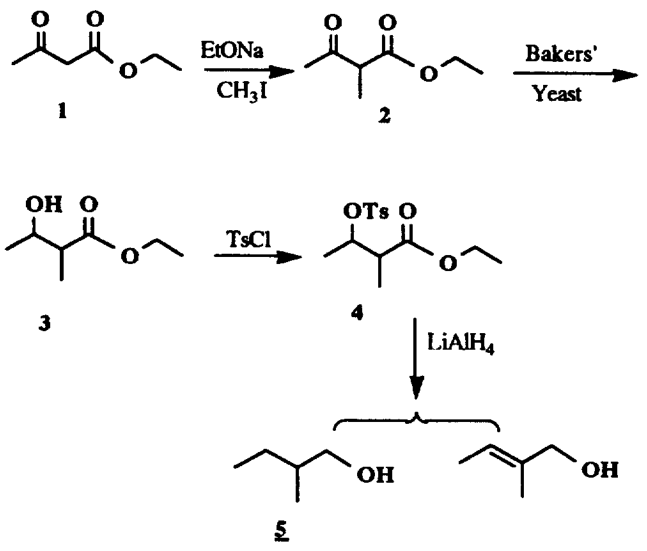
2.1. Preparation of the substrate

The preparation of the chiral synthon was performed by a chemoenzymatic synthesis based on the well-documented baker's yeast reduction of β-keto esters, especially those derived from alkyl acetoacetates.[10–13] Ethyl acetoacetate **1** was alkylated using sodium ethoxide as the base, followed by reaction with methyl iodide.[14] The purity of ethyl 2-methyl-3-oxobutyrate **2** (Scheme 2) was ascertained by GC and NMR analyses.

2.2. Reduction with immobilized and non-immobilized baker's yeast

Substrate **2** was reduced stereospecifically with baker's yeast (Scheme 2) and results similar to those published by other groups[12,13] were obtained. A mixture of (2*R*,3*S*)- and (2*S*,3*S*)-diastereomers was obtained, the major product being the (2*R*,3*S*)-diastereomer. In the biotransformation with baker's yeast, a number of parameters were varied with the aim of obtaining the best stereospecificity, the highest yield, and the most efficient procedure for bio-reduction (Table 1).

From the results in Table 1 it is evident that the stereoselectivity of the asymmetric reduction is very similar with both types of yeast — immobilized and non-immobilized. A significant reduction in the amount of yeast used was achieved by immobilization. The main difference between the two techniques was the ease of manipulation of the reaction mixture at the end of the reaction when immobilized baker's



Scheme 2.

Table 1
Reduction of $CH_3COCH(CH_3)COOCH_2CH_3$ **2** with baker's yeast

Type[2]	Yeast weight (g)	Substrate weight (g)	V_{H_2O} (ml)	Glucose (g)	Time (h)	Yield (%)	Diastereomeric ratio (2*R*,3*S*)/(2*S*,3*S*) (GC)
N	200	1.44	250	30	48	60	92/8
N	200	1.44	250	0	48	60	90/10
I	2.5	1.44	100	30	53	-[3]	79/21
I	2.5	1.44	100	0	53[4]	0	-
I	10	1.44	200	60	50	60	87/13
I	10	0.75	200	60	48	60	91/9
I[5]	5	0.36	100	30	50	69	42/58

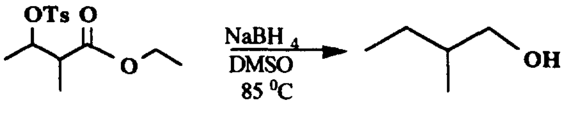
[1] The reactions were performed at room temperature with magnetic stirring. [2] N = nonimmobilized yeast, I = yeast immobilized by entrapment in calcium alginate.[3] Only 60% reduction. [4] No reduction took place. [5] The mixture was shaken on a gyrorotatary shaker at 27°C (180 rpm).

yeast was used. The work-up was straightforward with the immobilized yeast: there was no need to use aggregation agents or relatively large volumes of solvents to separate the yeast biomass from the reaction products. When glucose was not added to the reaction mixture, only with non-immobilized yeast was an asymmetric reduction observed.

The diastereomeric ratio of the products was determined by GC and ^1H NMR analyses. Research to improve the diastereomeric excess with various additives[13,15] was not attempted. The (2*R*,3*S*)-diastereomer was obtained by chromatography on a silica gel column.

2.3. Conversion to the chiral synthon

Since the ratio of diastereomers was about 9:1 in favor of the desired diastereomer, tosylation or mesylation was performed mainly with the diastereomeric mixture as previously reported,[16,17] and the products were purified by column chromatography. Due to possible diastereomer enrichment during purification, the specific rotation of the tosylate, for example, was measured before {$[\alpha]_D^{22}$=+9.87 (c 1.08, $CHCl_3$)} and after crystallization {$[\alpha]_D^{22}$=+10.60 (c 1.01, $CHCl_3$)}. The reduction of the tosyl or mesyl groups was not straightforward. The reagents conventionally used for this type of reduction, such as $LiAlH_4$[18] or NaI/Zn,[19] produced not only the desired synthon **5** but also significant quantities of olefin (Scheme 2). The only successful route involved the use of $NaBH_4$ in DMSO[20] at 85–90°C (Scheme 3), but the yield was relatively low (27% after purification by silica gel column chromatography). The specific rotation of the product (*R*)-2-methylbutan-1-ol obtained as described above was $[\alpha]_D^{22}$=+5.89 (c 1.08, $CHCl_3$) while that of the commercial (*S*)-enantiomer was {$[\alpha]_D^{22}$=−6.67 (c 2.4, $CHCl_3$} (optical purity of about 88%). The e.e. of the alcohol was estimated by GC using a Chiraldex G-TA chiral column at 31°C. The retention times of (*S*)- and (*R*)-2-methylbutan-1-ol were found to be 14.37 min and 14.86 min, respectively. The enantiomeric excess of (*R*)-2-methylbutan-1-ol was 82%.



4 **5**

Scheme 3.

2.4. Preparation of the pheromone

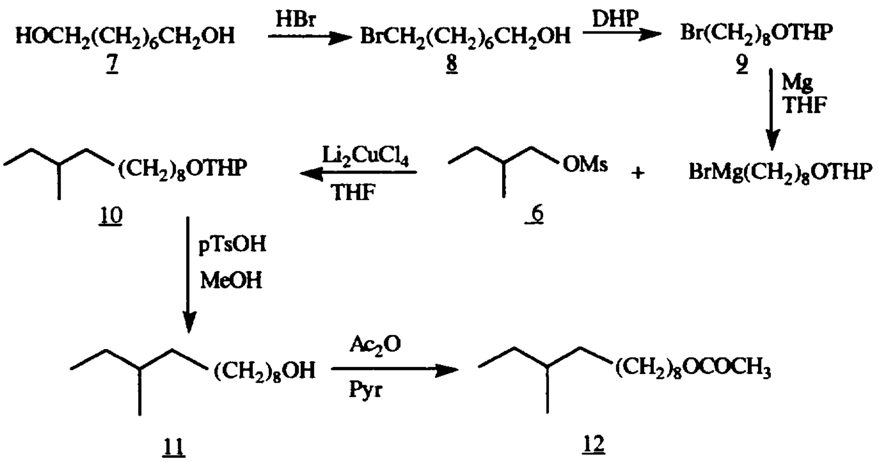
After obtaining the chiral synthon, (*R*)-2-methylbutan-1-ol **5**, the pheromone of *Adoxophyes* sp. was synthesized as previously described (Scheme 4).[5] (*R*)-2-Methylbutan-1-ol **5** was converted into the mesylate **6** and coupled with Li_2CuCl_4 as catalyst to a Grignard reagent prepared from the tetrahydropyrane (THP) derivative **9** of 8-bromooctan-1-ol, **8**. The latter compound was prepared separately by bromination of 1,8-octane diol **7** with HBr. After removing the THP-protecting group from **10** with *p*-TsOH, the resulting alcohol 10-methyldodecan-1-ol **11** was acetylated with acetic anhydride and pyridine to give (*R*)-10-methyldodecan-1-yl acetate **12** (75% yield). The specific rotation was $[\alpha]_D^{24}$=−4.80 (c 1.2, $CHCl_3$); {lit.[5] $[\alpha]_D^{23}$=−5.84 (c 2.21, $CHCl_3$)}.

In summary, the optically active pheromone of *Adoxophyes* sp. was prepared by a route based on the building block (*R*)-(+)-2-methylbutan-1-ol, which was in turn synthesized by an immobilized yeast-mediated reduction as the key-step in the asymmetric synthesis.

3. Experimental

3.1. General

Melting points are uncorrected and were determined in open-ended capillaries on a Capillary Melting Point Apparatus. ^1H NMR spectra were recorded on a Bruker 200 MHz instrument. The solvent in all cases was deuterochloroform, with tetramethylsilane added as the internal standard. Chemical shifts are given in δ, ppm. Optical rotation was measured on a Perkin–Elmer 141 polarimeter, either neat or as a



Scheme 4.

chloroform solution. Analytical GLC work was carried out on a Hewlett–Packard 417 gas chromatograph with a FID detector, on a column of 5% DEGS/Chromosorb W (60–80 mesh), 4.5 m, i.d. 1/8 in., with argon as the carrier gas. The enantiomeric excess was estimated on an HP 5890 gas chromatograph by means of a Chiraldex G-TA chiral column (30 m×0.25 mm) with helium as the carrier gas. Fresh baker's yeast was purchased from a local market.

3.2. *Ethyl 2-methyl acetoacetate 2*

Ethyl acetoacetate **1** (48.75 g, 0.375 mol) was methylated with methyl iodide (63.84 g, 0.45 mol) according to known procedures,[14] yielding **2** (48% after distillation). ^{1}H NMR: 1.25 (d+t, 6H), 2.25 (s, 3H), 3.5 (q, 1H), 4.22 (q, 2H).

3.3. *Ethyl 3-hydroxy-2-methylbutyrate 3*

3.3.1. *Reduction with non-immobilized baker's yeast*

Into a 1 L round-bottomed flask was added 250 ml of water, 200 g of baker's yeast, 1.44 g (10 mmol) of **2** and glucose (30 g, in 5 g portions every 6 hours). After 48 h with stirring at room temperature, Celite was added to the suspension which was further stirred for an additional hour. After centrifugation, the aqueous solution was saturated with NaCl and extracted with ethyl acetate (4 times). The organic phase was washed with water, dried with anhydrous $MgSO_4$, filtered, and evaporated to yield 800 mg product (54% yield). From the GC at 130°C, two peaks were obtained at 5.96 and 6.37 min, at a ratio of about 10:1. The optical rotation of this mixture was $[\alpha]_D^{22}=+8.8$ (c 1.14, $CHCl_3$). IR (neat) cm^{-1}: 3400 (OH) and 1740 (C=O). ^{1}H NMR: 1.18 (2d, 6H), 1.27 (t, 3H), 2.54 (dq, 1H), 2.83 (b, 1H), 4.1 (m, 1H), 4.22 (dq, 2H).

3.3.2. *Reduction with immobilized baker's yeast in alginate*

First, 10 g of baker's yeast suspended in 40 ml of Tris buffer 0.05 M, pH 8, were mixed with 40 ml of sodium alginate solution (5% w/v) and extruded into a 0.5 M $CaCl_2$ solution. The beads were left to stiffen for 16 h, decanted, washed with water and filtered off. The immobilized yeast was immersed in a 500 ml round-bottomed flask together with 200 ml of water, 10 g of glucose and 750 mg of **2**. An additional 50 g of glucose were added in portions of 10 g every 6 hours. After 72 h, the mixture was filtered. The solution was saturated with NaCl and extracted as described above. The crude product (690 mg) was chromatographed on a silica gel column with a mixture of petroleum ether:ethyl acetate (4:1) to yield 425 mg (60% yield). From the GC at 130°C, two peaks were obtained at 6.08 and 6.51 min, in a ratio of about 9:1. The mixture was chromatographed again on a silica gel column with a mixture of petroleum ether:ethyl acetate (6:1) to obtain an almost pure (2*R*,3*S*)-diastereomer (97.4% by GC).

3.3.3. Chemical reduction of ***2***

A sample of **2** was reduced with $NaBH_4$ in MeOH to prepare a mixture of diastereomers **3** as a standard. From the GC at 130°C, two peaks were obtained at 5.81 and 6.29 min, in a ratio of about 1:1.

3.4. Preparation of the tosylate ***4***

Tosylation of **3** was performed as described in the literature.[15] Starting from 1.2 g (8.2 mmol) of **3**, a crude product (2.86 g) was obtained with $[\alpha]_D^{22}=+9.87$ (c 1.08, $CHCl_3$). It was purified on a column of silica gel using a mixture of petroleum ether:ethyl acetate (96:4). The yield was 69%. The tosylate was recrystallized from chloroform:petroleum ether (m.p. 80–81°C). The specific rotation of **4** was $[\alpha]_D^{22}=+10.6$ (c 1.01, $CHCl_3$).

3.5. Preparation of the mesylate ***4a***

The mesylate of **3** was obtained by known procedures. A crude product (10.7 g) was obtained from 6.73 g (46.1 mmol) of **3**. After purification with petroleum ether:ethyl acetate (9:1) on a column of silica gel, 8.4 g of **4a** was obtained (81% yield). ^1H NMR: 1.28 (d+t, 6H), 1.47 (dd, 3H), 2.65 (m, 1H), 3.02 (s, 3H), 4.08 (q, 2H), 5.1 (m, 1H). The optical rotation of **4a** was $[\alpha]_D^{22}=+19.96$ (c 2.31, $CHCl_3$).

3.6. Reaction of ***4*** *with* $NaBH_4$

Into a triple-necked round-bottomed flask fitted with a thermometer and condenser was added **4** (1.2 g, 4 mmol), DMSO (8 ml), and $NaBH_4$ (800 mg, 22 mmol). The mixture was maintained at 85–90°C with magnetic stirring for 20 hours. The mixture was then cooled in an ice bath, and HCl (5%) was added carefully up to pH 7.2 to dissolve the salts. The obtained solution was extracted with CH_2Cl_2 (×4). The organic phase was washed with a saturated solution of NaCl, and then with water, dried on anhydrous $MgSO_4$, filtered and evaporated to yield 470 mg of crude material. This material was applied to a small column of silica gel and eluted with ether. The yield was 95 mg (27%). GC analysis at a column temperature of 60°C revealed a peak at 2.44 min, which is the same as that of the injected racemic 2-methylbutan-1-ol. Separation on a Chiraldex G-TA derivatized column at 31°C gave an enantiomeric excess of 82%. ^1H NMR: 0.87 (d+t, 6H), 1,15 (m, 2H), 1.45 (q, 1H), 3.45 (m, 2H), 3.65 (b, 1H). The optical rotation of the product was $[\alpha]_D^{22}=+5.89$ (c 1.08, $CHCl_3$). The specific rotation for the (*S*)-enantiomer was $[\alpha]_D^{20}=-5.87$ (neat). The same reduction procedure of the mesylate **4a** produced 81 mg of end product (23% yield): $[\alpha]_D^{23}=+6.1$ (c 1.4, $CHCl_3$).

3.7. Preparation of the bromohydrin of 1,8-octane diol 8

Into a triple-necked flask connected to a Dean–Stark trap and condenser was placed toluene (160 ml), 1,8-octane diol **7** (11.68 g, 80 mmol) and 48% HBr (14.84 g, 87.9 mmol). After refluxing for 13 h and measuring the volume of water that was collected, the reaction mixture was cooled to room temperature, and washed with a saturated solution of $NaHCO_3$, and then with a saturated solution of sodium chloride. The organic phase was dried, filtered off, and evaporated. The residue was distilled (bp 104/0.3 mmHg). The yield of **8** was 12.54 g (75%). IR (neat): 3400 cm^{-1} (OH); ^1H NMR: 1.35–1.95 (m, 12H), 2.43 (b, 1H), 3.39 (t, 2H), 3.61 (t, 2H).

3.8. *Preparation of THP of bromohydrin 9*

The THP derivative of bromohydrin **8** was prepared according to known procedures. Starting from 3.14 g (15 mmol) of **8**, a product of 4.57 g was obtained (100% yield). IR (neat): no hydroxyl present; ^1H NMR 1.20–1.70 (m, 12H), 1.90 (m, 6H), 3.45 (t, 2H), 3.76 (m, 2H), 3.91 (m, 2H), 4.56 (t, 1H).

3.9. *Preparation of 9–11*

The Grignard reagent of **9** (0.59 g, 2 mmol) was prepared in 1.5 ml of THF with Mg (51 mg, 2.1 mmol). This reagent was added dropwise into a precooled THF solution containing the mesylate **6** (obtained by the usual procedures) and 0.1 M of Li_2CuCl_4. Stirring at 0°C was continued for another 3 h. Then the mixture was left to stand at room temperature for another 17 h. Thereafter, HCl (5%) was added carefully to bring the solution to pH 4–5. After separation of the phases, the aqueous phase was extracted with ether (×4). The combined organic phase was washed first with a saturated bicarbonate solution and then with a saturated NaCl solution, dried, filtered and evaporated to yield an oil, **10**. This oil was mixed with 10 ml of methanol, which contained a catalytic amount of *para*-toluene sulfonic acid, and the mixture was left to stand at 40°C for 4 h. The solvent was evaporated off. The material obtained after the above-described work-up was chromatographed on a silica gel column with petroleum ether:ethyl acetate (96:4) to yield **11** (45 mg, 22% yield).

3.10. *Preparation of the acetate 12*

Compound **11** (45 mg, 0.25 mmol) was mixed at room temperature with acetic anhydride (0.7 ml) and pyridine (3 ml). The mixture was poured into cold water, and ether was used to extract compound **12**. The end product was chromatographed on a preparative silica gel plate with petroleum ether to yield 30 mg of product. ^1H NMR: 0.85 (t, 6H), 1.00 (bm, 18H), 1.56 (m, 1H), 2.05 (s, 3H), 4.05 (t, 2H).

Acknowledgements

This work was supported by the Moriah Fund.

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