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A Practical Method for the Stereochemical Analysis of Acyclic Terpenoid Carbonyl Compounds***

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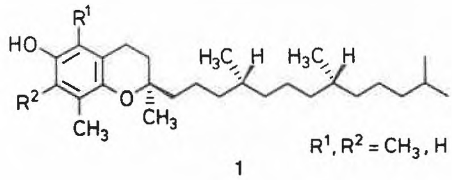
Abstract: The stereoisomeric composition of acyclic terpene aldehydes and ketones can be assayed by derivatization with L (+)-diisopropyl tartrate and separation of the ensuing acetal diastereomers by gas chromatography.

Unlike the comprehensive repertoire available for the stereochemical characterization of alcohols or acids[1], few methods to this purpose exist for aldehydes and ketones. Successful *ee*-determinations have so far been restricted to cyclic ketones, whereas a general method for the stereochemical analysis of chiral acyclic carbonyl compounds appears to be lacking.

As an outgrowth of our interest in the synthesis of optically active terpenoids, particularly naturally occurring tocopherols (**1**) and vitamin K_1 (**2**), we report in this communication the determination of the stereoisomeric composition of carbonyl compounds **3**–**6**[2] by using capillary gas chromatography to assay their respective L(+)-diisopropyl tartrate acetal derivatives **7**–**10**[3,4].

This derivatization can be achieved by either heating the carbonyl compound with L(+)-diisopropyl tartrate in toluene in the presence of a catalytic amount of toluenesulfonic acid with azeotropic removal of water, or preferably by triflate catalyzed condensation[5] with bis(*O*-trimethylsilyl)diisopropyl tartrate. The crude reaction mixture of either preparation is suitable for the analysis. Crude, as well as purified (column chromatography) samples from both procedures, yielded identical (± 0.2%) results in all cases examined.

Gas chromatography of the acetals **7**–**10** derived from (all)racemic **3**–**6** on a 100% cyanopropylsilicon[6] coated glass column, produced the resolution patterns shown in Fig. 1. Near to complete baseline separation is observed for the individual diastereomers. Their equal peak intensities in-



$R^1, R^2 = CH_3, H$

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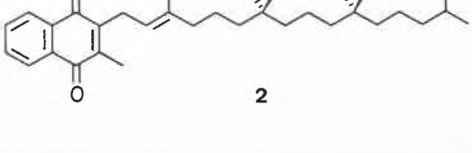

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dicate the absence of kinetic resolution in the derivatization step. Peak assignments were carried out by coinjection of the respective racemic acetal with either one of the corresponding homochiral diisopropyl tartrate acetal diastereomers[7].

Though expected under the experimental conditions used, the preservation of stereochemical integrity was demonstrated experimentally: Samples of enantiomerically pure *R* or *R,R* configurated carbonyl compounds **4**–**6** were obtained by degradation of natural phytol[8]. The corresponding acetals **8**–**10** did indeed produce clean, single-peak chromatograms, which corroborate the reliability of this protocol. A series of control experiments established a reproducibility of ±0.3% (percentage of total peak area). We therefore do consider this method safe for routine use, particularly for the analysis of highly (*R*)- or (*R,R*)-enriched samples, typically obtained by a number of present-day methods for the synthesis of chiral acyclic terpenoids[9].

Since compounds **3**–**6** are intermediates in various syntheses of (*R,R,R*)-α-tocopherol, the present method allows a complete stereochemical characterization at the C_{10}, C_{13}, C_{15}, and C_{18} chain length level of tocopherol building blocks. This represents a considerable improvement over existing methodologies, since only C_{10} intermediates (dihydrocitronelloic acid derivatives[10]) were hitherto amenable to a direct analysis. The stereoisomeric composition of C_{15} intermediates had to be inferred from a GC-analysis of the tocopherol obtained[11], or deduced from a determination of the diastereomeric ratio[12] in conjunction with either a derivatization selectively discriminating C-3 epimers (as hexahydrofarnesoic acid derivatives[13]) or information on the optical purity of the relevant starting materials. *ee*-Determinations of C_{13} and C_{18} chain intermediates have thus far not been possible.

The tartrate and the in-chain stereocenters of acetal **10** are separated by six, respectively ten single bonds. To the best of our knowledge, this is the maximum distance between discriminating stereocenters that has ever been observed to translate into an analytically useful separation of acyclic carbonyl compound diastereomers.

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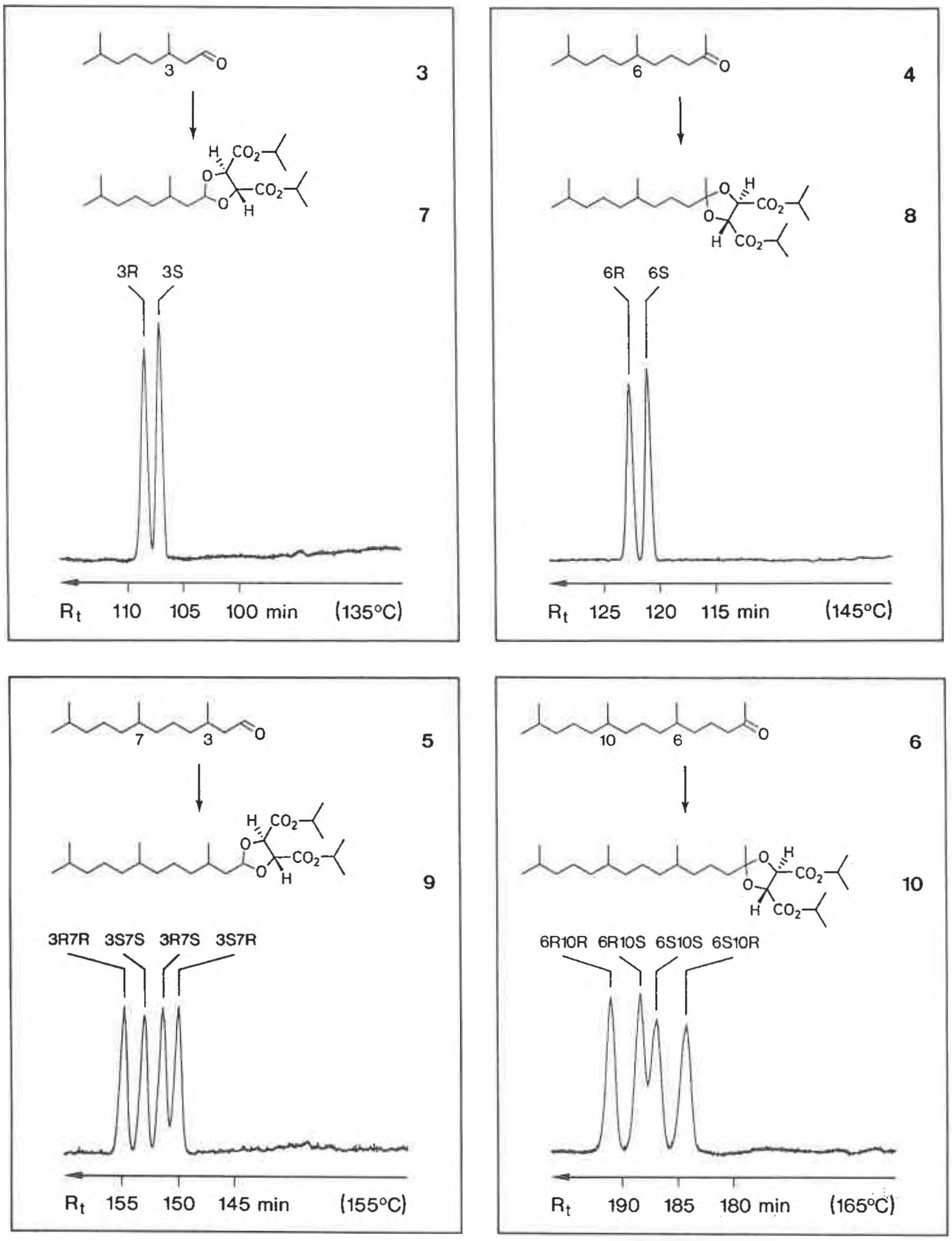

Fig. 1. Gas chromatographic analysis of L(+)*-diisopropyl tartrate acetals derived from terpenoid carbonyl compounds (column temperatures in parentheses).*

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[1] Review: V. Schurig, W. H. Pirkle, J. Finn, in J. D. Morrison (Ed.): *Asymmetric Synthesis, Vol. 1, Analytical Methods*, Academic Press, New York (1983), chapters 5 and 6.

[2] Trivial names: dihydrocitronellal (**3**), hexahydropseudoionone (**4**), hexahydrofarnesal (**5**), hexahydrofarnesylacetone (**6**).

[3] Acetals derived from the homologous diethyl, diisobutyl, di-*tert*-butyl, diisopentyl, dineopentyl, and dicyclohexyl tartrates performed inferior in this assay.

[4] Structures of all new compounds are consistent with spectroscopic (^{1}H- and ^{13}C-NMR, IR, MS) and microanalytical data. We thank our colleagues from Central Research Units for these analyses, and H. Willimann and N. Kuratli for skilful technical assistance.

[5] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett. 21* (1980) 1357; J. R. Hwu, L.-Ch. Leu, J. A. Robl, D. A. Anderson, J. M. Wetzel, *J. Org. Chem. 52* (1987) 188. – The reaction mixture was stirred 1–4 h at room temperature and quenched by adding triethylamine.

[6] Supelco SP-2340 column (95 m × 0.3 mm) mounted on a Hewlett-Packard HP-5890 chromatograph equipped with a flame ionization detector. Columns were operated isothermically under a hydrogen flow of 40 cm/s.

[7] Unnaturally configurated **5** and **6** were prepared from the corresponding hexahydrofarnesols by oxidation (pyridinium chlorochromate) or by a bromination (tosylation)/acetoacetate condensation/decarboxylation sequence. We wish to thank Drs. R. Schmid, E. A. Broger, and Y. Crameri for supplying optically active starting materials.

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