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Amano PS-catalysed enantioselective acylation of (±)-α-methyl-1,3-benzodioxole-5-ethanol: an efficient resolution of chiral intermediates of the remarkable antiepileptic drug candidate, (−)-talampanel☆

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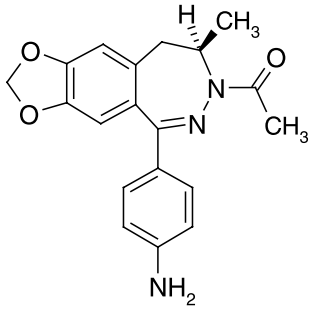
Dedicated to Dr. B. G. Hazra, OCS, NCL, Pune, India

Abstract—(*S*)-(+)-α-Methyl-1,3-benzodioxole-5-ethanol **5** is a chiral building block in the synthesis of the future drug (−)-talampanel **1**. Amano PS-induced enantioselective acylation of (±)-**3** at 50°C using vinyl acetate as acyl donor furnished (+)-**5** in 53% yield and 80% e.e., and the corresponding acetyl derivative (−)-(*R*)-α-methyl-1,3-benzodioxole-5-ethyl acetate **6** in 44% yield and 96% e.e. The base-catalysed methanolysis of (−)-**6** followed by Mitsunobu inversion and subsequent methanolysis of the product, (+)-**8** also gave the desired (+)-**5** in 38% overall yield (four steps) and 96% e.e.

1. Introduction

A group of scientists from the Hungarian Institute of Drug Research have recently discovered an orally active novel compound 7-acetyl-5-(4-aminophenyl)-8(*R*)-methyl-8,9-dihydro-7*H*-1,3-dioxolo[4,5-*b*][2,3]-benzodiazepine [(−)-talampanel, GYKI-53773, IDR-53773, LY-300164, **1**] with potential *antiepileptic*, *neuroprotectant* and *skeletal muscle relaxant* activities.[1–3] Phase II trials of the drug (−)-talampanel **1** in patients with severe epilepsy not responsive to other drugs have shown efficacy and phase III studies are in progress to confirm and use these results. Hence, (−)-talampanel **1** has been identified as a future drug.[4,5] The clinical potential of this new compound **1** has led to great interest in developing new syntheses.[5–7] The enantioselective synthesis of **1** has been completed via asymmetric reduction of the carbon–nitrogen double bond of 2,3-benzodiazepine using a borane–homochiral amino alcohol complex.[6] The stereoselective enzymatic reduction of 3,4-methylenedioxyphenylacetone to the corresponding (+)-(*S*)-α-methyl-1,3-benzodioxole-5-ethanol **5** is the first step of a new stereoselective route for the synthesis of the new drug candidate (−)-talampanel **1**.[5]



(−)-Talampanel **1**, CAS: 161832-65-1

$C_{19}H_{19}N_3O_3$ (337.3820)

Recently, an efficient large scale enantioselective reduction of 3,4-methylenedioxyphenylacetone has been elegantly accomplished by using an NAD(P)H-dependent oxidoreductase from *Zygosaccharomyces rouxii* together with polymeric hydrophobic resins both to supply substrate to the enzyme and remove the product from the reaction mixture as it is formed.[5,7] Chemical methods for the enantioselective reduction of methyl

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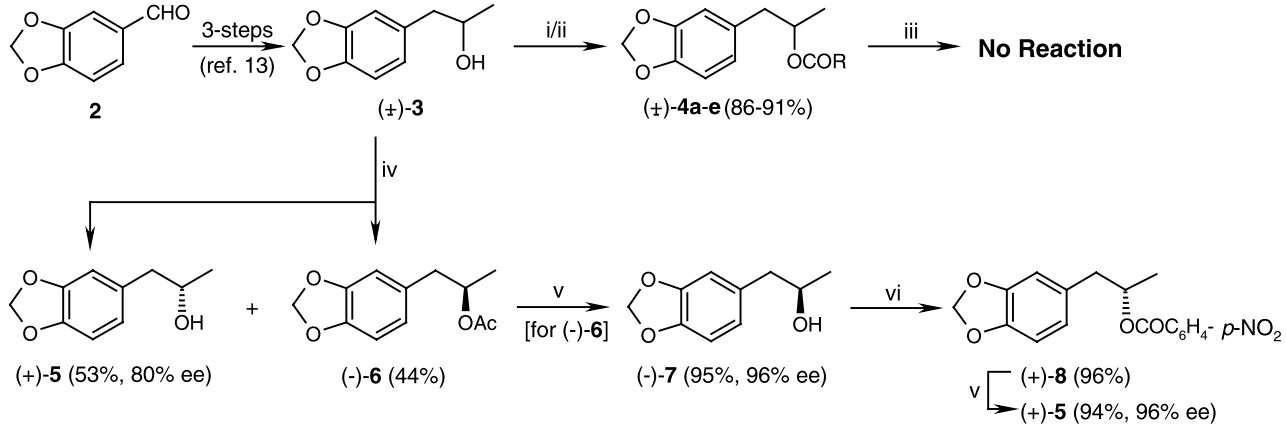
benzyl ketones require the stoichiometric use of costly reagents.[8] Selectivity and conversion of the corresponding ketone to (+)-**5** with Baker's yeast and other common microorganisms were found to be unsatisfactory.[5,9] Copper(I)-catalysed reaction of (*S*)-propylene oxide with the corresponding aryl Grignard reagent is known to produce the desired alcohol (+)-**5** in 91% yield. However, the cost of this method is high as the enantiomerically pure epoxide starting material is expensive.[5]

Biotransformations are often more efficient than chemical methods[10] and in continuation of our earlier studies[11] on the enzymatic resolutions of important chiral intermediates, we planned the enantioselective enzyme-catalysed acylation of (±)-**3** and hydrolysis of acyl derivatives of (±)-**3**.[12] We report herein an efficient enzyme-catalysed acylation of (±)-**3** to obtain enantiomerically pure (+)-**5** in high yields (Scheme 1).

2. Results and discussion

The (±)-α-methyl-1,3-benzodioxole-5-ethanol **3** was obtained in 3-steps from piperonal **2** using a known procedure involving nitroethane condensation, reductive hydrolysis and sodium borohydride reduction.[13] We prepared a systematic plan to study the enzyme-catalysed enantioselective hydrolysis of acyl derivatives of (±)-**3** and enzyme-catalysed enantioselective acylation of (±)-**3**. We first synthesised the acetyl, chloroacetyl, *p*-methoxybenzoyl, *p*-nitrobenzoyl and palmitoyl derivatives **4a**-**e** from (±)-**3** for screening enzyme-catalysed hydrolysis with the enzymes Amano PS, CCL and Amano AY but unfortunately the substrates **4a**–**e** were not recognised by these enzymes and all attempts at biphasic enantioselective enzymatic hydrolysis of **4a**–**e** met with failure. Interestingly, the Amano PS-catalysed acylation of (±)-**3** using vinyl acetate (5 equiv.) as an acyl donor at 25°C took place with 12% yield of (−)-**6** in 48 h. During these studies we noticed that the enzymatic resolution is time, temperature and vinyl acetate concentration dependent. Several experiments were carried out to obtain the maximum yield of (+)-**5** and (−)-**6** with high enantiomeric excess (Table 1). The best result from the acylation of (±)-**3** afforded (−)-**6** with 96% e.e. in 46% yield and (+)-**5** with 80% e.e. in 54% yield (Table 1, entry 5). These results were obtained using 5 equiv. of vinyl acetate at 50°C in a reaction time of 72 h. Under the present set of reaction conditions, the enzyme Amano PS had the highest activity at 50°C and showed a decline in its activity at 55 and 60°C (Table 1, entries 5–8). The formed hydroxy compound (+)-**5** and the acetyl derivative (−)-**6** were easily separated by silica gel column chromatography. On methanolysis in the presence of K_2CO_3 as a catalyst the acetyl derivative (−)-**6** gave alcohol (−)-**7** in 95% yield. The stereochemical assignment of (+)-**5** and (−)-**7** was done on the basis of comparison with literature information.[5] The ^{1}H NMR spectrum of diastereomeric mixture of Mosher's esters[14] obtained from (±)-**3** and (*R*)-Mosher's acid showed a very clean resolution of the –OCH_3 and 1,3-benzodioxole (-O-CH_2-O-) methylene protons. The ^{1}H NMR spectrum of Mosher's esters of (+)-**5** and (−)-**7** revealed that (+)-**5** possesses 80% e.e.[15] and (−)-**7** is formed with 96% e.e. Mitsunobu inversion[17] of alcohol (−)-**7** using DEAD, TPP and *p*-nitrobenzoic acid then afforded (+)-**8** in 96% yield and subsequent alcoholysis of (+)-**8** provided the desired alcohol (+)-**5** in 94% yield and 96% e.e. (from the ^{1}H NMR spectrum of the MTPA-ester). The conversion of the enantiomerically pure (*S*)-alcohol **5** to (−)-talampanel **1** in an impressive 54% overall yield (six steps) via exclusive generation of the seven-membered 2,3-benzodiazepine skeleton with inversion of configuration is a well established protocol.[5,7]



4a, R = Methyl; **4b**, R = Chloromethyl; **4c**, R = *p*-Anisyl; **4d**, R = *p*-Nitrophenyl; **4e**, R = Pentadecanyl

Scheme 1. *Reagents and conditions*: (i) Ac_2O/py, rt, 24 h; (ii) RCOOH, DCC, DMAP, DCM, rt, 8 h; (iii) petroleum ether/benzene (2:1), Amano PS or CCL or Amano AY, 50 mM sodium phosphate buffer (pH 7.0), rt, 24 h; (iv) *n*-hexane/benzene (2:1), Amano PS, vinyl acetate, 50°C, 72 h; (v) K_2CO_3/MeOH, 0°C, 4 h; (vi) DEAD, TPP, *p*-NO_2-C_6H_4COOH, THF, 0°C to rt, 8 h.

Table 1. Amano PS-catalysed enantioselective acylation of (±)-α-methyl-1,3-benzodioxole-5-ethanol **3**

Entry	Temp. (°C)	Time (h)	Vinyl acetate (equiv.)	(+)-**5** % remained (by ^{1}H NMR)	(−)-**6** % conversion (by ^{1}H NMR)	(+)-**5**[a] $[\alpha]_{589}^{20}$	(−)-**6**[a] $[\alpha]_{589}^{20}$	(+)-**5**% e.e.	(−)-**6**% e.e.
1	25	48	5	88	12	+3.1	−5.3	10[b]	95[b]
2	50	24	5	65	35	+11.6	−5.4	34[b]	96[b]
3	50	48	5	56	44	+26.1	−5.3	76[c]	95[d]
4	50	60	10	60	40	+19.3	−5.3	56[b]	95[b]
5	50	72	5	54	46	+27.6	−5.4	80[c]	96[d,e]
6	50	96	5	54	46	+27.5	−5.3	80[c]	95[d]
7	55	48	5	67	33	+10.7	−5.3	31[b]	95[b]
8	60	48	5	75	25	+6.9	−5.3	20[b]	95[b]

[a] Specific rotations were determined in $CHCl_3$ ($c=1$ in all cases).
[b] E.e. determined from the specific rotation value.
[c] E.e. determined by MTPA-ester preparation with (*R*)-Mosher's acid.
[d] % E.e. determined by conversion of -OAc to -OH followed by MTPA-derivatisation with (*R*)-Mosher's acid.
[e] *E* value: 125.

3. Conclusion

In summary, we have demonstrated an efficient practical enantioselective Amano PS-catalysed acylation of (±)-α-methyl-1,3-benzodioxole-5-ethanol **3** to obtain the potential chiral building block (+)-(*S*)-α-methyl-1,3-benzodioxole-5-ethanol **5** for promising antiepileptic future drug (−)-talampanel **1** in 53% yield and 80% e.e. The enantiomerically pure antipode, (−)-**6** was also transformed to the desired isomer (+)-**5** via Mitsunobu inversion in 38% overall yield (four steps) with 96% e.e. We feel that the present early stage enzymatic resolution will be of interest from a practical point of view to both academic and industrial chemists.

4. Experimental

4.1. General

Stereochemical assignments are based on the optical rotation of known compounds.[5] Melting points are uncorrected. Amano PS-1400 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[18] Column chromatographic separations were done on ACME silica gel (60–120 mesh). Commercially available acetic anhydride, DCC, DMAP, DEAD, TPP and (*R*)-Mosher's acid were used.

4.2. (±)-α-Methyl-1,3-benzodioxole-5-ethanol, 3

It was prepared in three steps using known literature procedures.[13] Analytical and spectral data obtained for (±)-**3** were identical with (+)-**5**.

4.3. (±)-α-Methyl-1,3-benzodioxole-5-ethyl acetate, 4a

To a stirred solution of alcohol (±)-**3** (900 mg, 5 mmol) in pyridine (10 mL) was added acetic anhydride (5 mL) and the reaction mixture was kept in the dark at rt for 24 h. The reaction mixture was poured into water and extracted with ethyl acetate (15 mL×5). The combined organic layer was washed with aq. $CuSO_4$ solution, water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9:1) gave **4a** (1.01 g, 91%). Analytical and spectral data obtained were identical with (−)-**6**.

4.4. General procedure for preparation of esters, 4b–e

To a solution/slurry of carboxylic acid (1.1 mmol), alcohol (±)-**3** (180 mg, 1 mmol) and catalytic amount of DMAP in dry CH_2Cl_2 (10 mL) was added a solution of DCC (1.1 mmol) in dry CH_2Cl_2 (5 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 8 h. The urea formed was filtered off and the organic layer was concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether and ethyl acetate (9.5:0.5) to give the desired esters **4b–e** in 86–90% yield.

4.4.1. (±)-α-Methyl-1,3-benzodioxole-5-ethyl chloro acetate, 4b. Oil; 226 mg (88% yield); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (d, $J=6$ Hz, 3H), 2.71 (dd, $J=14$ and 6 Hz, 1H), 2.87 (dd, $J=14$ and 6 Hz, 1H), 4.01 (s, 2H), 5.13 (sextet, $J=6$ Hz, 1H), 5.93 (s, 2H), 6.63 (dd, $J=8$ and 2 Hz, 1H), 6.69 (s, 1H), 6.74 (d, $J=8$ Hz, 1H); IR (Neat) ν_{max} 1751, 1740, 1502, 1491, 1443, 1250, 1188, 1040 cm^{-1}. Anal. calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.07. Found: C, 56.23; H, 5.11%.

4.4.2. (±)-α-Methyl-1,3-benzodioxole-5-ethyl *p*-methoxybenzoate, 4c. Viscous oil; 270 mg (86% yield); ^{1}H NMR

($CDCl_3$, 200 MHz) δ 1.32 (d, $J=6$ Hz, 3H), 2.79 (dd, $J=14$ and 6 Hz, 1H), 2.98 (dd, $J=14$ and 6 Hz, 1H), 3.86 (s, 3H), 5.27 (sextet, $J=6$ Hz, 1H), 5.91 (s, 2H), 6.60–6.80 (m, 3H), 6.91 (d, $J=8$ Hz, 2H), 7.98 (d, $J=8$ Hz, 2H); IR (Neat) ν_{max} 1709, 1607, 1502, 1256, 1038 cm^{-1}. Anal. calcd for $C_{18}H_{18}O_5$: C, 68.79; H, 5.73. Found: C, 68.88; H, 5.91%.

4.4.3. (±)-α-Methyl-1,3-benzodioxole-5-ethyl *p*-nitrobenzoate, 4d. 289 mg (88% yield); analytical and spectral data obtained were identical with (+)-**8**.

4.4.4. (±)-α-Methyl-1,3-benzodioxole-5-ethyl hexadecanoate, 4e. Viscous oil; 376 mg (90% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, $J=8$ Hz, 3H), 1.20 (d, $J=6$ Hz, 3H), 1.25 (bs, 24H), 1.45–1.65 (m, 2H), 2.24 (t, $J=8$ Hz, 2H), 2.66 (dd, $J=14$ and 6 Hz, 1H), 2.83 (dd, $J=14$ and 8 Hz, 1H), 5.06 (sextet, $J=6$ Hz, 1H), 5.92 (s, 2H), 6.63 (dd, $J=6$ and 2 Hz, 1H), 6.69 (s, 1H), 6.73 (d, $J=6$ Hz, 1H); IR (Neat) ν_{max} 1732, 1504, 1491, 1443, 1248, 1042 cm^{-1}. Anal. calcd for $C_{26}H_{42}O_4$: C, 74.64; H, 10.05. Found: C, 74.51; H, 10.13%.

4.5. Amano PS-catalysed acylation of (±)-3

A solution of alcohol (±)-**3** (900 mg, 5 mmol) in *n*-hexane/benzene (2:1) (25 mL) was added to Amano PS lipase (300 mg) followed by vinyl acetate (2.3 mL, 25 mmol). The reaction mixture was stirred at 50°C for 72 h and then allowed to reach rt. The enzyme was filtered off, washed with ethyl acetate and the organic layer was concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether and ethyl acetate (9:1) to obtain (+)-**5** (474 mg, 53%) and (−)-**6** (498 mg, 44%), respectively.

4.5.1. Alcohol (+)-5. Oil; $[\alpha]_{589}^{20}=+27.6$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, $J=6$ Hz, 3H), 1.63 (bs, 1H), 2.59 (dd, $J=14$ and 8 Hz, 1H), 2.72 (dd, $J=14$ and 4 Hz, 1H), 3.96 (sextet, $J=6$ Hz, 1H), 5.93 (s, 2H), 6.66 (d, $J=8$ Hz, 1H), 6.70 (s, 1H), 6.76 (d, $J=8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.3, 45.0, 68.5, 100.5, 107.9, 109.4, 122.0, 132.2, 145.7, 147.3; MS (*m*/*e*) 180, 148, 135, 121, 106, 91, 77, 63, 51, 45; IR (Neat) ν_{max} 3398, 1609, 1502, 1490, 1443, 1248, 1040 cm^{-1}. Anal. calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.52; H, 6.55%.

4.5.2. Acetate (−)-6. Oil; $[\alpha]_{589}^{20}=-5.4$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (d, $J=6$ Hz, 3H), 2.01 (s, 3H), 2.66 (dd, $J=14$ and 6 Hz, 1H), 2.84 (dd, $J=14$ and 6 Hz, 1H), 5.05 (sextet, $J=6$ Hz, 1H), 5.93 (s, 2H), 6.64 (d, $J=8$ Hz, 1H), 6.69 (s, 1H), 6.74 (d, $J=8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 21.0, 41.7, 71.3, 100.6, 107.9, 109.5, 122.1, 131.1, 146.0, 147.4, 170.3; MS (*m*/e) 222, 162, 147, 135, 121, 104, 91, 77, 69, 63; IR (Neat) ν_{max} 1736, 1609, 1505, 1491, 1443, 1373, 1246, 1042 cm^{-1}. Anal. calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 65.02; H, 6.49%.

4.6. (−)-(*R*)-α-Methyl-1,3-benzodioxole-5-ethanol, 7

To a solution of acetate (−)-**6** (444 mg, 2 mmol) in dry methanol (10 mL) was added anhydrous K_2CO_3 (5 mg) at 0°C with stirring. The reaction mixture was stirred at 0°C for a further 4 h and subsequently filtered through Celite. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9:1) yielded (−)-**7** (340 mg, 95%); viscous oil; $[\alpha]_{589}^{20}=-34.2$ (*c* 1.0, $CHCl_3$). Analytical and spectral data obtained were identical with (+)-**5**.

4.7. Mitsunobu inversion of (−)-7

A solution of DEAD (192 mg, 1.1 mmol) in dry THF (5 mL) was added dropwise to a solution of TPP (288 mg, 1.1 mmol), *p*-nitrobenzoic acid (184 mg, 1.1 mmol) and alcohol (−)-**7** (180 mg, 1 mmol) in dry THF (10 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 8 h. Concentration of reaction mixture in vacuo followed by silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9:1) gave (+)-**8**: 316 mg (96% yield); mp 57–59°C; $[\alpha]_{589}^{20}=+103.1$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, $J=6$ Hz, 3H), 2.84 (dd, $J=14$ and 6 Hz, 1H), 3.00 (dd, $J=14$ and 6 Hz, 1H), 5.34 (sextet, $J=6$ Hz, 1H), 5.92 (s, 2H), 6.60–6.80 (m, 3H), 8.17 (d, $J=8$ Hz, 2H), 8.29 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 41.9, 73.5, 100.9, 108.2, 109.7, 122.4, 123.5, 130.6, 130.8, 136.0, 146.3, 147.7, 150.4, 164.1; IR (Nujol) ν_{max} 1720, 1607, 1526, 1493, 1443, 1281 cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.56; N, 4.26. Found: C, 62.11; H, 4.60; N, 4.11%.

4.8. (+)-(*S*)-α-Methyl-1,3-benzodioxole-5-ethanol, 5

(+)-**8** On repetition of above procedure for conversion of (−)-**6** to (−)-**7** gave (+)-**5** in 94% yield. $[\alpha]_{589}^{20}=+34.0$ (*c* 1.0, $CHCl_3$).

4.9. General procedure for MTPA-ester preparation

To a solution of (*R*)-Mosher's acid (26 mg, 0.11 mmol), alcohol (±)-**3** or (+)-**5** or (−)-**7** (18 mg, 0.1 mmol) and DMAP (cat.) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (23 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 8 h. The formed urea was filtered off and the organic layer was concentrated in vacuo. Silica gel column chromatographic purification of the residue using petroleum ether and ethyl acetate (9.5:0.5) gave the MTPA-ester in quantitative yield.

4.9.1. MTPA-ester of (±)-α-methyl-1,3-benzodioxole-5-ethanol, 3. Viscous oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, $J=6$ Hz, 3H), 1.34 (d, $J=6$ Hz, 3H), 2.60–3.00 (m, 4H), 3.42 (s, 3H), 3.50 (s, 3H), 5.20–5.45 (m, 2H), 5.91 (s, 2H), 5.93 (s, 2H), 6.45–6.80 (m, 6H), 7.20–7.50 (m, 10H).

4.9.2. MTPA-ester of (+)-(*S*)-α-methyl-1,3-benzodioxole-5-ethanol, 5. Viscous oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (d, $J=6$ Hz, 0.30H), 1.34 (d, $J=8$ Hz, 2.70H), 2.60–2.95 (m, 2H), 3.42 (s, 0.30H), 3.51 (s, 2.70H), 5.34 (sextet, $J=6$ Hz, 1H), 5.92 (s, 1.80H), 5.93 (s, 0.20H), 6.45–6.80 (m, 3H), 7.25–7.55 (m, 5H).

4.9.3. MTPA-ester of (−)-(*R*)-α-methyl-1,3-benzodioxole-5-ethanol, 7. Viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (d, $J=6$ Hz, 3H), 2.70–3.00 (m, 2H), 3.42 (s, 2.94H), 3.51 (s, 0.06H), 5.32 (sextet, $J=6$ Hz, 1H), 5.93 (s, 2H), 6.60–6.80 (m, 3H), 7.15–7.50 (m, 5H).

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