How to be right and wrong

Rita H. Cornforth and John W. Cornforth*

School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, United Kingdom

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An historical article, recounting the circumstances in which the authors and Professor V. Prelog published their one collaborative paper.9 In that paper, the question of the absolute configurations of the naturally occurring terpene alcohols (+)- and (−)-linalool was finally cleared up.

In 1956, chemists from the Merck Sharpe and Dohme research laboratory at Rahway, New Jersey, reported that a growth factor for Lactobacilli, identified as 3,5-dihydroxy-3-methylpentanoic acid (1), was a precursor of cholesterol in rat liver slices.1 This experiment used a synthetic isochiral2 preparation of mevalonic acid, as the factor was called, labelled with radioactive carbon. So high was the incorporation of radioactivity into cholesterol that if only one enantiomer of the precursor was participating (as was likely), then mevalonic acid was being used by this tissue for cholesterol synthesis and for no other significant pathway, and it was not appreciably degraded to any product that could then be involved in general metabolism.

This beautiful discovery was a liberating event for all of us who were working on steroid and terpenoid biosynthesis. It was soon confirmed that

![Chemical structure of 3,5-dihydroxy-3-methylpentanoic acid](image)

* Author to whom correspondence should be addressed.
only one enantiomer of mevalonic acid was used in biosynthesis and that the »unnatural« enantiomer was inert metabolically. This was fortunate, since it meant that the labelled versions used for experiments on biosynthesis could be isochiral and therefore easier for chemists to make. Resolution of the synthetic acid to yield the monochiral »natural« enantiomer was achieved with difficulty, and enzymic resolution is also possible, but an easy synthesis of the natural enantiomer was desirable; and in 1958 we looked for a monochiral starting-point for such a synthesis.

The attractions of linalool (2) were soon obvious. Commercial supplies of this alcohol are often anisochiral, but an essentially monochiral supply of the (−) form, from Ho-leaf oil, was available. Linalool already contains, at its sole stereogenic centre, two of the groups at the sole stereogenic centre of mevalonic acid. The chemical task was to transform one of the two remaining groups into a carboxymethyl group and the other into a β-hydroxyethyl group. To design a synthesis leading directly to »natural« mevalonic acid from (−)-linalool, the absolute configurations of starting-point and destination must be known. Happily, there was recent information on both of them.

Eberle and Arigoni executed an ingenious and chemically unambiguous transformation of quinic acid (3) to »unnatural« mevalonic acid (4) and concluded that the »natural« acid has the 3R configuration (5). Although this work was not published until 1960 we knew about it. Prelog and Watanabe assigned in 1957 an absolute configuration to linalool on the basis of a synthesis of anisochiral tetrahydrolinalool. It appeared from these two assignments that if we started from (−)-linalool and transformed its vinyl group to a β-hydroxyethyl group, we would obtain »natural« 3R-mevalonic acid by oxidative degradation of the other carbon chain to carboxymethyl.
The work went well. The first and obvious step, a Brown hydroboration of both double bonds in (–)-linalool, yielded a triol (6) easily convertible by acid-catalysed condensation with acetaldehyde into a cyclic acetal (7). The unprotected hydroxyl group was oxidized to a ketone (8) with chromic acid in pyridine (this reagent, still known as the Cornforth reagent, was a modification of Sarett’s original chromium trioxide – pyridine reagent but is quicker and safer to make); the ketone by Claisen condensation with methyl formate – sodium methoxide gave a hydroxymethylene-ketone (9) which was immediately oxidized with sodium periodate. The acetal group was lost in the work-up and mevalonic acid was isolated as its low-melting crystalline lactone in 21% overall yield from linalool. The novel cleavage of a ketomethylene group to two carboxyl groups was smooth and convenient and we would still use it if another occasion arose. So, monochiral mevalonic acid was now readily available in quantity – but it was the »unnatural« 3S-mevalonic acid (4)! Instead of reaching our destination we had arrived in Looking-glass Land. One of the two assignments of absolute configuration was wrong.

![Chemical Structure](image)

We could not doubt the validity of the chemical correlation between quinic acid and mevalonic acid, so we set out to check the absolute configuration assigned to quinic acid. In those days, there was no atlas of stereochemistry in which one could turn up correlations, along with references to the experiments, in a few minutes. The pathway uniting quinic acid, by way of glucose, to Bijvoet’s tartaric acid (the source at that time of all absolute configurations) was long, tortuous and overgrown. It took one of us a week to force a way through. But in the end we had no reasonable doubt that the assignment was correct. It was time to look at the evidence for linalool.
Vlado Prelog’s rule for correlating absolute configurations has its origin in one of the earliest successful asymmetric syntheses. In 1904, McKenzie showed that when the monochiral ester (10) of (−)-menthol with benzoylformic acid was treated with the then novel methylmagnesium iodide, alkaline hydrolysis of the product (11) gave an anisochiral α-methylmandelic acid with an enantiomeric excess (e.e.) around 25%. Half a century later, and armed with more extensive knowledge of absolute and relative configurations, Vlado was able to seek, test and establish a rule connecting the chirality of the esterifying alcohol (menthol, in the original case) with the chirality of the major component of the anisochiral product formed. He summarized this magnificent work in a review. The key factor that determines the direction of attack of the Grignard reagent on the ketone carbonyl of the α-oxo ester, he concluded, is the relative »size« (that is, the demand for space) of the three groups immediately attached to the oxygenated carbon of the alcohol. If these three groups are ranked as large (L), small (S), and medium (M), then an α-oxo ester of general formula (12) will be attacked by a Grignard reagent to yield an α-hydroxy ester that is predominantly (13), and this will give on saponification an acid that has an excess of the enantiomer (14). Vlado strengthened his rule by many experiments using different alcohols, different α-oxo acids, and different Grignard reagents. He used it to determine the absolute configuration of a number of alcohols: experimentally, the spatial arrangement of the L, M and S groups was deduced simply from the sign of optical rotation of the derived α-hydroxy acid.
Linalool is an alcohol, but its absolute configuration was not deduced in this way. The difference in »size« between the three relevant groups was too small for a secure assignment to be made, and preparation of the requisite ester from an allylic tertiary alcohol could have been difficult. Instead (−)-menthol, an alcohol of known chirality and good LMS differentiation, was used, by reaction of its 2-oxobutyrate ester (15) with isohexylmagnesium bromide, to construct an anisochiral hydroxy acid (16) of predictable stereochemical preference, and this was converted chemically into tetrahydrolinalool (17) without disturbance of chirality, by conversion of its carboxyl group into methyl. This tetrahydrolinalool was laevorotatory, as was a specimen obtained by catalytic hydrogenation of (−)-linalool. The e.e. of the asymmetric synthesis was quite good, about 40%. According to rule, the preferred configurations are as shown in the figures and (−)-linalool (18) is R. But this was not the conclusion drawn in the paper. Somehow or other, perhaps because this was an unusual application of the rule, the preferred configuration of the hydroxy acid came out as the enantiomer (19). Thereafter, the logic was faultless and led to the mistaken conclusion that (−)-linalool was S.
Our very last expectation, in starting this inquiry, was having to tell a very great chemist that he had misapplied his own rule. What to do? In the event, we wrote to Vlado telling him the facts and offering to assist in putting the matter right. The ability to admit error is a good measure of a person’s quality and Vlado did not disappoint us. He made no attempt to blame his collaborator and he pointed out other observations that should have warned him that there might be something anomalous in this assignment. His paper was wrong, but his rule was right, and he was happy to see it vindicated. He wrote the correction and we published it together: our only paper with Vlado. And since then, we have been fast friends.

We might have modified our conversion of (–)-linalool to obtain natural mevalonic acid, converting its vinyl group into carboxymethyl and its isohexenyl group into β-hydroxyethyl instead of the other way round. That would have been a longer and harder way, but a kind fate made it unnecessary. We visited Australia, our native country, in 1960 and one of us mentioned our synthesis in a lecture. Afterwards, one of the audience arose and asked if we would like to have some (+)-linalool. We were soon in joyful possession of two litres of the essential oil of a tea-tree, Melaleuca quinquenervia, from which we distilled monochiral S (+)-linalool (20) and converted it into 3R mevalonolactone (21). One of us visited the Merck laboratories at Rahway on the way back to England and had the pleasure of presenting Dr. Karl Folkers with a 1 g specimen of the recrystallized, monochiral lactone, more than he had ever seen before. At home, George Popjak tested the two mevalonates with mevalonate kinase and verified that the 3R specimen was completely phosphorylated, whereas the 3S sample showed less than 1% reaction. We published the work as a full paper. We had solved a problem, cleared up an inconsistency, and gained a friend. May we enjoy many more years of his friendship.

REFERENCES


(In this proposed nomenclature »monochiral« means »consisting of one enantiomer«; »isochiral« means »containing both enantiomers in equal amounts«; and
»anisochiral« means »containing both enantiomers in unequal amounts«. These words replace »homochiral«, »racemic«, and »scalemic« respectively).


SAŽETAK

Kako biti u pravu i krivu

Rita H. Cornforth i John W. Cornforth

Povijesni članak koji opisuje uvjete u kojima su autori i profesor V. Prelog publicirali njihov jedini zajednički rad. U tom je radu definitivno razjašnjeno pitanje apsolutne konfiguracije prirodnih terpenskih alkohola (+)-i (-)-linalola.