Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2409–2420

TETRAHEDRON: *ASYMMETRY*

Synthesis of various 2*H*-benzopyran compounds and their kinetic resolution by asymmetric hydrolysis of their racemic acetates mediated by lipases

J. Y. Goujon, F. Zammattio* and B. Kirschleger

Laboratoire de Synthèse Organique, CNRS UMR 6513, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, 44072 Nantes Cedex 03, France

Received 21 April 2000; accepted 5 May 2000

Abstract

The preparation of 2*H*-benzopyrans from bromophenols and tertiary allylic alcohols is described. The reaction is characterised by its mildness, good yields and ease of work-up. Kinetic resolution of the latter up to 95% ee was obtained by using enzyme-catalysed enantioselective hydrolysis.

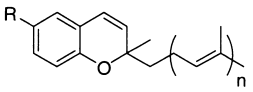
1. Introduction

The central role of heterocycles in life sciences and natural product chemistry provides a constant drive for the development of even more efficient methods for their preparation. Among them, benzopyran and 3,4-dihydrobenzopyran nuclei are present in many biologically active compounds, such as α-tocopherol or vitamin E,[1] levcromakalim,[2] cannabichromene[3] and ubichromenol or cordiachromene **1e**.[4] This latter compound was first isolated from *Cordia alliodora*, which is a tropical American tree whose wood is known for its durability in marine use. Moreover, cordiachromene exhibits high anti-inflammatory activity,[5] which seems to be due to a selective inhibition of cyclooxygenase.[5]

In the course of our interest concerning the development of new methods for the construction of benzopyran nuclei, we became interested in the preparation of substituted-3,4-dihydrobenzopyrans of type **1**, **2** and **3** with various *R* substituents. In addition, we also wanted to study the influence of relative and absolute stereochemistry of the stereogenic centre on the inhibition of cyclooxygenase.

* Corresponding author. Fax: 02 51 12 54 12; e-mail: fancoise.zammattio@chimie.univ-nantes.fr

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00176-2



1 : n = 1
2 : n = 2
3 : n = 3

(*RS*) **1a** : R = OBn
(*RS*) **1b** : R = OMe
(*RS*) **1c** : R = Me
(*RS*) **1d** : R = CN
(*RS*) **1e** : R = OH

(*RS*) **2a** : R = OBn
(*RS*) 2**b** : R = OH

(*RS*) **3** : R = OBn

The most used strategies for the synthesis of 3,4-dihydrobenzopyran nuclei involve a Claisen rearrangement of propargyl ethers[6] or a cyclisation of substituted quinones in refluxing pyridine.[7]

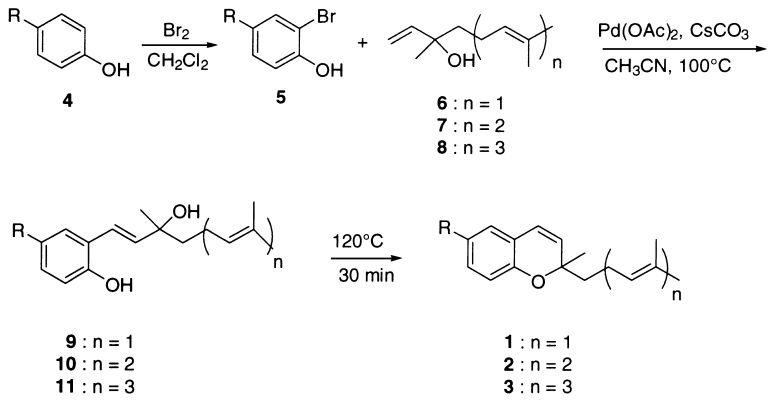
To try to introduce aryl diversity using readily available phenols, we envisaged a particularly attractive approach, similar to the one reported by Saà,[8] based on a palladium-catalysed reaction of a tertiary allylic alcohol with an *ortho*-bromophenol. This strategy has been used in order to circumvent the lack of availability of 2-iodophenols, which are the starting materials in the Saà[8] route. Moreover, to explore the scope and limitations of this process as well as its ability to facilitate the synthesis of various 3,4-dihydrobenzopyran, we systematically investigated the reaction of various tertiary allylic alcohols with diverse *ortho*-bromophenols using palladium acetate as the precatalyst.

In this paper, we are reporting our results concerning syntheses of compounds **1**, **2** and **3** and enzymatic kinetic resolution of **1e** and **2b** as an alternative for their stereocontrolled construction.

2. Results and discussion

2.1. Synthesis of 2H-1-benzopyran derivatives 1 to 3

Chiral racemic allylic alcohols **9**, **10** and **11** were prepared as shown in Scheme 1. The treatment of **4** with bromine[9] in methylene chloride provided the desired 2-bromophenols **5** in high yields. Heck reaction of **5** with 2 mol equiv. linalool **6** in CH_3CN in the presence of $CsCO_3$ (0.5 equiv.)



Scheme 1. Synthesis of compounds **1**, **2** and **3**

and 5 mol% of $Pd(OAc)_2$ at 100°C for 3 h gave the corresponding allylic alcohols **9** in satisfactory yields (Table 1: entries 1–4). These results show that the Heck coupling reaction works well with 2-bromophenols bearing electron withdrawing or donating groups. On the other hand, it is noteworthy that the same conditions could be applied to the preparation of analogues **10** and **11** (Table 1: entries 5 and 6) from the nerolidol **7** or the geranyl linalool **8**, respectively.

Table 1
Heck reaction of bromophenols **5** with allylic alcohols **6**, **7** and **8**

Entry	Bromophenols	Allylic alcohols	Products yields* (%)
1	**5a** : R = OBn	**6**	**9a** (77)
2	**5b** : R = OMe	**6**	**9b** (78)
3	**5c** : R = Me	**6**	**9c** (76)
4	**5d** : R = CN	**6**	**9d** (52)
5	**5a** : R = OBn	**7**	**10** (65)
6	**5a** : R = OBn	**8**	**11** (60)

* unoptimized

Finally, conversion of **9**, **10** and **11** to the corresponding 2*H*-1-benzopyrans **1**, **2** and **3** was simply achieved in quantitative yields by heating pure **9**, **10** or **11** at 120°C, under vacuum for 30 min.

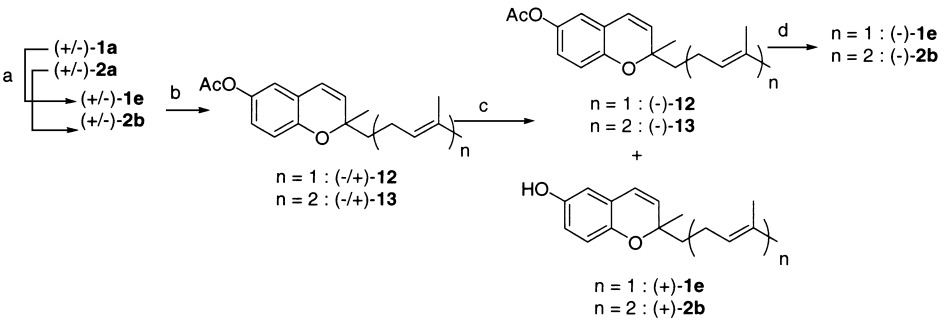
2.2. Kinetic resolution of *1e* and *2b*

With the desired **1a** and **2a** in hand, we turned our attention to their kinetic resolution as an alternative to their asymmetric synthesis. With this aim, removal of the benzyl-protecting group was first undertaken. The Lewis acid deprotection[10] of **1a** and **2a** afforded compounds **1e** and **2b** (Table 2) which served as key starting materials for our enzymatic resolution. Then, three lipases were tested for the enantioselective hydrolysis of racemic acetate (±)-**12** generated from **1e** (Table 2). As shown by the results listed in Table 2, the lipase from *Candida cylindracea* (CCL) was found to be the most effective one, even if (+)-**12** and (–)-**12** were not resolved with the same efficiency, leaving the enantiopure acetate (–)-**12** in satisfactory chemical yield and enantiomeric excess (Table 2: entry 2). Acetate (–)-**12** gave 2*H*-1-benzopyran (–)-**1e** in quantitative yield on K_2CO_3 mediated methanolysis. With the success of this kinetic resolution, we applied this methodology to the *trans* racemic acetate (±)-**13** generated from the *trans* (±)-**2b** (Table 2). Subsequently, enzymatic hydrolysis and methanolysis of the pure *trans* enantiomer (–)-**13** afforded the corresponding *trans* 2*H*-1-benzopyran (–)-**2b** (>98% ee) in 20% yield (Table 2: entry 4). The hydrolysis of substrates was followed by HPLC analysis. As an example, the HPLC analysis of a sample of acetate **12** is reported in Figs. 1 and 2.

2.3. Absolute configuration of *1e* and *2b*

Since optically active 2*H*-1-benzopyrans **1e**, **2b**, **12** and **13** have never been described, we could not, at this stage of our study, assign the absolute configuration of the stereogenic centre (C2). Nevertheless, the (*S*) preference observed with lipase AY in the case of enantioselective hydrolysis of (*RS*)-tocol acetate,[11] which is very similar to substrates (*RS*)-**12** and (*RS*)-**13**, supports the hypothesis that these latter substrates could be hydrolysed with the same enantioselectivity. To

Table 2
Lipase-catalysed kinetic resolution of 2*H*-1-benzopyran acetates (±)-**12** and **13**



a : $AlCl_3$, EtSH, Et_2O, -30°C; b : Ac_2O, Et_3N, DMAP, 25°C; c : enzyme, H_2O, IPE; d : K_2CO_3 / CH_3OH

Entry	Enzyme	Substrate	Time (hours)	Products			
				IY(%)[a]	EE(%)	IY(%)[a]	EE(%)
1	PPL	(+/-)-**12**	24	(-)**12**(80)	(18)	(+)-**1e**(16)	(34)
2	CCL	(+/-)-**12**	2	(-)**12**(30)	(95)	(+)-**1e**(55)	(13)
3	AY	(+/-)-**12**	12	(-)**12**(35)	(90)	(+)-**1e**(52)	(15)
4	CCL	(+/-)-**13**	1	(-)**13**(20)	(98)	(+)-**2b**(65)	(20)

Substrates and products were purified by column chromatography and the enantiomeric excesses were determined by HPLC analysis using a chiral column (CHIRALCEL OD-H, iPrOH-hexane (90/10 in the case of (+/-)-**12**) and (95/05 in the case of (+/-)-**13**). a : Isolated yield.

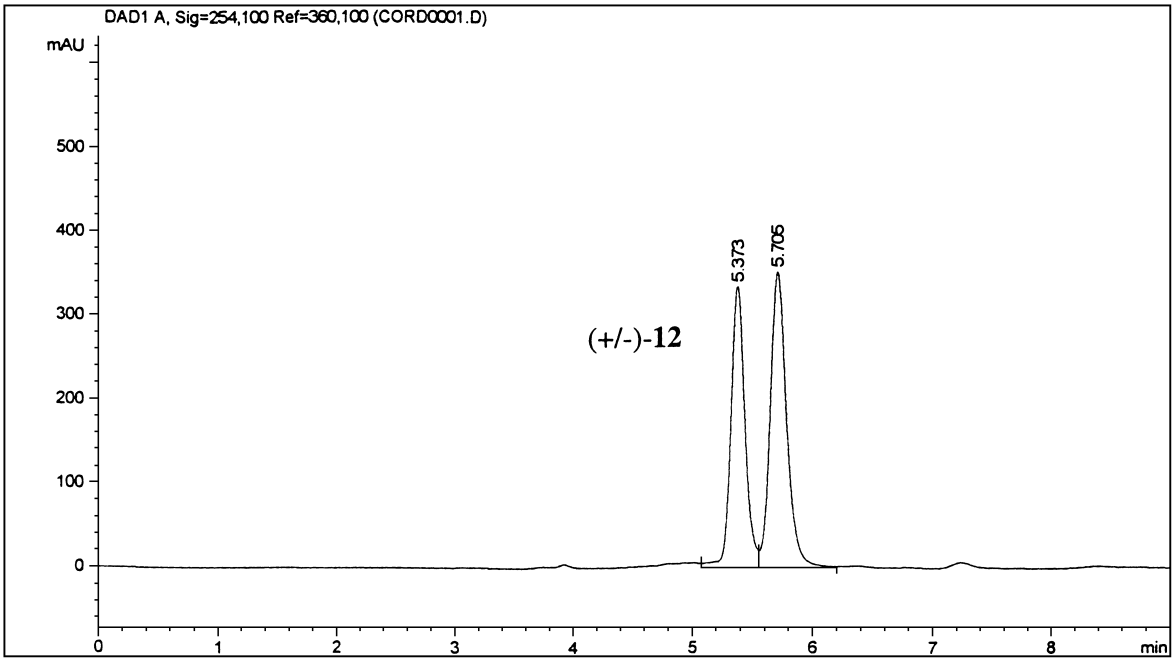


Figure 1. HPLC analysis of racemic acetate **12**

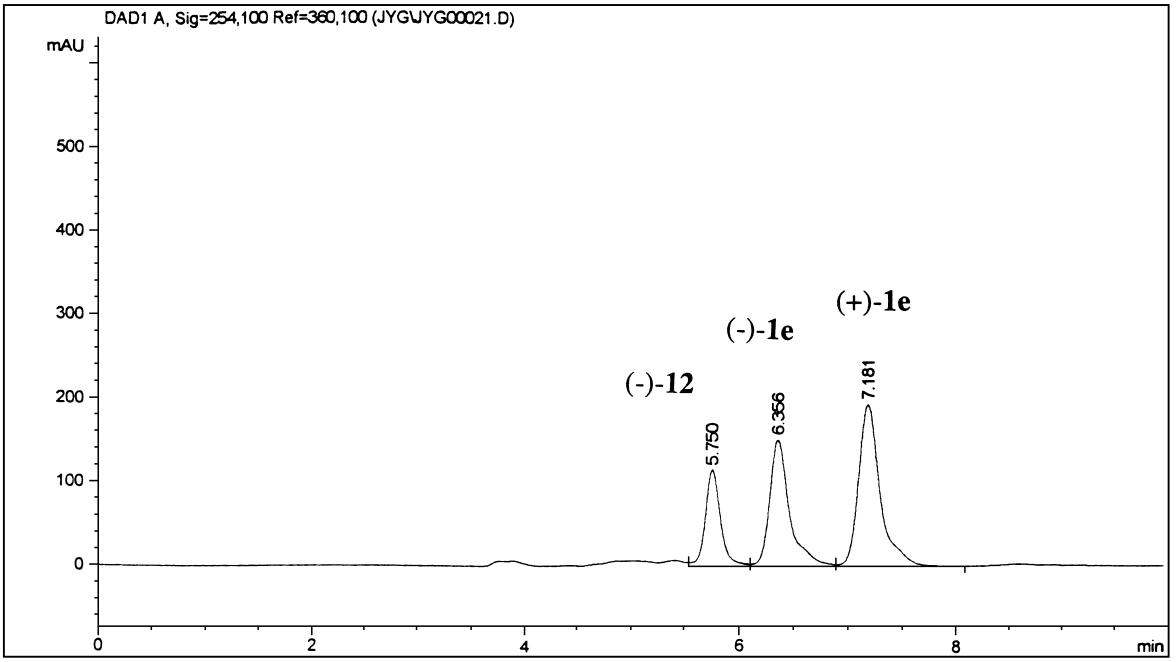
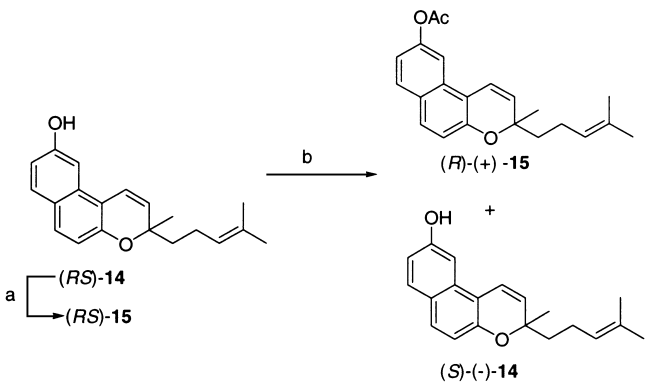


Figure 2. HPLC analysis of hydrolysis reaction mixture containing (–)-**12** and (±)-**1e** (Chiralcel OD-H, hexane:propan-2-ol, 95:5, flow 0.5 ml/min, λ 254 nm)

confirm the enantiopreference of lipases AY and CCL, kinetic resolution of racemic acetate **15**, of which both the relative and absolute configuration of each enantiomer were known,[12b] was carried out. Racemic acetate **15** was prepared as reported[12a] and submitted to lipase hydrolysis. From the reaction mixture, recovered (+)-**15** could be isolated in 15% yield and 70% ee (Scheme 2). The configuration of the pure enantiomer (+)-**15** was unequivocally established as (*R*) by comparison of its specific rotation with that of an authentic sample of (*R*)-(+)-**15**.[12b] This result confirmed the (*S*) enantiopreference of the enzyme and allows us to assign the (*R*) configuration at C2 for (–)-**12** and (–)-**13** as well as for (–)-**1e** and (–)-**2b**.



Scheme 2. Lipase-catalysed kinetic resolution of (*RS*)-**15**. (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 25°C; (b) lipase CCL, IPE/H_2O

In conclusion, we have developed a practical and efficient general route to 2*H*-1-benzopyrans in quite good yields and up to 95% enantioselectivity by using lipase-mediated kinetic resolution as an alternative to their asymmetric synthesis.

3. Experimental

3.1. Apparatus

^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 200 and Bruker AMX 400 spectrometers in chloroform-*d*[1]; chemical shifts are expressed in ppm. IR spectra were recorded on a Bruker vector 22 spectrometer. Mass spectra (*m*/*e* (% base peak)) were recorded on HP 5889A spectrometer EI (70 eV). For high performance liquid chromatography (HPLC) analysis a Hewlett–Packard model (HP 1050) equipped with a UV detector (254 nm) and a Chiralcel OD-H column were employed. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Melting points were determined on a C. Reichert microscope apparatus and are uncorrected. Elemental analyses were carried out on a Perkin–Elmer 2400 C,H,N elemental analyser.

3.2. Chemicals

Dichloromethane and ethyl acetate were dried by distillation over P_2O_5. Hexane was dried by distillation over $CaCl_2$. Lipase from *Candida rugosa* (AY) and porcine pancreas (PPL, type II) were obtained from Sigma. Lipase from *Candida cylindracea* (CCL, type VII) was obtained from Aldrich. Linalool, nerolidol and geranyl-linalool were purchased from Acros. Bromophenols **5** were prepared following classical procedures.[9]

3.3. General procedure for the preparation of tertiary allylic alcohols **9**, **10** and **11**

To a solution of 2-bromophenol **5** (3.5 mmol) in acetonitrile (9 ml), $CsCO_3$ (0.7 g, 1.5 mmol), $Pd(OAc)_2$ (0.03 g, 0.13 mmol) and 1.1 g (7.0 mmol) of linalool were added. The reaction mixture was stirred under argon at 100°C for 3 h, then diluted with dichloromethane and finally washed with brine. The organic layer was dried ($MgSO_4$), concentrated under vacuum and chromatographed on silica gel, eluting with a 80:20 (v/v) mixture of hexane:EtOAc.

3.3.1. 1-(2-Hydroxy-5-benzyloxyphenyl)-3,7-dimethylocta-1,6-dien-3-ol **9a**

Compound **9a** was obtained as a brown solid from **5a** in 77%; mp 42°C; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.57–1.69 (m, 2H, CH_2), 2.04–2.09 (m, 2H, CH_2), 4.98 (s, 2H, OCH_2), 5.08–5.15 (m, 1H, –CH=), 6.16–6.24 (d, 1H, J = 16.1 Hz, =CH–), 6.71 (m, 1H, $C_{ar}H$), 6.79–6.87 (d, 1H, J = 16.1 Hz, =CH–), 6.96 (m, 2H, $C_{ar}H$), 7.28–7.38 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 17.7, 22.9, 25.6, 28.2, 42.5, 70.7, 74.1, 113.2, 115.0, 116.8, 121.8, 124.2, 124.2, 127.5, 127.8, 128.4, 130.7, 132.2, 137.9, 147.5, 152.7; IR 3355, 3033, 2965, 2926, 2856, 1500, 1445, 1196 cm^{-1}; MS (*m*/*e*) 352 ($M^{+\cdot}$, 0), 334 (14), 251 (100), 91 (20).

3.3.2. 1-(2-Hydroxy-5-methoxyphenyl)-3,7-dimethylocta-1,6-dien-3-ol **9b**

Compound **9b** was obtained as a white solid from **5b** in 78% yield; mp 41°C; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.63 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 2.04–2.10 (m, 2H, CH_2),

3.74 (s, 3H, OCH_3), 5.10 (m, 1H, –CH=), 6.19–6.23 (d, 1H, J = 16.1 Hz, =CH–), 6.62–6.65 (m, 1H, $C_{ar}H$), 6.72–6.74 (m, 1H, $C_{ar}H$), 6.82–6.84 (d, 1H, J = 16.1 Hz, =CH–), 6.87–6.88 (m, 1H, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 22.9, 25.6, 28.0, 42.5, 55.7, 74.0, 111.7, 114.1, 116.9, 121.9, 124.2, 125.1, 131.8, 147.4, 153.4; MS (*m*/*e*) 276 ($M^{+\cdot}$, 0), 258 (8), 175 (100).

3.3.3. 1-(2-Hydroxy-5-methylphenyl)-3,7-dimethylocta-1,6-dien-3-ol ***9c***

Compound **9c** was obtained as a white solid from **5c** in 76% yield; mp 37°C; δ_H ($CDCl_3$) 1.36 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.60–1.68 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 2.02–2.10 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 5.04–5.08 (m, 1H, –CH=), 6.14–6.22 (d, 1H, J = 16.2 Hz, =CH–), 6.68–6.87 (m, 2H, $C_{ar}H$), 6.72–6.79 (d, 1H, J = 16.2 Hz, =CH–), 7.10–7.11 (m, 1H, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 20.4, 22.9, 25.6, 27.9, 42.4, 74.2, 115.9, 122.1, 124.1, 124.1, 127.3, 128.9, 128.9, 131.7, 137.0, 153.4; MS (*m*/*e*) 260 ($M^{+\cdot}$, 0), 242 (3), 202 (18), 159 (27), 43 (100).

3.3.4. 1-(2-Hydroxy-5-cyanophenyl)-3,7-dimethylocta-1,6-dien-3-ol ***9d***

Compound **9d** was obtained as a yellow oil from **5d** in 52% yield; δ_H ($CDCl_3$) 1.42 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.66–1.74 (m, 2H, CH_2), 1.74 (s, 3H, CH_3), 2.04–2.14 (m, 2H, CH_2), 5.07–5.14 (m, 1H, –CH=), 6.26–6.34 (d, 1H, J = 16.3 Hz, =CH–), 6.79–6.87 (d, 1H, J = 16.3 Hz, =CH–), 6.90–6.94 (m, 1H, $C_{ar}H$), 7.30–7.59 (m, 1H, $C_{ar}H$), 7.58 (m, 1H, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 22.8, 25.6, 27.8, 42.3, 74.4, 102.3, 116.7, 119.4, 120.6, 123.0, 125.8, 131.2, 132.1, 132.2, 138.7, 158.1; IR 3300, 2971, 2928, 2226, 1601, 1277 cm^{-1}; MS (*m*/*e*) 271 ($M^{+\cdot}$, 0), 253 (19), 210 (33), 170 (100), 43 (24), 41 (26).

3.3.5. 1-(2-Hydroxy-5-benzyloxyphenyl)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol ***10***

Compound **10** was obtained as a brown oil from **5a** in 65% yield; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.57 (s, 6H, $2CH_3$), 1.63–1.69 (m, 2H, CH_2), 1.66 (s, 3H, CH_3), 1.98–2.06 (m, 6H, $3CH_2$), 4.96 (s, 2H, OCH_2), 5.07–5.14 (m, 2H, 2CH=), 6.14–6.22 (d, 1H, J = 16.1 Hz, =CH–), 6.70–6.71 (m, 2H, $2C_{ar}H$), 6.79–6.87 (d, 1H, J = 16.1 Hz, =CH–), 6.96 (s, 1H, $C_{ar}H$), 7.31–7.47 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 16.0, 17.5, 22.6, 25.6, 26.4, 28.0, 39.6, 42.3, 70.7, 73.9, 113.2, 115.0, 116.8, 121.8, 124.0, 124.2, 125.0, 127.4, 127.8, 128.4, 131.3, 135.2, 137.2, 137.8, 147.5, 152.7; IR 3355, 3032, 2966, 2925, 2856, 1503, 1437, 1196 cm^{-1}; MS (*m*/*e*) 420 ($M^{+\cdot}$, 0), 402 (19), 251 (100), 91 (50).

3.3.6. 1-(2-Hydroxy-5-benzyloxyphenyl)-3,7,11,15-tetramethylhexdeca-1,6,10,14-tetraen-3-ol ***11***

Compound **11** was obtained as a brown oil from **5a** in 65% yield; δ_H ($CDCl_3$) 1.36 (s, 3H, CH_3), 1.57 (s, 6H, $2CH_3$), 1.64 (m, 2H, CH_2), 1.66 (s, 6H, $2CH_3$), 2.02 (m, 10H, $5CH_2$), 4.96 (s, 2H, OCH_2), 5.05 (m, 3H, 3CH=), 5.93 (d, 1H, J = 13.0 Hz, =CH–), 6.36 (m, 2H, $2C_{ar}H$), 6.44 (d, 1H, J = 13.0 Hz, =CH–), 6.57 (m, 1H, $C_{ar}H$), 7.31 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 15.9, 17.6, 22.9, 23.4, 25.6, 25.9, 26.7, 28.1, 31.9, 39.7, 42.5, 70.7, 74.0, 113.2, 115.0, 116.8, 121.8, 124.0, 124.1, 124.9, 124.9, 127.5, 127.8, 128.5, 130.5, 131.5, 135.8, 137.8, 138.6, 147.5, 152.7; IR 3356, 3033, 2965, 2925, 2855, 1499, 1453, 1196 cm^{-1}; MS (*m*/*e*) 488 ($M^{+\cdot}$, 0), 470 (9), 317 (21), 251 (37), 91 (100), 41 (62).

3.4. General procedure for the cyclisation of tertiary allylic alcohols ***9,10*** *and* ***11*** *to 2H-1-benzopyran*

The tertiary allylic alcohol was warmed at 120°C under vacuum to obtain the corresponding pure racemic 2*H*-1-benzopyran without any further purification.

*3.4.1. 6-Benzyloxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran* ***1a***

Compound **1a** was obtained from **9a** as a brown oil in 95% yield; δ_H ($CDCl_3$) 1.36 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.61–1.71 (m, 2H, CH_2), 2.11–2.19 (m, 2H, CH_2), 4.98 (s, 2H, CH_2), 5.04–5.13 (m, 1H, –CH=), 5.54–5.59 (d, 1H, J = 9.9 Hz, =CH–), 6.26–6.31 (d, 1H, J = 9.9 Hz, =CH–), 6.61–6.73 (m, 3H, $C_{ar}H$), 7.28–7.42 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 12.5, 14.7, 20.5, 20.9, 35.8, 65.4, 72.9, 107.6, 110.1, 111.4, 116.6, 117.7, 119.0, 122.3, 122.4, 123.3, 125.6, 126.4, 132.2, 142.1, 147.7; IR 3033, 2968, 2924, 2856, 1489, 1267, 1225 cm^{-1}; MS (*m*/*e*) 334 ($M^{+\cdot}$, 11); 251 (100); 91 (38); anal. calcd for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84; O, 9.57. Found: C, 82.51; H, 7.80.

*3.4.2. 6-Methoxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran* ***1b***

Compound **1b** was obtained from **9b** as a brown oil in 92% yield; δ_H ($CDCl_3$) 1.36 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.65–1.73 (m, 2H, CH_2), 1.69 (s, 3H, CH_3), 2.04–2.16 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 5.04–5.13 (m, 1H, –CH=), 5.55–5.60 (d, 1H, J = 9.9 Hz, =CH–), 6.27–6.32 (d, 1H, J = 9.9 Hz, =CH–), 6.52–6.72 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 17.5, 22.7, 25.6, 26.0, 40.9, 55.6, 78.0, 111.5, 114.1, 116.5, 121.7, 122.8, 124.1, 130.1, 131.5, 146.9, 153.5; IR 2968, 2925, 2856, 1492, 1266, 1226, 1198, 1041 cm^{-1}; MS (*m*/*e*) 258 ($M^{+\cdot}$, 10); 175 (100); 41 (9); anal. calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; O, 12.39. Found: C, 79.00; H, 8.48.

*3.4.3. 2,6-Dimethyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran* ***1c***

Compound **1c** was obtained from **9c** as a yellow oil in 95% yield; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.58–1.74 (m, 2H, CH_2), 1.66 (s, 3H, CH_3), 2.00–2.13 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 5.09–5.12 (m, 1H, –CH=), 5.51–5.56 (d, 1H, J = 9.9 Hz, =CH–), 6.28–6.32 (d, 1H, J = 9.9 Hz, =CH–), 6.64–6.90 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 20.4, 22.7, 25.6, 26.3, 41.1, 78.2, 115.8, 120.8, 122.8, 124.1, 126.7, 129.4, 129.5, 129.7, 131.5, 150.9; IR 2969, 2923, 2860, 1492, 1256 cm^{-1}; MS (*m*/*e*) 243 ($M^{+\cdot}$, 2), 159 (100), 41 (14); anal. calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15; O, 6.60. Found: C, 84.14; H, 9.11.

*3.4.4. 6-Cyano-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran* ***1d***

Compound **1d** was obtained from **9d** as a yellow oil in 94% yield; δ_H ($CDCl_3$) 1.33 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.58–1.66 (m, 2H, CH_2), 1.95–2.06 (m, 2H, CH_2), 4.95–5.03 (m, 1H, –CH=), 5.54–5.59 (d, 1H, J = 10.1 Hz, =CH–), 6.21–6.26 (d, 1H, J = 10.1 Hz, =CH–), 6.67–6.71 (d, 1H, J = 8.4 Hz, $C_{ar}H$), 7.13–7.14 (d, 1H, J = 2.0 Hz, $C_{ar}H$), 7.25–7.30 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 22.5, 25.5, 27.0, 41.2, 80.2, 103.4, 116.8, 121.1, 121.4, 123.4, 130.0, 131.0, 131.9, 146.9, 133.2, 157.0; IR 3301, 2971, 2927, 2857, 2226, 1601, 1487, 1276 cm^{-1}; MS (*m*/*e*) 253 ($M^{+\cdot}$, 13); 170 (100); 41 (22); anal. calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; O, 6.32. Found: C, 80.49; H, 7.58; N, 5.45.

*3.4.5. 6-Benzyloxy-2-methyl-2-(4,8-dimethylnona-3,7-dienyl)-2*H*-1-benzopyran* ***2a***

Compound **2a** was obtained from **10** as a brown oil in 90% yield; δ_H ($CDCl_3$) 1.36 (s, 3H, CH_3), 1.56 (s, 3H, $1CH_3$), 1.66 (s, 6H, $2CH_3$), 1.66–1.75 (m, 2H, CH_2), 1.89–2.09 (m, 6H, $3CH_2$), 4.98 (s, 2H, CH_2), 5.06–5.13 (m, 2H, 2CH=), 5.54–5.59 (d, 1H, J = 9.8 Hz, =CH–), 6.26–6.31 (d, 1H, J = 9.8 Hz, =CH–), 6.6–6.71 (m, 3H, $C_{ar}H$), 7.36–7.40 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 16.0, 17.6, 22.7, 23.3, 25.6, 26.4, 31.8, 39.6, 70.6, 78.0, 112.5, 115.2, 116.5, 122.8, 124.0, 125.0, 127.4, 127.5, 128.4, 130.6, 132.1, 135.5, 137.0, 145.9, 153.3; IR 3034, 2966, 2924, 2856, 1489, 1222 cm^{-1}; MS (*m*/*e*) 402 ($M^{+\cdot}$, 12); 251 (100); 91 (21); anal. calcd for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51; O, 7.95. Found C 83.45; H, 8.48.

*3.4.6. 6-Benzyloxy-2-methyl-2-(4,8,12-trimethyltrideca-3,7,11-trienyl)-2*H*-1-benzopyran **3***

Compound **3** was obtained from **11** as a brown oil in 88% yield; δ_H ($CDCl_3$) 1.33 (s, 3H, CH_3), 1.56 (s, 6H, $2CH_3$), 1.66 (s, 6H, $2CH_3$), 1.66–1.75 (m, 2H, CH_2), 1.94–2.06 (m, 10H, $5CH_2$), 4.96 (s, 2H, CH_2), 5.09–5.11 (m, 3H, 3CH=), 5.55–5.58 (d, 1H, J = 9.8 Hz, =CH–), 6.26–6.28 (d, 1H, J = 9.8 Hz, =CH–), 6.59–6.70 (m, 3H, $C_{ar}H$), 7.32–7.40 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 15.9, 17.5, 22.0, 23.3, 25.6, 26.0, 26.2, 26.6, 31.8, 39.6, 41.1, 70.6, 77.9, 112.6, 115.2, 116.5, 121.2, 122.8, 123.9, 124.3, 124.9, 127.3, 127.7, 128.3, 130.6, 131.0, 134.9, 135.6, 137.4, 147.1, 152.7; IR 3033, 2965, 2924, 2856, 1489, 1452, 1224 cm^{-1}; MS (*m*/*e*) 470 ($M^{+\cdot}$, 8), 251 (100), 91 (24); anal. calcd for $C_{33}H_{42}O_2$: C, 84.21; H, 8.99; O, 6.80. Found: C, 84.15; H, 8.89.

*3.5. General procedure for debenzylation of 2*H*-1-benzopyran*

To a solution of benzylated compound (2 mmol), EtSH (6 ml) in diethylether, was added $AlCl_3$ (6 mmol) at –30°C. After stirring for 30 min, the reaction mixture was poured into water and extracted with diethylether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated under vacuum and chromatographed on silica gel, eluting with a 80:20 (v/v) mixture of hexane:EtOAc.

*3.5.1. 6-Hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran **1e** (cordiachromene)*

Compound **1e** was obtained from **1a** as a brown oil in 82% yield; δ_H ($CDCl_3$) 1.35 (s, 3H, CH_3), 1.57 (s, 3H, $1CH_3$), 1.65 (s, 3H, CH_3), 1.66–2.06 (m, 4H, $2CH_2$), 4.75 (s, 1H, OH), 5.08 (m, 1H, CH=), 5.60–5.65 (d, 1H, J = 9.8 Hz, =CH–), 6.28–6.33 (d, 1H, J = 9.8 Hz, =CH–), 6.62–6.71 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 17.5, 22.5, 25.5, 25.8, 40.7, 78.0, 112.8, 115.6, 121.8, 122.5, 124.0, 130.8, 131.5, 146.7, 149.1; IR 3394, 3017, 2971, 2920, 2853, 1620, 1580, 1490, 1455, 1221 cm^{-1}; MS (*m*/*e*) 244 ($M^{+\cdot}$, 41), 161 (100); anal. calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25; O, 13.10. Found: C, 78.56; H, 8.33.

*3.5.2. 6-Hydroxy-2-methyl-2-(4,8-dimethylnona-3,7-dienyl)-2*H*-1-benzopyran **2b** (dictyochromenol)*

Compound **2b** was obtained from **2a** as a brown oil in 80% yield; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.58 (s, 6H, $2CH_3$), 1.67 (s, 3H, CH_3), 1.68–2.10 (m, 8H, $4CH_2$), 4.56 (s, 1H, OH), 5.00–5.15 (m, 2H, 2CH=), 5.54–5.59 (d, 1H, J = 9.9 Hz, =CH–), 6.22–6.27 (d, 1H, J = 9.9 Hz, =CH–), 6.47–6.62 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 16.3, 18.0, 22.9, 26.0, 26.3, 27.0, 40.0, 41.2, 78.5, 113.2, 115.7, 117.0, 115.6, 122.3, 124.3, 124.6, 131.3, 132.6, 135.6, 147.2, 149.6; IR 3350, 2966, 2923, 2855, 1590, 1495, 1240 cm^{-1}; MS (*m*/*e*) 312 ($M^{+\cdot}$, 41), 203 (100), 161 (70); anal. calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03; O, 10.24. Found C 80.65; H, 8.96.

*3.6. 6-Acetoxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran **12***

To a solution of **1e** (490 mg, 2 mmol), Et_3N (0.35 ml, 2.5 mmol), and DMAP (12 mg, 0.1 mmol) in dichloromethane (6 ml) was added acetic anhydride (0.24 ml, 2.5 mmol) dropwise. The reaction mixture was stirred for 3 h at room temperature. The reaction was then diluted with brine, and the organic layer was washed with 1N HCl, 10% $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed under vacuum, yielding 550 mg (96%) of **12** as a brown oil; δ_H ($CDCl_3$) 1.37 (s, 3H, CH_3), 1.57 (s, 3H, $1CH_3$), 1.66 (s, 3H, CH_3), 1.68–2.06 (m, 4H, $2CH_2$), 2.25 (s, 3H, CH_3CO), 5.09 (m, 1H, CH=), 5.55–5.60 (d, 1H, J = 9.8 Hz, =CH–), 6.26–6.30 (d, 1H, J = 9.8 Hz, =CH–), 6.68–6.77 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 17.5, 20.9, 22.7, 25.6, 26.4, 41.2, 78.7, 116.4, 119.0,

121.5, 122.2, 123.3, 124.0, 130.5, 131.5, 143.9, 150.7; IR 2966, 2922, 2856, 1763, 1486, 1204 cm^{-1}; MS (*m*/*e*) 286 ($M^{+\cdot}$, 7), 203 (100), 161 (94), 69 (6); anal. calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; O, 16.76. Found: C, 75.09; H, 7.83.

3.7. 6-Acetoxy-2-methyl-2-(4,8-dimethylnona-3,7-dienyl)-2H-1-benzopyran **13**

To a solution of **2b** (624 mg, 2 mmol), Et_3N (0.35 ml, 2.5 mmol), and DMAP (12 mg, 0.1 mmol) in dichloromethane (6 ml) was added acetic anhydride (0.24 ml, 2.5 mmol) dropwise. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then diluted with brine, and the organic layer was washed with 1N HCl, 10% $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed under vacuum, yielding 686 mg (97%) of **13** as a brown oil; δ_H ($CDCl_3$) 1.38 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.68–2.10 (m, 8H, $4CH_2$), 2.26 (s, 3H, CH_3CO), 5.00–5.15 (m, 2H, 2CH=), 5.56–5.61 (d, 1H, J = 9.9 Hz, =CH–), 6.26–6.31 (d, 1H, J = 9.9 Hz, =CH–), 6.68–6.77 (m, 3H, $C_{ar}H$); δ_C ($CDCl_3$) 14.9, 21.0, 21.1, 25.6, 26.4, 26.6, 39.6, 41.4, 78.7, 80.2, 116.5, 115.7, 118.9, 121.5, 123.0, 123.1, 123.8, 124.3, 124.6, 135.7, 143.9, 150.7, 169.8; IR 2967, 2924, 2856, 1764, 1486, 1204 cm^{-1}; MS (*m*/*e*) 354 ($M^{+\cdot}$, 9), 312 (13), 203 (92), 161 (100), 69 (33), 41 (58); anal. calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53; O, 13.54. Found: C, 77.88; H, 8.48.

3.8. Kinetic resolution of 2H-1-benzopyran acetate (R)-**12**

Racemic acetate **12** (400 mg, 1.4 mmol) was dissolved in diisopropyl ether (26 ml) saturated with water and lipase CCL (200 mg) was added. The reaction was followed by HPLC and stopped at 60% of hydrolysis (reaction time: 1.05 h). Then, the enzyme was filtered off, and the organic layer was dried ($MgSO_4$), concentrated under vacuum and chromatographed on silica gel, eluting with a 90:10 (v/v) mixture of hexane:EtOAc to provide *R*-(–)-**12** (60 mg, 0.42 mmol, ee 95%, $[\alpha]_D = -75.7$ (*c* 1.18, acetone)) and (*S*)-(+)-**1e** (187 mg, 0.76 mmol, ee 13%, $[\alpha]_D = +22.0$ (*c* 1.38, acetone)).

3.9. Deacetylation of 2H-1-benzopyran acetate **12**

Compound *R*-(–)-**12** (50 mg, 0.17 mmol) was dissolved in 2 ml of MeOH and sat. K_2CO_3 (2 ml) was added. The reaction mixture was stirred for 4 h until the analysis by TLC revealed complete disappearance of starting material. The reaction was then acidified with 1N HCl and diluted with diethyl ether (20 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under vacuum, yielding (*R*)-**1e** (42.2 mg, 99%) as a pale yellow oil; $[\alpha]_D = -109.1$ (*c* 0.95, $CHCl_3$); ee 95%.

3.10. Kinetic resolution of 2H-1-benzopyran acetate (R)-**13**

Racemic acetate **13** (1 g, 2.82 mmol) was dissolved in diisopropyl ether (55 ml) saturated with water and lipase CCL (485 mg) was added. The reaction was followed by HPLC and stopped at 60% of hydrolysis (reaction time: 1.10 h). Then the enzyme was filtered off, and the organic layer was dried ($MgSO_4$), concentrated under vacuum and chromatographed on silica gel, eluting with a 90:10 (v/v) mixture of hexane:EtOAc to provide (*R*)-**13** (200 mg, 0.56 mmol,

ee 98%, $[\alpha]_D = -74.3$ (*c* 1.24, $CHCl_3$)) and (*S*)-(+)-**2b** (520 mg, 1.6 mmol, ee 18%, $[\alpha]_D = +19.0$ (*c* 1.20, $CHCl_3$)).

3.11. Deacetylation of 2H-1-benzopyran acetate **13**

Compound (*R*)-**13** (190 mg, 0.53 mmol) was dissolved in 3 ml of MeOH and sat. K_2CO_3 (3 ml) were added. The reaction mixture was stirred for 4 h until the analysis by TLC revealed complete disappearance of starting material. The reaction was then acidified with 1N HCl and diluted with diethyl ether (30 ml).The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under vacuum, yielding (*R*)-**2b** (164 mg, 98%) as a pale yellow oil; $[\alpha]_D = -103.8$ (*c* 1.21, $CHCl_3$); ee 98%.

3.12. 9-Hydroxy-3-methyl-(4-methylpent-3-enyl)-3H-naphtho[2,1-b]pyran **14**

A mixture of 2,7-naphthalenediol (5 g, 31.2 mmol) and citral (4.9 g, 32 mmol) in 4-picoline (10 ml) was heated to reflux for 20 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (80 ml), and then washed with 1N HCl and brine. The organic layer was dried ($MgSO_4$), concentrated under vacuum and chromatographed on silica gel, eluting with a 80:20 (v/v) mixture of hexane:EtOAc to provide **14** (8.2 g, 90%) as an orange oil; δ_H ($CDCl_3$) 1.44 (s, 3H, CH_3), 1.58 (s, 3H, $1CH_3$), 1.66 (s, 3H, CH_3), 1.71–1.79 (m, 2H, CH_2), 2.13–2.17 (m, 2H, CH_2), 5.08–5.10 (m, 1H, CH=), 5.63–5.65 (d, 1H, J = 10 Hz, =CH–), 6.88–6.90 (d, 1H, J = 10 Hz, =CH–), 6.90–7.65(m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 17.5, 22.7, 25.6, 40.7, 78.4, 103.9, 112.4, 115.9, 118.5, 124.0, 124.5, 127.9, 129.0, 130.3, 131.6, 151.8, 154.2; IR 3386, 2968, 2924, 2855, 1636, 1210 cm^{-1}; MS (*m*/*e*) 294 ($M^{+\cdot}$, 12), 211 (100), 41 (5).

3.13. 9-Acetoxy-3-methyl-(4-methylpent-3-enyl)-3H-naphtho[2,1-b]pyran **15**

To a solution of **14** (4 g, 13.6 mmol), Et_3N (2.4 ml, 17 mmol), and DMAP (81 mg, 0.68 mmol) in dichloromethane (40 ml) were added dropwise acetic anhydride (1.6 ml, 17 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with brine, the organic layer was washed with 1N HCl, 10% $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed under vacuum, yielding 4.47 g (98%) of **15** as a yellow oil; δ_H ($CDCl_3$) 1.43 (s, 3H, CH_3), 1.56 (s, 3H, $1CH_3$), 1.66 (s, 3H, CH_3), 1.67–1.81 (m, 2H, CH_2), 2.12–2.15 (m, 2H, CH_2), 2.34 (s, 3H, CH_3CO), 5.07–5.09 (m, 1H, CH=), 5.63–5.65 (d, 1H, J = 10 Hz, =CH–), 6.90–6.92 (d, 1H, J = 10 Hz, =CH–), 7.00–7.72 (m, 5H, $C_{ar}H$); δ_C ($CDCl_3$) 17.6, 21.2, 22.7, 25.6, 26.0, 40.8, 78.5, 112.5, 113.5, 118.3, 118.4, 124.1, 127.0, 128.4, 129.0, 129.9, 131.8, 169.5; IR 2968, 2925, 2856, 1764, 1674, 1206 cm^{-1}; MS (*m*/*e*) 336 ($M^{+\cdot}$, 12), 253 (100), 211 (75), 43 (12), 41 (14).

3.14. Kinetic resolution of **15**

Racemic acetate **15** (900 mg, 2.6 mmol) was dissolved in diisopropyl ether (60 ml) saturated with water and lipase CCL (1.8 g) was added. The reaction was followed by HPLC and stopped after 96 h of hydrolysis. Then the enzyme was filtered off, and the organic layer was dried ($MgSO_4$), concentrated under vacuum and chromatographed on silica gel, eluting with a 90:10 (v/v) mixture of hexane:EtOAc to provide (*R*)-(+)-**15** (140 mg, mmol, ee 70%, $[\alpha]_D = +3.3$ (*c* 1.38, acetone)) and (*S*)-(–)-**14** (630 mg, mmol, ee 7%, $[\alpha]_D = -0.3$ (*c* 1.20, acetone)).

References

1. (a) Ames, S. R.; Ludwig, M. I.; Nelan, D. R; Robeson, C. D. *Biochemistry* **1963**, *2*, 188–190. (b) Machin, L. J.; Gabriel, E.; Brin, M. *J. Nutr*. **1982**, *112*, 1437–1440.
2. Ashood,V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. T.; Stemp, G.; Wihcoks, K. *J. Med. Chem*. **1986**, *29*, 2194–2201.
3. Holley, J. H.; Hadley, K. W.; Turner, C. E. *J. Pharm. Sci*. **1975**, 892–985.
4. Mc Hale, D.; Green, *J. Chem. & Ind.* **1962**, 1867.
5. Benslimane, A. F.; Pouchus, Y. F.; Le Boterff, J.; Verbist, J. F.; Roussakis, C.; Monniot, F. *J. Nat. Prod*. **1988**, *51*, 582–583.
6. (a) Iwai, I.; Ide, J. *Chem. Pharm. Bull*. **1962**, *10*, 926–933. (b) Iwai, I.; Ide, *J. Chem. Pharm. Bull*. **1963**, *11*, 1042–1049. (c) Anderson, W. K.; Lavoie, E. J. *J. Org. Chem*. **1973**, *38*, 3832–3835. (d) Anderson, W. K.; Lavoie, E. J.; Whitkop, P. J. *J. Org. Chem*. **1974**, *39*, 881–884. (e) Brown, P. E.; Lewis, R. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 573–577. (f) Zsindley, J.; Schmid, H. *Helv. Chim. Acta*. **1968,** *51*, 1510–1514. (g) Kahn, H. P.; Cossy, J. *Tetrahedron Lett*. **1999**, *40*, 8113–8114.
7. (a) Elsohly, M. A.; Boeren, E. G.; Turner, C. E. *J. Heterocyclic Chem*. **1978**, *15*, 699–700. (b) Kane, V. V.; Razdan, R. K. *J. Am. Chem. Soc*. **1968**, *90*, 6551–6553. (c) Crombie, L.; Ponsford, R. *J. Chem. Soc., Chem. Commun*. **1968**, 894–895. (d) Crombie, L.; Ponsford, R. *J. Chem. Soc. (C)* **1971**, 796–804.
8. Garcias, X.; Ballester, P.; M. Saà, J. *Tetrahedron Lett*. **1991**, *52*, 7739–7742.
9. (a) Hoger, S. *Liebigs Ann./Recueil* **1997**, 273–277. (b) Oberhausser, T. *J. Org. Chem*. **1997**, *62*, 4504–4506.
10. Fuji, K.; Ichikawada, K.; Node, N.; Fujita, E. *J. Org. Chem*. **1979**, 1661–1663.
11. Mizuguchi, E.; Takemoto, M.; Achiwa, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1961–1964.
12. (a) Cannon, J. R.; Joshi, K. R.; McDonald, I. A.; Retallack, R. W.; Sierakowski, A. F.; Wong, L. C. *Tetrahedron Lett*. **1975**, 32, 2795–2798. (b) Jacobsen, E. N.; Vander Velde, S. L. *J. Org. Chem*. **1995**, *60*, 5380–5381.