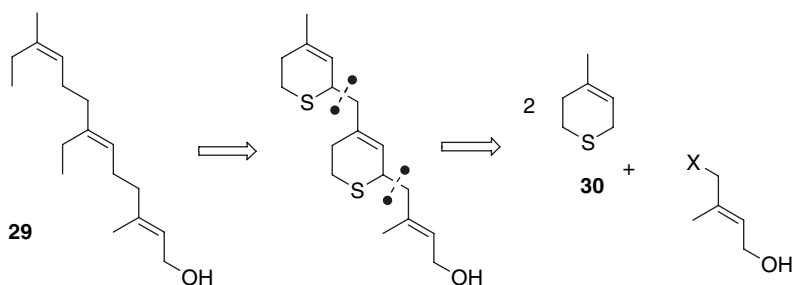


## Chapter 4

# Building Block Oriented Synthesis

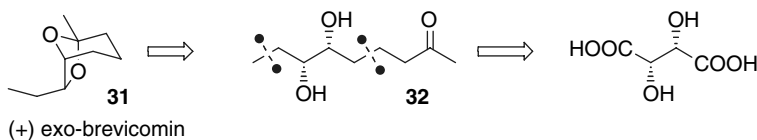
**Abstract** If substructures with special features (branches, stereogenic centers) of the target correspond to readily available starting materials, it is advisable to incorporate those as building blocks in the synthesis. Guidelines are given as to how to identify suitable building blocks.

One tends to pursue a building block oriented synthesis when building blocks are available that contain characteristic structural elements present in the target structure. Frequently, such structural elements are stereochemistry related, e.g., the defined configuration of a multiply-substituted double bond or a certain sequence of contiguous stereogenic centers. When the synthesis of compound **29** (the cecropia juvenile hormone) was considered, the thiapyrane **30** was identified as a suitable precursor, since this subunit contains the appropriate number of carbon atoms along with the correct double bond configuration [1, 2] (Scheme 4.1).



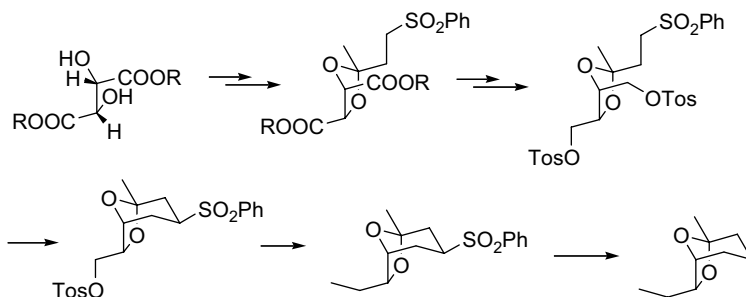
**Scheme 4.1** Identification of a building block containing the correct double bond configuration

When the methodology of stereoselective synthesis was still in its infancy, it was considered advantageous to utilize sequences of stereogenic centers available from enantiomerically pure natural products as building blocks [3, 4]; this so-called chiral pool synthesis strategy is exemplified in Scheme 4.2. The bicyclic acetal structure of *exo*-brevicomin (**31**) can be retrosynthetically linked to the chiral ketodiol **32**, which can be derived from (*S,S*)-(-)-tartaric acid, a readily available chiral starting material. This leads to the building block oriented bond-set depicted in intermediate **32**.



**Scheme 4.2** Building block oriented (ex chiral pool) retrosynthesis of *exo*-brevicomin

Several syntheses of *exo*-brevicomin have been executed according to this bond-set [5, 6, 7, 8, 9]. Their step count varies between 7 and 12, illustrating that, for a given bond-set, there is still ample room for intelligent planning of a synthesis in the forward direction. One [9] of these syntheses is illustrated in Scheme 4.3.

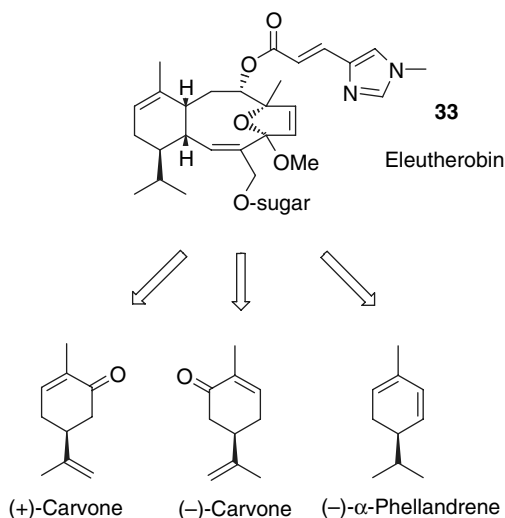


**Scheme 4.3** Building block oriented synthesis of *exo*-brevicomin from tartaric acid

This synthesis uses an auxiliary sulfonyl group (FGA, see Sect. 3.1) to enable the formation of one of the skeletal bonds.

The choice of a suitable chiral precursor is often obvious for a given target structure. However, the obvious choice is not necessarily the only meaningful

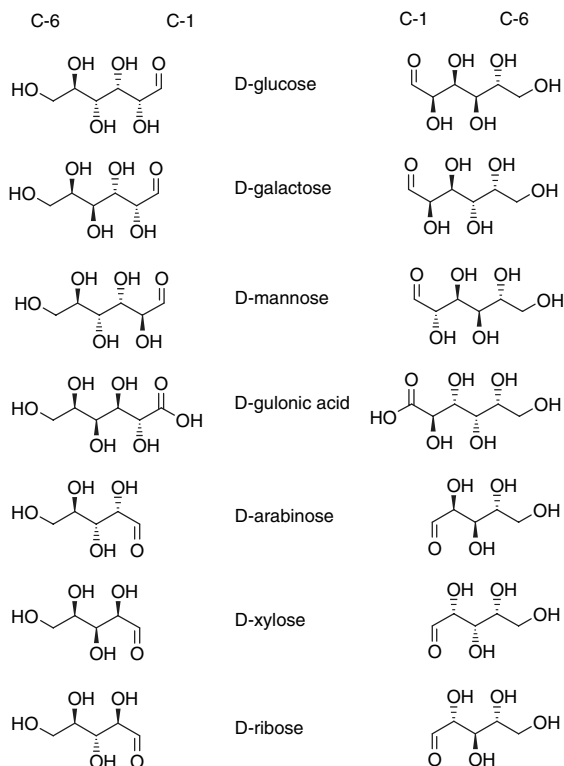
or possible solution. In the case of eleutherobin **33**, one tends to immediately envision (+)-carvone as a suitable chiral precursor [10]. However, a different adaptation reveals that (–)-carvone could also be an attractive precursor [11]. Even  $\alpha$ -phellandrene has been chosen as the starting point for an efficient synthesis of eleutherobin [12] (Scheme 4.4).



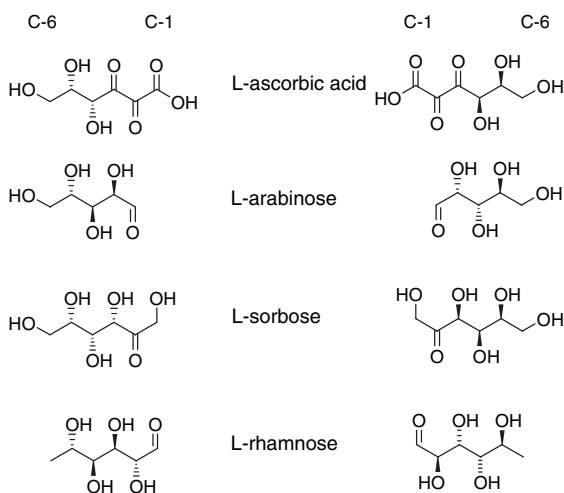
**Scheme 4.4** Suitable chiral building blocks for the synthesis of eleutherobin

In order to make the optimal choice from among suitable chiral precursors, one needs a compilation of all available chiral natural products. A selection of these is published in a review by Scott [13]. However, because one tends to write a target structure in a distinct arrangement, and the potential chiral precursors are often depicted quite differently, it can be difficult to recognize similarities or differences in constitution and configuration between target and precursor structures. Such comparisons can be effected reliably by computer programs [14]. Yet when one writes both target structure and precursor structures in the same spatial arrangement, even pedestrian solutions become readily apparent. This is illustrated by a list of common sugar building blocks, written in a zig-zag arrangement of the backbone, from C-6 to C-1 and also in the opposite sense (Schemes 4.5 and 4.6).

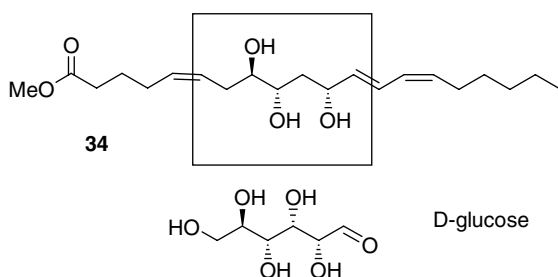
## D-Sugars

**Scheme 4.5** Readily available D-sugars in zig-zag arrangement of the main skeleton

## L-sugars

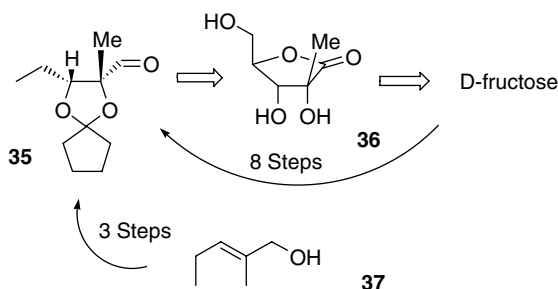
**Scheme 4.6** Readily available L-sugars in zig-zag arrangement of the main skeleton

It is advisable to copy these schemes as a transparency. When a target structure has several oxygenated stereogenic centers along its main chain, one should write the target structure in a zig-zag arrangement of the main chain. Then it will be possible by an overlay of the transparency to check which readily available sugar molecules possess a complete or partial congruence regarding the stereogenic centers. For example, consider the arachidonic acid derivative **34**. The comparison shown in Scheme 4.7 indicates that D-glucose could be a useful precursor. A synthesis along these lines would require deoxygenation at C-3 of glucose, as well as chain extensions at C-1 and C-6. In fact, an efficient synthesis of compound **34** was accomplished via this strategy [15].



**Scheme 4.7** Identification of D-glucose as a suitable precursor for synthesis of **34**

During a synthesis of erythronolide A, carried out by our group at Marburg, we needed the chiral aldehyde **35** as starting material. Perusal of the list of commercially available chiral starting materials [13] suggested a synthesis of lactone **36** from D-fructose (Scheme 4.8). With this in mind, aldehyde **35** was prepared from fructose in eight steps [16].



**Scheme 4.8** Identification of suitable precursors for the synthesis of **35**

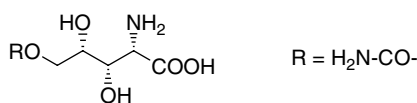
Yet, by today's standards, an effort of eight steps to create a molecule with just two stereogenic centers is decidedly inefficient! Due to the significant

enhancements in stereoselective synthesis methodology, it is now possible to access the aldehyde **35** in three steps via Sharpless asymmetric epoxidation beginning with the allylic alcohol **37** [17]. Thus, a principle drawback of ex chiral pool synthesis is illustrated: an excessive number of steps is required in order to trim down an overfunctionalized natural product during a synthesis in which it is employed. Ex chiral pool synthesis is only justified when the chiral building block contains a considerable measure of complexity (e.g., three or more stereogenic centers) that can be incorporated into the target structure. Long reaction sequences, after which only one stereogenic center remains intact from a complex sugar [18, 19], are justified only if the aim is to establish absolute configuration by chemical correlation.

The search for suitable chiral precursor molecules, which can be incorporated into a target structure with minimum effort, is an important part of planning a synthesis. When the target structure contains multiple stereogenic centers, it may be advantageous to take not all, but just the first stereogenic center from the chiral pool and then install the others by asymmetric synthesis, preferably by substrate-based asymmetric induction. In any case, one should think critically about any ex chiral pool synthesis of a target structure, bearing in mind the number of steps needed to remodel and incorporate a readily available chiral building block.

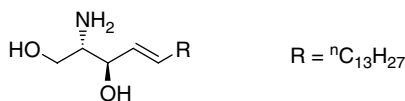
## Problems

**4.1** In Scheme 4.9 the core structure of polyoxamic acid is shown. Suggest suitable chiral building blocks for its synthesis.



**Scheme 4.9** Structure of polyoxamic acid

**4.2** Scheme 4.10 displays the structure of *D-erythro*-sphingosine. Suggest suitable chiral building blocks for its synthesis [20].



**Scheme 4.10** *D-erythro*-sphingosine, a target that invites synthesis from the chiral pool

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Elements of Synthesis Planning

Hoffmann, R.W.

2009, X, 227 p. 297 illus., Softcover

ISBN: 978-3-540-79219-2