Pergamon

Tetrahedron Letters 39 (1998) 1759–1762

TETRAHEDRON LETTERS

A New Approach for the Determination of the Absolute Configuration of Secondary Alcohols by ^{1}H NMR with *O*-Substituted Mandelate Derivatives.

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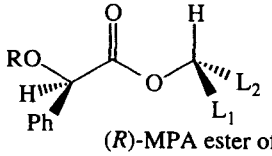
Received 13 November 1997; accepted 1 January 1998

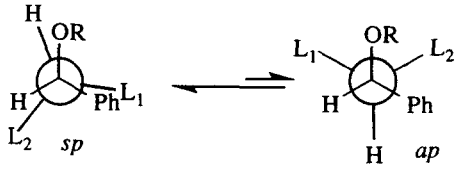
Abstract: It is shown that the cheap and easily prepared mandelic acid esters (or their OAc analogues) are best suited than the expensive, although usually employed, OMe mandelic acid esters to assess both the enantiomeric excesses and absolute configurations of secondary alcohols.

Proton NMR is widely used to determine the absolute configuration and/or enantiomeric purity of chiral materials due to the widespread occurrence of asymmetric reactions in organic synthesis.[1] In the case of chiral secondary alcohols, the studies are mostly carried out by comparison of the chemical shifts of the diastereomeric esters derived from alcohols and the two enantiomers of methoxyphenylacetic acid (**1**, MPA[2]) or methoxytrifluoromethylphenylacetic acid (**2**, MTPA, Mosher's reagent[2a]). In the model proposed to explain the NMR spectra of secondary *O*-methylmandelates, it is generally accepted that, in solution, the most stable conformation for these esters is the one where the methine proton, the carbonyl, and the methoxy groups are all *syn* and coplanar (see Figure 1).[2,3] Consequently, certain groups (L_1 or L_2) of the alcohol moiety are, according to their position in the anisotropic magnetic field around the phenyl ring, either shielded or non-shielded. Thus, the difference between the chemical shift ($\Delta\delta$) for the same proton in the (*R*)- and (*S*)-ester derivatives allows to determine the absolute configuration of the chiral alcohol. For each diastereomer, due to the conformation exchange, the observed NMR spectrum is averaged between the *ap* (*anti*periplanar) and *sp* (*syn*periplanar) conformers. If this empirical method is largely used[1], the success obviously depends on the $\Delta\delta$ value, which should be higher than 0.05 ppm.



(*R*)-MPA ester of **1** (R=Me)

Figure 1



To determine the absolute configuration and/or enantiomeric purity of a large number of chiral alcohols, use of MPA **1** or MTPA **2** may be hampered by high cost and difficult access. Also, it occurred to us that other *O*-R substituted mandelic acid derivatives, easier to obtain, might well serve this purpose. To our knowledge, no systematic study has been reported[2a] to date in this way.

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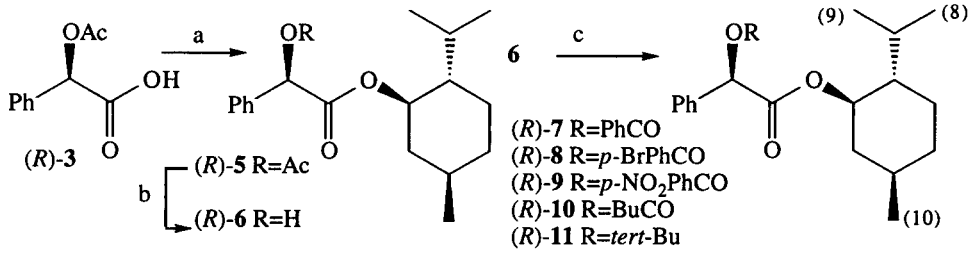
0040-4039/98/$19.00
PII: S0040-4039(98)00059-8

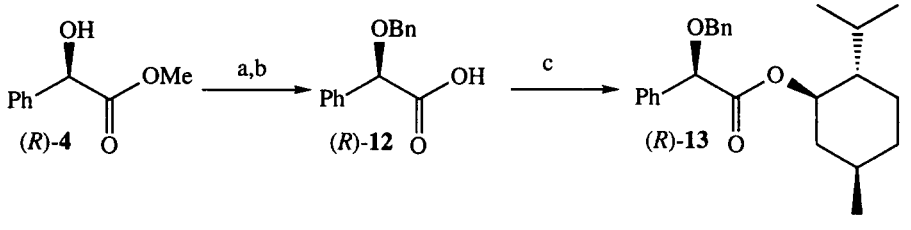
However, a few examples with chiral *O*-acetylmandelic acid **3** as chiral derivatizing agent for ^1H NMR determination of enantiomeric purity[4a,b,c] and absolute stereochemistry[4a,d,e] of secondary alcohols are mentioned. Recently, Riguiera[5] and colleagues reported the use of new arylmethoxyacetic acids displaying higher $\Delta\delta$ values compared to MPA **1** or MTPA **2** derivatives. Because these chiral acids are difficult to prepare, we focused our attention on the preparation of new *O*-R substituted mandelic ester derivatives (e.g. **5-11, 13**), and we investigated with them the steric and electronic effects of the R substituents on $\Delta\delta$ values. The ability of *O*-R substituted mandelic acid derivatives to separate the signals of the stereoisomers was first examined with *iso*-propanol and (-)-menthol. As shown in Schemes 1 and 2, (-)-menthol derivatives were prepared from chiral *O*-acetylmandelic acid **3**[6] or chiral methyl mandelate **4** using standard procedures.[7] For *iso*-propanol derivatives the same procedures were used from racemic materials.

Scheme 1.



Conditions : a) 1.1 eq DCC, 1 eq (-)-menthol, 0.2 eq DMAP, CH_2Cl_2, rt, 12h. b) 0.05eq K_2CO_3, MeOH, 0°C, 20 min.. c) For R = PhCO, *p*-BrPhCO, *p*-NO_2PhCO : 1.1 eq RCl, 1.2 eq Pyr., CH_2Cl_2, 0°C to rt, 10-12h. For R = *tert*-BuCO : 1.1 eq (*tert*-BuCO)$_2$O, 1.2 eq Et_3N, 0.2 eq DMAP, CH_2Cl_2, rt, 24h. For R=*tert*-Bu : 1.6 eq *tert*-BuO-C(NH)-CCl_3, 0.1 eq TfOH, CH_2Cl_2/cyclohex. (1/3), rt, 12h.

Scheme 2.



Conditions : a) 1.1 eq BnO-C(NH)-CCl_3, 0.1 eq BF_3-OEt_2, CH_2Cl_2, rt, 12h. b) 1M NaOH, THF/H_2O (7/3), rt, 2h. c) 1.1 eq DCC, 1 eq (-)-menthol, 0.2 eq DMAP, CH_2Cl_2, rt, 12h.

Chemical shifts for the Me groups of *iso*-propanol and (-)-menthol ester derivatives with the corresponding $\Delta\delta$ values defined as above are displayed in the Table.

Our results merit the following comments. First of all, it can be seen that significantly higher $\Delta\delta$ values are noted for the OAc-mandelic ester derivatives as compared to those displayed by the OMe analogues. Furthermore, it was yet possible to increase the $\Delta\delta$ values (up to 0.4 ppm!) by the simple expedient of transforming the OAc group into a OH one. Taken into account that the OAc-mandelic ester derivatives are prepared much more easily than their OMe analogues and that the OAc $\longrightarrow$ OH transformation can be effected, without apparent trace of epimerization, by simply exposing the acetate derivative to the action of dilute potassium carbonate in methanol, this two-step

procedure represents a significant improvement over the usually utilized procedure. Also noteworthy in the Table is the fact that, compared to R = OMe or OAc, bulkier R groups (O *tert*-Bu, OCO*tert*-Bu) induce smaller Δδ values. These observations can be rationalized on steric grounds in considering that the *ap* conformer is disfavoured over the *sp* conformer (Figure 1) as the R group is made bulkier. Finally, electronic effects have no detectable consequence on the Δδ values as shown by the last three entries in the Table.

Table : Selected chemical shifts[a] (ppm) of *O*-R substituted mandelic esters.

R group	(-)-menthol							*iso*-PrOH
	Conf.	δMe8	δMe9	δMe10	Δδ8	Δδ9	Δδ10	Δδ
Me[b]	(*R*)	0.63	0.43	0.89	-0.22	-0.26	0.05	0.11
	(*S*)	0.85	0.69	0.84				
Bn	(*R*)-**13**	0.63	0.45	0.89	-0.21	-0.26	0.05	0.11
	(*S*)-**13**	0.84	0.71	0.84				
tert-Bu	(*R*)-**11**	0.70	0.49	0.88	-0.12	-0.11	0.03	0.07
	(*S*)-**11**	0.82	0.60	0.85				
H	(*R*)-**6**	0.57	0.38	0.91	**-0.25**	**-0.40**	**0.01**	**0.17**
	(*S*)-**6**	0.82	0.78	0.90				
CH_3CO	(*R*)-**5**	0.63	0.44	0.89	-0.28	-0.32	0.04	0.15
	(*S*)-**5**	0.91	0.76	0.83				
tert-BuCO	(*R*)-**10**	0.62	0.42	0.86	-0.19	-0.27	0.02	0.13
	(*R*)-**10**	0.81	0.69	0.84				
p-NO_2PhCO	(*R*)-**9**	0.57	0.42	0.81	-0.23	-0.33	0.07	0.17
	(*S*)-**9**	0.80	0.75	0.88				
PhCO	(*R*)-**7**	0.58	0.43	0.87	-0.22	-0.32	0.01	0.16
	(*S*)-**7**	0.80	0.75	0.88				
p-BrPhCO	(*R*)-**8**	0.60	0.45	0.87	-0.20	-0.29	0.02	0.16
	(*S*)-**8**	0.80	0.74	0.89				

a) ^1H NMR spectra were recorded at 400MHz on a Bruker AMX-400 spectrometer at 298K in $CDCl_3$. TMS (δ=0) was used as an internal standard and all chemical shifts (δ) are given in ppm downfield of TMS. b) see ref. 5a.

In order to demonstrate the utility of our method, the above two-step protocol has been also tested with other representative chiral secondary alcohols, e.g.; (*R*)-2-butanol **14**, (*S*)-1-phenethyl alcohol **15**, (-)-borneol **16**, (-)-isopulegol **17**. The results displayed in Figure 2 once again show that

the Δδ values are arranged in the following order, Δδ(OH) >> Δδ(OAc) > Δδ(OMe), and that the Mosher-Trost model correctly predict the absolute configurations.

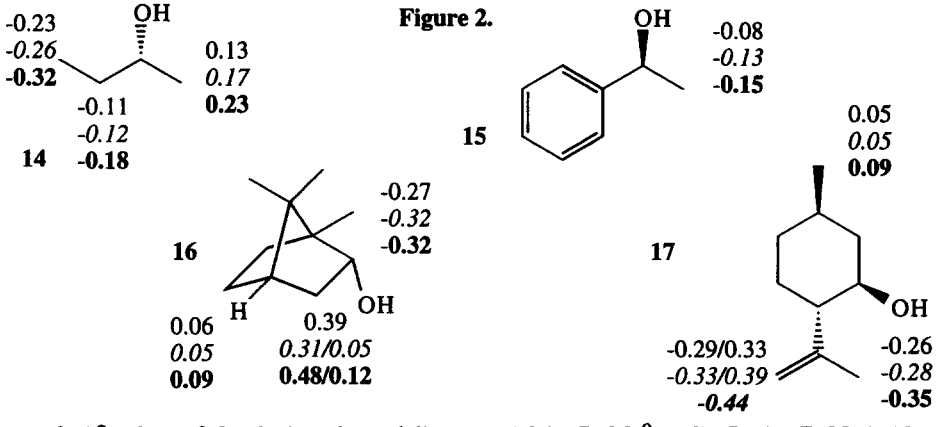


Figure 2.

Figure 2: Δδ values of *O*-substituted mandelic esters (plain: R=Me[9], *italic*: R=Ac, **Bold**: R=H).

In order to ensure the relabiability of the method, further investigations with complex chiral alcohols are currently underway.

Acknowledgments : We thank Mr Gilbert Nourrisson for his valuable help in NMR analysis.

References and notes

1. For reviews see : (a) S. Yamaguchi, S.; *Nuclear Magnetic Resonance Analysis Using Chiral Derivatives*, in *Asymmetric Synthesis* in ed Morrison, J. D., Vol 1, Academic Press, New York, **1983**, 125. (b) Parker, D.; *Chem. Rev.*, **1991**, *91*, 1441-1457. For more recent references see : (c) Pehk, T.; Lippmaa, E.; Lopp, M.; Paju, A.; Borer, B. C.; Taylor, R. J.; *Tetrahedron: Asymmetry*, **1993**, *4*, 1527-1532. (d) Fukushi, Y.; Yajima, C.; Mitzutani, J.;*Tetrahedron Lett.*, **1994**, *35*, 599-602. (e) Hoye, T. R.; Renner, M. K.; *J. Org. Chem.*, **1996**, *61*, 8489-8495. (f) Chinchilla, R.; Falvello, L. R.; Nájera, C.; *J. Org. Chem.*, **1996**, *61*, 7285-7290. (g) Ferreiro, M. J.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *Tetrahedron: Asymmetry*, **1997**, *8*, 1015-1018. (h) Kobayashi, M.; *Tetrahedron*, **1997**, *53*, 5973-5994. (h) Buist, P. H.; Behrouzian, B.; Cassel, S.; Lorin, C.; Rollin, P.; Imberty, A.; Perez, S.; *Tetrahedron: Asymmetry*, **1997**, *8*, 1959-1961.
2. (a) Dale, J. A.; Mosher, H. S.; *J. Am. Chem. Soc*, **1973**, *95*, 512-519. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; Mc Dougal, P.G.; Balkorec, M.; Baldwin, J.J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P.; *J. Org. Chem.*, **1986**, *51*, 2370-2374.
3. Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R.; *J. Org. Chem.*, **1996**, *61*, 8569-8577 and references cited therein.
4. (a) Parker, D.; *J. Chem. Soc. Trans II*, **1983**, 83-88. (b) Parker, D.; Taylor, R. J.; *Tetrahedron* , **1987**, *43*, 5451-5456. (c) Whitesell, J. K.; Reynolds, D.; *J. Org. Chem.*, **1983**, *48*, 3548-3551. (d) Panek, J. S.; Sparks, M. A.; *Tetrahedron: Asymmetry*, **1990**, *1*, 801-816. (e) Spino, C.; Weiler, L.;*Tetrahedron Lett*, **1987**, *28*, 731-734.
5. (a) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *Tetrahedron Lett*, **1994**, *35*, 2921-2924. (b) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *J. Org. Chem.*, **1995**, *60*, 504-515. (c) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *Tetrahedron: Asymmetry*, **1995**, *6*, 107-110. (d) Ferreiro, M. J.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *Tetrahedron: Asymmetry*, **1996**, *7*, 2195-2198. (e) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R.; *Tetrahedron* , **1997**, *53*, 8541-8564.
6. Thayer, F. K.; *Organic Syntheses*, **1932**, Vol I, 12-13.
7. Greene, T. W.; Wuts, P. G. M.; *Protective Groups in Organic Synthesis* ; Wiley, J. & Sons, New York, **1991**.
8. Typical procedure : to a solution of ester in dry MeOH (0.1 mmol/ml) at 0°C was added 5-10 mol% of K_2CO_3. The reaction was carefully monitored by TLC (less than 1 h). Then, ether was added followed by 1N aq. HCl. The organic layer was washed with water and brine. The crude mandelate ester was used without further purification. Under these condtions, no epimerization and/or mandelate cleavage were detected.
9. Data for MPA derivatives **14-17** taken from ref. 5a.