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Note

Gas chromatography-based method for assigning the configurations of allylic and benzylic alcohols and for determining their optical purities

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We recently demonstrated that it is possible, with rare exceptions, to account for the optical purities[1], as well as the configurations, of alcohols prepared by enantioselective hydrolysis of the corresponding racemic acetates using the mold *Rhizopus nigricans*[1–4]. Estimates of enantiomeric excesses of alcohols formed in these kinetic resolutions were based on electrical, steric and polarizability parameters obtained from the literature and on quantitative hydrolysis data. The experimental values for enantiomeric excess were obtained from rotation measurements; consequently, the data employed in formulating the correlations would be subject to large errors. The desire for a more precise analytical technique prompted a search for a better method. That search was also influenced by a recent observation[4] that the configuration of one allylic alcohol formed in these hydrolyses was not the expected one based on the rule given in ref. 1. Thus, an independent method of assigning the configurations of allylic alcohols was also sought. A recently developed reaction by Sharpless *et al.*[5] is now widely used by organic chemists for the preparation of chiral allylic and epoxy alcohols of a predictable configuration. While we are unaware of any discrepancies between predicted and observed configurations of alcohols prepared using this reaction, a simple method of verifying a configurational assignment of an allylic alcohol, obtained using the Sharpless procedure, should prove useful. We describe here a method of assigning the configurations of allylic and benzylic alcohols that employs the relative retention times of the diastereomeric esters formed with (−)-camphanic acid, from an Ultra 1 (Hewlett-Packard) capillary gas chromatography (GC) column. In addition, the GC separation provides analytical data on the optical purity of the alcohol.

Many of our preparations of chiral alcohols employ microbial transformations; thus it is frequently necessary to analyze small quantities of impure alcohols. To avoid the extensive purification necessary for optical and NMR methods, a chromatographic procedure to separate and characterize diastereomers appeared ideal. Although milligram quantities were employed to prepare the camphanate esters, reaction conditions can be modified to use much less material.

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While separations of diastereomeric esters have been used to determine optical purity, many of the derivatives were developed for the analysis of saturated alcohols[6–8] and for correlating the elution order of diastereomers with their configuration[9–11]. The procedure developed by Doolittle and Heath[7] employes (*S*)-tetrahydro-5-oxo-5-furancarboxylic acid while Brooks and Gilbert[10] utilizes α-phenylbutyric acid in a modification on a microscale of Horeau and Kagan's procedure[11]. Analogous studies using elution order from high-performance liquid chromatography (HPLC) columns have been described[12–16]. Thus, there is ample precedent for employing chromatographic procedures for determining enantiomeric excess and for making configurational assignments based on elution order. Camphanate esters of allylic alcohols have been employed by several investigators to resolve allylic alcohols[17,18] and by others to assign a molecules configuration[19]. Deger *et al.*[16] employed HPLC and GC for the separation of camphanate esters of allylic alcohols. Deger *et al.*[16] and Bergot *et al.*[20] have cautioned against overestimating the reliability of configurational assignments based on elution order. Despite these cautionary comments a series of thirteen racemic cyclic allylic alcohols were esterified with (−)-camphanyl chloride. We found that all of the diastereomeric esters could be separated on a 25 m × 0.2 mm I.D. Ultra capillary GC column. The configuration of the more rapidly eluted diastereomer was assigned using samples of known configuration. The resulting data were examined to determine if the elution order of a diastereomer could be correlated with the configuration of the alcohol.

EXPERIMENTAL

General procedure for the preparation of camphanate esters

A solution of 0.002–0.010 g of the alcohol in methylene chloride (1–2 ml) was reacted overnight at room temperature with 1.2 equiv. of camphanyl chloride in the presence of 1 equiv. of 4-dimethylaminopyridine. The reaction mixture was treated with water (1 ml), the methylene chloride layer was separated, washed, dried and concentrated. The crude ester was then purified by flash chromatography on silica gel.

Analysis

The analyses were done using a Hewlett Packard 5890A gas chromatograph equipped with a 25 m × 0.2 mm I.D. Ultra 1 capillary column and an HP 3392A integrator. The alcohols employed for this study were all prepared by literature methods and their spectroscopic properties were in agreement with those expected for their structures. The peaks in the chromatogram were identified using camphanates of alcohols enriched in one enantiomer, the absolute stereochemistry of which had previously been established. Data on the specific rotations and the configurations of the alcohols used to identify the diastereomeric camphanate ester more rapidly eluted from the column is given in Table I.

RESULTS AND DISCUSSION

The data obtained for the chromatographic behavior of camphanate esters of a series of (*E*)- and (*Z*)-cycloalk-2-en-1-ols (compounds **1**–**13**) on a 25 m × 0.2 mm I.D. Ultra 1 cross-linked capillary column is summarized in Table II. Success in

TABLE I

DATA ON THE SPECIFIC ROTATIONS AND ABSOLUTE STEREOCHEMISTRIES OF THE ALCOHOLS EMPLOYED IN ASSIGNING THE ABSOLUTE STEREOCHEMISTRY OF THE DIASTEREOMERIC CAMPHANATES

Compound	*Specific rotation in chloroform (enantiomeric excess)*	*Absolute stereochemistry of enantiomer in excess*	*Compound*	*Specific rotation in chloroform (enantiomeric excess)*	*Absolute stereochemistry of enantiomer in excess*
1	+5.7 (14)	*R*	**13**	−4.6 (49)	*R*
2	+18 (15)	*R*	**14**	+23 (91)	*S*
3	−17 (22)	*S*	**15**	+27 (81)	*S*
4	−28 (79)	*R*	**16**	+30 (91)	*R*
5	−7.5 (35)	*S*	**17**	−89 (>95)	*S*
6	+55 (97)	*R*	**18**	−71 (99)	*S*
7	−24 (52)	*R*	**19**	+45 (91)	*R*
8	−38 (78)	*R*	**20**	−1.5 (91)	*R*
9	−85	*R*	**21**	+37 (61)	*R*
10	−118 (46)	1*R*, 2*R*	**22**	+26 (53)	*R*
11	−49 (85)	*R*	**23**	+26 (77)	*S*
12	−2.0	*R*	**24**	−17 (98)	*R*

separating diastereomeric camphanates of cyclic allylic alcohols prompted us to extend this study to include benzylic alcohols. Camphanate esters of several benzylic alcohols were prepared (compounds **14**–**19**) and their chromatographic properties examined. The esters were readily separated; data are included in Table II. Although no systematic effort was made to explore the scope and limitations of the GC-based method, the chromatographic behavior of several other camphanates were examined. The esters of saturated acyclic alcohol **25** and of the cyclohexanol derivative **26** were *not* separated on the Ultra 1 capillary column. However, esters of the homobenzylic alcohol **21** were readily separated.

Since the method proved valuable in determining enantiomeric excesses of benzylic and allylic alcohols, an effort was made to learn whether the elution order of a diastereomer correlated with the configuration of the alcohol. As mentioned briefly in the introduction, chiral allylic alcohols are important synthetic intermediates and their configurations are frequently assigned from the method of preparation. It is therefore important to identify compounds where the configuration might have been incorrectly assigned. Information on the configuration of the ester preferentially eluted (first peak) is given in Table II; it shows that the alcohol has the configuration shown in Fig. 1. The presence of substituents on C-2 or C-3 of a cycloalk-2-en-ol does *not* alter this correlation between elution order and configuration of the ester. Furthermore, the correlation between the configuration of the alcohol and the elution order of the ester is also independent of the *cis* or *trans* nature of the double bond.

The configuration of a benzylic alcohol preferentially eluted from the column is also accounted for by the structure in Fig. 1, if the double bond is incorporated into an aromatic ring. For phenylalkyl carbinols, replacing an ethyl group by a trifluoromethyl group (compounds **22** and **23**) does not affect the relation between elution order and configuration. Since critical factors which affect the differential binding of diastereomeric esters to the column are unknown, *assignments based on this correla-*

TABLE II

SEPARATION BY GC OF DIASTEREOMERIC CAMPHANATES OF ALLYLIC, BENZYLIC AND MISCELLANEOUS ALCOHOLS ON A 25-m ULTRA 1 COLUMN

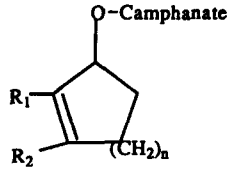
Compound	*Oven temp. (°C)*	*First peak*		*Second peak*		*Alpha value*	*Ref.*
		Retention time (min)	*Absolute stereochemistry*	*Retention time (min)*	*Absolute stereochemistry*		
1	140[a]	10.13		10.23		1.02	4
2	160[a]	7.52	*R*	7.71	*S*	1.03	4
3	200	11.79	*R*	12.23	*S*	1.04	4
4	175[a]	10.55	*R*	11.26	*S*	1.07	4
5	170	7.78	*R*	7.92	*S*	1.02	4
6	200	5.43	*R*	5.76	*S*	1.06	4
7	170	11.85	*R*	12.05	*S*	1.02	18
8	190[a]	8.97	*R*	9.13	*S*	1.02	13
9	200[a]	12.81	*R*	13.09	*S*	1.02	13
10	180–220[b]	32.33	*R*	32.77	*S*	1.01	21, 22
11	210–240[b]	19.06	*R*	19.16	*S*	1.01	21, 22
12	250–270[b]	12.41	*R*	12.53	*S*	1.01	21, 22
13	250–270[b]	14.76	*R*	14.97	*S*	1.01	26
14	190	7.46	*R*	7.88	*S*	1.06	3
15	190	10.50	*R*	11.26	*S*	1.07	3
16	210	5.89	*R*	6.34	*S*	1.08	3
17	210	7.65	*R*	7.92	*S*	1.04	24
18	250–270[b]	15.55	*R*	15.88	*S*	1.02	13
19	230[a]	7.06	*R*	7.35	*S*	1.04	13
20	230	7.03	*R*	7.35	*S*	1.04	25
21	240	15.46	*R*	15.87	*S*	1.03	27
22	220	12.15	*R*	12.71	*S*	1.05	2
23	150	9.64	*S*	9.79	*R*	1.02	2
24	240	13.56	*S*	15.19	*R*	1.12	2
25	160	9.07		9.07		1.00	–
26	200	11.01		11.01		1.00	–

[a] Temperature programmed to rise 1°C/min.

[b] The column used for these measurements was physically different one from that used for the other measurements, although it was purchased from the same source with the same specifications.

tion must be treated as tentative. There are several reports in which the elution order of one member of a homologous series unexpectedly differs from that of the others in the series[16,20]. Configurational assignments based on elution order data therefore should be verified using an independent method, *i.e.*, chiroptical measurements or the use of enzymic or microbially mediated reactions. If independent assignments differ, the configuration must be rigorously determined by a direct method, *i.e.*, chemical conversion into a compound of established configuration or by an X-ray crystallographic determination.

One factor that has been found to alter the relationship between the relative



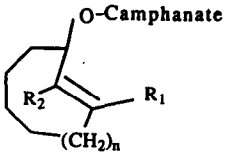
1 n = 1, $R_1 = R_2 = H$ **6** n = 3, R_1 = Br, $R_2 = H$

2 n = 2, $R_1 = R_2 = H$ **7** n = 4, $R_1 = R_2 = H$

3 n = 2, R_1 = Ph, $R_2 = H$ **8** n = 5, $R_1 = R_2 = H$

4 n = 2, $R_1 = H$, R_2 = Br **9** n = 6, $R_1 = R_2 = H$

5 n = 3, $R_1 = R_2 = H$

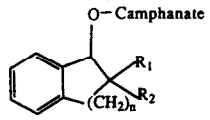


10 n = 1, $R_1 = R_2 = H$ **12** n = 4, $R_1 = R_2 = H$

11 n = 2, $R_1 = R_2 = H$ **13** n = 5, $R_1 = R_2 = H$

retention time of diastereomeric benzylic camphanates is the presence of substituents on the methylene group adjacent to the carbinol carbon, *e.g.*, 4,4-dimethyl-1,2-benzocyclohexen-3-ol (**24**). The configuration of the enantiomer more rapidly eluted from the column *differed* from that predicted using the relationship proposed in ref. 4. Since we have no data on the elution order of other 4-substituted 1,2-benzocycloalken-3-yl camphanates, this observation should alert other investigators to be extremely careful in assigning the configurations of 4-substituted cyclic benzylic camphanates from their elution order. Surprisingly, a similar change in the relationship between elution order and configuration of 4-substituted 1,2-benzocycloalken-3-ols and the unsubstituted parent compounds was noted for the elution of enantiomers of these alcohols from type 1A chiral Pirkle HPLC column[2].

The ability to separate diastereomeric camphanates has been helpful in solving several problems. In the course of resolving 1-acenaphthenol, a metabolite of acenaphthene[21], this separations technique was used to monitor the resolution and make a tentative configurational assignment of the (−)-enantiomer. The ester of (−)-1-acenaphthenol was the more rapidly eluted diastereomer, suggesting that it was the (*R*)-alcohol. This deduction was confirmed by an X-ray structure analysis[22]. This procedure was also used to establish enantiomeric excesses of substituted and unsubstituted 1,2-benzocycloalken-3-ols (**13** and **16**). The alcohols were not resolved on a type 1A Pirkle HPLC column[1–4,23,24]. Finally, the analytical method was used to assign the configuration of (−)-(*E*)-cyclooct-2-en-1-ol[25]. Treatment of the (*E*)-isomer with silver ion to convert it into the (*Z*)-isomer yielded a mixture of isomers

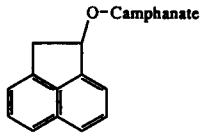


14 n = 1, $R_1 = R_2 = H$ **17** n = 4, $R_1 = R_2 = H$

15 n = 2, $R_1 = R_2 = H$ **18** n = 5, $R_1 = R_2 = H$

16 n = 3, $R_1 = R_2 = H$ **19** n = 6, $R_1 = R_2 = H$

24 n = 2, $R_1 = R_2 = CH_3$



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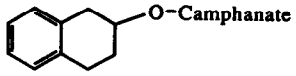

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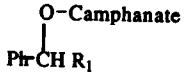
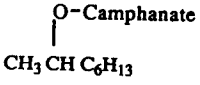


22 $R_1 = C_2H_5$

23 $R_1 = CF_3$



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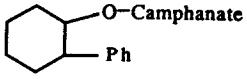

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whose separation was very difficult. When the camphanate esters of this mixture were prepared it was possible to separate all of the diastereomeric esters by GC. The chromatogram was also used to assign the configuration of the predominant diastereomer of (*Z*)-cyclooct-2-en-1-ol. The use of these GC-based separations with sensitive detection systems, *e.g.*, mass spectrometers would result in far greater sensitivity than is possible with NMR-based methods.

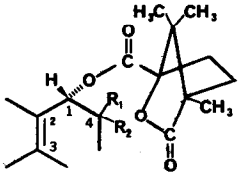

Fig. 1. Configuration at the carbinol carbon of the ester formed with (−)-camphanic that is more rapidly eluted from an Ultra 1 capillary column.

CONCLUSION

It is possible to identify the predominate enantiomer and to analyze the enantiomeric excesses of a large number of allylic and benzylic alcohols by esterifying them with (−)-camphanic acid and separating the resulting diastereomers on a capillary GC column. Data on the relative retention times of a diastereomer have been correlated with the configurations about the carbinol carbon.

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