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 thia-pyrane 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](image-url)
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](image)

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](image)

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 α-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](image)

**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](image)

**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 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](image)

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](image)
References

Elements of Synthesis Planning
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