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The tetrahydropyranyl-protected mandelic acid: a novel versatile chiral derivatising agent

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Abstract

A simple synthesis of (2R)-2-phenyl-2-[(2S)-tetrahydro-2-pyranyloxy]ethanoic acid, a versatile chiral derivatising agent (CDA), is proposed. The derivatisation of secondary alcohols aimed at the absolute configurational assignment, determination of enantiomeric purity as well as semipreparative resolution is described. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The routine tasks encountered in studying chiral compounds are: (1) the absolute configurational assignment of stereogenic centres; (2) determination of the enantiomeric purity of the substances obtained; and (3) semipreparative separation of the enantiomers of bioactive compounds (potential drugs, insect attractants, etc.), all of them to be tested as samples of high enantiomeric excess.[1] The goal of our recent studies has been the development of techniques using a CDA for an integrated approach to these tasks[2] resulting often in the optimal preparation of samples with required enantiomeric excess (up to gram-scale) together with their stereochemical characterisation.

For analytical purposes α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA; Mosher's acid)[3] is the most preferable CDA for the derivatisation of secondary alcohols and amines because of its resistance to racemisation. α-Methoxyphenylacetic acid (MPA) as a CDA has been found to satisfy the needs of all three procedures (despite the more stringent requirements to derivatisation methodology in order to avoid racemisation)[2] being increasingly popular especially for absolute configurational assignment using

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NMR spectroscopy.[2,4] In addition, chiral solvating agents offer a useful method for NMR analysis of chiral compounds without derivatisation.[4a]

However, in certain cases, the use of these CDAs can be considered disadvantageous because: (1) they are relatively expensive to be used in preparative applications; (2) differences between the NMR spectra[5] of diastereomers tend to be less in the case of O-methylated derivatives of mandelic acid (MA) than for those having an unprotected hydroxyl group; and finally, (3) the possibility of further derivatisation[6] of the diastereomer prepared is practically ruled out for the derivatives of O-methylated MA.

The use of unprotected MA as a CDA has been documented by only a few examples.[7–9] This is evidently related to the harsh conditions needed for the direct esterification, as well as the problem of controlling the composition of the product due to the presence of the hydroxyl group alongside the carboxylic acid moiety in MA. The direct esterification has given satisfactory results in the resolution of simple chiral secondary alcohols[7,8] being evidently unsuitable for the mandoylation of more labile complex molecules. The shortcomings related to the esterification of acid-sensitive compounds as well as to the uncontrolled chemoselectivity of the direct mandoylation were overcome by using O-acetyl MA as a CDA[7a] (often giving rise to higher NMR chemical shift non-equivalence of diastereomers than the O-methyl MA). To produce free mandelates the acetyl group has to be selectively removed by thiolysis which is the drawback of the method.

Treatment of a chiral bicyclic hydroxyketone[9] and nonchiral aldehydes[10] with an enantiomerically pure MA under catalysis by a strong acid with simultaneous azeotropic removal of water has been reported to afford readily separable isomers of the corresponding dioxolanone in a regio- or (and) stereoselective, respectively, manner along with a minute amount (<5%) of diastereomeric mandelates in the former case.

The esterification procedure via bissilylation[11] of a homochiral MA followed by the selective chlorination of the dimethyl(*tert*-butyl)silyl ester moiety with an oxalyl chloride–DMFA mixture affording the acid chloride to be further coupled with a hydroxy compound has been studied by us.[12] Unfortunately, yields of the esters obtained varied due, most probably, to complications connected with the removal of residues of the highly reactive oxalyl chloride. Attempts to analyse the silylated diastereomeric mandelates by HPLC failed. Although the corresponding homochiral mandelates (for instance, **10** and **11**, Scheme 3) were readily obtained upon the cleavage of silyl ether by a dilute hydrofluoric acid[13] followed by chromatography, this approach had to be rejected as being unreliable, not technically simple or inexpensive enough.

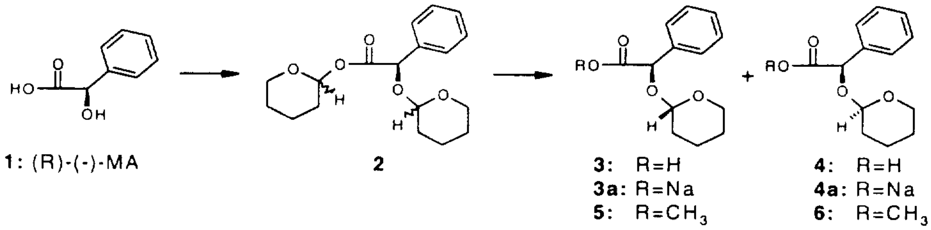
Our further search for a better approach resulted in the finding that tetrahydropyranylation is a suitable protecting method for MA to be used for derivatisation under mild conditions. The present study was aimed at: (1) the preparation of an individual diastereomer of tetrahydropyranyl-protected MA (THPMA); (2) the description of the stereochemistry of the diastereomers of THPMA by using NMR spectrometric approach combined with computational chemistry methods; and (3) the characterisation of some applications of THPMA as a CDA to the preparation of diastereomeric THP-mandelates and mandelates for the absolute configurational assignment and semipreparative resolution of secondary alcohols, as well as the estimation of their enantiomeric purity.

2. Results and discussion

2.1. Synthesis and the absolute configurational assignment of THPMA

The THPMA methyl esters have been prepared,[14,15] starting from (+)-MA, by the tetrahydropyranylation of the enantiomerically pure ester. Diastereomers obtained were separated by chromatography and the absolute configuration of the THP group of one of the diastereomers was assigned by X-ray crystallography.[16]

Our initial goal was to prepare a diastereomeric mixture of THPMA to be used in the preparative synthesis of MA esters. (−)-MA **1** was tetrahydropyranylated[17] (Scheme 1) to afford a diastereomeric mixture of THP-esters **2** which was hydrolysed by alkali to sodium carboxylates **3a+4a**. The product was washed with $CHCl_3$ to remove non-acidic contaminants from the alkaline water solution of **3a+4a**, which was further acidified under simultaneous extraction with $CHCl_3$. Washing the $CHCl_3$ extract of **3+4** with water to remove hydrophilic impurities (MA, etc.) afforded a crude diastereomeric mixture of THPMA suitable for preparative derivatisation without further purification. No detectable racemisation was found to occur under the conditions of the synthesis.[18]



Scheme 1. Tetrahydropyranylation of mandelic acid

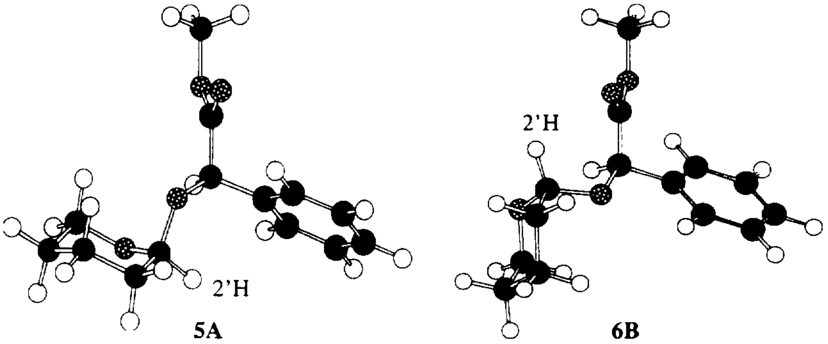
Somewhat unexpectedly, one of the acid diastereomers, the THPMA **3**, was readily separated (up to 94–98% purity) from the crude product by single crystallisation over 2–3 h (crystallisation during a prolonged period has given the product of a significantly lower diastereomeric purity in some cases). The recrystallisation of **3** afforded the target compound in over 99% diastereomeric purity estimated by the HPLC of the corresponding methyl esters **5** and **6**.[19] The enantiomeric excess (e.e.) of THPMA **3** was found to be >98%.[20] The pure crystalline diastereomer **3** was stable during a prolonged storage at 4°C while the crystalline mixture of **3** and **4** (3:1) decomposed to a significant extent under the same conditions.

The preliminary absolute configurational assignment of the THP group in THPMA **3** was based on the statement that on TLC the methyl ester **5** derived[21] from the acid **3** was the more polar diastereomer. The less polar THPMA methyl ester diastereomer was assigned by X-ray analysis to be of a 2S,2′S configuration[16] allowing us to assign the THPMA **3** as being the (2R,2′S)-THPMA, respectively.

The independent assignment of the absolute configuration of **3** was performed by using computational chemistry methods combined with NMR studies[22] of diastereomeric THPMA methyl esters relying on the X-ray crystallographic data for the methyl ester.

The conformational analysis of esters **5** and **6** were performed by the AM1 minimisation of energies[23] of the numerous conformers generated by the DGEOM95 program.[24] The minimum energy geometries **5A** and **6B** (Scheme 2) obtained from calculations for **5** and **6**, respectively, were compared with the results of NMR analysis (Table 1). The ring-current effects caused by the phenyl group were in good agreement with the geometries **5A** and **6B**. This conclusion can best be explained by the difference in the chemical shifts corresponding to the 2′-hydrogen atom of **5** and **6** being 4.58 and 4.90 ppm, respectively. Examination of the conformers **5A** and **6B** shows that in the former case the 2′H is shielded by the phenyl ring, while the shielding of 2′H is ruled out for **6B**. The same is also true for 3′-hydrogens: chemical shift values are 1.71 ppm for **5** and 1.83 ppm for **6**. The energetically most favoured conformer **6B** of the 2R,2′R diastereomer was also found to be very close (a mirror image) to that determined by the X-ray analysis for the THPMA methyl ester of the 2S,2′S configuration.[16] The results of NMR measurements of the above ring-current effect in the case of the parent THPMAs (**3**) and (**4**) (Table 1) are in very good agreement with the data recorded for the methyl esters **5** and **6**.

Thus, by comparison of conformers **5A** and **6B**, evidently being close to those occurring for the



Scheme 2. The most favoured conformers **5A** and **6B** calculated for the diastereomeric THPMA methyl esters **5** and **6**, respectively

Table 1
The ^{13}C and ^{1}H chemical shifts[a] of THPMAs **3**, **4** and THPMA methyl esters **5**, **6**[25]

Comp.	(2R)-2-Phenyl-2-[(2S)-tetrahydro-2-pyranyloxy]ethanoic acid (3)		(2R)-2-Phenyl-2-[(2R)-tetrahydro-2-pyranyloxy]ethanoic acid (4)		Methyl (2R)-2-Phenyl-2-[(2S)-tetrahydro-2-pyranyloxy]-ethanoate (5)		Methyl (2R)-2-Phenyl-2-[(2R)- tetrahydro-2-pyranyloxy]ethanoate (6)	
Atom	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$
1	174.53	—	176.17	—	171.04	—	171.71	—
2	76.59	5.27	75.56	5.35	76.71	5.243	75.52	5.345
s	135.58	—	136.16	—	136.24	—	136.71	—
ortho	127.53	7.45	127.20	7.51	127.24	7.46	127.11	7.50
meta	128.64	7.37	128.84	7.35	128.47	7.36	128.40	7.37
para	128.50	7.37	128.52	7.34	128.50	7.32	128.28	7.34
2' [b]	96.95	4.61 (3.6)	97.39	4.93 (3.0)	96.51	4.58 (3.6)	97.03	4.90 (3.1)
3'	30.19	1.71/1.73	30.08	1.81	30.14	1.71	30.08	1.83
4'	19.16	1.54/1.92	18.60	1.55/1.86	18.96	1.53/1.94	18.58	1.56/1.88
5'	25.11	1.59	25.17	1.48/1.60	25.20	1.57	25.23	1.49/1.62
6'	62.74	3.55/3.96	62.02	3.50/3.69	62.20	3.51/3.95	61.80	3.51/3.70
OCH_3	—	—	—	—	52.06	3.698	52.05	3.708

a: $CDCl_3$, RT (see ref. 22);
b: The $^{3}J_{HH}$ value to 3'H protons is given in parentheses. It indicates that 2'H is equatorial.

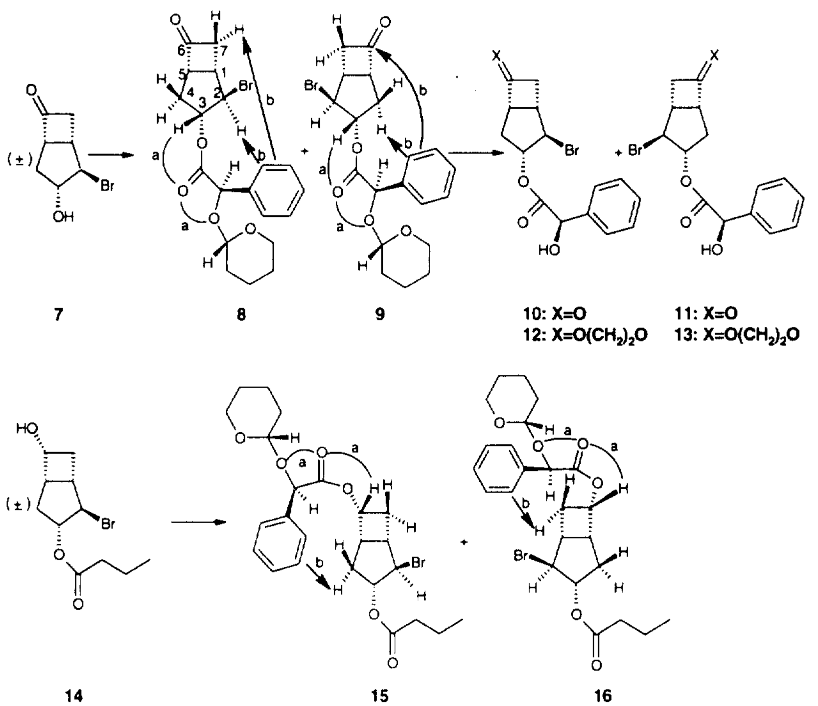
corresponding acid diastereomers, we should conclude that the exceptional crystallisability of the THPMA **3** may be related to the ease of stacking of the acid molecules having the cyclic fragments parallel as for conformer **5A**.

2.2. Derivatisation of bicyclic alcohols

Two bicyclic secondary alcohols, bromohydrin **7**[26] and hydroxy butyrate **14**,[27,28] were derivatised with THPMA (**3**) in order to study diastereomeric esters for NMR spectroscopic as well as chromatographic behaviour.

The esterification of **7** and **14**[20] (Scheme 3) with THPMA **3** proceeded readily under the conditions of the carbodiimide method[21] giving quantitative access to the THP-mandelates[25] **8**, **9** and **15**, **16**, respectively, when 1.5 eq. of **3** was used. Neither the kinetic differentiation of the optical antipodes of bromohydrin **7** by the reagent[29] nor the detectable racemisation of the THP-mandoyl moiety was found to occur throughout esterification.[20]

The ratio of diastereomeric THP-mandelates **8**/**9** and **15**/**16** was found to be easily estimated by both NMR spectroscopy and HPLC.[30] The preparative separation of diastereomers **8** and **9** can be performed by conventional column chromatography over silica, while for the separation of diastereomers **15** and **16** only the HPLC approach can be suggested. The mandelates[9,31] **10** and **11** obtainable upon acidic



a: the arc line indicates coplanar fragments of the molecule;
b: the atoms showing the greatest differential shielding effects in the NMR spectra caused by the ring-current influence of the phenyl group are indicated by the arrows.

Scheme 3. Derivatisation of bicyclic alcohols with THPMA **3**

deprotection[32] of THP-mandelates **8** and **9** have been ketalised under conventional conditions to afford diastereomers **12** and **13** of good separability on silica. The separation factor, α, of up to 1.55 has been obtained when using a C_6H_6/EtOAc mixture as an eluent.[31] The diastereomer **12** has been further treated with alkali[33] to afford the corresponding homochiral endo-epoxide, a known synthon for a number of biologically active compounds.[34]

NMR spectroscopic studies of diastereomeric THP-mandelates **8**, **9** and **15**, **16** have proved the validity of the same conformational model for the absolute configurational assignment by NMR as stated for the MA esters (in good approximation; see the ^{13}C NMR spectra[25] of **10**, **11**) as well as MPA esters[2] of secondary alcohols. Thus, the carbinyl hydrogen, the carbonyl oxygen of the THP-mandoyl moiety and the oxygen atom attached to the C_2 of the THP-mandoyl group can be considered to be coplanar (Scheme 3) for the preferred conformer in solution. The most significant appearance of the ring-current diamagnetic shielding effect caused by the phenyl group (Scheme 3: indications with arrows) on ^1H chemical shifts were observed for the 7-endo hydrogen atom of **8** situated close to the phenyl ring (stated also by the examination of molecular models) and showed therefore an exceptionally large upfield shift: 2.28 ppm for **8** versus 2.92 ppm for **9** (Table 2). For the diastereomers **15** versus **16** the most prominent upfield shift of ^{13}C and ^1H resonances can be observed for C_4 and the endo-hydrogen attached to C_4.

In conclusion, the above NMR results prove the suitability of THPMA **3** as a CDA for the derivatisation of bicyclic secondary alcohols aimed at the absolute configurational assignment. It has been stated that diastereomeric THP-mandelates can readily be analysed by HPLC; some of them are separable by low-pressure liquid chromatography over silica gel, while the corresponding diastereomeric MA esters usually show better separability on silica.

Table 2
The ^{1}H and ^{13}C NMR chemical shifts of the diastereomeric THP-mandelates of alcohols **7** and **14**

Compound No	**8**		**9**		**15**		**16**	
Atom No.	δ^{13}C	δ^1H	δ^{13}C	δ^1H	δ^{13}C	δ^1H	δ^{13}C	δ^1H
bicyclic skeleton: 1	38.94	3.27	39.09	3.32	42.24	2.83	42.33	2.85
2	53.91	4.09	54.02	4.34	56.31	4.13	56.31	4.15
3	83.08	5.51	83.39	5.45	84.18	5.39	84.24	5.45
4	33.60	2.547x/2.273n	33.60	2.550x/2.205n	28.55	2.27x/1.67n	28.90	2.45x/1.97n
5	63.68	3.79	63.74	3.82	44.29	3.32	44.38	3.41
6	209.42	—	209.06	—	65.00	5.09	65.41	5.05
7	52.23	2.94x/2.28n	52.46	3.16x/2.92n	32.64	2.53x/2.24n	32.45	2.49x/2.21n
mandelate: CO	168.81	—	169.31	—	169.79	—	169.98	—
α	76.55	5.11	77.65	5.03	76.42	5.19	76.88	5.16
s	135.43	—	135.50	—	136.27	—	136.23	—
ortho	127.76	7.39	127.01	7.40	127.59	7.43	127.40	7.44
meta	128.78	7.38	128.61	7.37	128.62	7.36	128.58	7.36
para	128.89	7.33	128.68	7.34	128.77	7.34	128.66	7.34
THP: 2	96.48	4.50	97.70	4.60	96.29	4.13	96.94	4.15
3	30.12	1.64	30.12	1.72	30.22	1.71	30.22	1.71
4	19.19	1.49/1.90	18.87	1.52/1.93	19.03	1.54/1.93	19.04	1.54/1.93
5	25.16	1.56	25.13	1.59	25.29	1.58	25.25	1.58
6	62.57	3.50/3.91	62.32	3.47/3.94	62.31	3.50/3.93	62.31	3.50/3.93
butyrate: CO					172.14	—	172.20	—
α					36.25	2.27	36.22	2.24
β					18.29	1.66	18.26	1.66
ω					13.71	0.99	13.71	0.98

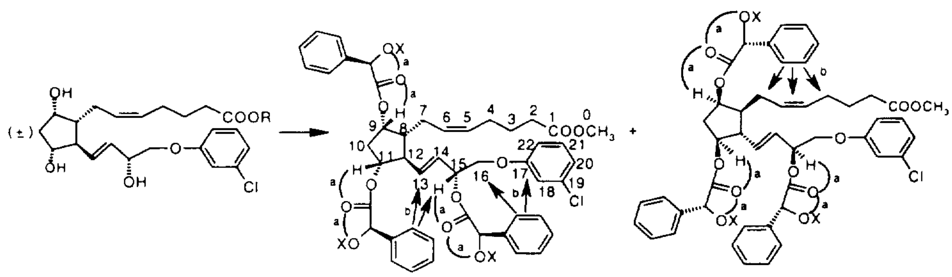
2.3. *Derivatisation of polyol compounds*

The derivatisation of cloprostenol **17** with THPMA was aimed at the semipreparative resolution of this highly potent luteolytic drug[35] as well as at the stereochemical studies of the derivatives.

A racemic cloprostenol[36] (Scheme 4) was esterified under pTsOH catalysis in methanol, the corresponding methyl ester **18** was purified and THP-mandoylated with the diastereomeric mixture of THPMA.[21] The diastereomeric mixture of CDA was used because based on the previous results we suggested better chromatographic separability of free trismandelates **21**/**22** than of THP-protected ones. Thus, the THP groups of **19** and **20** were cleaved on the acidic hydrolysis.[32] The resulting cloprostenol methyl ester trismandelates **21** and **22** were separated by short-column chromatography over silica (TLC: R_f 0.18 and 0.27, eluent $CHCl_3$:EtOAc=2:1 were determined for **21** and **22**, respectively) and further purified by semipreparative HPLC[37] in order to isolate the minute amounts of impurities detected. HPLC as well as NMR analysis established the resulting trismandelates **21** and **22** to be pure compounds. The alkaline hydrolysis of esters **21** and **22** afforded (D)-(+)-cloprostenol and (L)-(−)-cloprostenol, respectively, in satisfactory yield.[38] This final assignment of the absolute configuration of these known products by polarimetric results was in accordance with our results of the absolute configurational assignment by the NMR spectra of trismandelates **21** and **22** (Table 3; Scheme 4). Regions of the molecules affected by the ring-current influence of the phenyl groups of the mandoyloxy moieties were identified.

2.4. *Derivatisation of aliphatic alcohols*

The derivatisation of aliphatic secondary alcohols with THPMA **3** as a CDA was first checked on 2-butanol **23** (Scheme 5). The diastereomeric THP-mandelates[25] **24** and **25** obtained were separable by HPLC[30] showing differences of expected regularity[20] between their NMR spectra.[39] The derivatisation[20,29] of 1-octyn-3-ol[40] **26** with THPMA **3** and related chiral moieties were aimed at a



17: R=H
18: R=CH3

19: X=THP
21: X=H

20: X=THP
22: X=H

a: the arc line indicates coplanar fragments of the molecule;
b: the atoms showing the greatest differential shielding effects in the NMR spectra caused by the ring-current influence of the phenyl group are indicated by the arrows.

Scheme 4. Synthesis of diastereomeric cloprostenol methyl ester trismandelates

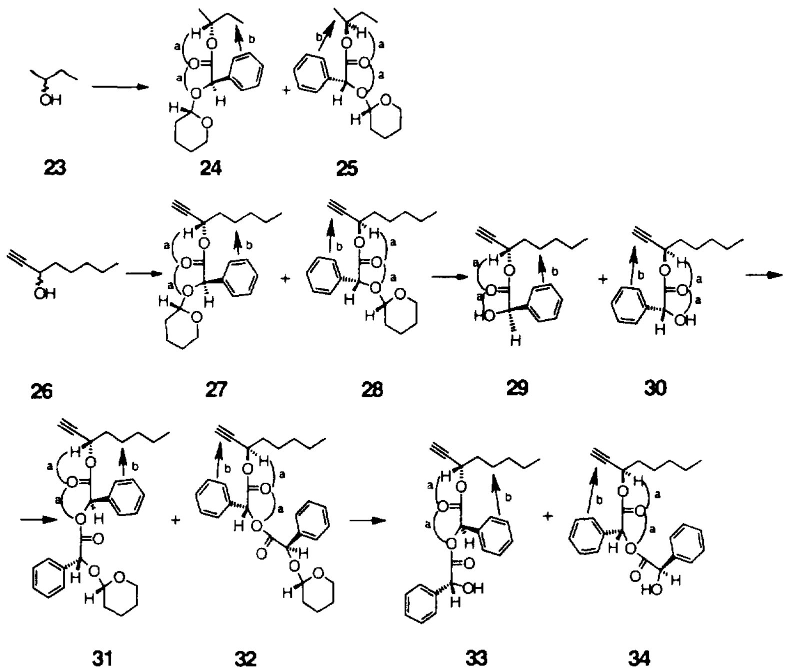
Table 3
The ^{1}H and ^{13}C NMR chemical shifts of diastereomeric cloprostenol methyl ester trismandelates **21** and **22**

Atoms of the cloprostenol framework									
Comp. No.	**21**		**22**		Comp. No	**21**		**22**	
Atom No.	δ^{13}C	δ^{1}H	δ^{13}C	δ^{1}H	Atom No.	δ^{13}C	δ^{1}H	δ^{13}C	δ^{1}H
0	51.59	3.82	51.53	3.82	12	51.84	2.44	51.85	2.37
1	174.14	—	174.11	—	13	134.40	5.69	133.27	5.04
2	33.29	2.47	33.23	2.35	14	126.50	5.22	126.04	5.54
3	24.56	1.82	24.46	1.69	15	72.83	5.60	72.96	5.77
4	26.53	2.18	26.15	1.74	16	68.44	3.74/3.76	68.80	4.15/4.17
5	130.62	5.54	130.05	5.26	17	158.58	—	158.88	—
6	127.05	5.44	126.83	4.94	18	115.02	6.75	115.06	7.06
7	24.71	2.18/2.25	23.87	1.30/1.69	19	134.71	—	134.91	—
8	47.70	1.84	48.28	1.29	20	121.42	7.09	121.58	7.14
9	76.03	5.35	76.09	5.16	21	130.10	7.30	130.31	7.38
10	38.22	1.61s/2.62a	38.52	1.64s/2.37a	22	112.93	6.65	113.16	6.94
11	78.32	5.06	79.36	4.83					

Atoms of mandoyloxy groups				
Comp. No.	**21**		**22**	
Atom No.	δ^{13}C	δ^{1}H	δ^{13}C	δ^{1}H
CO	173.04 / 172.77 / 172.59	—	173.10 / 172.74 / 172.51	—
α	72.88 / 72.86 / 72.27	5.30 / 5.36 / 5.01	72.90 / 72.86 / 72.56	5.26 / 5.37 / 4.79
s	138.18 / 138.12 / 137.96	—	138.52 / 138.11 / 138.11	—
ortho	126.22 / 126.34 / 126.60	7.44 / 7.54 / 7.62	126.43 / 126.58 / 126.70	7.43 / 7.54 / 7.57
meta	128.37 / 128.47 / 128.64	7.49 / 7.43 / 7.59	128.39 / 128.54 / 128.75	7.47 / 7.49 / 7.55
para	128.33 / 128.40 / 128.62	7.50 / 7.41 / 7.52	128.39 / 128.44 / 128.78	7.47 / 7.47 / 7.55

comparison of differential shielding effects from THPMA esters[25,41] **27** and **28**, MA esters[25,41] **29** and **30**, MPA esters[25,41] **35** and **36**, MTPA esters[4] as well as from THP-mandoylmandelic acid (THPMMA) esters[25,42] **31** and **32** and mandoylmandelic acid (MMA) esters[25,42] **33** and **34**.

The compilation of differential ^{1}H and ^{13}C shielding values from different CDAs on 1-octyn-3-ol is given in Table 4. It should be stressed that a complete picture gives a reliable basis for the assignment of the absolute configuration and it can generally be obtained by using ^{1}H–^{1}H and ^{13}C–^{1}H 2D FT diagrams only.[4] Data given in Table 4 show that MA, THPMA, THPMMA and MMA all follow the regularities observed in MPA esters and are opposite to those of MTPA esters. The shielding effects observed for the ^{1}H and ^{13}C atoms along the octynol chain of the molecule are the greatest for MA esters due probably to the existence of the energetically most stabilised (by the intramolecular hydrogen bond) basic conformation. It should also be noted that the greatest differential shielding values are observed for both ^{1}H and ^{13}C at the β position to the carbinyl carbon for all the esters studied.



a: the arc line indicates coplanar fragments of the molecule;
b: the atoms showing the greatest differential shielding effects in the NMR spectra caused by the ring-current influence of the phenyl group are indicated by the arrows.

Scheme 5. Derivatisation of aliphatic secondary alcohols with THPMA 3

Table 4
A differential shielding (in ppm) on the ^{1}H and ^{13}C nuclei in the diastereomeric 1-octyn-3-ol esters

Atom No.		Δδ						
Derivatives		1	2	4	5	6	7	8
MPA **(35)**, **(36)**	C	-0.019	0.373	0.002	0.345	0.122	0.091	0.059
	H	0.091	—	0.146	0.239	0.152	0.123	0.071
MA **(29)**, **(30)**	C	0.072	0.456	-0.060	0.400	0.209	0.125	0.094
	H	0.139	—	0.170	0.310	0.190	0.160	0.097
THPMA **(27)**, **(28)**	C	0.008	0.310	0.011	0.270	0.161	0.093	0.068
	H	0.096	—	0.135	0.236	0.148	0.122	0.074
MTPA[4]	C	0.055	0,252	-0.010	0.259	0.091	0.050	0.032
	H	0.050	—	0.060	0.122	0.070	0.060	0.040
THPMMA **(31)**, **(32)**	C	0.151	0.192	0.061	0.261	0.107	0.074	0.048
	H	0.086	—	0.189	0.226	0.139	0.110	0.060
MMA **(33)**, **(34)**	C	0.158	0.199	<0.02	0.257	0.099	0.075	0.051
	H	0.090	—	0.167	0.239	0.140	0.121	0.067

The positive differences indicate regular behaviour according to the accepted conformational model of MPA (MA, THPMA, THPMMA, MMA) and MTPA. The negative values indicate deviations from this model.

The differential shielding effects observed for the THPMMA and MMA esters can be used for the absolute configurational assignment of a stereogenic centre despite the influence of the phenyl group of the terminal mandoyl moiety diminishing primary shielding effects.

Thus, it can be concluded that the best possibilities for the absolute configurational assignment are afforded by using MA esters. THP-mandelates, in turn, are comparable to MTPA esters giving somewhat worse results than MPA esters.

3. Conclusions

- A simple method for the preparation of an enantiomerically pure THP-protected mandelic acid **3** has been proposed.
- THPMA **3** has been shown to be a versatile chiral derivatising agent for secondary alcohols allowing us to prepare diastereomeric THP-protected mandelates and mandelates suitable for analysis, the absolute configurational assignment and the semipreparative optical resolution.
- The absolute configurational assignment of chiral secondary alcohols has been discussed in the case of some THPMA and MA esters. The conformational model of THPMA esters was found to be close to that of mandelates and O-methyl mandelates.

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6. MMA esters have been described[8] as being readily separable from diastereomeric impurities by crystallisation affording a simple way to diminish (gradually) the influence of the optical impurity of CDA on the enantiomeric excess of the target alcohol by introduction of two (or more) CDA molecules. See also Refs. 1 and 38.
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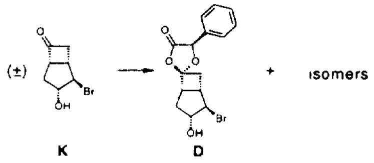

Characterisation of D: ^{13}C NMR ($C_{1\text{-}7}$, $C_{1',2',5',\text{ortho,meta,para}}$); 39.68, 58.77, 82.65, 32.28, 51.70, 109.37, 41.40, 170.44, 76.24, 133.70, 126.46, 129.01, 129.55; IR; 3500, 3060, 3030, 2970, 2935, 2920, 1780, 1500, 1330, 1300, 1200, 1130, 960, 770, 700, 610, 500 cm^{-1}; mp=92±1°C; $[\alpha]_{546}^{20}$ − 52.5 (c 0.7, C_6H_6); TLC, R_f=0.381 (C_6H_6:EtOAc:pyridine 100:3:0.5); R_f-s 0.314, 0.266, 0.238 were measured for three other isomeric products under the same conditions.
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17. Synthesis of (2R)-2-phenyl-2-[(2S)-tetrahydro-2-pyranyloxy]ethanoic acid: To benzene (100 ml) in a single-necked round-bottomed flask (R)-(−)-MA (5 g, 32.86 mmol) was added followed by 3,4-dihydro-2H-pyran (9.4 ml, 103 mmol) and pTsOH (10 mg). MA dissolved over one hour, stirring was continued for one more hour at RT. Et_3N was added and the volatile material was carefully removed under vacuum on a rotary evaporator; the oily residue was dissolved in acetone (100 ml) and the NaOH solution (40 ml, 1 N) was added. After stirring at RT for two hours acetone was evaporated, H_2O (50 ml) was added and the alkaline solution was extracted with $CHCl_3$ (3×50 ml). To the remaining water solution $CHCl_3$ (120 ml) was added. The flask was introduced in a water-bath at RT and the $NaHSO_4$ water solution (45 ml, 1 M) was added under vigorous stirring. The organic layer was separated and the water solution was extracted with $CHCl_3$ (2×50 ml). The $CHCl_3$ extracts were combined and washed with H_2O (2×50 ml) and the brine. The extract was dried over anhydrous Na_2SO_4, filtered, evaporated and the oily residue was crystallised on stirring at +4°C from CCl_4/n-hexane solution (the crude product was dissolved in 8 ml of CCl_4 and 12 ml of n-hexane was added). The **THPMA** (**3**) (3.4 g) was obtained in ~95% diastereomeric purity. The recrystallisation of this product afforded THPMA (**3**) (2.9 g; yield 37%) with homogeneity >99% (mp=104°C; C 66.02%, H 6.79%; theor.; C 66.09%, H 6.83%). The dissolution of the product to be recrystallised should be assisted by a low-boiling, more powerful solvent than CCl_4 (acetone, for instance) that could easily be evaporated prior to addition of n-hexane.
18. A sample of individual THPMA **3** was stirred in the NaOH water solution (2 N) at RT for 48 hrs. The solution was acidified with $NaHSO_4$ and THPMA was isolated.[17] The specific rotation value of the product was established to be close to that of the starting material. The product was further methylated[21] and analysed by HPLC.[19] The diastereomeric purity (~99/1) was found to have remained practically unchanged during the alkaline treatment proving the occurrence of no detectable racemisation throughout the above procedures.
19. The HPLC analysis of THPMA methyl esters was performed instead of that of free acids **3** and **4** because of the complications encountered on looking for HPLC conditions for the analysis of the latter which still remained unreliable in our hands.
20. The absolute configurational assignment of diastereomers by NMR was verified by the HPLC identification of the major/minor components of the samples using the standards synthesised starting from the enantiomerically pure (+)-(**7**)[26] and the enantiomerically enriched (+)-(**14**)[27,28] and (−)-(**26**)[40] of known configuration. The individual diastereomer (**8**) of >99% diastereomeric purity (by HPLC) was obtained showing the high optical purity of (**3**) as well as the occurrence of undetectable racemisation throughout derivatisation. The assignment of 2-butanol esters (**24**), (**25**) is based on the NMR study and it fits nicely the systematic study of the regularities found in the MPA esters of homological secondary aliphatic alcohols from butanol to decanol.
21. The procedure used for the acylation of alcohols with THPMA (**3**): synthesis of the THP-mandelates **8** and **9**. N,N′-Dicyclohexylcarbodiimide (464 mg; 2.25 mmol) was introduced to dry THF (4.5 ml) stirred by a magnetic stirrer. THPMA **3** (354 mg; 1.5 mmol) was added followed by bromohydrin **7** (206 mg; 1.0 mmol) and 4-dimethylaminopyridine (12 mg; 0.1 mmol). The mixture was stirred at RT for 16 h. A quantity (30 ml) of EtOAc was added, the N,N′-dicyclohexylurea was filtered off and the solution was washed with $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered and evaporated to afford crude THP-mandelates (**8**) and (**9**) which were purified over silica (eluent; benzene:EtOAc 98:2). The total yield of esters was 96.3% (408 mg).
22. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution at room temperature on a Bruker AMX500 instrument. ^1H–^1H and ^1H–^{13}C 2D FT correlation diagrams were used for the full assignment of ^1H and ^{13}C chemical shifts.
23. Energy minimisations were carried out using a semi-empirical method: Austin Method 1 (AM 1), M. J.S. Dewar et al. *J. Am. Chem. Soc.*, **1985**, 107, 3902.
24. Conformational space of **5** and **6** was scanned by using the DGEOM95 package (Chiron Corp.©95).
25. Characterisation of compounds. **1**: (R)-(−)-mandelic acid, a commercial product (Merck, Germany); **3**: for NMR data see Table 1; **IR** (KBr) 3440, 3040, 2950, 2870, 1730, 1640, 1500, 1460, 1420, 1400, 1360, 1300, 1270, 1210, 1180, 1140, 1120, 1080, 1060, 1030, 1020, 980, 950, 910, 870, 810, 800, 780, 720, 700, 680, 580 cm^{-1}; mp=104°C; $[\alpha]^{20}_{546}$ −254 (c 1.0, $CHCl_3$); **4:** for NMR data see Table 1; **5/6**: for NMR data see Table 1, see also Ref. 15; TLC R_f=0.226/0.283 (C_6H_6:EtOAc=50:1); $[\alpha]^{20}_{546}$ −280/ +56 (c 0.3, CH_3OH); **8/9**: for NMR data see Table 2; TLC R_f=0.116/0.134 (C_6H_6:EtOAc=100:2); **10/11**: ^{13}C NMR ($C_{1\text{-}7;\,\text{mandoyl}}$) 39.00/39.22, 53.58/53.74, 84.35/84.48, 33.70/33.81, 63.71/63.72, 209.40/209.12, 52.35/52.77, 172.21/171.79, 73.13/73.28, 137.53/137.27, 127.00/126.31, 128.93/128.75, 129.00/128.81; IR 3540/3550, 2930/2940, 3070, 3040, 1790, 1740 cm^{-1}; TLC R_f=0.192/0.163 (C_6H_6:EtOAc=10:1); **12/13**: IR 3450/3460,

Table 5
The ^1H and ^{13}C NMR spectra of diastereomeric THPMA **3** esters of 2-butanol

Comp. No.	24		25			24		25	
Atom No.	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	Atom No.	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H
1	19.32	1.19	18.90	1.05	ortho	127.32	7.45	127.19	7.45
2	72.83	4.85	72.80	4.85	meta	128.31	7.33	128.29	7.33
3	28.48	1.437	28.53	1.51/1.60	para	128.30	7.29	128.25	7.29
4	9.13	0.635	9.39	0.852	THP 2	96.36	4.58	96.66	4.60
CO	170.25	—	170.27	—	3	30.13	1.71	30.13	1.71
α	76.75	5.17	79.96	5.17	4	18.90	1.52/1.94	18.87	1.52/1.94
s	136.60	—	136.49	—	5	25.31	1.56	25.28	1.56
					6	62.07	3.95/3.49	62.03	3.95/3.49

2960, 2890, 1740, 1460, 1425, 1300, 1180, 1100, 1070, 700 cm^{-1}; TLC R_f=0.333/0.240 (C_6H_6:acetone=10:1); **14**: Ref. 28; **15/16**: for NMR data see Table 2; TLC R_f=0.243 (C_6H_6:EtOAc=100:2); **21/22**: for NMR data see Table 3; TLC R_f=0.18/0.27 ($CHCl_3$:EtOAc=2:1); **24/25**: for NMR data see Ref. 39; TLC R_f=0.202 (C_6H_6); **26**: Ref. 40; **27/28**: for NMR data see Ref. 41; TLC R_f=0.298 (C_6H_6); **29/30**: for NMR data see Ref. 41; TLC R_f=0.157 (C_6H_6:EtOAc=100:2); **31/32**: for NMR data see Ref. 42; TLC R_f=0.200 (C_6H_6); **33/34**: for NMR data see Ref. 42; TLC R_f=0.226/0.245 (C_6H_6:n-hexane:EtOAc 5:5:1); **35/36**: for NMR data see Ref. 41

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29. A sample of (±)-**7** was acylated with 0.3 eq. of THPMA **3**.[21] The diastereomers **8**, **9** were obtained in the ratio of 53/47 by HPLC, while the remaining **7** had an specific rotation close to zero. Contrary to this, the above trial for (±)-**26** proved the occurrence of some kinetic differentiation that was not studied further because the quantitative conversion of the starting alcohol took place in all derivatisations with **3**.
30. HPLC analysis: column: 3×300 mm Separon SGX (5 μm). Detector: UV-spectrophotometer (λ=254 nm). Eluent: n-hexane:EtOAc (95:5) for **5**, **6**; **15**, **16**; **24**, **25**; **27**, **28**; n-hexane:EtOAc (90:10) for **8**, **9**; n-hexane:2-propanol (98:2) for **10**, **11**; **12**, **13**; **29**, **30**; **33**, **34**; n-hexane:2-propanol:H_2O (80:19:1) for **17** and $CHCl_3$:EtOH (99:1) for **21**, **22**.
31. The chromatographic separation of the diastereomers **10/11** and **12/13** has been studied. See: Lõhmus, M.; Parve, O.; Kanger, T.; Lopp, M.; Lille, Ü. Resolution of diastereomers as a key step in obtaining optically pure prostanoids In: Abstracts. The 13th Symp. of Column Liquid Chromatography. Stockholm, 1989, 47.
32. THP groups were cleaved by the treatment of a sample in CH_3CN:0.2 N H_2SO_4 (3:1) for 16 h.
33. The alkaline hydrolysis was performed stirring the sample during 16 h in a MeOH:1 N NaOH (3:1) mixture.
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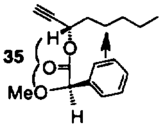
36. The sample of (±)-cloprostenol was kindly provided by Kemasol Ltd, Tallinn.
37. Semipreparative HPLC: column: 30×300 mm Separon SGX (7μm). Detector: UV-spectrophotometer (λ=254 nm). Eluent: $CHCl_3$:EtOH (99:1) for (**21**), (**22**) and $CHCl_3$:EtOH:H_2O (90:9.6:0.4) for **17**.
38. The alkaline hydrolysis[33] of **21** and **22** afforded (D)-(+)-cloprostenol (32 mg; $[\alpha]^{20}_{546}$ + 27 (c 1.0, $CHCl_3$)) and (L)-(−)-cloprostenol (35 mg; $[\alpha]^{20}_{546}$ − 27 (c 1.0, $CHCl_3$)), respectively, after semipreparative HPLC purification[37]. The optical resolution procedure was started from 100 mg of (±)-**17**: total yield 67%. The present process for the optical resolution of cloprostenol is supposed to allow a very high control of the enantiomeric purity of the product: the optical purity of the CDA (e.e.) was ≥98% and all minor diastereomers were separated by semipreparative HPLC (as concluded by HPLC and NMR analysis). Then the content of the enantiomeric contamination could be calculated as follows: 0.01×0.01×0.01×100%=0.0001%. The value calculated characterises the expected enantiomeric excess of the target enantiomeric cloprostenols to be as high as 99.9998%. This consideration should be proved by further analysis using proper methodologies. Compounds of a very high enantiomeric purity can also be obtained by using the repetition of any of the optical resolution procedure (see also Ref. 6).
39. See Table 5.

Table 6
The ^1H and ^{13}C NMR chemical shifts of diastereomeric mandoyl derivatives of 1-octyn-3-ol

Comp.	27		28		29		30		35		36	
Atom	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H
1	73.63	2.45	73.63	2.35	74.30	2.52	74.22	2.38	73.83	2.46	73.84	2.37
2	80.89	—	80.58	—	80.39	—	79.93	—	80.80	—	80.43	—
3	64.13	5.39	64.39	5.38	65.49	5.38	65.77	5.40	64.33	5.41	64.60	5.39
4	34.35	1.65	34.36	1.78	34.32	1.64	34.26	1.81	34.37	1.64	34.37	1.78
5	24.06	1.17	24.33	1.41	24.00	1.12	24.40	1.43	24.08	1.15	24.42	1.39
6	30.96	1.13	31.12	1.28	30.88	1.11	31.09	1.30	30.96	1.12	31.08	1.27
7	22.28	1.18	22.38	1.30	22.25	1.16	22.37	1.32	22.29	1.17	22.38	1.29
8	13.80	0.80	13.87	0.88	13.78	0.81	13.88	0.90	13.82	0.81	13.88	0.88
CO	169.56	—	169.70	—	172.79	—	172.54	—	169.62	—	169.77	—
α	76.41	5.25	77.08	5.21	72.87	5.22	72.84	5.20	82.31	4.80	82.59	4.80
OH/OCH_3	—	—	—	—	—	3.51	—	3.42	57.37	3.43	57.37	3.44
b	136.17	—	135.96	—	138.06	—	137.82	—	136.03	—	135.76	—
ortho	127.51	7.46	127.34	7.47	126.52	7.44	126.54	7.45	127.23	7.45	127.13	7.46
meta	128.49	7.35	128.43	7.36	128.52	7.38	128.49	7.37	128.58	7.37	128.53	7.37
para	128.59	7.33	128.51	7.30	128.46	7.38	128.29	7.38	128.77	7.34	128.71	7.34
THP 2	96.33	4.61	97.02	4.65								
3	30.12	1.72	30.17	1.73								
4	18.88	1.54/1.96	18.84	1.54/1.95								
5	25.28	1.59	25.29	1.59								
6	62.13	3.96/3.52	62.13	3.98/3.53								

35



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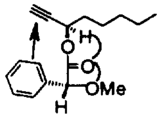

Table 7
The ^1H and ^{13}C NMR spectra of 1-octyn-3-ol THPMMA and MMA esters

Comp.	31		32		33		34	
Atom	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H	$\delta^{13}C$	δ^1H
1	74.05	2.42	73.90	2.34	74.20	2.45	74.04	2.36
2	80.27	—	80.08	—	80.15	—	79.95	—
3	64.89	5.30	64.96	5.28	65.17	5.29	65.22	5.28
4	34.07	1.48	34.13	1.67	34.13	1.48	34.13	1.65
5	24.02	1.12	24.28	1.35	24.03	1.07	24.29	1.31
6	30.91	1.12	31.02	1.26	30.91	1.09	31.01	1.23
7	22.24	1.18	22.31	1.29	22.26	1.16	22.34	1.28
8	13.80	0.82	13.85	0.88	13.81	0.82	13.86	0.88
THP 2	96.46	4.66	96.34	4.65	—	—	—	—
3	30.07	1.73	30.07	1.74	—	—	—	—
4	18.70	1.55/1.96	18.72	1.55/1.96	—	—	—	—
5	25.24	1.57/1.59	25.24	1.57/1.59	—	—	—	—
6	61.92	3.45/3.94	62.94	3.47/3.94	—	—	—	—
CO'	169.78	—	169.86	—	172.65	—	172.72	—
CO"	167.01	—	167.08	—	166.73	—	166.82	—
α'	76.28	5.38	76.22	5.38	72.86	5.32	72.93	5.51
α"	74.71	5.99	74.67	5.97	75.53	6.01	75.58	5.98

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41. See Table 6.
42. See Table 7.