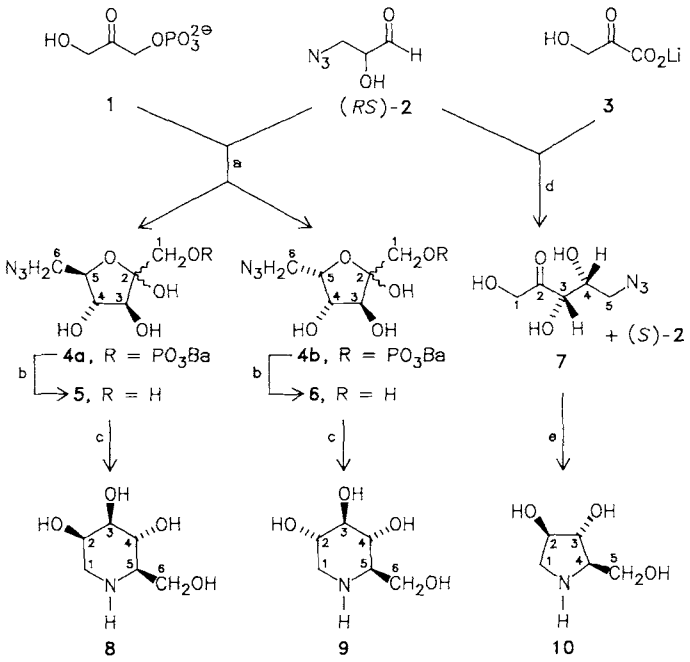
Enzyme-Catalyzed Synthesis of 1-Deoxymannojirimycin, 1-Deoxynojirimycin, and 1,4-Dideoxy-1,4-imino-D-arabinitol**

By *Thomas Ziegler, Alexander Straub,* and *Franz Effenberger**

1-Deoxymannojirimycin (1,5-dideoxy-1,5-imino-D-mannitol) **8**, 1-deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol) **9**, and 1,4-dideoxy-1,4-imino-D-arabinitol **10** are very effective glycosidase inhibitors.[1,2] The piperidine derivatives **8** and **9** have been known for some time,[1] whereas the pyrrolidine derivative **10** was first discovered in 1985 in two types of leguminoses, from which it was isolated.[3]

Because of their great importance as active agents a considerable number of methods have been developed for the synthesis of **8** and **9**, almost all of them starting from naturally occurring carbohydrates so as to introduce as many chirality centers from the very beginning.[4] Recently a synthesis of **9** from L-(+)-tartaric acid was described.[5] In the case of **10**, only one synthesis has been published so far;[6]



Scheme 1. a) **1** + (*R,S*)-**2**/pH 6/aldolase (EC 4.1.2.13)/12 h/25°C; pH 7/$BaCl_2 \cdot 2H_2O \rightarrow$ **4** (≡ **4a** + **4b**) (70%). b) **4**/phosphatase/pH 4.5/48 h/38°C/chromatography on Dowex 1×8 $HCO_3^{\ominus}$ with $H_2O \rightarrow$ **5** and **6** (each 80%). **5**: $[\alpha]_D^{20} = +52.49°$ ($c = 2.1$, H_2O), **6**: $[\alpha]_D^{20} = -53.78°$ ($c = 2.9$, H_2O). c) **5** or **6**/K_2CO_3/H_2O/Pd/C/80 bar H_2/4 h/50°C/HCl → **8** · HCl and **9** · HCl (each 65%). d) (*RS*)-**2** + **3**/$MgCl_2$/thiamine pyrophosphate/pH 8/transketolase (EC 2.2.1.1)/15 h/30°C/chromatography on Dowex 50 WX8 $Ca^{2\oplus}$ with $H_2O \rightarrow$ (*S*)-**2** (62%) and **7** (71%). (*S*)-**2**: $[\alpha]_D^{20} = -19°$ ($c = 0.4$, D_2O), **7**: $[\alpha]_D^{20} = -13.9°$ ($c = 0.4$, D_2O). e) **7**/K_2CO_3/H_2O/Pd/C/80 bar H_2/12 h/25°C → **10** · HCl and (4*S*)-**10** · HCl (11:1), after recrystallization from methanol/ether **10** · HCl (63%). $[\alpha]_D^{20} = +35.6°$ ($c = 0.4$, H_2O), m.p. 113°C (113–115°C [6]), ^{1}H-NMR-, ^{13}C-NMR-spectra identical with those given in [6].

it starts from D-xylose. Common to all these methods is the involvement of an extensive protecting group technique, which consequently requires a large number of reaction steps and thus leads to low overall yields.

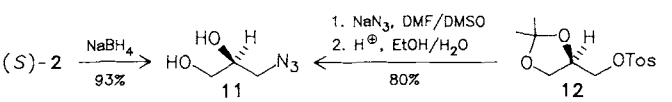
We recently reported on a simple synthesis of dihydroxyacetone phosphate (DHAP) **1** and its use in aldolase-catalyzed aldol additions.[7] We have now used this stereochemically unambiguous CC coupling as key reaction for the synthesis of the compounds **8** and **9** from a chiral precursor (Scheme 1).

In the reaction of **1** with (*R,S*)-3-azido-2-hydroxypropanal **2** catalyzed by rabbit-muscle aldolase we have isolated a diastereomeric mixture **4** of the barium sugar phosphates **4a** and **4b** in 70% yield. The enzymatically determined conversion was >99%. By acid or enzymatic cleavage of phosphate we obtained a diastereomeric mixture which could be readily resolved chromatographically on Dowex 1×8 into the D-fructo- and L-sorbo-compounds **5** and **6**, respectively (each in 80% yield). The purity and composition of the diastereomers **5** and **6** were confirmed by GC-MS analysis of the persilylated compounds (29% α-**5**, 71% β-**5**; 88% α-**6**, 12% β-**6**).

The anomers **5** and **6** were hydrogenated analogously to the method used for the preparation of hydroxypiperidines from 6-aminohexuloses.[4a–c] Thereby we obtained exclusively deoxymannojirimycin **8** from **5** and exclusively deoxynojirimycin **9** from **6**. The diastereomeric purity of **8** and **9** was confirmed by GC-MS analysis of the persilylated compounds; the ^{1}H-NMR, ^{13}C-NMR and MS data are consistent with the published data for **8** and **9**.[4f–h]

For the analogous synthesis of the pyrrolidine derivative **10**, azidoacetaldehyde, which, however, has so far proved impossible to prepare in pure form, had to be used in place of (*R,S*)-**2**. We have now succeeded, however, in preparing the 5-azido-5-deoxy-D-xylulose **7** in good yields from lithium hydroxypyruvate **3** and (*R,S*)-**2** via a transketolase-catalyzed CC coupling (Scheme 1). Upon hydrogenation, the azido sugar **7** furnishes the pyrrolidine derivative **10** in high yields (76%), containing less than 10% of the undesired (4*S*)-diastereomer. The latter byproduct can be removed by simple recrystallization of the hydrochloride from methanol/ether.

Transketolases have thus far found little preparative use.[8] This example demonstrates, not only their utility in the synthesis of sugars, but can also serve for the separation of racemic aldehydes, e.g. (*R,S*)-**2**. The configuration of the aldehyde (*S*)-**2** isolated besides **7** was confirmed



by reduction to the (*S*)-3-azido-1,2-propanediol **11** ($[\alpha]_D^{20} = -15°$). **11** ($[\alpha]_D^{20} = -15.8°$) was prepared via an independent route from the commercially available (*R*)-isopropylideneglycerol tosylate **12**.

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Competition of Endoperoxide and Hydroperoxide Formation in the Reaction of Singlet Oxygen with Cyclic, Conjugated Dienes**

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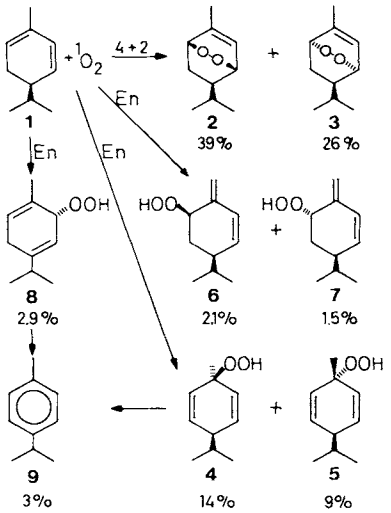
Singlet oxygen ($^1O_2$) usually reacts with cyclic, conjugated dienes in the sense of a [4+2] cycloaddition to give endoperoxides, whereas non-conjugated olefins with allylic hydrogen atoms undergo a double-bond shift with formation of hydroperoxides. In the following we show that both reactions can occur, and that a common intermediate can be formulated in the case of cyclic, conjugated dienes.

In the search for biologically active plant constituents we isolated the two endoperoxides **2** and **3** as active components which are accessible synthetically by reaction of $^1O_2$ with (*R*)-(−)-α-phellandrene **1**[1] and were previously considered to be the sole products of this reaction. To our surprise, however, not only the peroxides **2** and **3** are formed but also all theoretically possible hydroperoxides **4**, **5**, **6**, **7**, and **8**, together with the aromatization product *p*-cymol **9**.[2] Scheme 1 shows the distribution of all products after a preparative HPLC separation (data in wt-%).



Scheme 1.

Two facts emerge therefrom: First, hydroperooxides are formed to a considerable extent; that is, [4+2] cycloaddition and ene reaction compete. Second, the *cis-trans* ratio (based on the position of the peroxide function to the isopropyl group) is constant for both the endoperoxides as well as the diastereomeric hydroperoxides; it is 3:2.

The latter finding suggests the existence of a common intermediate for endo- and hydroperoxides. *Monroe*[3] has postulated this for the reaction of $^1O_2$ with acyclic dienes; for cyclic dienes, however, he proposed a concerted [4+2] cycloaddition exclusively, since only endoperoxide formation was observed.

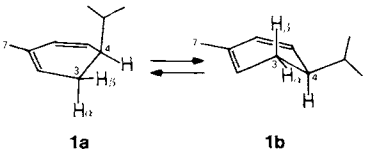


Fig. 1. Conformations **1a** and **1b** of (*R*)-(−)-α-phellandrene **1**.

Dreiding models show that α-phellandrene **1** can assume two conformations (Fig. 1). At room temperature a considerable amount of **1** is present in the conformation **1a**.[4] In a concerted [4+2] cycloaddition with attack of $^1O_2$ from above, steric interactions of the isopropyl group with the dienophile should be considerable for **1a** and negligible for **1b**. On the other hand, both conformers are equally likely to react with $^1O_2$ from below. In summary, therefore, more *trans*-endoperoxide **3** should result. The observed higher proportion of the *cis*-endoperoxide **2** thus contradicts an endoperoxide formation by concerted [4+2] cycloaddition.

Especially interesting concerning the hydroperoxides is the preferred *cis*-conformation of **6** compared to **7**. Since the abstracted H atom here comes from a methyl group, a *cis-trans* ratio of 1:1 would be expected, irrespective of the conformation,[5] if the $^1O_2$ does not preferably approach from above.

How then does this *cis*-directing effect come about? The point is that $^1O_2$ preferably abstracts axial allylic H atoms in an ene reaction, whereas equatorial allylic H-atoms remain undisturbed.[6]

Regarding the *cis* sides of **1a** and **1b** in respect to the formation of **4** and **5**, H-3β being the only proton that could react in an ene reaction has the unreactive equatorial position in the case of **1a** and, additionally, the isopropyl group disfavors abstraction because of unfavorable steric interactions. In contrast this H-3β is axial in the conformer **1b**. Exactly the opposite holds true on the *trans* side for H-3α: in **1a** it is axial, and in **1b** it is equatorial. We therefore presumed that the *cis* products are mainly formed from the conformer **1b** and the *trans* products mainly from the conformer **1a**. To substantiate our assumption we carried out the reaction at −50°C. Since conformer **1a** is the energetically less favorable,[4c] the amount of *trans* products should decrease further. As expected the *cis-trans* ratio increases from 3:2 to 4:2, both in the case of the endo- as well as the hydroperoxides.

According to the above observations the mechanism of the ene reaction must first be considered. In the recent literature[7] a loose complex **10** is proposed in which $^1O_2$ interacts with the olefinic C atoms and with the allylic H atoms to be abstracted. If, as in the present case, both endo- as well as hydroperoxides are formed from a diene,

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