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An experimental/theoretical approach to determine the optical purity and the absolute configuration of *endo*- and *exo*-norborn-5-en-2-ol using mandelate derivatives

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ABSTRACT

The *O*-acetylmandelates and mandelates of *endo*- and *exo*-norborn-5-en-2-ol were prepared, both as a mixture and also as separate diastereomers. ^{1}H NMR spectroscopy of these derivatives was efficiently used to determine the enantiomeric ratios and to predict the absolute configuration of the alcohols. Theoretical calculations were performed to locate the predominant conformations of the mandelate derivatives and GIAO ^{1}H NMR Boltzmann-weighted average chemical shifts were computed, correctly reproducing the experimental δ and $\Delta\delta$ values.

Bicyclo[2.2.1]heptane systems are interesting from the structural and synthetic points of view due to their occurrence as natural products and their utility as versatile building blocks for the synthesis of diverse chemical structures.[1] Chiral norborn-5-en-2-ol (bicyclo[2.2.1]hept-5-en-2-ol) (**1**) has been prepared in a number of ways, including the asymmetric hydroboration of norbornadiene[2] and various chemical and enzymatic resolutions.[3] However, no general method has been developed to determine its enantiomeric purity and to assign its absolute configuration. In most cases, the optical purity has been estimated based on optical rotations.[2b,3a,b,g,h] However, the values found in the literature are variable and, moreover, the *exo* isomer has a very small $[\alpha]_D$, which can lead to inaccurate results.[4] Other techniques such as chiral GC of the acetates,[3e] chiral HPLC of the 3,5-dinitrobenzoates,[3f] and ^{1}H NMR using the chiral shift reagent $Eu(hfc)_3$ as well as ^{19}F NMR of the Mosher esters[3c,d] have been applied to determine the enantiomeric excess of the *endo* isomer. In 1968, Sandman and Mislow synthesised the *O*-methylmandelates of racemic norborn-5-en-2-ol (*endo*/*exo* 13:87) as a means to determine the optical purity of norborn-5-en-2-one.[5] The signals for the methoxymethine protons of the *endo* isomer were resolved, appearing at 4.59 and 4.55 ppm (60 MHz, benzene). In a related and more recent Letter, Guan and Li investigated the preparation and the optical properties of optically pure 1-methyl-7-oxabicyclo[2.2.1]heptan-2-one via resolution of the reductive products with (+)-mandelic acid, followed by saponification and oxidation.[6]

Our interest in the asymmetric synthesis of cyclohexenols has led us to examine the properties of the mandelate derivatives of *endo*- and *exo*-norborn-5-en-2-ol (**1**), both as a mixture and also as separate diastereoisomers, as a means to develop a direct method to determine their enantiomeric ratios and to assign their absolute configurations.

Due to the key role played by enantiomerically pure compounds in different fields of chemistry, many efforts have been devoted to the development of simple and reliable methods for the determination of the optical purities and the absolute configurations. Among the existing methods available, ^{1}H NMR spectroscopy has emerged as one of the most useful and widely used techniques for this purpose.[7] We have focused our attention on the use of readily available mandelic acid and its *O*-substituted analogues as chiral derivatising agents (CDA).[8] The cheap and easily prepared mandelates and their *O*-acetyl analogues have been found to be best suited than the expensive, although more frequently used, *O*-methylmandelates to assess the enantiomeric excesses and absolute configurations of secondary alcohols.[8d] For this reason, we decided to prepare the mandelates and the *O*-acetyl analogues derived from *endo* and *exo*-norborn-5-en-2-ol (**1**) and analyse their NMR spectra in detail. Reaction of commercially available racemic norborn-5-en-2-ol (*endo*/*exo* 75:25) with (*S*)-*O*-acetylmandelic acid,[9] DCC and catalytic DMAP in dichloromethane gave the mixture of diastereomeric *O*-acetylmandelates **2** in quantitative yield (Scheme 1). By integration of the ^{1}H NMR spectrum, we corroborated that the 75:25 *endo*/*exo* and 1:1 *R*/*S* ratios were maintained. We were delighted to note that the signals of the bridgehead protons attached to C1 of the four diastereomers were well resolved (Fig. 1, spectrum a). In addition, the signals of C3–H were clearly separated, and the same was observed for the olefinic protons attached to C6 for the *endo* isomer. Subsequent selective hydrolysis of the acetate group gave the mixture of mandelates **3** without apparent epimerisation. The spectra of the mandelates showed $\Delta\delta$s($\Delta\delta = \delta_R - \delta_S$) which were even higher than those of the

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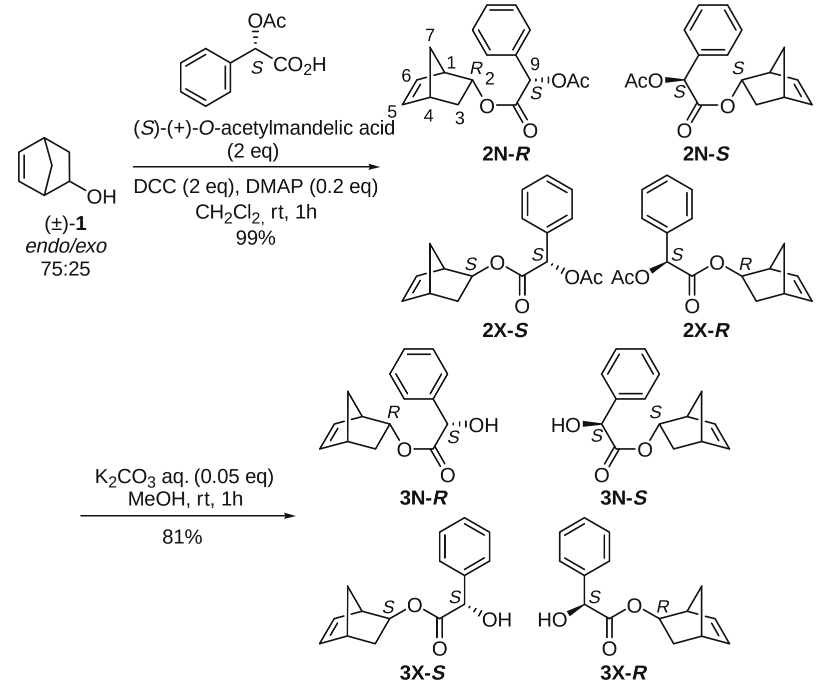


Scheme 1.

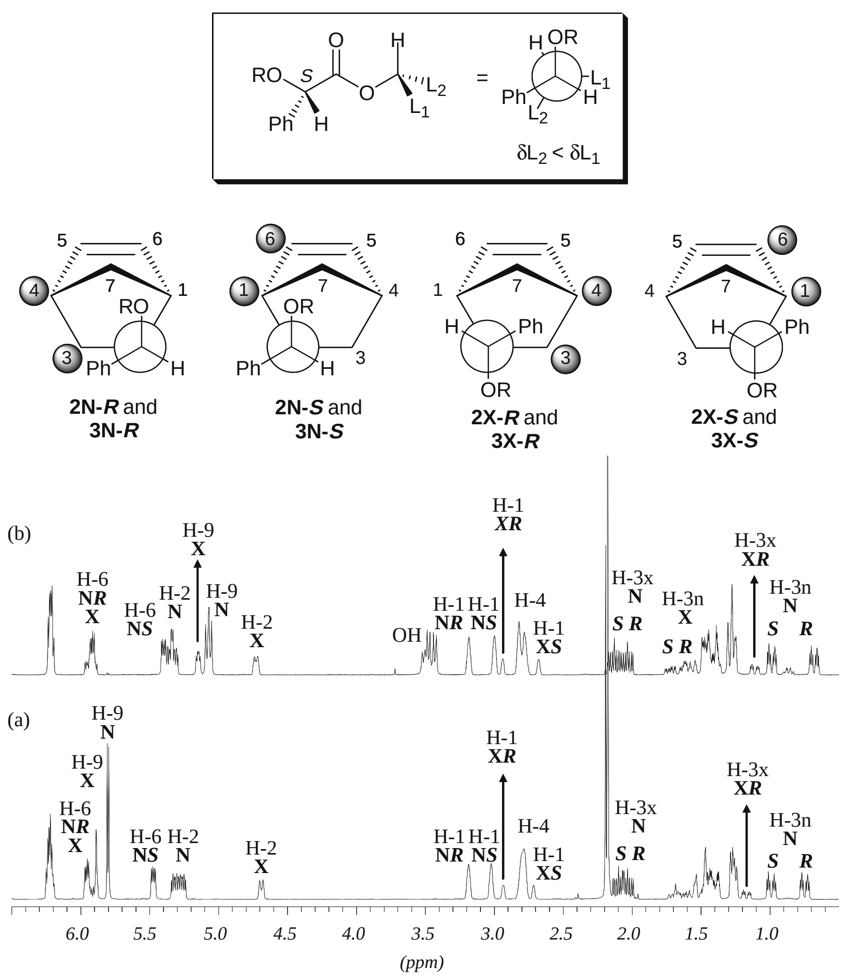


Figure 1. Models proposed to assign the absolute configuration and partial ^{1}H NMR spectra of *O*-acetylmandelates **2** (spectrum a) and mandelates **3** (spectrum b) at 300 MHz in $CDCl_3$.

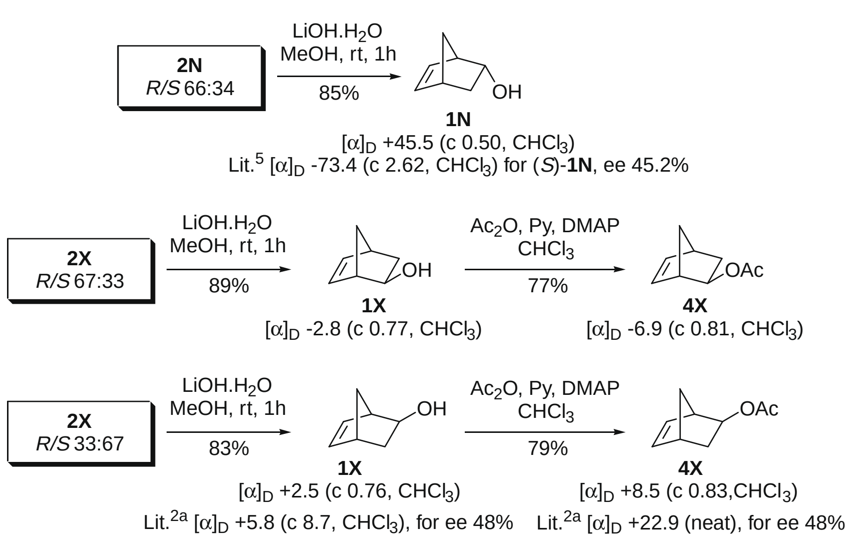
O-acetylmandelate analogues (Fig. 1, spectrum b). According to the model proposed to explain the NMR spectra of secondary *O*-methylmandelates,[8a,c] the most stable conformation in solution is the *syn*periplanar (*sp*) conformation, in which the methine proton, the carbonyl and the methoxy group are all *syn* and coplanar. As a consequence of the anisotropic magnetic field created by the phenyl ring, the groups L_1 and L_2 of the alcohol moiety can be either shielded or deshielded. Based on this model, we predicted the absolute configuration of the diastereomers of *O*-acetylmandelates **2** and mandelates **3** as shown in Figure 1. For example, the protons attached to C1 and C6 were predicted to be more shielded in the *endo* and *exo* isomers having the *S* absolute configuration at C2 (**2N-*S*** and **2X-*S***: spectrum a, **3N-*S*** and **3X-*S***: spectrum b). On the other hand, C3–H were predicted to be more shielded in the diastereoisomers having the *R* stereochemistry at C2.

In order to confirm the absolute configurations, we decided to synthesise the mandelate derivatives of the separate *endo* and *exo* epimers. After chromatographic separation on silica gel (pentane/diethyl ether), the sequence shown in Scheme 1 was repeated individually for *endo* and *exo*-norborn-5-en-2-ol (**1N** and **1X**, respectively) without difficulty. A 1:1 mixture of the *endo*-*O*-acetylmandelates was enriched in the 2*R* diastereomer by column chromatography on silica gel (hexane/ethyl acetate) and hydrolysed to *endo*-norborn-5-en-2-ol (**1N**) with lithium hydroxide (Scheme 2). The optical rotation of the 66:34 *R*/*S* mixture thus obtained confirmed that the absolute configuration of the *endo* isomer was correctly assigned by NMR of the mandelate derivatives.[4] The *exo* isomer was subjected to the same protocol and the optical rotation of the product of hydrolysis of a 67:33 *R*/*S* mixture of **2X** corroborated the absolute configuration of **1X**. However, since the $[\alpha]_D$ was very small we converted the alcohol into its acetate **4X**, which has a higher value of optical rotation. Although the experimental value was slightly lower than expected, the negative sign of the optical rotation provided further support to the proposed stereochemistry. The same was repeated with a 33:67 *R*/*S* mixture of the *O*-acetylmandelate **2X**, giving consistent results. The spectra of the *O*-acetylmandelates and the mandelates of separate *endo* and *exo*-norborn-5-en-2-ol are shown in the Supplementary data.

To validate these experiments, we performed theoretical calculations for the *endo* and *exo*-*O*-acetylmandelates (**2N** and **2X**) and mandelates (**3N** and **3X**). Conformational searches were run to locate the minimum energy conformers of all the structures. Initially, a large number of geometries were generated using the conformational search module of Hyperchem[10] with the MM+ method. Selected structures were then successively reoptimised at the RHF/AM1, RHF/3-21G and B3LYP/6-31G* levels of theory using GAUSSIAN 03.[11] Normal coordinate analyses were used to confirm the nature of the stationary points and to evaluate the thermochemical properties at 1 atm and 298.15 K. For all significantly populated conformers of each stereoisomer, free energies in solution were computed on the structures optimised in the gas phase at the B3LYP/6-311++G** level of theory with the Polarisable Continuum Model (PCM) as implemented in GAUSSIAN 03 using chloroform as the solvent.[12]

Figure 2 gathers the optimised geometries of the major conformers for each compound (for all conformers, see the Supplementary data). In agreement with the empirical model,[8a,c] all global minima correspond to conformations in which the methine proton, the carbonyl and the acetate or hydroxy group are *syn*periplanar.[13] For each compound, we found two *syn*periplanar conformers of similar energies, having H–C2–O–C8 torsion angles of ca. 40° and −40°. In addition, conformers having *syn* or *anti*periplanar arrangements of the acetate and the carbonyl oxygen were located for *O*-acetylmandelates **2N** and **2X**, but the *anti* counterparts were considerably less stable and account for 15–30% of the population. On the other hand, the free hydroxy group in mandelates **3N** and **3X** is H-bonded to the carbonyl oxygen, so the hydroxyl and the carbonyl are *syn*periplanar. The conformational preferences towards the *syn*periplanar conformers are maintained in solution. NOE experiments support these theoretical results since they confirmed the proximity of the aromatic protons and H-6 of **2N-*S***, H-6 and H-1 of **3N-*S*** and H-3n of **3N-*R***. In addition, irradiation of the aromatic protons enhanced the signals of H-3*n* of **2X-*R***, H-1 of **2X-*S*** and H-1 of **3X-*S***. We also carried out NMR experiments at low temperature (−40 °C) for *O*-acetylmandelates **2N** and noticed that the $\Delta\delta$ for H-6 was increased in 0.12 ppm, which suggests that conformational equilibria are important for these compounds and affect the chemical shifts significantly. For *O*-acetylmandelates **2X**, H-6 and H-3*x* become 0.02 and 0.04 ppm more shielded for the diastereomers having the *S* and *R* configurations at C-2, respectively.

Finally, we performed GIAO NMR calculations at the B3LYP/6-31G* level of theory for all significantly populated conformers of each diastereoisomer and compared the calculated Boltzmann-weighted average ^{1}H NMR chemical shifts obtained using relative free energies in the gas phase with the experimental values



Scheme 2.

(Table 1).[14,15] Gratifyingly, the experimental δ and $\Delta\delta$ values were correctly reproduced.

These computational results support the stereochemical assignment predicted by ^{1}H NMR spectroscopy based on the empirical model. In our case, this was unequivocally confirmed by optical rotation measurements. However, this might not always be possible. When the optical rotations of the enantiomerically pure secondary alcohols are not known, the theoretical prediction of the chemical shifts of the derivatives obtained with CDAs might be crucial.

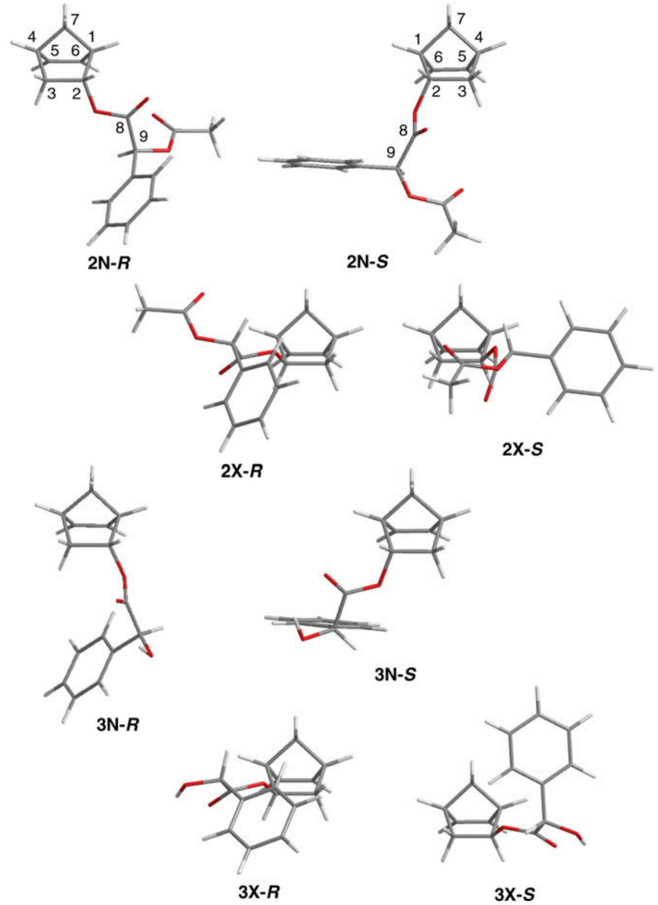


Figure 2. B3LYP/6-31G* optimised geometries of the major conformers for *O*-acetylmandelates **2** and mandelates **3**.

Table 1
Experimental and calculated ^{1}H NMR δ and $\Delta\delta$ values (in ppm) for selected nuclei

		H-1		H-3n		H-3x		H-6	
		Exp.	Calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.	Calcd.
2N	δ_R	3.19	3.12	0.75	1.03	2.03	1.99	5.95	6.20
	δ_S	3.02	2.90	0.99	1.20	2.10	2.12	5.47	5.73
	Δδ	**0.17**	**0.22**	**−0.24**	**−0.17**	**−0.07**	**−0.13**	**0.48**	**0.47**
2X	δ_R	2.93	2.83	1.62	1.63	1.17	1.44	5.93	6.02
	δ_S	2.71	2.52	1.70	1.71	1.47	1.68	5.89	5.87
	Δδ	**0.22**	**0.31**	**−0.08**	**−0.08**	**−0.30**	**−0.24**	**0.04**	**0.15**
3N	δ_R	3.19	3.01	0.68	0.89	2.04	2.09	5.92	6.29
	δ_S	3.00	2.81	0.99	1.27	2.13	2.22	5.40	5.76
	Δδ	**0.19**	**0.21**	**−0.31**	**−0.38**	**−0.09**	**−0.13**	**0.52**	**0.53**
3X	δ_R	2.94	2.83	1.62	1.64	1.11	1.28	5.95	6.00
	δ_S	2.68	2.54	1.72	1.78	1.47	1.68	5.90	5.92
	Δδ	**0.26**	**0.29**	**−0.10**	**−0.14**	**−0.36**	**−0.40**	**0.05**	**0.08**

$\Delta\delta = \delta_R - \delta_S$.

In summary, the *O*-acetylmandelates and the mandelate derivatives have been efficiently used to determine the optical purity and to predict the absolute configuration of *endo*- and *exo*-norborn-5-en-2-ol. The conformational, stereochemical and NMR properties of these derivatives have been studied using an experimental/theoretical approach. In accordance with the empirical model proposed for secondary *O*-methylmandelates, all major conformers are *syn*periplanar. GIAO ^{1}H NMR Boltzmann-weighted average chemical shifts correctly reproduced the experimental δ and $\Delta\delta$ values. Preliminary studies show that this protocol can be successfully applied to determine the enantiomeric ratios and to predict the absolute configurations of other bicyclic and monocyclic secondary cyclohexenols. These results will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures, spectroscopic, analytic and computational data and NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.056.

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