Retrosynthetic Analysis: Excerpts from Hoffmann*

Chapter 1
Introduction

Abstract Any synthesis of a target structure requires a plan, which is derived from the target structure by a retrosynthetic analysis. This analysis identifies the bonds to be made in the forward synthesis, i.e., the bond-set. Guiding principles are listed, along which synthesis plans may be developed.

When looking at a target structure, three main aspects should be given attention: the molecular skeleton, the kind and placement of functional groups, and the kind and placement of stereogenic centers. All three aspects impart the planning process for a synthesis; they are interdependent, yet they are not of equal importance. Functional groups may be readily interconverted [1] and, moreover, may be generated from existing C=O and C=C double bond entities. Also, the techniques of stereoselective synthesis have reached a standard [2] such that considerations regarding the generation of stereogenic centers, while an important aspect of synthesis planning, are no longer a paramount problem. In most cases, efficient access to the molecular skeleton remains the major challenge.

Hence, one normally focuses first on the molecular skeleton when planning a synthesis. Consider, for example callystatin A, a target molecule of medium complexity (Scheme 1.1). Try to identify building blocks from which this molecule could be assembled. To do this, one cuts the structure into smaller fragments using *retrosynthetic disconnections*.

There is actually no meaningful alternative in synthesis planning, as S. J. Danishefsky [3] puts it: “It would be improbable, to say the least, to plan the synthesis of a complex target structure through a cognitive process which is fully progressive in nature. Given the stupefying number of ways in which one might begin and proceed, it would seem unlikely that the human mind would go anywhere but in the retrosynthetic direction wherein, at least generally, complexity is reduced as the planning exercise goes on.”

Retrosynthetic disconnections are done best in a manner that produces resulting pieces of approximately similar size [4]. Such a tactic will enable the

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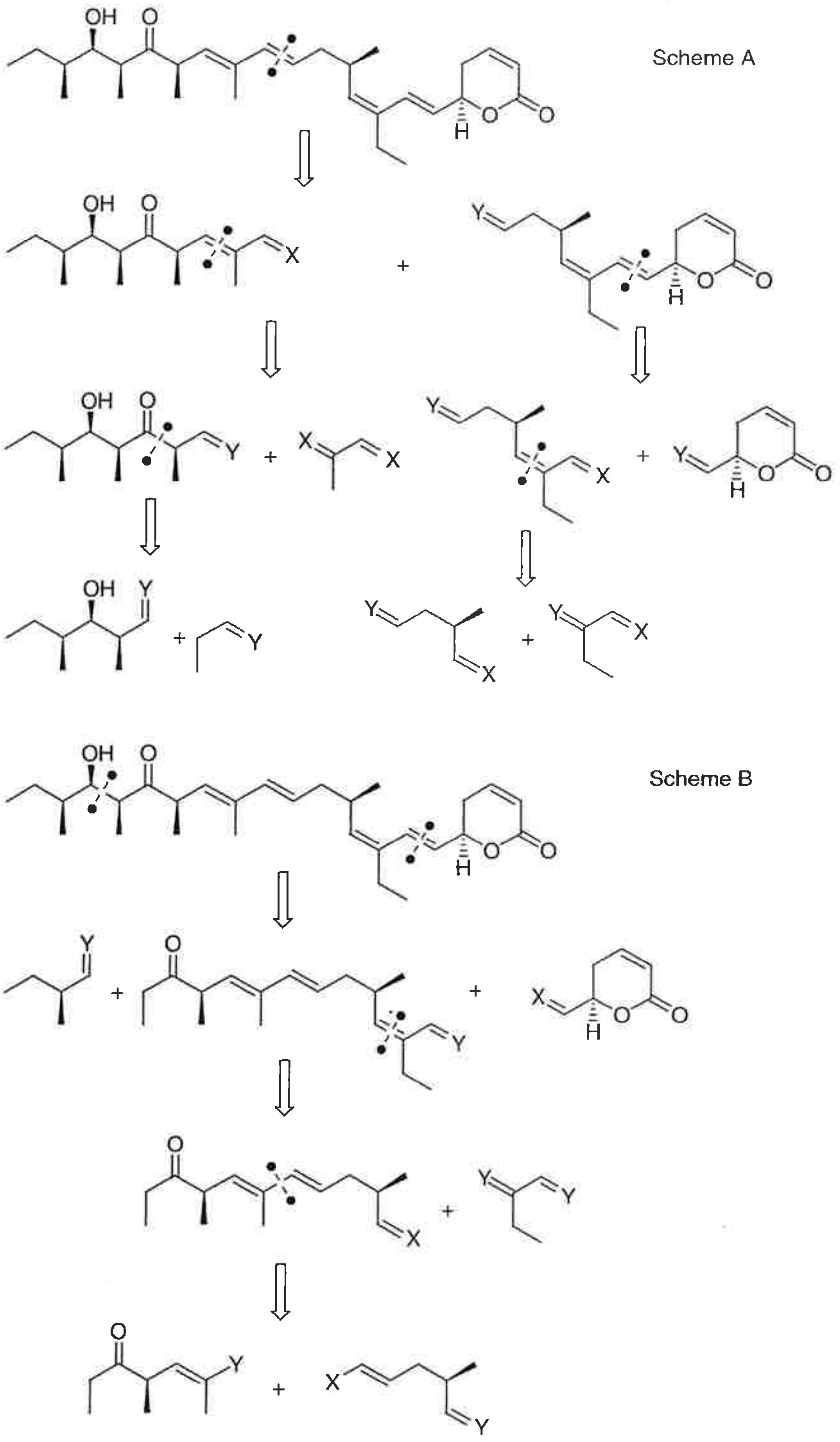


Scheme 1.1 Two (of many conceivable) retrosynthetic schemes for callystatin A, a cytostatic compound of limited natural supply

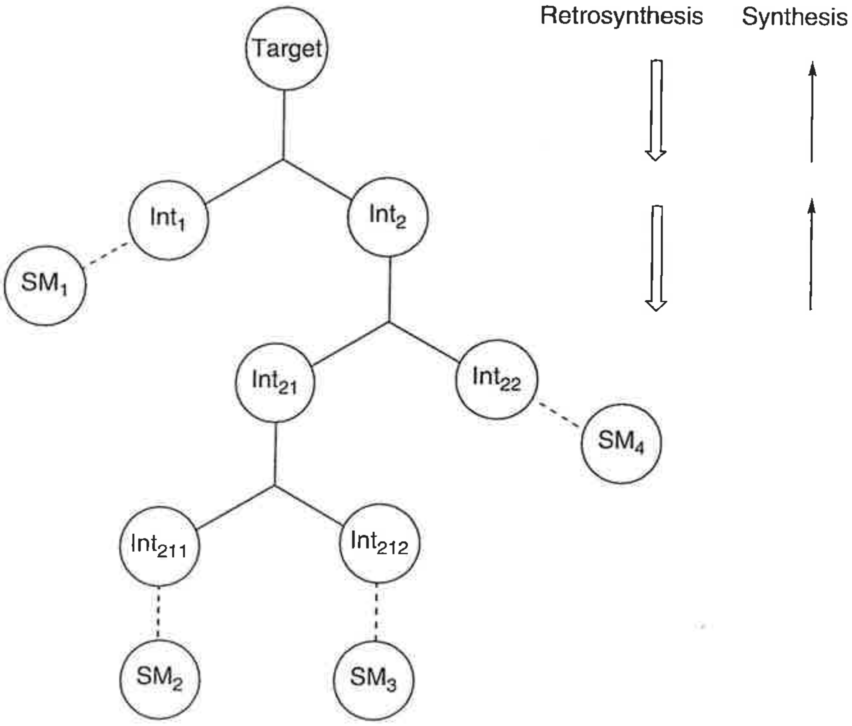
forward synthesis to proceed in a highly convergent manner (cf. Chap. 8). When one does these cuts based solely on the topology of the target structure, one neglects the knowledge of how to execute bond formation in the forward direction. As the experienced chemist knows which type of bonds he can easily form in actual synthesis, this information, together with the topological considerations, guides the retrosynthetic disconnections. Hence, selecting cuts in retrosynthesis means striking a balance between topological considerations and the availability of easily attainable forward synthetic operations.

At this stage of the planning process, the pieces resulting from the cuts do not have to be fully defined with regard to specific functional groups. Rather, the planning process at this stage yields a highly generalized synthesis plan, as illustrated in Scheme 1.1 for callystatin A [5]. Each conceived retrosynthetic cut is symbolized by a hollow arrow ("retrosynthetic arrow"), whereas each planned forward synthetic step is indicated by a normal arrow. The not yet defined functionalities, enabling bond formation in the synthetic direction, have been designated by the symbols X and Y.

The completion of actual syntheses of callystatin A by these and further routes can be found in reference number [5].

The two retrosynthetic schemes for callystatin A reveal significant differences. In Scheme A, the cuts are done to separate the target into pieces of roughly similar size. By contrast, in Scheme B, the cuts have been done at the periphery of the target structure; thus failing to provide optimal retrosynthetic simplification.

Retrosynthesis schemes generally have the shape of an upside-down tree. At the root is the target structure, while the outer branches constitute the ensemble of starting materials (cf. Scheme 1.2).

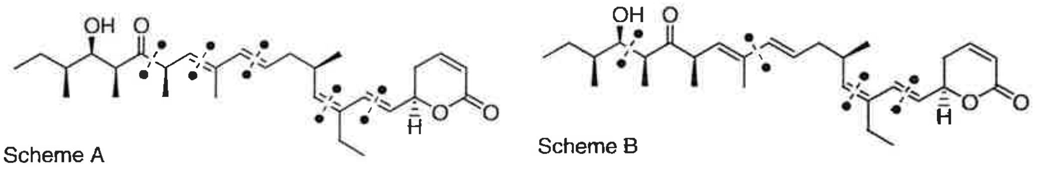


Scheme 1.2 Synthesis tree; Int = intermediate product, SM = starting material

Inasmuch as the starting materials are only vaguely defined at this level of the planning process, one stops when the retrosynthetic cuts have yielded pieces of five to eight skeletal atoms. Building blocks of that size are often commercially available or can be readily obtained by known literature procedures.

The formulation of a retrosynthesis scheme is a process in which each step (cut) is consequential for the possibilities available for the next step (cut). This is a hierarchical process, because the synthesis tree defines a temporal sequence in which the bonds are to be formed. Yet obviously there is the possibility for permutation in the sequences of bond formation.

The ordering of the synthesis steps and the detailed nature of the starting materials are left open in a frequently used depiction of the retrosynthetic analysis. Simply put, bonds that are projected to be formed by synthesis are marked with a dashed line. This generates a set of marked bonds, which are referred to as a *bond-set* [4]. Such notation is perfectly suited for comparing several syntheses of a given target structure (cf. Scheme 1.3).

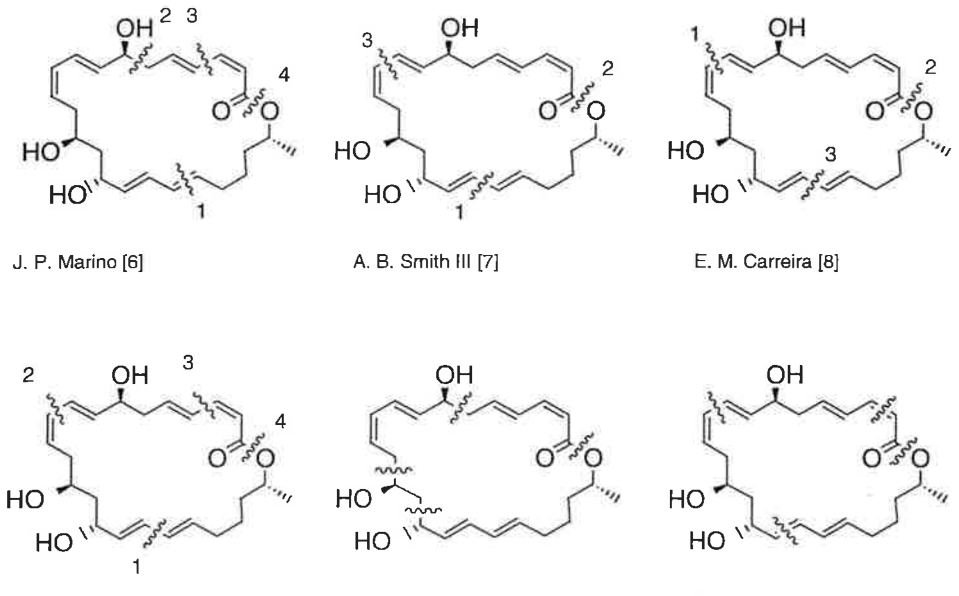


Scheme A

Scheme B

Scheme 1.3 Bond-sets for two realized syntheses of callystatin A

Bond-set notation is further exemplified in Scheme 1.4, wherein six actual syntheses of macrolactin A are organized for ready comparison.



J. P. Marino [6]

A. B. Smith III [7]

E. M. Carreira [8]

J. Pattenden [9]

J. Vilarrasa [10]

S. Tanimori [11]

Scheme 1.4 Realized syntheses (or syntheses in progress) of macrolactin A, an antibiotic of limited availability

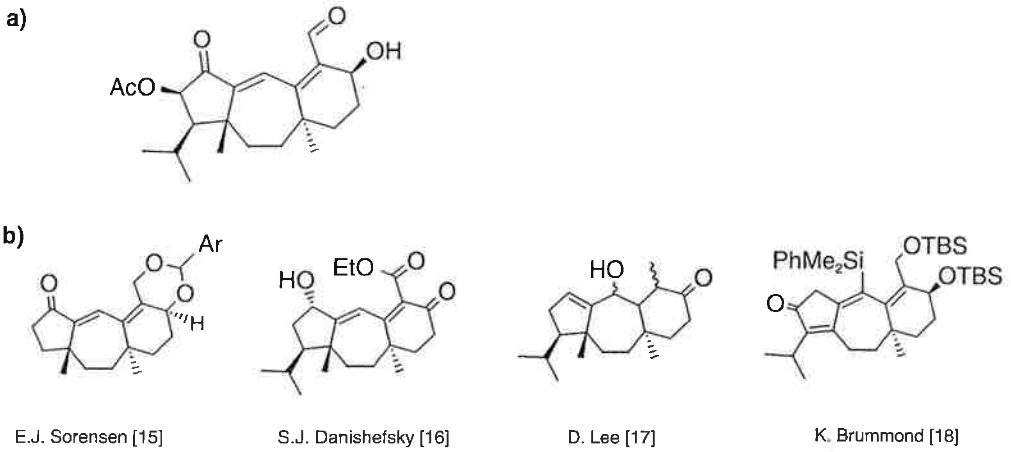
In almost all cases, the retrosynthetic cuts are performed until pieces of five to eight skeletal atoms result, which are either commercially available or readily synthesized with the appropriate functionality. Comparison of the different bond-sets reveals not only differences in the retrosynthetic approaches, but also common features that originate from particular structural moieties, suggesting certain construction reactions. The expert recognizes the generation of 1,3-diene units by Pd(0)-catalysed coupling reactions. One equally appreciates the options opened by allyl metal addition to aldehydes, by aldol additions, or by carbonyl-olefination reactions. One also notes that olefin metathesis, one of the best methods of forming macrocyclic rings [12], will be problematic in this case, as the target structure contains a plethora of similarly substituted olefinic bonds.

The core of planning a synthesis is to select the individual bonds of a bond-set and the sequence of bond-forming steps in such a manner that in the end an efficient synthesis of the target structure can be realized. Several (quite different) guidelines help in this process. A survey of a multitude of published syntheses reveals that bonds in a bond-set are marked according to:

- the kind and arrangement of functional groups in the target structure = *FG oriented*;
- the peculiarities (branches, rings) of the skeleton of the target structure = *Skeleton oriented*;
- the availability of certain (frequently chiral) building blocks = *Building block oriented*;
- the expertise in certain synthetic methodologies = *Method oriented*.

An optimal synthesis plan rarely follows one of the above options exclusively. Rather, it results from a virtuoso combination of all four of the guidelines. Accordingly, we aspire to learn the basics underlying all of these guidelines and how they relate to the selection of a reasonable bond-set (see Chaps. 2–6). The efficiency of a synthesis not only depends on the bond-sets, but also on the sequence by which the individual bonds are formed (i.e., convergent vs. linear syntheses). In Chap. 8 we will address criteria for rating different synthesis plans. This reveals the sorts of steps that reduce synthetic efficiency (i.e., refunctionalization steps, and the introduction as well as removal of protecting groups or auxiliaries). When the use of protecting groups cannot be avoided completely, there are possibilities by which to minimize the drawbacks of protecting groups, as discussed in Chap. 7.

The points stressed earlier should be highlighted once more: Construction of the skeleton of the target structure is the prime task in synthesis planning, not the placement of functionalities or stereogenic centers. This priority is best reflected when a newly reported target structure arouses the interest of the synthetic community. In such a situation, possible approaches to the skeleton of the new target structure are evaluated with respect to (functionally) trimmed down versions of the target structure. For example, various inroads to guanacastepene [13] have been explored via construction of trimmed down guanacastepene congeners [14] (Scheme 1.5).



E.J. Sorensen [15] S.J. Danishefsky [16] D. Lee [17] K. Brummond [18]

Scheme 1.5 (**a**) guanacastepene A, active against antibiotic-resistant bacteria, natural source no longer accessible; (**b**) representative trimmed down skeletal versions

The preliminary goals shown in Scheme 1.5b contain the whole or major parts of the target skeleton (Scheme 1.5a), but lack the complete endowment of functional groups present in guanacastepene. This was reserved for a second phase of the synthesis effort.

References

1. R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, New York, **1989**.
2. *Houben-Weyl Methods of Organic Chemistry, Vol E21, Stereoselective Synthesis*, (Ed. G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann) Thieme, Stuttgart, **1995**.
3. R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2007**, *72*, 4293–4305.
4. J. B. Hendrickson, *J. Am. Chem. Soc.* **1977**, *99*, 5439–5450.
5. M. Kalesse, M. Christmann, *Synthesis* **2002**, 981–1003.
6. J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto, F. C. Tucci, *J. Am. Chem. Soc.* **2002**, *124*, 1664–1668.
7. A. B. Smith III, G. R. Ott, *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948.
8. Y. Kim, R. A. Singer, E. M. Carreira, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1261–1263. (*Angew. Chem.* **1998**, *110*, 1321–1323).
9. R. J. Boyce, G. Pattenden, *Tetrahedron Lett.* **1996**, *37*, 3501–3504.
10. A. González, J. Aiguadé, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1996**, *37*, 8949–8952.

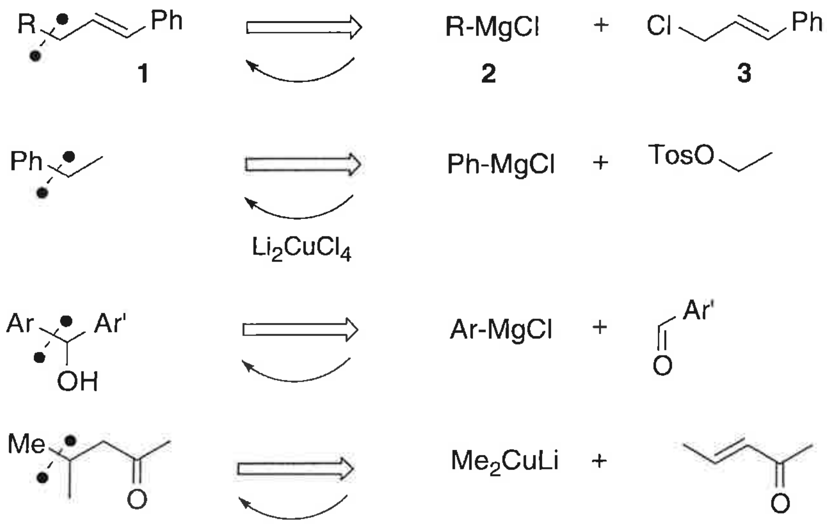
11. S. Tanimori, Y. Morita, M. Tsubota, M. Nakayama, *Synth. Commun.* **1996**, *26*, 559–567.
12. M. E. Maier, *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (*Angew. Chem.* **2000**, *112*, 2153–2157).
13. M. Mandal, H. Yun, G. B. Dudley, S. Lin, D. S. Tan, S. J. Danishefsky, *J. Org. Chem.* **2005**, *70*, 10619–10637.
14. S. V. Maifeld, D. Lee, *Synlett* **2006**, 1623–1644.
15. W. D. Shipe, E. J. Sorensen, *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.
16. D. S. Tan, G. B. Dudley, S. J. Danishefsky, *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188. (*Angew. Chem.* **2002**, *114*, 2289–2292).
17. T. M. Nguyen, D. Lee, *Tetrahedron Lett.* **2002**, *43*, 4033–4036.
18. K. M. Brummond, D. Gao, *Org. Lett.* **2003**, *5*, 3491–3494.

Chapter 2
Functional Group Oriented Bond-Sets

Abstract During synthesis most skeletal bonds are made by polar bond formation in the vicinity of functional groups. The distance between the bond being formed and the functional group determines the sign of the polarity of the bond forming reaction; distance relationships from 1,1 to 1,3 are considered. When bond formation occurs between two functional groups, a mismatch in polarity may result and has to be corrected by using "umpoled" synthons.

2.1 Polar Bond Formation

When we identify a certain bond in the target structure as one to be made in synthesis (i.e., including it in the bond-set), we should reflect upon the possibilities for constructing such a skeletal bond in the forward synthetic direction. Skeletal bonds are primarily made by polar bond-forming reactions, as illustrated in Scheme 2.1.



Scheme 2.1 Examples of polar bond-forming reactions

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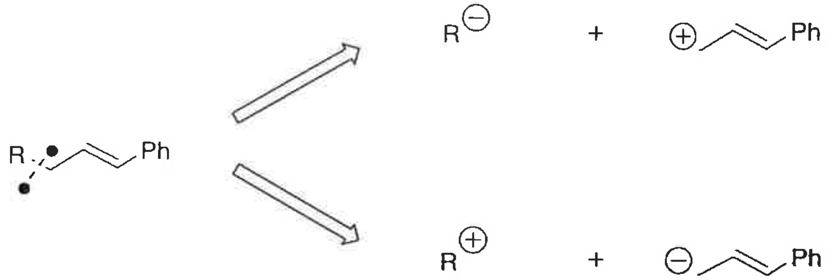
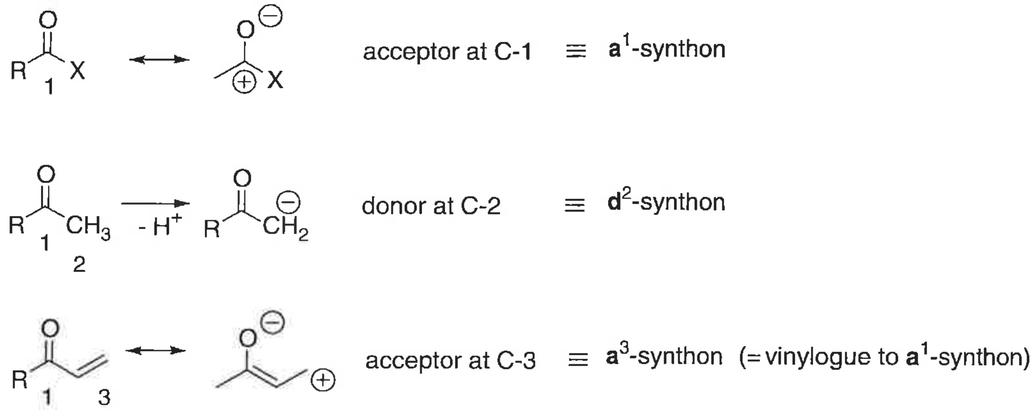
We call the disconnection of compound **1** into potential precursor building blocks **2** and **3** a *retrosynthetic transformation* [1]. In this manner, we capture our knowledge about a synthetic reaction that leads from **2** and **3** to compound **1**. A retrosynthetic transformation is written in the direction opposite to that of a synthetic transformation. As the overwhelming number of synthetic reactions is based on polar bond-forming events, these feature prominently in delineating retrosynthetic transformations of target structures.

During a polar bond-forming reaction, one of the partners (the nucleophile) provides the electron pair that is to form the new bond. The other partner (the electrophile) can, on account of an energetically low-lying empty orbital (LUMO), accommodate the bond-forming electrons. One can choose between two different polarity patterns in order to form a skeletal bond in this manner (Scheme 2.2):



Scheme 2.2 The two different polarity patterns for the formation of a skeletal bond

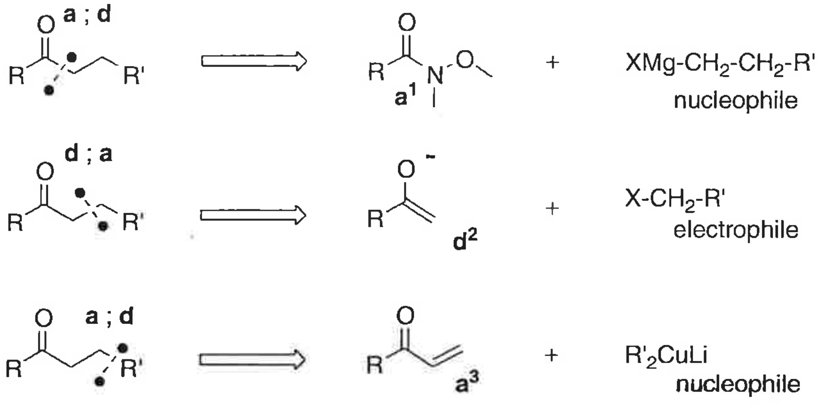
Which of these options turns out to be more attractive? This depends on how easily a negative or positive (partial) charge can be stabilized in the real synthesis reactants. Here is the point at which the functional groups present in the target structure have to be considered. Seebach [2] demonstrated in a



Scheme 2.3 (Partial) charges at or near a carbonyl group; **a** = acceptor, **d** = donor. The number designates the position of the reactive center with respect to the skeletal atom of the functional group

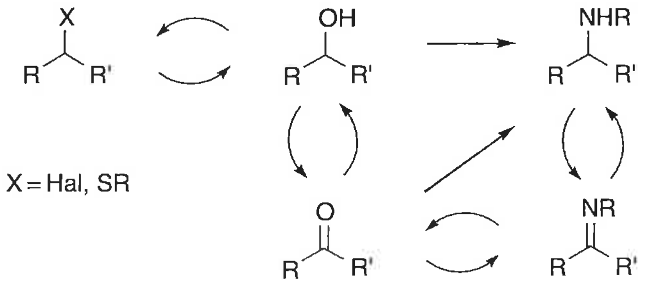
fundamental study that a functional group, e.g., a carbonyl group, can help to stabilize either positive or negative charges, depending on the distance from this functional group (Scheme 2.3). In doing this, the removal (or addition) of a proton to accentuate the reactivity pattern—as is done in actual synthetic transformations—is implied.

This leads to clear preferences for the polarity of bond formation at or near a carbonyl group in the target structure (Scheme 2.4):



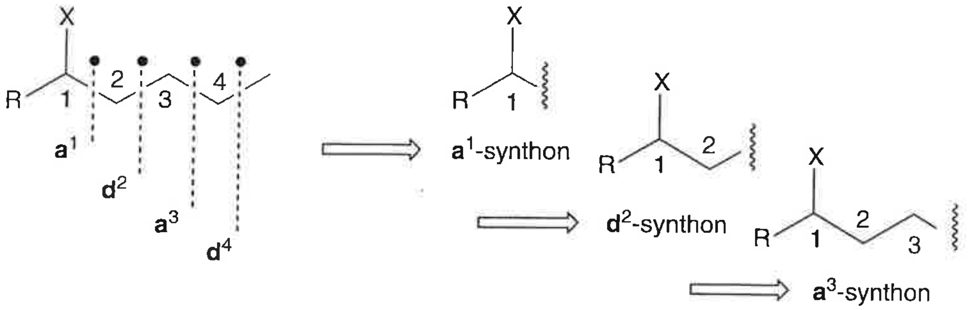
Scheme 2.4 Different polarity in bond-forming reactions depending on the distance from a carbonyl group

This illustrates how a carbonyl group present in the target structure affects the possible types of bond formation in its vicinity. Other functional groups will possess related polarity patterns. To establish such polarity patterns separately for every functional group that commonly occurs in target structures would, however, overcomplicate the exercise, for it would overload the early-planning phase of the synthesis with too many details. Rather, at this stage one relies on the knowledge that most of the important functional groups can be readily (frequently in one-step operations) interconverted [3] (Scheme 2.5).



Scheme 2.5 Interconversion of functional groups

As a consequence, one uses a heteroatom substituent X as a generic placeholder for the basic garden varieties of functional groups. This placeholder marks the position of a functional group in the retrosynthetic planning process and determines the preferred polarity for bond formation in the vicinity of such a generalized functional group [4, 5, 6] (Scheme 2.6).



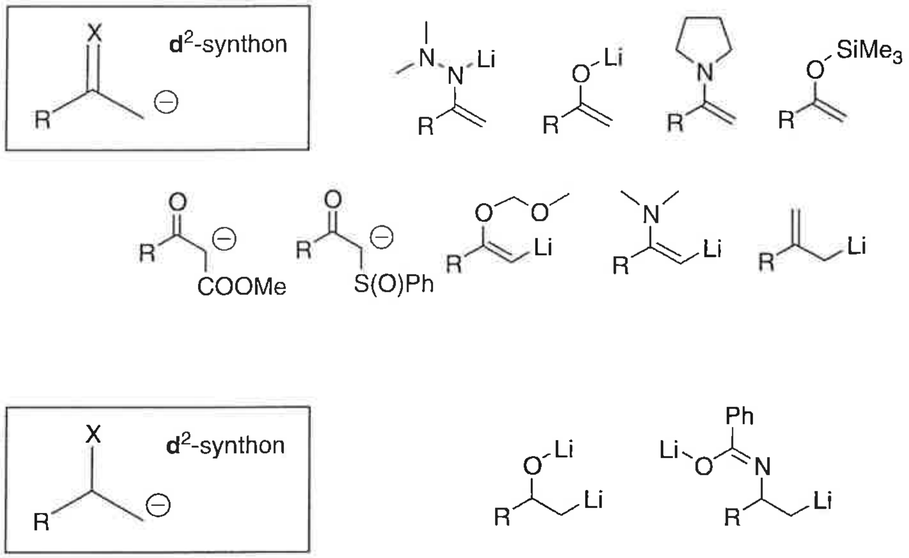
Scheme 2.6 General rule for the polarity of bond formation in the vicinity of a heteroatom substituent

2.1.1 *Polar Synthons*

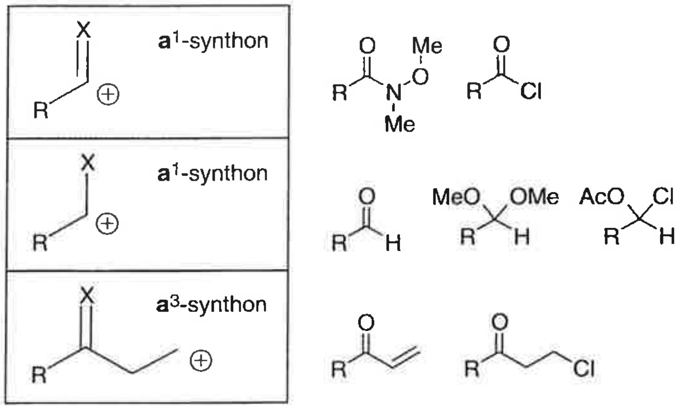
In order to develop a general rule for synthesis planning as depicted in Scheme 2.6, we had to make considerable simplifications of the target structure. The relation to the original target structure should, however, be possible at every moment. This implies the ability to connect generalized synthon formulas to existing reactions or reagents.

Retrosynthetic analysis leads to generalized building blocks, which incorporate a reaction principle. These generalized building blocks are called "synthons" [7]. This notation was first employed by Corey [8]. Unfortunately, usage of this term [9] by the chemical community is not consistent. We prefer the usage promoted by Seebach [2], in which a quasi-real axiomatically defined synthon is related to a series of corresponding real reagents. This is illustrated with regard to a $\mathbf{d}^2$-synthon in Scheme 2.7.

In order to carry out the forward synthetic reactions, one has only to choose the most appropriate reagent, depending on whether a hard or soft nucleophile is best compatible with the bystanding functionalities in the intermediates, and depending on whether these functionalities prefer a reaction to be run in strongly basic, neutral, or mildly acidic media. Unfortunately, there does not yet exist a compilation of standard synthons and their corresponding real reagents. Some hints are found in references [2, 7]. Reagents corresponding to donor synthons are listed in references [10, 11]. Some reagents corresponding to $\mathbf{a}^1$- respectively $\mathbf{a}^3$-synthons are given in Scheme 2.8.



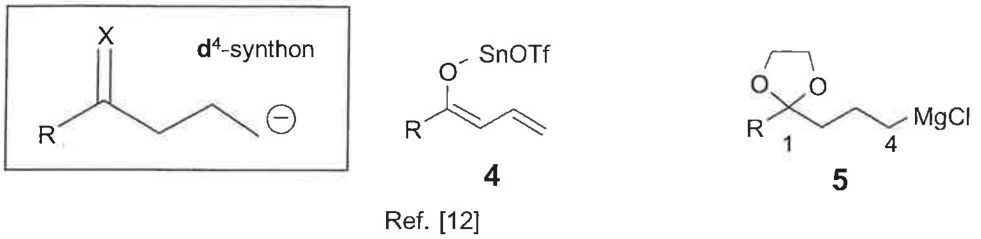
Scheme 2.7 $\mathbf{d^2}$-Synthons and corresponding real reagents



Scheme 2.8 $\mathbf{a^1}$- respectively $\mathbf{a^3}$-synthons and corresponding reagents

Logically, an extension of this sequence would lead to $\mathbf{d^4}$-synthons, for which a few corresponding reagents exist (Scheme 2.9). In practice, compound **4** is likely to display competing $\mathbf{d^2}$- and $\mathbf{d^4}$-reactivity [12]. In the case of compound **5**, there is no relation of the reactivity at C-4 to the functionality at C-1; rather the acetal moiety is masking the carbonyl group, protecting it from the donor reactivity at C-4.

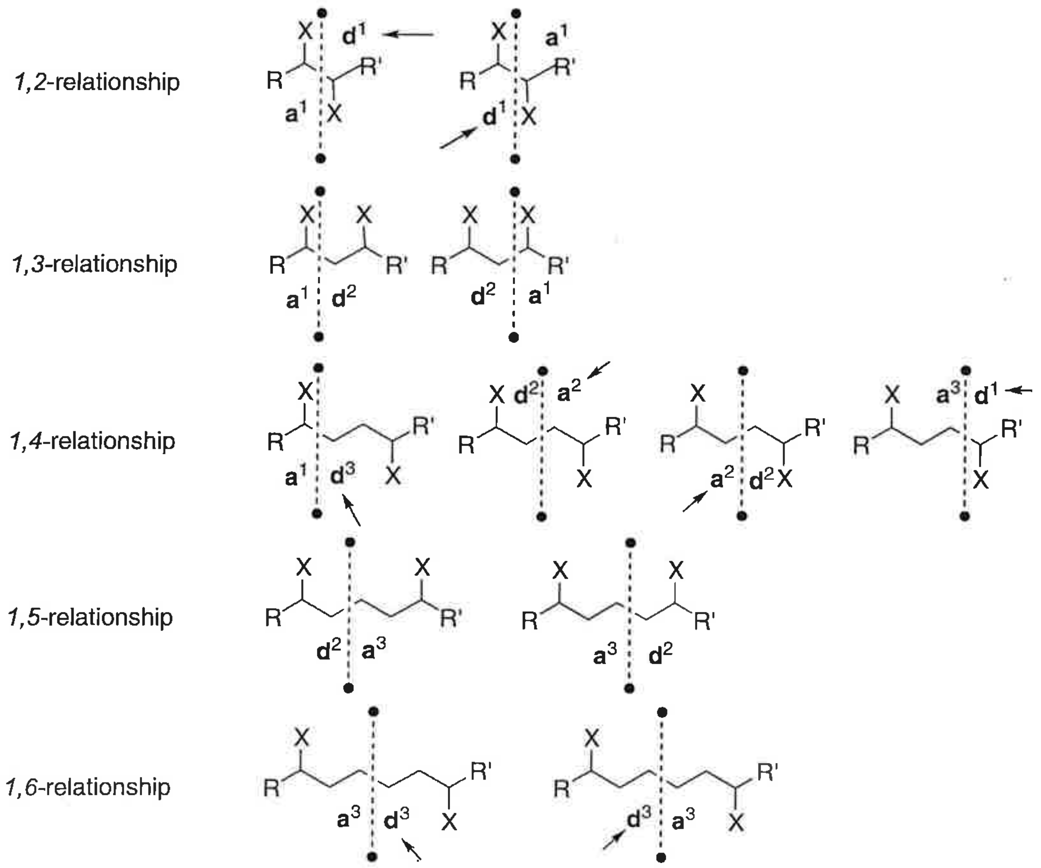
The connection between functionality at C-1 and reactivity at C-n is no longer present. Generally speaking, the synthon concept applies predominantly to distances between the functionality and reactive center of 1–3 skeletal atoms. Thus, the *reach of a functional group* in governing remote reactivity extends no further than the skeletal atom “3”.



Scheme 2.9 $\mathbf{d}^4$-synthons and corresponding reagents

2.1.2 Bond Formation Between Two Functional Groups

The synthons with $\mathbf{a}^1$-, $\mathbf{d}^2$-, and $\mathbf{a}^3$-reactivity are not all the synthons one encounters in synthesis planning. Further synthons show up when one considers target structures with two or more functional groups, provided their distance ranges from 1,2 to 1,6 (counting the skeletal atoms that carry the heteroatom of the functional group). One can select any bond in between these two functional groups for retrosynthetic scission, as summarized in Scheme 2.10.



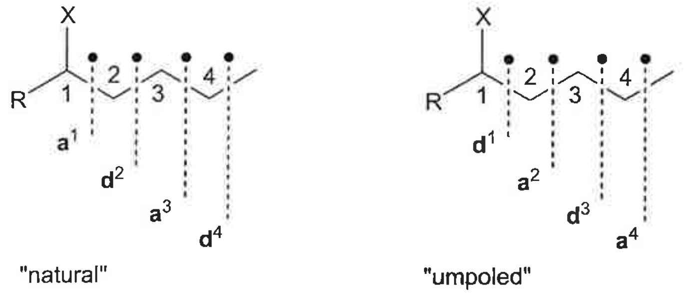
Scheme 2.10 Bond formation between two functional groups in relationships from *1,2* to *1,6*

Scheme 2.10 demonstrates that:

skeletal bond formation between two functional groups is possible using the hitherto introduced (natural) synthons, as long as the relationship between the functional groups is *1,3* or *1,5*.

skeletal bond formation between two functional groups in a relationship *1,2, 1,4*, or *1,6* requires in addition a different set of (unnatural) synthons, which are called umpoled synthons [2].

The umpoled synthons are marked in Scheme 2.10 by arrows. The types of synthons that occur in Scheme 2.10 are summarized in Scheme 2.11.



"natural" "umpoled"

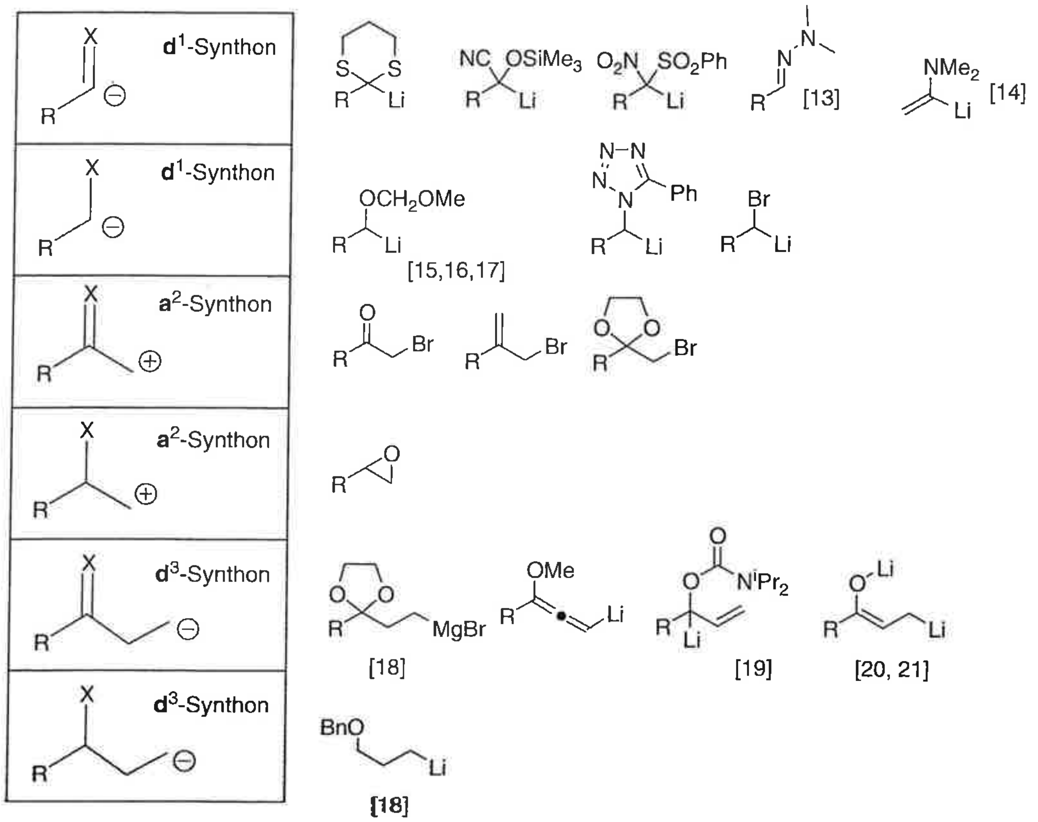
Scheme 2.11 Natural and non-natural (=umpoled) synthons

2.1.3 Umpolung

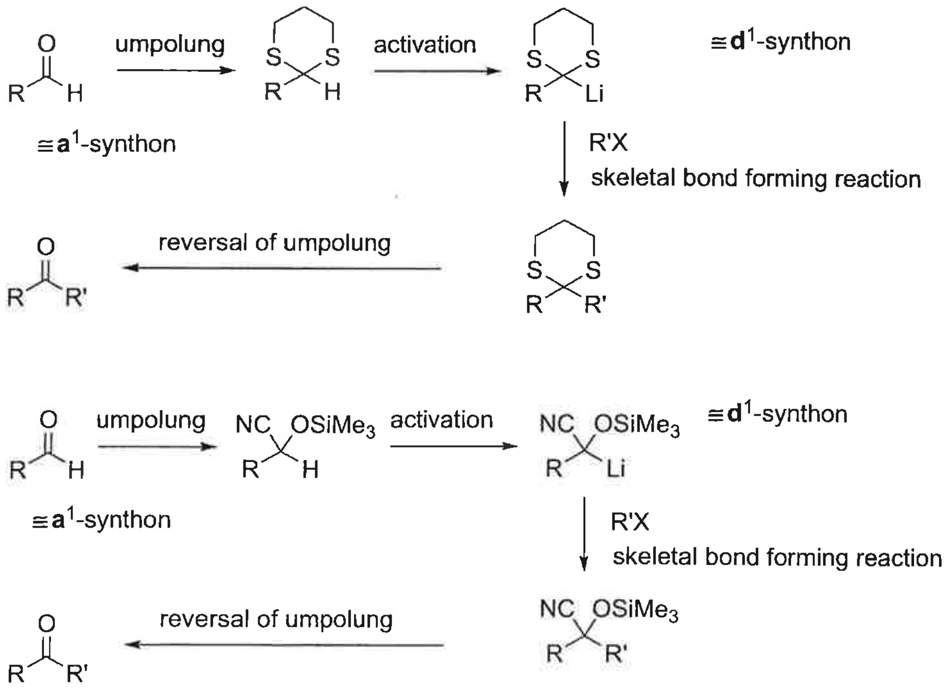
The conception and development of umpoled synthons were a direct consequence of the above rational concepts for synthesis planning [2]. Before discussing the principles of umpolung and their consequences for planning and efficiency of syntheses, some examples of umpoled synthons are presented in Scheme 2.12.

What is umpolung [2], and how does one use it in synthesis planning? The transformations of an $\mathbf{a}^1$-synthon to a $\mathbf{d}^1$-synthon and the reverse, shown in Scheme 2.13, illustrate this aspect.

Umpolung is a process by which one converts a synthon of natural reactivity into one of "umpoled" or "inverted" reactivity. The accomplishment of this step enables a skeleton bond-forming reaction which, without umpolung, would not have been possible. At the end of the reaction sequence one must reverse the umpolung in order to liberate the functional group with which one started. Thus, the incorporation of an umpoled synthon in a reaction sequence requires at least two additional steps than reaction sequences that



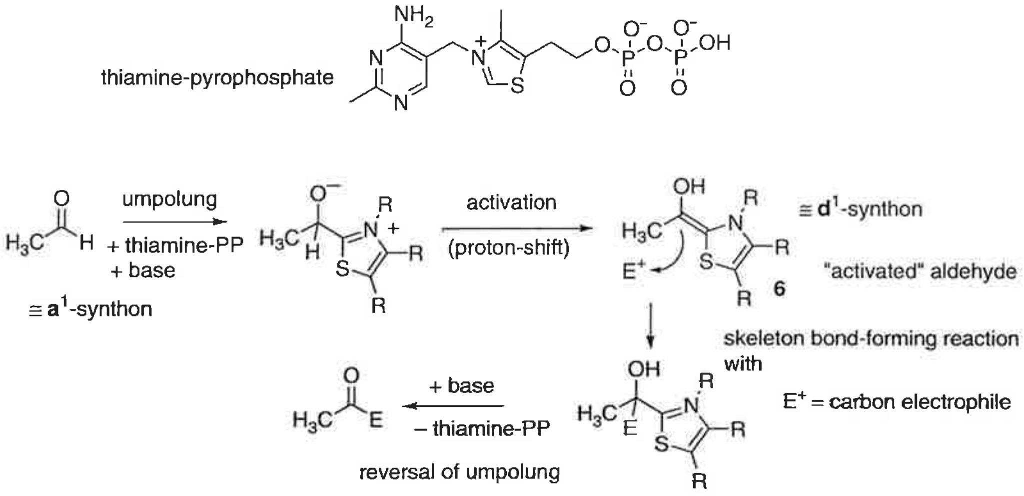
Scheme 2.12 d^1-, a^2-, respectively d^3-synthons and corresponding real reagents



Scheme 2.13 Steps by which umpolung of a reagent is realized

rely only on natural synthons. This drawback can be avoided if one succeeds in attaining umpolung in situ by the aid of a catalyst [22].

Nature, in fact, does just that when it converts the $\mathbf{a}^1$-reagent acetaldehyde into a $\mathbf{d}^1$-reagent by thiamine-pyrophosphate. The latter adds to the aldehyde. A subsequent proton shift generates the thiamine conjugate **6**, which on account of its enamine unit becomes a $\mathbf{d}^1$-reagent (with reference to the original aldehyde). Nature utilizes this umpolung in situ in a reaction cascade that is continued by skeletal bond formation and reversal of the umpolung to regenerate the aldehyde carbonyl as well as the catalyst (Scheme 2.14).



Scheme 2.14 Example of catalytic umpolung in a biosynthetic pathway

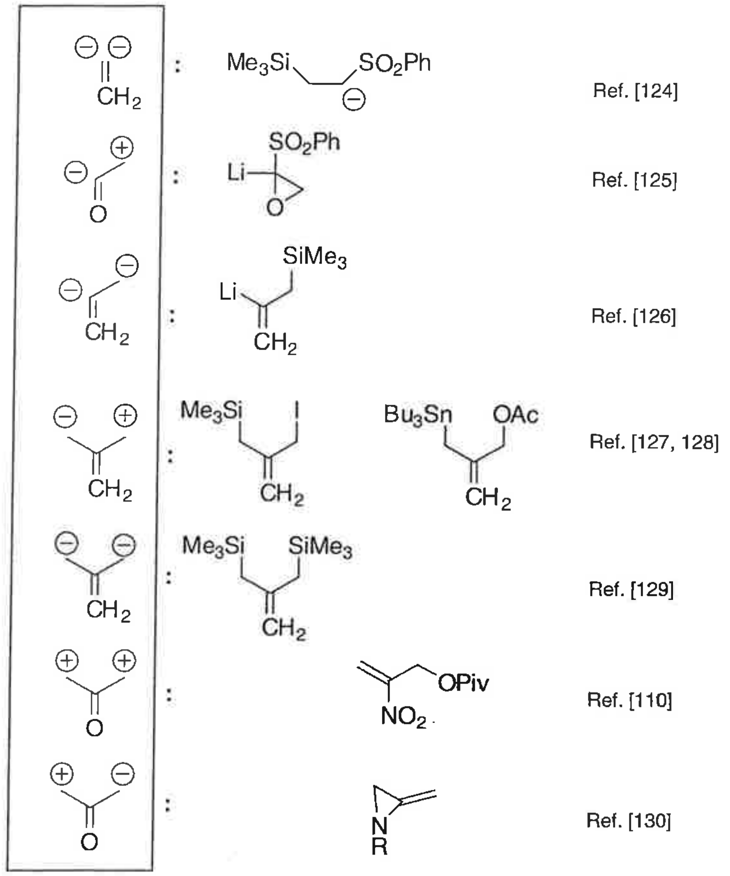
The principle ways by which one can attain umpolung have been summarized in a comprehensive paper by Seebach [2]. One far-reaching principle in this context is "*redox-umpolung*." An **a**-synthon may be converted into a **d**-synthon simply by the addition of two electrons (2e-reduction); in reverse, a **d**-synthon is converted into an **a**-synthon by a two-electron oxidation (Scheme 2.15).

$$\mathbf{a}\text{-synthon} \underset{-\,2e}{\overset{+\,2e}{\rightleftarrows}} \mathbf{d}\text{-synthon}$$

Scheme 2.15 Principle of redox-umpolung

Redox-umpolung can be achieved under actual synthesis conditions. One limitation, though, arises from the fact that the **d**-synthon, for example, is generated via redox-umpolung in the presence of its precursor **a**-synthon.

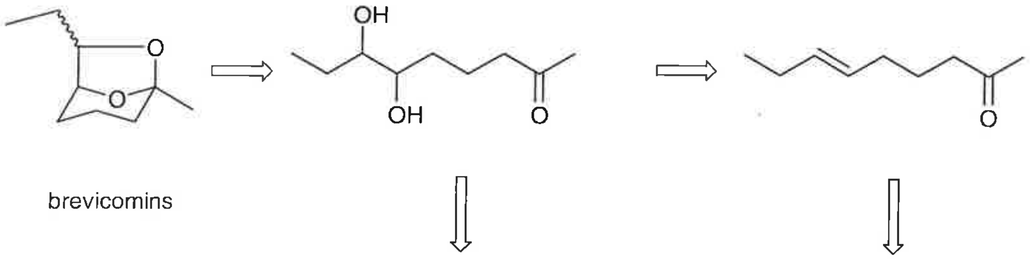
Other useful conjunctive reagents are listed in Scheme 2.63 (cf. also Scheme 5.7 on p. 78).



Scheme 2.63 Examples of *1,1*-, *1,2*-, and *1,3*-bivalent conjunctive reagents

Problems

2.1 exo-Brevicomin is a pheromone of the insect Dendroctonus brevicomis; the endo-epimer is the pheromone of a Dryocoetus species. Various



Scheme 2.64 Retrosynthesis of the brevicomins

routes to the syntheses of the brevicomins have been explored [131]. Most syntheses proceed via the dihydroxyketone shown in Scheme 2.64.

Develop a retrosynthesis of the brevicomins along these lines and discuss the pros and cons of going retrosynthetically back to a double bond as the profunctionality of the diol unit (consult references [132, 133, 134, 135, 136]).

2.2 A versatile intermediate for the synthesis of indolizidine alkaloids is the compound shown in Scheme 2.65.

Scheme 2.65 Intermediate for indolizidine alkaloid synthesis

Follow the skeletal bonds around the molecule. Which distances between heteroatom groups can you delineate? Which of them are unproblematic in synthesis? Consider the carbon-carbon bonds marked A–C for construction of this molecule. Evaluate the polarity options for making these bonds.

References

1. E. J. Corey, X.-M. Cheng *The Logic of Chemical Synthesis*, J. Wiley & Sons, New York, **1989**.
2. D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258. (*Angew. Chem.* **1979**, *91*, 259–278).
3. R. C. Larock *Comprehensive Organic Transformations*, Wiley-VCH, New York, **1989**.
4. D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147–155
5. F. Serratosa *Organic Chemistry in Action*, 1st ed., Elsevier, Amsterdam, **1990**
6. G. S. Zweifel, M. H. Nantz *Modern Organic Synthesis: An Introduction*, W. H. Freeman and Co., New York, **2007**.
7. S. Warren *Organic Synthesis: The Disconnection Approach*, J. Wiley & Sons, Chichester, **1982**.
8. E. J. Corey, *Pure Appl. Chem.* **1967**, *14*, 19–37.
9. W. A. Smit, A. F. Bochkov, R. Caple *Organic Synthesis: The Science behind the Art*, Royal Society of Chemistry, **1998**, Chapt. 2.16, p. 152.
10. D. Seebach *Organolithium Compounds in Organic Synthesis* in *New Applications of Organometallic Reagents in Organic Synthesis* (Ed.: D. Seyferth), Elsevier, Amsterdam, **1976**, pp. 1–92.

11. M. Braun *Houben Weyl, Methoden der Organischen Chemie* vol. E19d, (Ed.: M. Hanack), G. Thieme, Stuttgart, **1993**, pp. 853–1138.
12. R. W. Stevens, T. Mukaiyama, *Chem. Lett.* **1985**, 851–854.
13. R. Fernández, J. M. Lassaletta, *Synlett.* **2000**, 1228–1240.
14. M. Yus, J. Ortiz, C. Najera, *ARKIVOC* **2002**(v), 38–47.
15. W. C. Still, *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.
16. W. C. Still, C. Sreekumar, *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202.
17. J. M. Chong, E. K. Mar, *Tetrahedron Lett.* **1990**, *31*, 1981–1984.
18. J. C. Stowell, *Chem. Rev.* **1984**, *84*, 409–435.
19. D. Hoppe, *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948. (*Angew. Chem.* **1984**, *96*, 930–946).
20. H. Nakahira, M. Ikebe, Y. Oku, N. Sonoda, T. Fukuyama, I. Ryu, *Tetrahedron* **2005**, *61*, 3383–3392.
21. I. Ryu, G. Yamamura, S. Omura, S. Minakata, M. Komatsu, *Tetrahedron Lett.* **2006**, *47*, 2283–2286.
22. J. S. Johnson, *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328. (*Angew. Chem.* **2004**, *116*, 1348–1350).
23. B. K. Banik, *Eur. J. Org. Chem.* **2002**, 2431–2444.
24. H. C. Aspinall, N. Greeves, C. Valla, *Org. Lett.* **2005**, *7*, 1919–1922.
25. T. Wirth, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61–63. (*Angew. Chem.* **1996**, *108*, 65–67).
26. Y. Taniguchi, M. Nakahashi, T. Kuno, M. Tsuno, Y. Makioka, K. Takaki, Y. Fujiwara, *Tetrahedron Lett.* **1994**, *35*, 4111–4114.
27. D. S. Surry, D. R. Spring, *Chem. Soc. Rev.* **2006**, *35*, 218–225.
28. T. Shono, N. Kise, T. Fujimoto, A. Yamanami, R. Nomura, *J. Org. Chem.* **1994**, *59*, 1730–1740.
29. R. K. Dieter, S.-J. Li, N. Chen, *J. Org. Chem.* **2004**, *69*, 2867–2870.
30. Y.-I. Yoshida, M. Itoh, S. Isoe, *J. Chem. Soc., Chem. Commun.* **1993**, 547–549.
31. Y.-I. Yoshida, Y. Ishichi, S. Isoe, *J. Am. Chem. Soc.* **1992**, *114*, 7594–7595.
32. J. B. Sperry, D. L. Wright, *Chem. Soc. Rev.* **2006**, *35*, 605–621.
33. K. Naraska, Y. Kohno, S. Shimada, *Chem. Lett.* **1993**, *22*, 125–128.
34. K. Otsubo, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 5763–5764.
35. E. J. Enholm, H. Satici, A. Trivellas, *J. Org. Chem.* **1989**, *54*, 5841–5843.
36. G. Masson, P. Cividino, S. Py, Y. Vallée, *Angew. Chem., Int. Ed.* **2003**, *42*, 2265–2268. (*Angew. Chem.* **2003**, *115*, 2367–2370).
37. E. J. Corey, A. K. Ghosh, *Chem. Lett.* **1987**, *16*, 223–226.
38. B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363.
39. T. Linker, *J. Prakt. Chem.* **1997**, *339*, 488–492.
40. F. A. Davis, B.-C. Chen, *Chem. Rev.* **1992**, *92*, 919–934.
41. C. Greck, J. P. Gênet, *Synlett* **1997**, 741–748.
42. P. Dembech, G. Seconi, A. Ricci, *Chem. Eur. J.* **2000**, *6*, 1281–1286.
43. C. D. Johnson, *Acc. Chem. Res.* **1993**, *26*, 476–482.
44. P. C. Wälchli, C. H. Eugster, *Helv. Chim. Acta* **1978**, *61*, 885–898.
45. S. R. Angle, R. M. Henry, *J. Org. Chem.* **1998**, *63*, 7490–7497.
46. Y. Hirai, J. Watanabe, T. Nozaki, H. Yokoyama, S. Yamaguchi, *J. Org. Chem.* **1997**, *62*, 776–777.
47. O. Muraoka, B.-Z. Zheng, K. Okumura, G. Tanabe, T. Momose, C. H. Eugster, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1567–1575.

48. B. Nader, T. R. Bailey, R. W. Franck, S. M. Weinreb, *J. Am. Chem. Soc.* **1981**, *103*, 7573–7580.
49. R. S. Mali, M. Pohmakotr, B. Weidmann, D. Seebach, *Liebigs Ann. Chem.* **1981**, 2272–2284.
50. J. W. Labadie, D. Tueting, J. K. Stille, *J. Org. Chem.* **1983**, *48*, 4634–4642.
51. J. E. Baldwin, R. M. Adlington, S. H. Ramcharitar, *Synlett* **1992**, 875–877.
52. P. Bakuzis, M. L. F. Bakuzis, T. F. Weingartner, *Tetrahedron Lett.* **1978**, *19*, 2371–2374.
53. F. Derguini, G. Linstrumelle, *Tetrahedron Lett.* **1984**, *25*, 5763–5766.
54. B. M. Trost, F. W. Gowland, *J. Org. Chem.* **1979**, *44*, 3448–3450.
55. B. Seuring, D. Seebach, *Liebigs Ann. Chem.* **1978**, 2044–2073.
56. K. F. Burri, R. A. Cardone, W. Y. Chen, P. Rosen, *J. Am. Chem. Soc.* **1978**, *100*, 7069–7071.
57. M. Asaoka, N. Yanagida, N. Sugimura, T. Takei, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061–1064.
58. E. W. Colvin, T. A. Purcell, R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1,* **1976**, 1718–1722.
59. H. Gerlach, K. Oertle, A. Thalmann, *Helv. Chim. Acta* **1977**, *60*, 2860–2865.
60. E. J. Corey, K. C. Nicolaou, T. Toru, *J. Am. Chem. Soc.* **1975**, *97*, 2287–2288.
61. H. J. Bestmann, R. Schobert, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 791–792. (*Angew. Chem.* **1985**, *97*, 784–785).
62. H. Stetter, *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–647. (*Angew. Chem.* **1976**, *88*, 695–704).
63. P. S. Baran, M. P. DeMartino, *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086. (*Angew. Chem.* **2006**, *118*, 7241–7244).
64. H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005.
65. K. Narasaka, N. Miyoshi, K. Iwakura, T. Okauchi, *Chem. Lett.* **1989**, *18*, 2169–2172.
66. C.-G. Yang, N. W. Reich, Z. Shi, C. He, *Org. Lett.* **2005**, *7*, 4553–4556.
67. T. A. Hase, A. Ourila, C. Holmberg, *J. Org. Chem.* **1981**, *46*, 3137–3139.
68. J.-E. Bäckval, *Bull. Soc. Chim. Fr.* **1987**, 665–670.
69. H. H. Wasserman, J. L. Ives, *Tetrahedron* **1981**, *37*, 1825–1852.
70. A. Defoin, H. Fritz, G. Geffroy, G. Streith, *Tetrahedron Lett.* **1986**, *27*, 4727–4730.
71. D. L. Boger, M. Patel, F. Takusagawa, *J. Org. Chem.* **1985**, *50*, 1911–1916.
72. D. J. Dixon, S. V. Ley, D. J. Reynolds, *Angew. Chem., Int. Ed.* **2000**, *39*, 3622–3626. (*Angew. Chem.* **2000**, *112*, 3768–3772).
73. Y. Yamamoto, H. Yamamoto, *Angew. Chem., Int. Ed.* **2005**, *44*, 7082–7085. (*Angew. Chem.* **2005**, *117*, 7244–7247).
74. R. S. Garigipati, A. J. Freyer, R. R. Whittle, S. M. Weinreb, *J. Am. Chem. Soc.* **1984**, *106*, 7861–7867.
75. J. K. Whitesell, D. James, J. F. Carpenter, *J. Chem. Soc., Chem. Commun.* **1985**, 1449–1450.
76. J.-E. Baeckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619–4631.
77. K. Kondo, M. Matsumoto, *Tetrahedron Lett.* **1976**, *17*, 4363–4366.
78. T. L. Gilchrist, D. A. Lingham, T. G. Roberts, *J. Chem. Soc., Chem. Commun.* **1979**, 1089–1090.

Chapter 3
Skeleton Oriented Bond-Sets

Abstract Branches in the target structure mark points at which bonds should be made during synthesis. If no functional group is close to the branching point, an auxiliary functional group has to be introduced temporarily in order to allow construction of the desired skeletal bond. A substantial reduction in the number of construction steps may be realized, if the target structure or an intermediate has c_2 or σ-symmetry.

Only in rare cases does the target molecule possess an unbranched linear molecular skeleton. More often than not, one is faced with target structures that display branched chains, rings, and substituted rings. In a synthesis, unless branches come with the starting materials, they result from bond formation. This leads to two more approaches worth considering during synthesis planning. In the first, skeleton oriented bond-sets, the bond-set for a molecule with a branched skeleton has to be chosen such that the branches are being formed. Alternatively, the second approach is to move to a building block oriented bond-set, when suitable building blocks containing the required kind of branches are available. Bond-sets following each directive are shown in Scheme 3.1. Both will be discussed below.

skeleton oriented

building block oriented

Scheme 3.1 Bond-sets with skeleton orientation and with building block orientation

When one deals with molecules having a branched skeleton, one checks the distance between the branching point and any existing functionality. When this distance falls within the normal reach of the functional group, one tends primarily to use natural synthons in order to create a skeletal bond at the branching point (Scheme 3.2).

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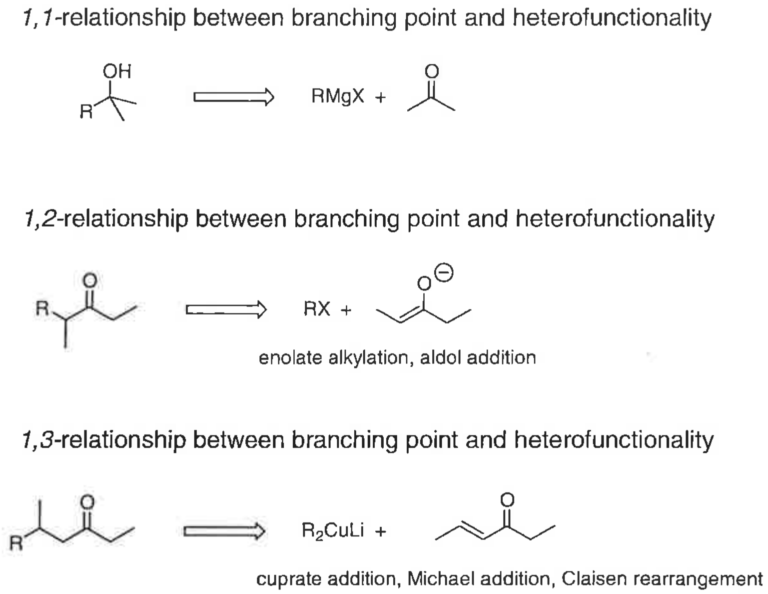
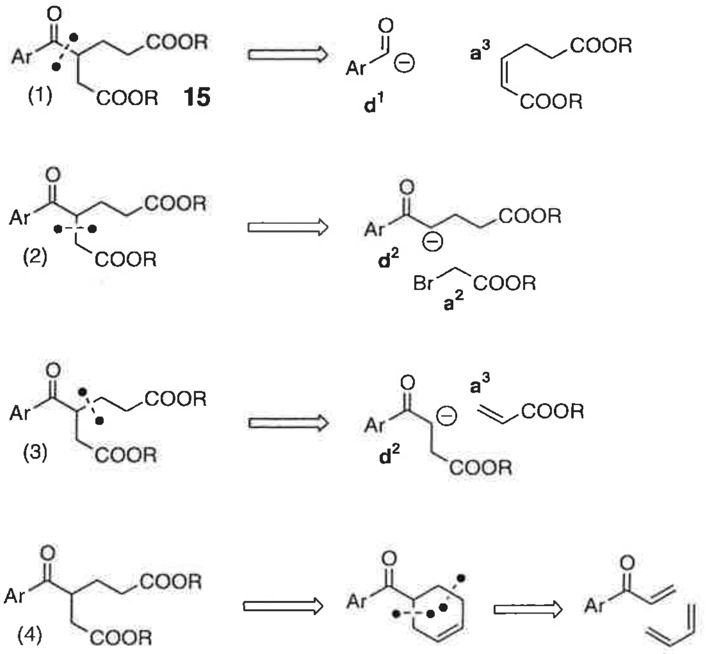


Scheme 3.2 Bond formation according to the distance betweeen branching point and heteroatom functionality

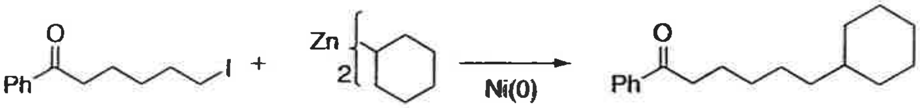
The available options are exemplified in Scheme 3.3 by a multifunctionalized but simply branched intermediate **15** taken from the tetracycline synthesis of Woodward [1]. Remember to always choose the cut at the branching point.



Scheme 3.3 Bond formation at the branching point according to the heterofunctionalities present

Of the possibilities shown in Scheme 3.3, (1) is the least attractive since it requires an umpoled **d^1**-synthon to generate a *1,4*-relationship of functionalities. The approach reflected by (2) is better since it also uses an umpoled, but readily available, **a^2**-synthon in addition to a natural **d^2**-synthon. Approach (3) is better still, since it aims at a *1,5*-relationship of functionalities and avoids the use of umpoled synthons. This is the tactic that was employed by Woodward in a modified version [1]. In hindsight, one recognizes an even more attractive route (4) that relies on a *1,6*-relationship of the ester functionalities and a "reconnect" transformation, opening an entry via a Diels-Alder cycloaddition.

When a branching point in the skeleton falls outside the reach of a functional group, one can rely on skeletal bond-forming reactions which do not require the presence of a functional group. A nearly ideal solution to this problem is provided by the transition metal-catalyzed coupling reactions of alkylzinc or alkylmagnesium reagents with alkyl iodides [2, 3, 4, 5] (Scheme 3.4).

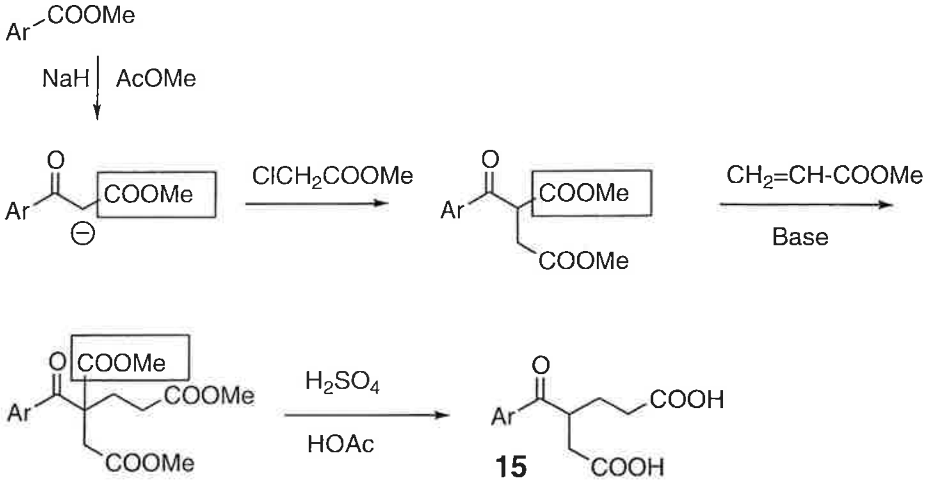


Scheme 3.4 Skeletal bond formation remote from preexisting functionality

3.1 The FGA-Strategy for Preparing Branched Skeletons

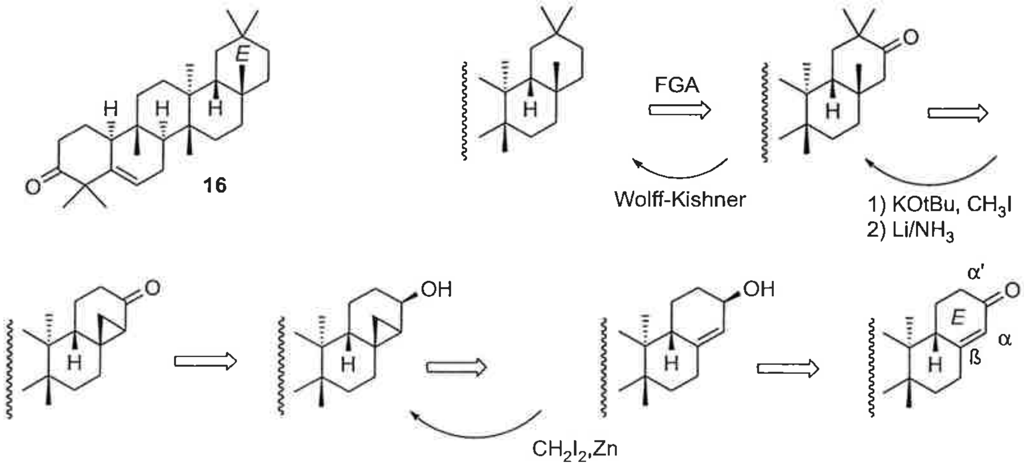
On perusal of many natural product syntheses, one notes that detours are frequently taken in order to generate branches in the skeletons. Additional functionality is placed at or close to the point where the bond is to be made. The purpose of this functional group addition (FGA) is to facilitate bond formation at the desired position. This auxiliary functionality has to be removed by an extra step later in the synthesis. In his synthesis of the intermediate **15,** Woodward used a methoxycarbonyl group as an auxiliary functionality [1] (Scheme 3.5).

Of course, introduction and later removal of the methoxycarbonyl group adds two extra steps to the overall synthesis.



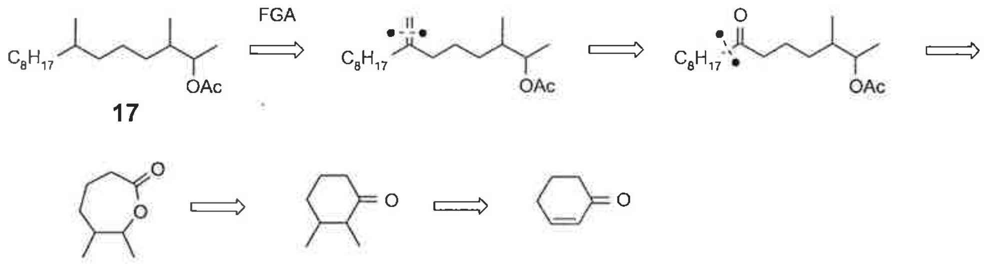
Scheme 3.5 Use of a methoxycarbonyl group as an auxiliary functionality to facilitate bond formation for a branched sekeleton

A standard auxiliary functional group allowing the introduction of branches into a molecular skeleton is the carbonyl group. The synthesis of alnusenone [6] (**16**) (Scheme 3.6) illustrates how a single enone function in ring E serves in a twofold manner to introduce methyl branches. First, the enone serves as precursor to an allylic alcohol that permits a hydroxyl-directed Simmons-Smith cyclopropanation to eventually generate a methyl branch in the ß-position, a tactic which capitalizes on the equivalency of a carbonyl and an alcohol function in retrosynthetic analysis. Second, after reoxidation to a ketone, the carbonyl group allows two consecutive enolate alkylations to introduce two methyl branches directly in the α'-position. Finally, after having orchestrated all these branch-forming steps, the carbonyl group is reductively removed.



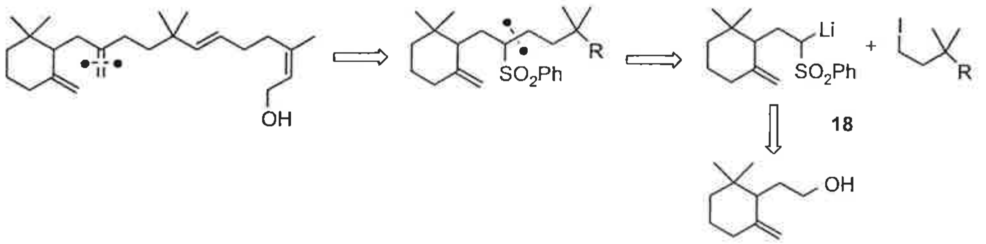
Scheme 3.6 Introduction of methyl groups into ring E of alnusenone via a cabonyl group as auxiliary function

The utility of a carbonyl group as an auxiliary to introduce branches in a skeleton is underscored by a suggested synthesis of the insect pheromone **17** [7] (Scheme 3.7). The plan of this synthesis is clearly skeleton oriented.



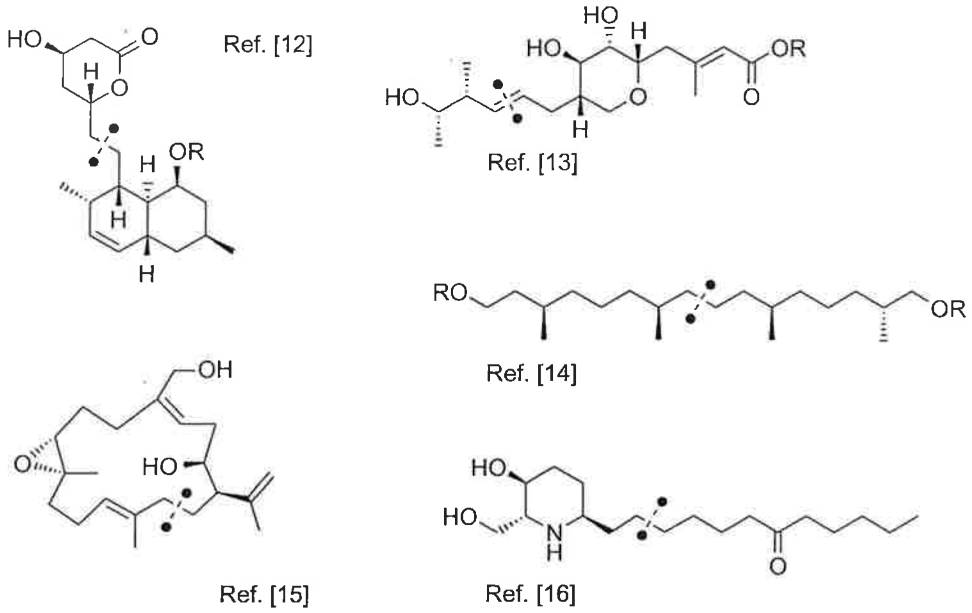
Scheme 3.7 Carbonyl group as auxiliary functionality to generate branches in a molecular skeleton

More recently, arylsulfonyl groups have found use as auxiliary functionalities to allow access to branches in molecular skeletons. Alkylation of an α-sulfonylalkyllithium species such as **18** is quite useful to make skeletal bonds remote from any other controlling functionality. An example is given by the synthesis of diumycinol [8]. In this case, the auxiliary sulfonyl group is disposed of in a skeleton and branch forming Julia–Lythgoe olefination (Scheme 3.8).



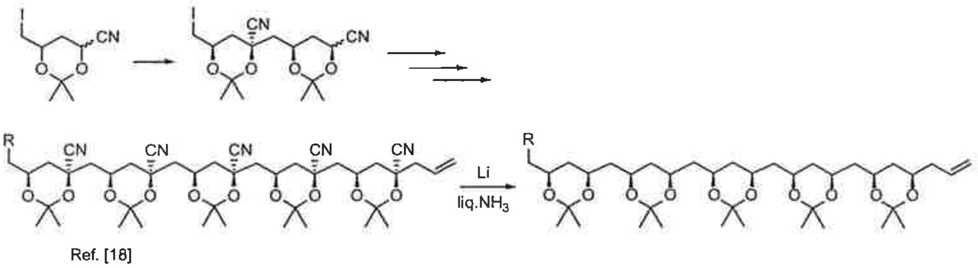
Scheme 3.8 Sulfonyl group-mediated access to a branching point during a synthesis of diumycinol

The attractivness of a sulfonyl group as an auxiliary function in building molecular skeletons is enhanced by its ease of removal. It may serve as a precursor for Julia–Lythgoe olefination [9], or it can be removed reductively under mild conditions [10, 11]. Several cases of bond formation remote from controlling functionality aided by a sulfonyl group are summarized in Scheme 3.9.



Scheme 3.9 Target structures whose syntheses rely upon sulfonyl group mediated bond formation

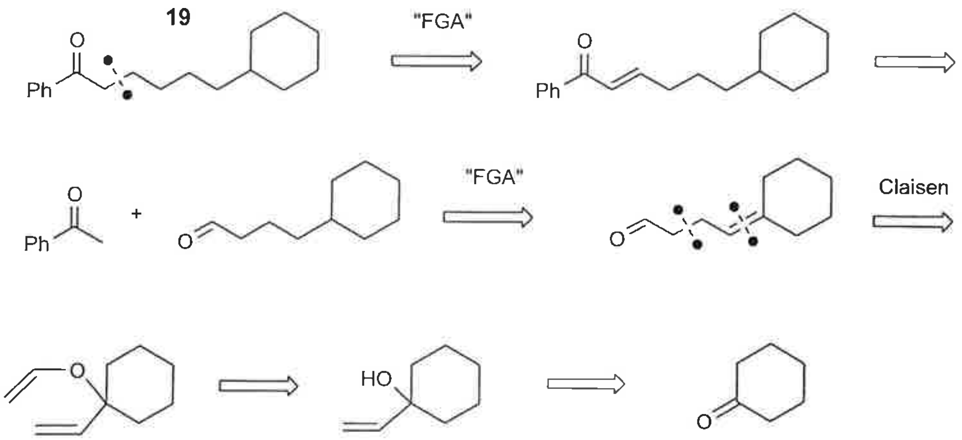
The fact that the utilization of a sulfonyl group generally requires two extra steps does not appear to detract from its popularity. Nevertheless, there are other functional groups such as the triphenylphosphonium moiety or nitrile groups that may serve in exactly the same manner [17] (Scheme 3.10).



Scheme 3.10 Use of nitrile groups as auxiliary functions for the formation of molecular skeletons

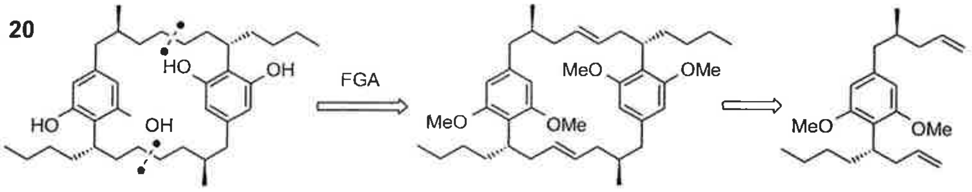
Nitrile groups may be be removed reductively either with LiDBB [19] or with Li in liquid ammonia [18, cf. also 20]. Conditions for nitrile removal are not as mild, however, as those required to remove sulfonyl groups, which explains the popularity of the latter.

Another auxiliary functionality which can serve well for making bonds remote from a controlling functionality is a carbon-carbon double bond. A double bond facilitates bond formation in its vicinity and may in the end be removed by catalytic hydrogenation. Considering target molecule **19,** the following retrosynthetic analysis is suggested (Scheme 3.11).



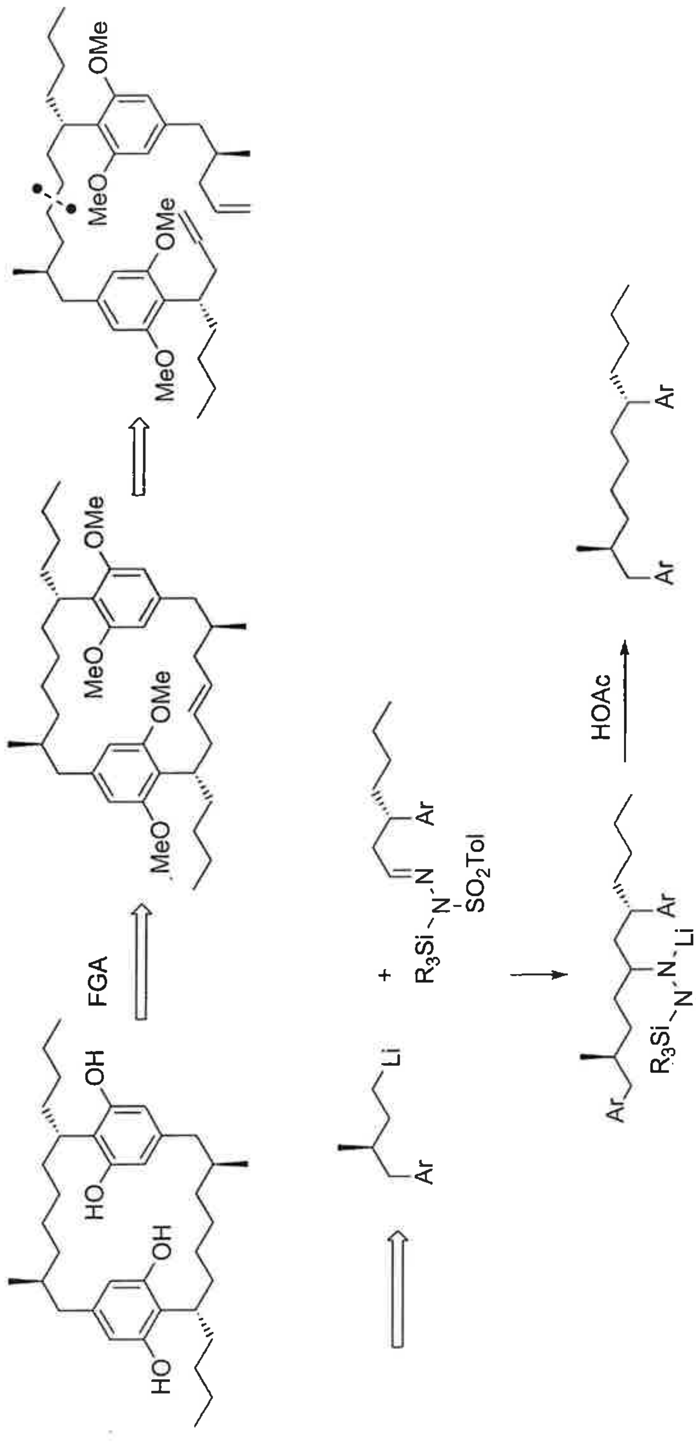
Scheme 3.11 Use of a carbon-carbon double bond as an auxiliary function to allow the introduction of a branch far from a preexisting functionality

Bond formation remote from functional groups is frequently required when following a building block oriented approach to a molecular skeleton. On considering a synthesis of cylindrocyclophane [21] (**20**) (cf. Scheme 3.12), the symmetry of the target suggests a dimerization of identical building blocks. This should give rise to a macrocycle indicating olefin metathesis as the key reaction. Therefore an olefinic double bond becomes the auxiliary structural element to enable linkage of the two units.



Scheme 3.12 Concept of the synthesis of cylindrocyclophane using carbon-carbon double bonds as auxiliary groups to effect macrocyclzation

The intended macrocyclization is threatened, in theory, by a regioselectivity problem. In practice, the ring-closing metathesis proceeded with a high regioselectivity in favor of the desired head-to-tail dimerization [21]. Since this was not clear at the outset, the exploration of the synthesis route was initiated by a stepwise linkage of the building blocks (Scheme 3.13) to ascertain the correct regioselectivity in the overall process [22].

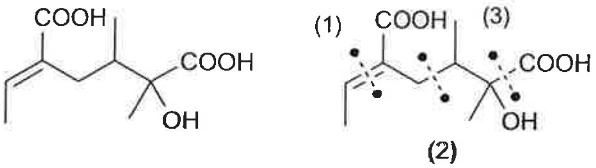


Scheme 3.13 Stepwise formation of the ring system of cyclindrocyclophane

available, one should first consider an approach involving a c_2-symmetrical precursor [36].

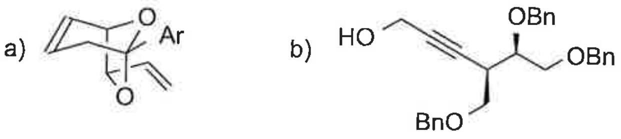
Problems

3.1 Integerrinecic acid (Scheme 3.25), despite its small size, has branches and functional groups enough to practise meaningful retrosynthesis. The construction plan of three very similar syntheses [40, 41, 42] (sequence of bond formation (1), (2), (3)) shows that all cuts are made to create branches with the aid of the existent functionality. Work backwards (3) → (2) → (1) to recognize by which reactions a synthesis can be realized. For a completely different approach, see reference [43].



Scheme 3.25 Integerrinecic acid and bond-set for synthesis

3.2 Look for symmetrical building blocks as potential precursors to the following compounds (Scheme 3.26).



Scheme 3.26 Target molecules incorporating hidden symmetry

References

1. J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, R. B. Woodward, *J. Am. Chem. Soc.* **1968**, *90*, 439–457.
2. A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79–85.
3. J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.
4. N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805–3807.

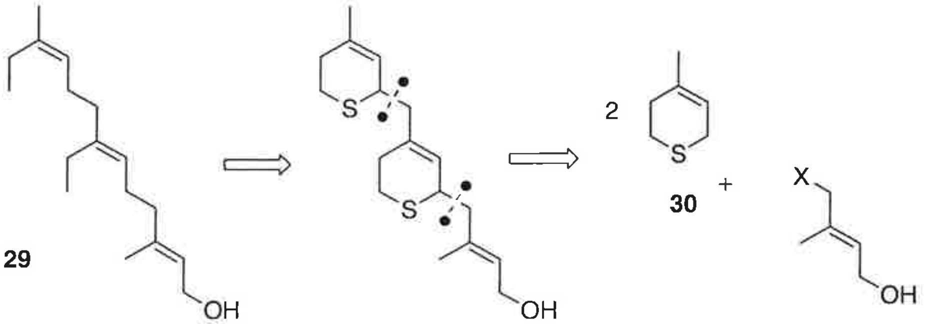
5. C. Herber, B. Breit, *Angew. Chem., Int. Ed.* **2005**, *44*, 5267–5269. (*Angew. Chem.* **2005**, *117*, 5401–5403).
6. R. E. Ireland, M. I. Dawson, S. C. Welch, A. Hagenbach, J. Bordner, B. Trus, *J. Am. Chem. Soc.* **1973**, *95*, 7829–7841.
7. G. Magnusson, *Tetrahedron* **1978**, *34*, 1385–1388.
8. P. Kocienski, M. Todd, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1783–1789.
9. P. J. Kocienski, *Chem. & Ind.* **1981**, 548–551.
10. C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547–10658.
11. I. Das, T. Pathak, *Org. Lett.* **2006**, *8*, 1303–1306.
12. J. R. Falck, Y.-L. Yang, *Tetrahedron Lett.* **1984**, *25*, 3563–3566.
13. G. E. Keck, D. F. Kachensky, E. J. Enholm, *J. Org. Chem.* **1984**, *49*, 1462–1464.
14. C. H. Heathcock, P. A. Radel, *J. Org. Chem.* **1986**, *51*, 4322–4323.
15. M. A. Tius, A. Fauq, *J. Am. Chem. Soc.* **1986**, *108*, 6389–6391.
16. T. N. Birkinshaw, A. B. Holmes, *Tetrahedron Lett.* **1987**, *28*, 813–816.
17. Y. Fall, M. Torneiro, L. Castedo, A. Mourino, *Tetrahedron Lett.* **1992**, *33*, 6683–6686.
18. S. D. Rychnovsky, G. Griesgraber, *J. Org. Chem.* **1992**, *57*, 1559–1563.
19. D. Guijarro, M. Yus, *Tetrahedron* **1994**, *50*, 3447–3452.
20. T. Ohsawa, T. Kobayashi, Y. Mizuguchi, T. Saitoh, T. Oishi, *Tetrahedron Lett.* **1985**, *26*, 6103–6106.
21. A. B. Smith III, S. A. Kozmin, C. M. Adams, D. V. Paone, *J. Am. Chem. Soc.* **2000**, *122*, 4984–4985.
22. A. B. Smith III, S. A. Kozmin, D. V. Paone, *J. Am. Chem. Soc.* **1999**, *121*, 7423–7424.
23. A. G. Myers, M. Movassaghi, *J. Am. Chem. Soc.* **1998**, *120*, 8891–8892.
24. B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
25. J. Clayden, S. Warren, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 241–270. (*Angew. Chem.* **1996**, *108*, 261–291).
26. P. Wipf, S. Lim, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068–1071. (*Angew. Chem.* **1993**, *105*, 1095–1097).
27. Y. Gao, K. Harada, T. Hata, H. Urabe, F. Sato, *J. Org. Chem.* **1995**, *60*, 290–291.
28. A. Ullmann, J. Schnaubelt, H.-U. Reissig, *Synthesis* **1998**, 1052–1066.
29. C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665–681. (*Angew. Chem.* **1992**, *104*, 675–691).
30. T. R. Hoye, D. R. Peck, P. K. Trumper, *J. Am. Chem. Soc.* **1981**, *103*, 5618–5620.
31. C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9–17.
32. S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167–2213.
33. J. M. Holland, M. Lewis, A. Nelson, *Angew. Chem., Int. Ed.* **2001**, *40*, 4082–4084. (*Angew. Chem.* **2001**, *113*, 4206–4208).
34. M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938.
35. T. Nakata, *J. Synth. Org. Chem., Jpn.* **1998**, *56*, 940–951.
36. R. W. Hoffmann, *Angew. Chem., Int. Ed.* **2003**, *42*, 1096–1109. (*Angew. Chem.* **2003**, *115*, 1128–1142).
37. M. Ball, M. J. Gaunt, D. F. Hook, A. S. Jessiman, S. Kawahara, P. Orsini, A. Scolaro, A. C. Talbot, H. R. Tanner, S. Yamanoi, S. V. Ley, *Angew. Chem., Int. Ed.* **2005**, *44*, 5433–5438. (*Angew. Chem.* **2005**, *117*, 5569–5574).
38. D. J. Critcher, S. Connolly, M. Wills, *J. Org. Chem.* **1997**, *62*, 6638–6657.
39. A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307–2320.

40. S. E. Drewes, N. D. Emslie, *J. Chem. Soc., Perkin Trans. 1,* **1982**, 2079–2083.
41. U. Pastewka, H. Wiedenfeld, E. Röder, *Arch.Pharm.* **1980**, *313*, 846–850.
42. C.C. J. Culvenor, T. A. Geissman, *J. Am. Chem. Soc.* **1961**, *83*, 1647–1652.
43. K. Narasaka, T. Uchimaru, *Chem. Lett.* **1982**, 57–58.

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

R.W. Hoffmann, *Elements of Synthesis Planning*,
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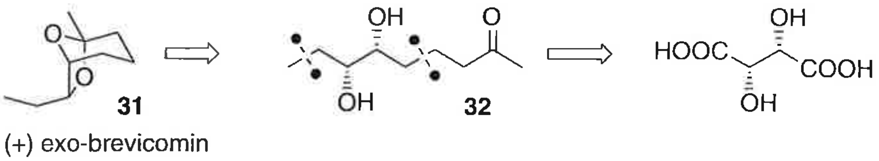
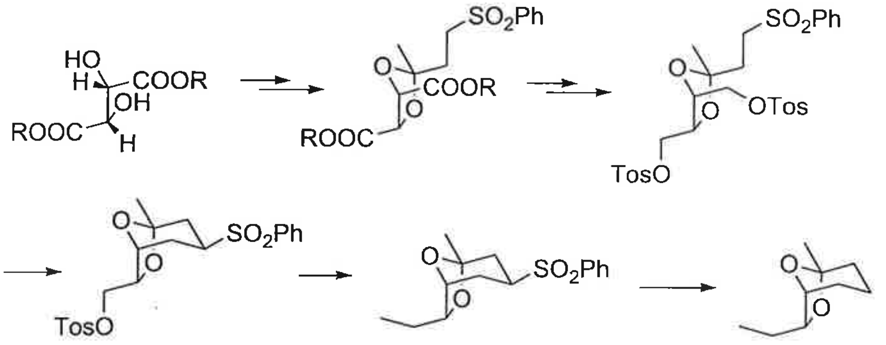
When the methodology of stereoselective synthesis was still in its infancy, it was considered advantageous to utilize sequences of stereogenic centers available from enantiomerically pure natural products as building blocks [3, 4]; this so-called chiral pool synthesis strategy is exemplified in Scheme 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

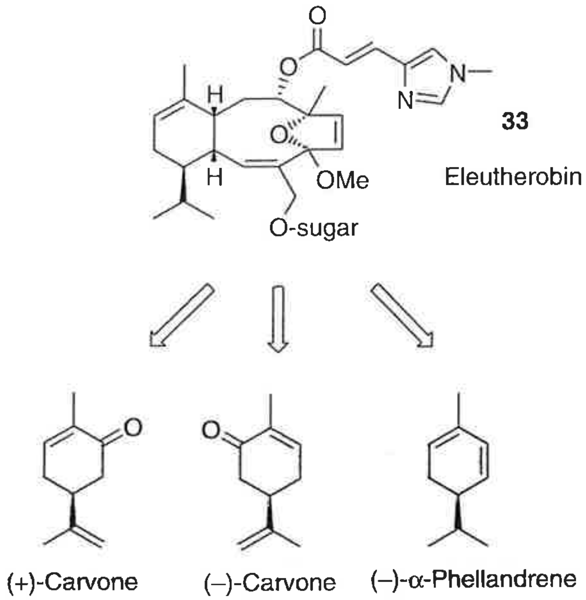
Several syntheses of exo-brevicomin have been executed according to this bond-set [5, 6, 7, 8, 9]. Their step count varies between 7 and 12, illustrating that, for a given bond-set, there is still ample room for intelligent planning of a synthesis in the forward direction. One [9] of these syntheses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



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

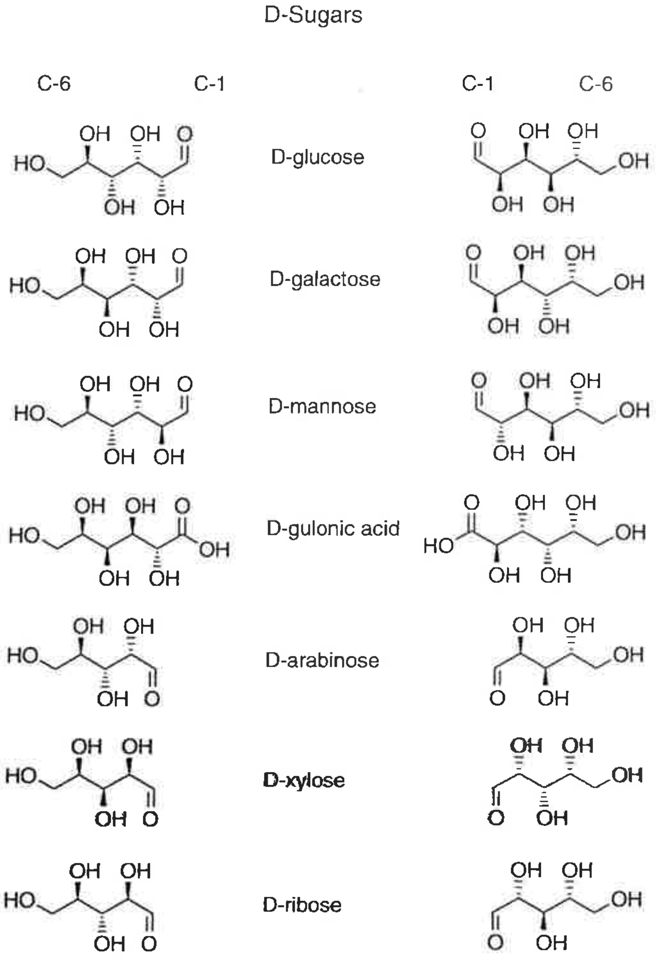
This synthesis uses an auxiliary sulfonyl group (FGA, see Sect. 3.1) to enable the formation of one of the skeletal bonds.

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 α-phellandrene has been chosen as the starting point for an efficient synthesis of eleutherobin [12] (Scheme 4.4).

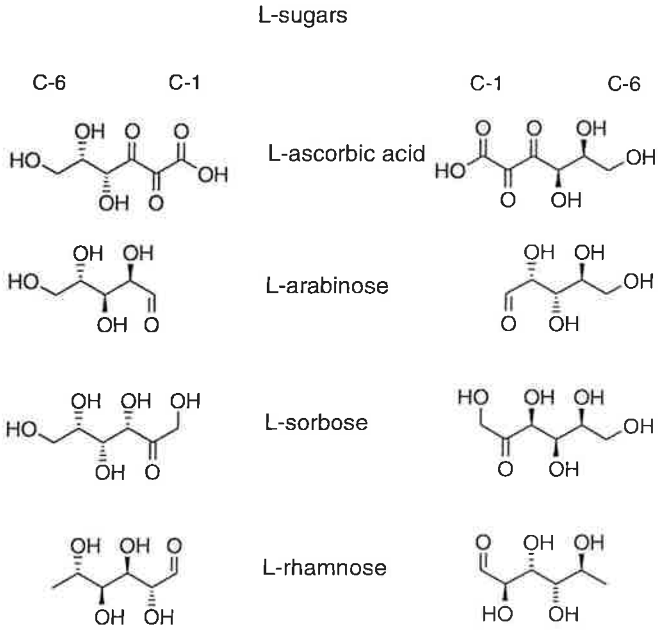


Scheme 4.4 Suitable chiral building blocks for the synthesis of eleutherobin

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).

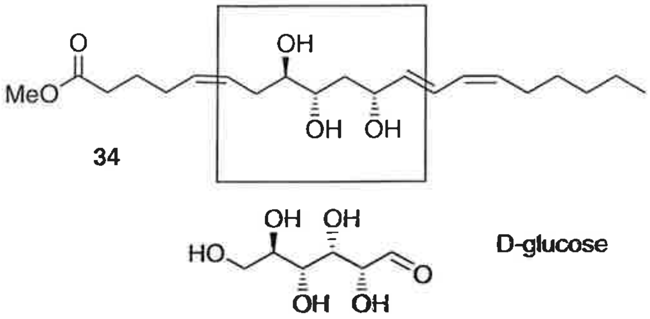


Scheme 4.5 Readily available D-sugars in zig-zag arrangement of the main skeleton



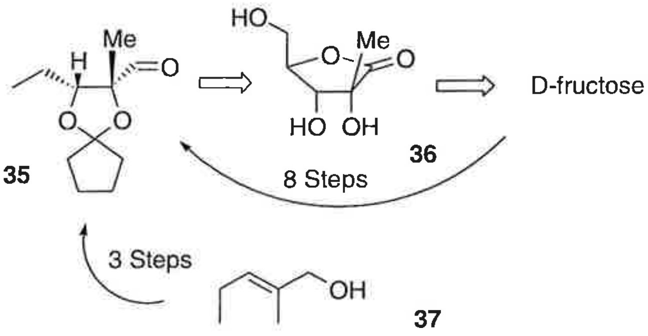
Scheme 4.6 Readily available L-sugars in zig-zag arrangement of the main skeleton

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].



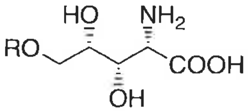
Scheme 4.8 Identification of suitable precursors for the synthesis of **35**

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 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

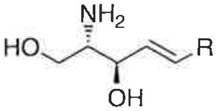
4.1 In Scheme 4.9 the core structure of polyoxamic acid is shown. Suggest suitable chiral building blocks for its synthesis.



R = H_2N-CO-

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].



R = $^{n}C_{13}H_{27}$

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

References

1. P. L. Stotter, R. E. Hornish, *J. Am. Chem. Soc.* **1973**, *95*, 4444–4446.
2. K. Kondo, A. Negishi, K. Matsui, D. Tunemoto, S. Masamune, *J. Chem. Soc., Chem. Commun.* **1972**, 1311–1312.
3. D. Seebach, H.-O. Kalinowski, *Nachr. Chem. Tech. Lab.* **1976**, *24*, 415–418.
4. S. Hanessian, *Aldrichimica Acta* **1989**, *22*, 3–14.
5. B. Giese, R. Rupaner, *Synthesis* **1988**, 219–221.
6. H. H. Meyer, *Liebigs Ann. Chem.* **1977**, 732–736.
7. K. Mori, Y.-B. Seu, *Liebigs Ann. Chem.* **1986**, 205–209.
8. H. Kotsuki, I. Kadota, M. Ochi, *J. Org. Chem.* **1990**, *55*, 4417–4422.
9. Y. Masaki, K. Nagata, Y. Serizawa, K. Kaji, *Tetrahedron Lett.* **1982**, *23*, 5553–5554.
10. K. C. Nicolaou, T. Ohshima, S. Hosokawa, F. L. van Delft, D. Vourloumis, J. Y. Xu, J. Pfefferkorn, S. Kim, *J. Am. Chem. Soc.* **1998**, *120*, 8674–8680.
11. S. M. Ceccarelli, U. Piarulli, C. Gennari, *Tetrahedron* **2001**, *57*, 8531–8542.
12. X.-T. Chen, C. E. Gutteridge, S. K. Bhattacharya, B. Zhou, T. R. R. Pettus, T. Hascall, S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 185–186. (*Angew. Chem.* **1998**, *110*, 195–197).
13. J. W. Scott in *Asymmetric Synthesis* (Eds.: J. D. Morrison, J. W. Scott), Academic Press, New York, vol. 4, **1984**, pp. 1–226.
14. S. Hanessian, J. Franco, B. Larouche, *Pure. Appl. Chem.* **1990**, *62*, 1887–1910.
15. G. Just, C. Luthe, *Can. J. Chem.* **1980**, *58*, 1799–1805.
16. R. W. Hoffmann, W. Ladner, *Chem. Ber.* **1983**, *116*, 1631–1642.
17. R. Stürmer, *Liebigs Ann. Chem.* **1991**, 311–313.
18. H. Redlich, W. Francke, *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 630–631. (*Angew. Chem.* **1980**, *92*, 640–641).
19. H. Redlich, J. Xiang-jun, *Liebigs Ann. Chem.* **1982**, 717–722.
20. P. M. Koskinen, A. M. P. Koskinen, *Synthesis* **1998**, 1075–1091.