Pergamon

Tetrahedron 57 (2001) 6855–6875

TETRAHEDRON

Tetrahedron report number 577

Increase in intricacy—a tool for evaluating organic syntheses

P. L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

Received 22 December 2000

Contents

1. Introduction

Understanding organic synthesis is a lifetime endeavor. Teaching it in one semester is an exercise in discussing a subject that is expanding rapidly.[1] Providing an overall strategy and demonstrating its application with illustrative examples enables the construction of an essential frame of reference. Comparing and contrasting existing information allows assimilation of new data. As learning proceeds, this framework becomes broader and deeper.

One of the more challenging aspects of this developmental process is planning an original synthesis. The problem is exacerbated by the multitude of potential pathways, which can easily overwhelm an individual during the middle to late planning stages. Synthetic plans are often rendered impractical because the planner has evolved a lengthy approach, which may include speculative or impossible chemistry in a subconscious effort to effect closure of the synthesis. Guidelines, which correlate the operational length of a synthesis with the structural intricacy of the target and starting materials, can provide focus for the synthetic planner. Such discipline fosters aggressive new chemistry and can engender graceful and efficient access to the target.

The dawn of the third Millennium is an appropriate juncture to propose several simple analytical tools for assessment of both projected and completed syntheses.[2] The information revolution empowers access to ever-greater quantities of chemical data, but the essential step is still the act of isolating crucial facts without being inundated or misled. Synthetic organic chemists are often accused of sharing a common heritage with used car salespersons. Both groups of individuals extol the virtues of their product but ignore or actively obfuscate areas of information that cast less favorable light on their wares. In the case of synthesis, the task of analyzing the quality of the outcome is strongly effected by the perspective of the observer. For example, an academic practitioner concerned with achieving the first total synthesis of a topographically complex and biologically important target has vastly differing goals from

Keywords: synthetic analysis; synthetic design; increase in intricacy; intricacy factors; intricacy quotient; complexity; efficiency quotient; synthetic blueprint; total synthesis.

* Tel.: +1-765-494-5242; fax: +1-765-494-7679;
e-mail: pfuchs@purdue.edu

PII: S0040-4020(01)00474-4

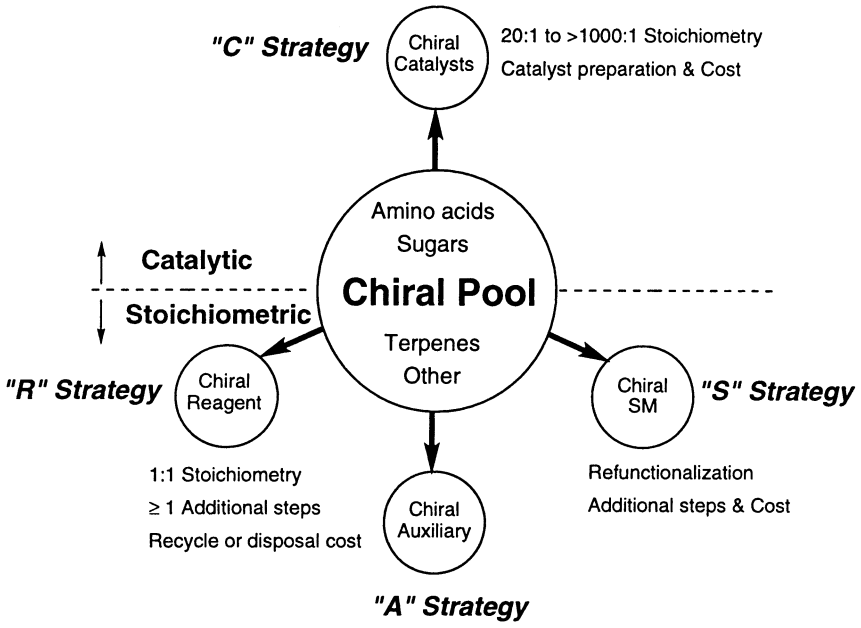


Figure 1.

the organic chemist/chemical engineer working in a pharmaceutical process development group where success is measured in terms of kilograms (or tons) of high-purity material delivered within defined cost and time constraints.

As Service discussed in *Science*,[3] this philosophical schism can be detrimental to advancing the boundaries of synthetic organic chemistry. Nevertheless, individuals at both extremes intersect at the crucial point of having to construct an explicitly defined target. The first synthesis of any important target, whether performed in academia or industry, is likely to suffer by contrast to later syntheses which are usually substantially improved by applying the lessons of the pioneers who achieved the initial preparation.

The pivotal synthetic operations which *increase molecular complexity* include (hetero) arene alkylations, formation of chiral centers, rings, and multiple bonds.[4] Focusing on these factors was held to emphasize the essence of organic synthesis, namely the creation of a target molecule in a highly efficient manner.[5] Because of the biological importance of enantiopure compounds, analysis shall be restricted to only those syntheses that deliver a single enantiomer. Requiring an enantiodefined synthesis combined with high efficiency significantly increases the complexity of the problem and requires creative solutions.

All syntheses that target a single enantiomer ultimately can be related to one or more substances obtained from the chiral pool (Fig. 1). One of the most important considerations in planning a total synthesis is to decide how to introduce absolute stereochemistry. While one can categorically assert that 'all things being equal', syntheses that generate their asymmetry via a chiral catalyst are most desirable because one molecule of catalyst will be responsible for the creation of a multitude of new chiral progeny. Unfortunately, in many cases, issues such as catalyst cost (length of catalyst synthesis, patent royalty, etc.) may detract from the inherent attractiveness of this option. If constrained to use one of the stoichiometric chiral strategies, it is often difficult to identify which of the three options to adopt. The problem is further compounded by syntheses that require establishment of a number of independent chiral centers as this increases the number of times one must access the chiral pool. Specific chiral strategies involved in all syntheses used for defining the analytical method are given in Table 1.

2. An intricacy based technique for synthetic analysis

Corey's insightful treatment of synthetic planning[6] fostered deliberation on the entire process of how a chemist conceives and evolves a synthetic plan. Important contributions by Bertz,[7] Hendrickson,[8] Jorgensen[9] and Long[10] further expanded the domain of synthetic analysis, especially those aspects that featured the human–computer interface.

A recent paper by Whitlock describes a complexity-based synthetic analysis[11] that employs many of the same structural features with a protocol that we evolved over several years. The Whitlock method weights structural features in the following manner: rings=4; unsaturations=2; heteroatoms=1; chiral centers=2. Whitlock affirms that these weighting factors are somewhat arbitrary, but they satisfactorily describe the examples he analyzed.

Our own experience in attempting to develop tools for synthetic analysis initially involved investigation of the compositional and structural features present in a set of total syntheses. In practice, this generated an unwieldy equation with far too many variables, but it was clear that

wide-ranging weighting factors seemed to give reasonable descriptions of a small collection of syntheses. Ultimately we elected to adopt an analysis system that postulates 1:1:1:1 weighting factors for olefinic stereogenic centers, chiral centers, rings, and heteroatoms because of their chemical interconvertability.

The essence of organic synthesis is creation and stereospecific functionalization of π-systems. Concomitant installation of functionality suitable for reiteration of the process engenders highly efficient syntheses.

3. The intricacy quotient

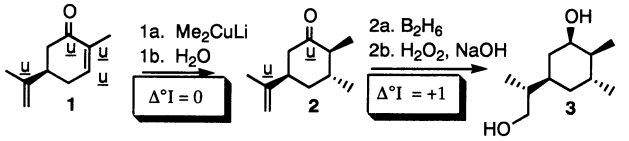
In the context of total synthesis of optically active target molecules, the *intricacy quotient* (IQ) is defined to be average number of *intricacy factors* created per operation. This value is comprised of chiral *centers*+*unsaturations* (*including rings*)+(*hetero*) *aryl substitution*+*heteroatoms* generated per synthetic operation during the transformation of a set of starting materials to the final target. IQ is set mathematically equal to the degree of intricacy ($^{\circ}I$) of the target ($^{\circ}I_t$) minus the degree of intricacy of the sum of the starting materials ($\sum^{\circ}I_{sm}$), all divided by the *total number of operations* (*O*) *in the entire synthesis* (Eq. (1)). $^{\circ}I_t$ and $^{\circ}I_{sm}$ are, in turn, both defined as equal to $C^*+\underline{U}+AR+X$, where C^* is the number of chiral centers, $\underline{U}$ the number of prochiral unsaturations plus rings, AR the number of aryl or heteroaryl C–C or C–X bonds, and *X* is the number of heteroatoms (Eq. (2)). In the context of this analysis, all non-C–C and C–H bonds are considered heteroatoms.

$$IQ = (^{\circ}I_t - \Sigma^{\circ}I_{sm})/O \tag{1}$$

$$^{\circ}I = C^* + \underline{U} + AR + X \tag{2}$$

In devising a synthesis it is useful to calculate $\Delta^{\circ}I$ for each operation (i.e. the IQ for a single operation). Processes with positive $\Delta^{\circ}I$ indicate progress toward the ultimate goal, while reactions with zero or negative values signal areas to be considered for possible revision. Strictly accounting for every chiral center, prochiral unsaturation, ring, arene C–X bond, and heteroatom in all starting materials by subtracting $\sum^{\circ}I_{sm}$ from $^{\circ}I_t$ enables sharp focus upon those intricacy factors which have specifically been created during each operation as well as cumulatively at the end of the synthesis. This method of intricacy factor bookkeeping discounts the intricacy value of the starting materials. This is not to say that recognition and efficient inclusion of such molecular arrays is unimportant,[4] but the reward for such judicious choices is reflected in the EQ calculation which deals with average yield per operation (see Eq. (13)).

While counting chiral centers and unsaturations due to rings is straightforward, *assignment of the unsaturation value of double bonds requires consideration of the symmetry properties of the olefin*. This accounting method assigns a $\underline{U}$ value of **2** for unsaturations bearing a pair of prochiral atoms. For example, the cuprate conjugate–addition step shown in Eq. (3) transforms enone **1** to ketone **2**. The increase in intricacy ($\Delta^{\circ}I$) for this conversion is equal to zero; that is, the two prochiral carbons of the trisubstituted olefin are smoothly converted to two chiral centers, but no *net complexity* has been introduced. The second operation involves concomitant ketone reduction and hydroboration of the disubstituted olefin. This transformation converts the remaining two prochiral centers to a pair of chiral centers. However, the hydroboration also introduces an alcohol heteroatom, which ultimately could be further functionalized to a ring, chiral center, or oxidized to introduce another unsaturation. Thus, it is reasonable that the second step has $\Delta^{\circ}I = +1$ to reflect the *increase in intricacy* in going from **2** to **3** (Eq. (3)).



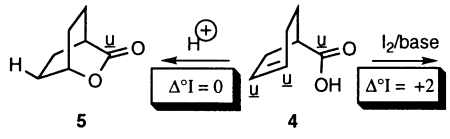
°I = C* + U + AR + X °I = 1 + 5 + 0 + 1 U = 4u + 1 ring

°I = C* + U + AR + X °I = 3 + 3 + 0 + 1 U = 2u + 1 ring

°I = C* + U + AR + X °I = 5 + 1 + 0 + 2 U = 1 ring

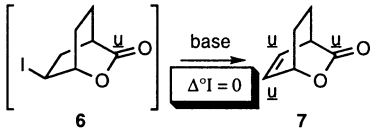
(3)

Acid-catalyzed lactonization is compared with halolactonization in Eq. (4). The former process consumes the bis-stereogenic olefin of acid **4** and creates one new stereocenter and one new ring in lactone **5**. This *isomerization* has a $\Delta^{\circ}I = 0$. The halolactonization reaction is a net oxidation, and incorporates an iodine heteroatom as well as creating a new ring and two new stereocenters ($\Delta^{\circ}I = 2$) in iodide **6**. If run in the presence of an appropriate base, this process would further transform iodide **6** to olefin **7** having an $^{\circ}I$ value equal to that of **6**. The oxidative process has, in one operation, effected the desired cyclization as well as providing new olefin functionality appropriate for subsequent functionalization. The value-added nature of this transformation is apparent from the increase in intricacy ($\Delta^{\circ}I = 2$).



°I = C* + U + AR + X °I = 2 + 3 + 0 + 2

°I = C* + U + AR + X °I = 1 + 4 + 0 + 2



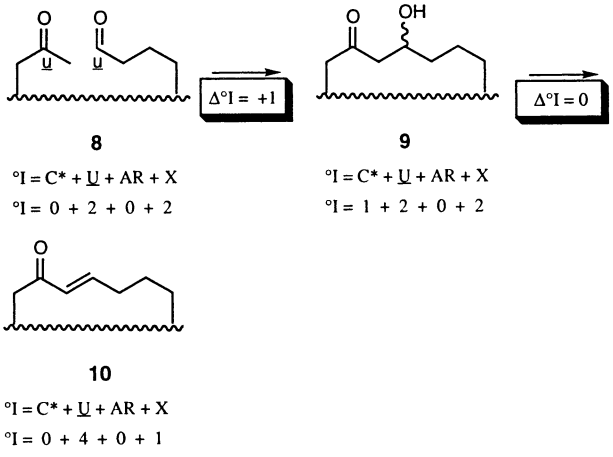
°I = C* + U + AR + X °I = 3 + 3 + 0 + 3

°I = C* + U + AR + X °I = 2 + 5 + 0 + 2

(4)

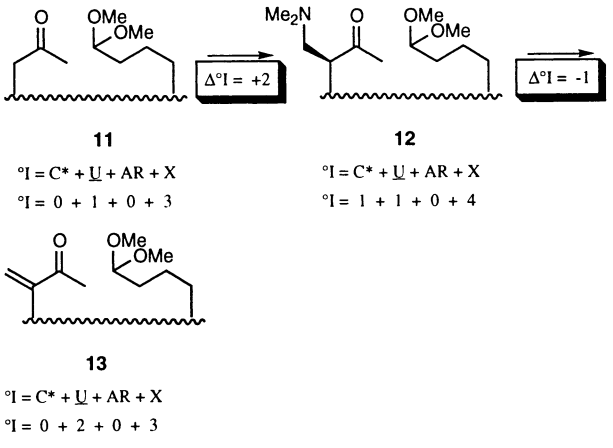
The intramolecular aldol reaction shown in Eq. (5) converts **8**, which bears two carbonyl groups, each composed of one stereogenic center and one heteroatom ($^{\circ}I$=4) to the cyclic β-hydroxyketone **9** having one chiral center, one new ring,

one stereogenic center, and two heteroatoms ($^{\circ}I$=5). Further dehydration of **9** gives cyclic enone **10** which bears three stereogenic centers, the ring, and the carbonyl heteroatom. Thus, the dehydration is a value-neutral transformation ($\Delta^{\circ}I = 0$), since the olefin bears a latent pair of stereogenic centers. It is noted that intermediate **9** is a mixture of diastereomers, but this is irrelevant to the transformation at hand.



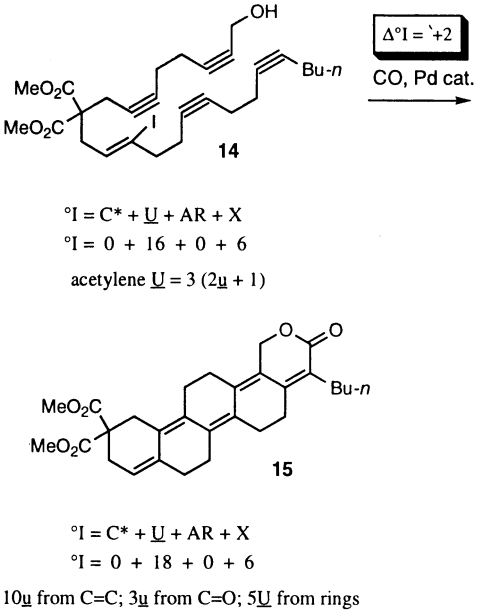
(5)

A contrasting example is shown in Eq. (6). In this instance, the protected keto-aldehyde **11** undergoes a Mannich reaction to generate β-aminoketone **12** which is more intricate ($\Delta^{\circ}I = 2$) by virtue of the creation of a new stereocenter and the introduction of the nitrogen heteroatom. Elimination to enone **13** *decreases* $\Delta^{\circ}I$ of the product since the newly formed 1,1-disubstituted olefin bears only a single prochiral center ($\underline{u} = 1$), while both a chiral center and a heteroatom have been lost.



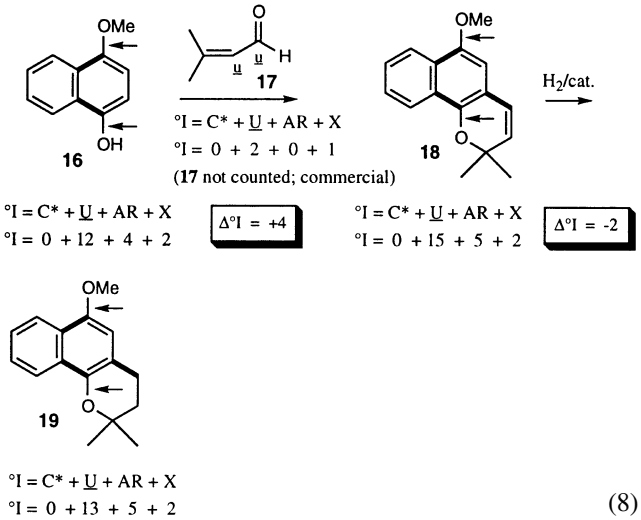
(6)

Triple bonds, both terminal and internal, are counted as $\underline{U} = 3$, that is, one unit of unsaturation in addition to two potentially stereogenic carbons. The Negishi cascade cyclization[12] of vinyl iodide **14** to pentaenyl lactone **15** provides a striking example, which illustrates the generation of olefins and rings from the embedded alkynes (Eq. (7)).



(7)

Eq. (8) demonstrates calculation of arenes. This example features a phenylboronic acid mediated annulation reaction from Snieckus' synthesis of β-lapachone.[13] The first point concerns the high $\underline{U}$ value for the naphthalene starting material **16**. It might initially appear that this reaction, which does not perturb the naphthalene core, overvalues the arene sp^2 centers by counting them all as prochiral centers. *The intricacy value is not intended to characterize the fundamental complexity of a target molecule.* This is clearly seen in the case of **18**, which is a much simpler molecule than an acyclic hydrocarbon containing 22 stereocenters, although both have $^{\circ}I = 22$. The *increase in intricacy* concept relies upon *chemical interconvertability* of the individual structural features and requires subtraction of the intricacy of the starting materials in order to provide a meaningful assessment of a given transformation. Thus, if arene π-unsaturations are not converted to sigma centers they are irrelevant, since their intricacy is equally weighted in both starting material and product of a given transformation.



(8)

The second point deals with how to count increases in arene

(or heteroarene) substitution. This is referred to as the AR value and is defined as the number of arene regiocenters which bear (or have been converted to) C–C or C–X bonds. In Eq. (8), the starting arene **16** bears two C–O bonds (arrows) and two internally fused C–C bonds (bold, Eq. (8)), while the product **18** has one additional external C–C bond; therefore their AR values are 4 and 5, respectively. Inclusion or omission of the two bolded bonds is irrelevant in this instance, as they occur in both the starting material **16** and the target **18**. In cases where new arene rings are *created* from the existing C–C or C–X bonds, the rationale for inclusion of the resultant bonds in the product becomes apparent.

Conversion of **16** to **18** has $\Delta^{\circ}I = 4$, which over-rewards this single operation. It is further noted that while all chiral centers and arene features (C^{*}+AR) need to be included as contributing starting materials, over-zealous accounting for all heteroatoms and unsaturations in commercially available reagents like ethyl acetate, oxidizing agents, and simple fragments is not necessary. Compounds like methyl vinyl ketone and vinyl aldehyde **17** are not included unless they are excessively expensive or are prepared rather than purchased. Conversely, if the $^{\circ}I$ value of **17** were included, the $\Delta^{\circ}I$ would equal +1, which would appear low for this efficient annulation reaction. While a transformation having a zero or negative value can pave the way to the final product, the $\Delta^{\circ}I$ for the *entire synthesis* is the ultimate measure of the degree of success, since it avoids the above 'local extrema' problem.

The final synthetic transformation in Eq. (8) involves hydrogenation of a bis-prochiral olefin in **18** to dihydro derivative **19**. The unsaturation has been consumed without concomitant structural elaboration, and the negative intricacy value indicates this reality. This does not necessarily reflect poorly on the design of the synthesis, but highlights the fact that the olefinic substructure was incorporated without being further exploited. This indicates that the *synthesis might be achieved with a less intricate substrate*, or more importantly, the strategy developed has the potential to deliver even more intricate congeners.

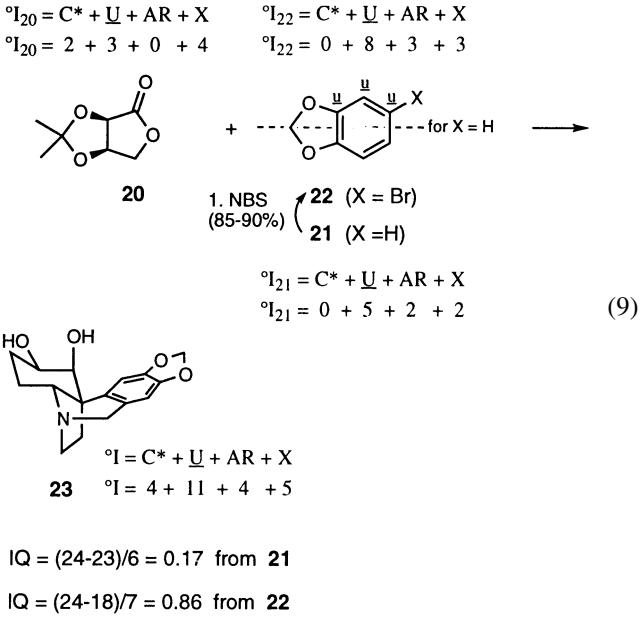
4. Definition of starting materials

Intricacy factors of the following species *must* be counted as 'starting materials':

- $^{\circ}I$ values for all enantiopure materials bearing chiral centers that are incorporated into the target. Note this excludes commercially available enantiopure auxiliaries and reagents.
- $^{\circ}I$ values for all non-trivial materials bearing unsaturations (rings, multiple bonds, arenes, or heteroarenes).
- $^{\circ}I$ values for all materials that require synthesis or are excessively costly.
- The highest $^{\circ}I$ primary starting material, even if commercially available.

As with the case of vinyl aldehyde **17**, there is some temptation to second-guess the above 'rules'; however, inspection of the equations in conjunction with the additional examples from Table 1 (supplemental material) further elucidates which compounds are starting materials, and which to exclude.

Another consideration with respect to commercially available starting materials is recognition of their genesis. Superficial application of the rules suggests that the Pearson synthesis of Amabiline[32] **23** from enantiopure lactone **20** and commercial aryl bromide **21** results in an IQ of 0.17 (Table 1). However, comparison of the (longer) synthesis that includes preparation of **21**[14] from the less intricate arene **22** provides an outstanding IQ of 0.86 (Eq. (9)). This retrospective analysis simply illustrates that an extraordinary synthetic design should not be negatively portrayed if further consideration reveals its true value. Similarly, the importance of carefully chosen (simple and symmetric) starting materials cannot be understated with respect to planning new syntheses.

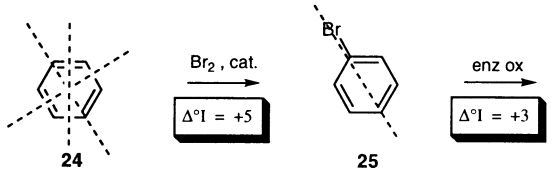


(9)

5. Rationale for counting prochiral π-centers in arenes

While the plane of symmetry in methyenedioxybenzene **21** (Eq. (9)) resulted in a *decreased* number of prochiral centers ($\underline{u} = 3$) relative to bromoarene **22** ($\underline{u} = 6$), further support for assigning full integral weight to each of the prochiral π-unsaturations of arenes is provided by the Hudlicky enantiospecific oxidation of bromobenzene **25** to diol **26**.[15] This spectacular enzymatic reaction converts two of the four prochiral arene centers of **25** to the diol functionality with simultaneous introduction of the two oxygen heteroatoms (Eq. (10)). The power of this transformation becomes especially apparent when one recognizes that the precursor of **25** is benzene **24** itself. Thus, $\Delta^{\circ}I = +8$ for the two-operation synthesis of **26** if one includes the intricacy of benzene. Conversion of **25** to **26** is the kind of standard-setting transformation that prompts the organic chemist to re-evaluate alternative plans for the synthesis of highly functionalized

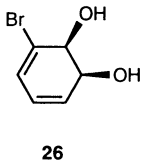
enantiopure six-membered rings.



°I = C* + U + AR + X
°I = 0 + 2 + 0 + 0

°I = C* + U + AR + X
°I = 0 + 5 + 1 + 1

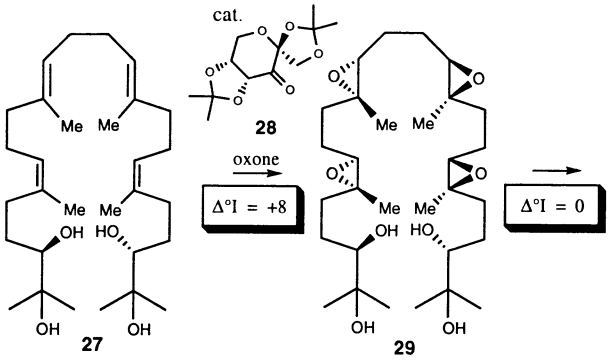
(10)



°I = C* + U + AR + X
°I = 2 + 5 + 0 + 3

6. The advantage of multiple reactions

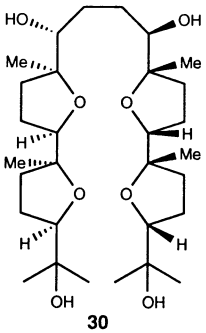
Eq. (11) shows a portion of a recent synthesis of glabrescol by Xiong and Corey.[16] At the heart of the strategy, tetraene **27** is epoxidized using oxone with a catalytic amount of the enantiopure Shi ketone **28**. This example converts four doubly prochiral olefins to four chiral epoxides, each having a ring, two stereocenters, and an oxygen heteroatom. Thus, $\Delta^{\circ}I = +8$ for synthesis of tetraepoxide **29**, an outstanding increase for a single operation. While the beautiful cascade cyclization of **29** to the tetrakis tetrahydrofuran **30** is a noteworthy reaction, it can be seen that all the necessary structural information was introduced in the previous step, thus only resulting in $\Delta^{\circ}I = 0$ for the final *isomerization*.



°I = C* + U + AR + X
°I = 2 + 8 + 0 + 4

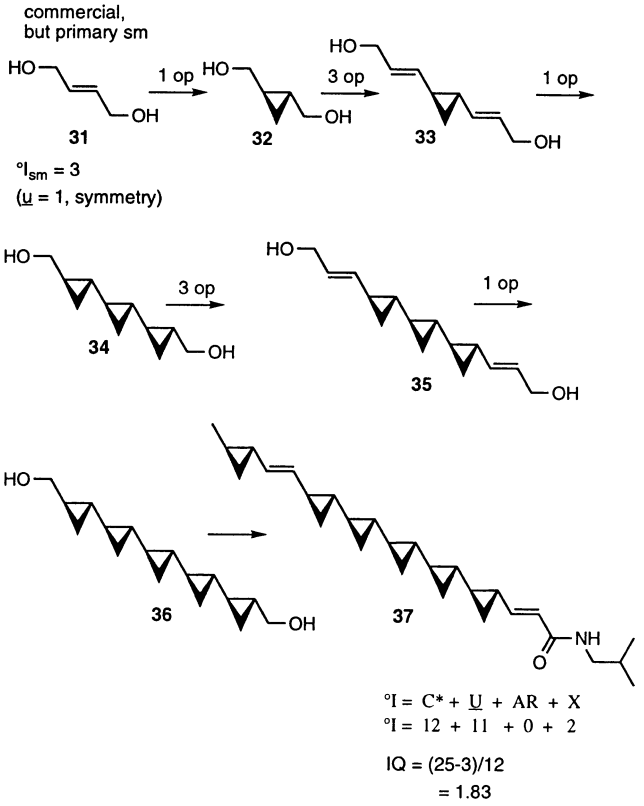
°I = C* + U + AR + X
°I = 10 + 4 + 0 + 8

(11)



°I = C* + U + AR + X
°I = 10 + 4 + 0 + 8

Another striking example demonstrating the power of multiple reactions was provided by the groups of Charette and Barrett by their independent and essentially identical syntheses of the polycyclopropane U-106305 (Eq. (12)).[23] This synthesis featured reagent-based enantiospecific cyclopropanation of ene–diol **31** to cyclopropyl diol **32** followed by bi-directional oxidation/olefination/reduction to **33**. Repeating the process gave **36** which was monofunctionalized and further converted to target **37** with the highest IQ (1.83) we have observed thus far.



(12)

7. The efficiency quotient

We adopt *average yield per operation*, defined as the sum of all yields (including preparation of starting materials) divided by the total number of operations (Eq. (13)). This is referred to as the *efficiency quotient* (EQ). This number provides an excellent measure of the tactical proficiency of a completed synthesis. This number has been recently used by a number of research groups and is gaining momentum.[17] The EQ value demonstrates the potential of a synthesis for material throughput, and when applied to a collection of syntheses, (see Table 1) enables comparison between syntheses. For intricacy analysis, an *operation* is defined as a *sequence of steps terminating in purification* (distillation,

crystallization, or chromatography). Schemes are numbered to designate individual operations and are further subdivided by letter suffixes to indicate addition of reagents, co-reactants, or workup (without purification).

$$EQ = \Sigma Y/O \quad (13)$$

Counting operations rather than steps is intended to approximate the industrial ethic, where unnecessary purification and handling of intermediates is routinely avoided (see Hoechst synthesis: Table 1).[25] The experimental section of Overman's synthesis of Isocrambescidin 800 (Table 1) provides an excellent example of a hybrid reporting format where intermediates are characterized in the traditional stepwise academic fashion, parallel to an operational sequence which minimized loss of time and material.[54]

8. Convergency

The order of operations is intimately involved with the ability of a synthesis to accommodate material throughput. Consideration of three synthetic sequences, each of which uses 22 operations to accomplish the objective, can dramatically illustrate this point. The mathematical consequences of the fully linear sequence are particularly devastating as the overall yield is calculated to be less than one percent, based upon an 80% average yield (the current standard of reference, Table 1). As is well known to the synthetic community, employing more highly convergent plans of attack can ameliorate this bottleneck (Fig. 2).[18]

While there is currently no uniform editorial standard for the presentation of information associated with a total synthesis, it is relatively common for authors to provide an overall yield for the 'longest linear sequence'. This information gives an indication of the limiting yield for the material supply line. However, by not including yield information for the shorter supporting legs of the synthesis, it is difficult or impossible to obtain a complete overview of what has been accomplished. It is strongly asserted that comprehensive synthetic analysis must include all operations undertaken in a multiply–convergent synthesis *including the construction of all starting materials, be they 'readily-available' or not*!

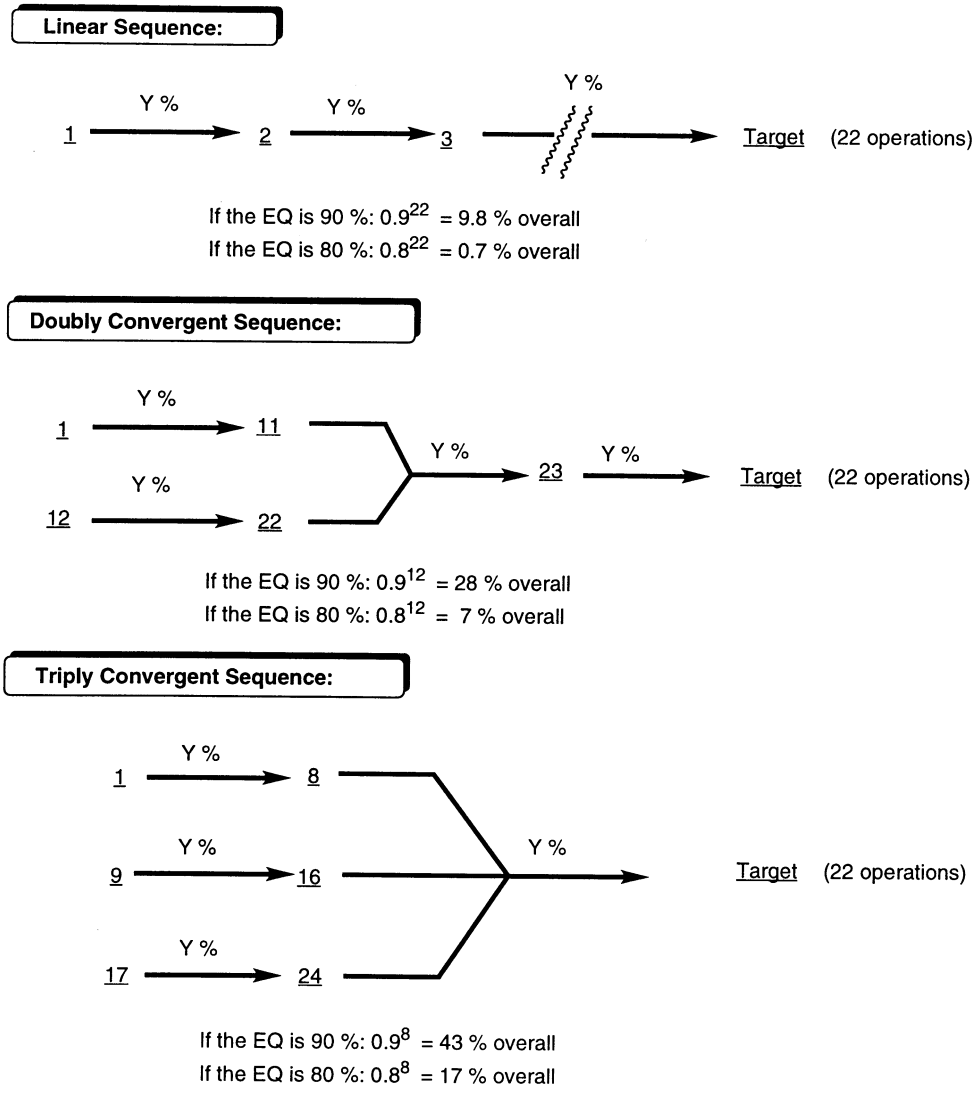


Figure 2.

9. The overhead problem

An important question is how to treat molecular fragments, such as chiral auxiliaries and protecting groups, which contain intricacy factors *peripheral to the final target*. This subject relates to the issue of atom economy. Trost convincingly argues that an ideal synthetic process is one that catalytically transforms substrate(s) into product without the generation or consumption of organic or inorganic byproducts.[19] This is an especially important goal in industry where environmental considerations strongly influence the disposal costs of reaction residues. While the scenario of all organic reactions conducted in water with chemical or biological catalytic orchestration represents a utopian future limit, the desire to minimize generation of molecular detritus is an issue whose import is proportional to reaction scale.[20] In order to increase cognizance of this important topic, the term 'overhead' is introduced to indicate intricacy factors necessary to effect a synthesis. To maintain consistency with the general philosophy, the overhead present in starting materials, chiral auxiliaries, chiral reagents, and protecting and activating groups can be designated by appending a trailing superscript to the $^{\circ}I$ value (see Eqs. (14)–(17)). The overhead number indicates departure from an ideal synthesis, but it is currently impossible to quantitatively apportion liability without a substantially larger database, including material costs, time, and recycling efficiency. Consequently, for this paper, the overhead number will be ignored, and only those intricacy factors that appear in the final target will be used in intricacy calculations.

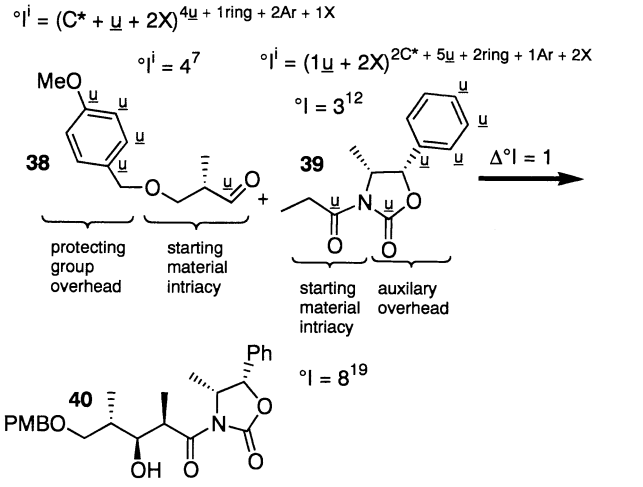
Although a considerable number of bonds, stereocenters, and rings may be created in a single transformation, it is important to reemphasize that *all the fundamental structural information necessary for elaboration of a target resides in the planar stereochemistry of its precursor π-system.* Several transformations, with overhead included, are shown in Eqs. (14)–(17). The first example is an auxiliary controlled Evans' aldol condensation used by Smith in his highly efficient discodermolide synthesis (Eq. (14)).[35] The basis of this $\Delta^{\circ}I = 1$ conversion is the consumption of an aldehyde carbonyl ($^{\circ}I = 2$) with concomitant generation of two stereocenters plus the attendant alcohol heteroatom (**40**, $^{\circ}I = 3$).

The Diels–Alder cycloaddition is routinely revered as one of the most outstanding and powerful reactions discovered. Eq. (15) shows a beautiful intramolecular Diels–Alder reaction by the Evans group.[44] This reaction employs an enantiopure Lewis acid catalyst to generate two rings, four stereocenters, and the new olefin **42**, all as a single enantiomer. The net increase in intricacy for this process is $\Delta^{\circ}I = 2$ since three bis-stereogenic olefins were consumed in the process.

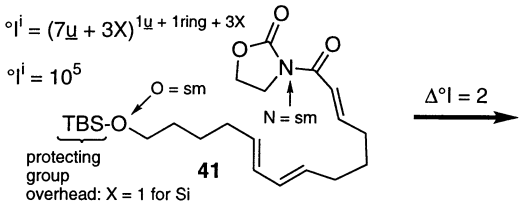
The third example, provided by Corey,[40] exploits the cation–olefin cyclization to deliver tricyclic **44** bearing three new rings, six stereocenters, and a pendant alcohol (Eq. (16)). This outstanding transformation also has a net intricacy increase of $\Delta^{\circ}I = 2$ after subtracting the three bis-stereogenic olefins and the mono-stereogenic epoxide ring, which were consumed.

Denmark provides a fourth study which features a highly efficient hetero Diels–Alder reaction of vinyl ether **46** bearing a chiral auxiliary with vinyl nitro compound **45** attached to a silyl dienyl ether via a silicon tether.[30] After the initial cyclization the incipient aci-nitro intermediate suffers an intramolecular 3+2 cycloaddition to deliver **47**, bearing all requisite stereocenters and heteroatoms for a superbly conceived synthesis of castanospermine (Eq. (17)).

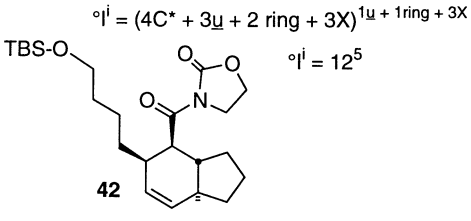
Eq. (18) dramatically makes the point that intricacy factors not directly involved in the chemical transformation must only be counted as overhead (or ignored). Glucose anomer **48** has $^{\circ}I$=12, while pentaacetate **49** would have an apparent $^{\circ}I$=22 if the five acyl units were included as contributing factors. Clearly, this is inappropriate, since the acyl groups are simply acting as protecting groups and are not retained in the final product. Therefore, Eq. (18) is seen to have $\Delta^{\circ}I$=+0[10] which indicates that the overhead has increased, but the intricacy value of the substrate has not fundamentally changed.

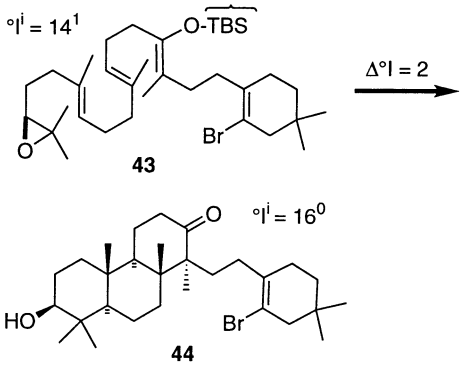


(14)

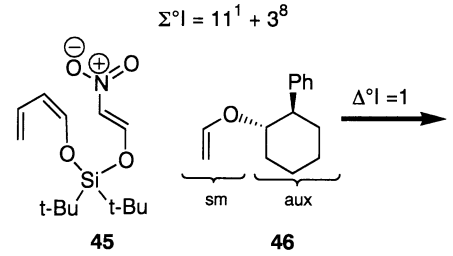


(15)

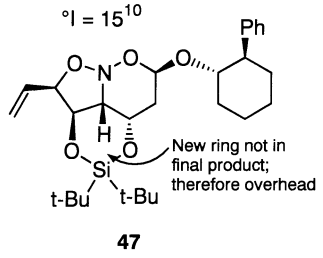


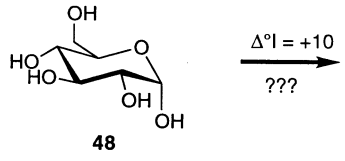


(16)



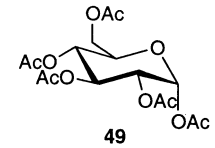
(17)





°I = C* + U + AR + X
°I = 5 + 1 + 0 + 6

°I = 12^0



(18)

°I = C* + U + AR + X
°I = 5 + 6 + 0 + 11

°I = 12^{10}

10. Counting arene and heteroarene creation and substitution

The final example deals with overhead and intricacy counting for arene and heteroarene formation and substitution. Wood's superb synthesis of K252a demonstrates many of these features (Eq. (19)).[26] Oxalic acid diamide **50** bears 16 unsaturations, 4 arene substitutions (bold), and 4 heteroatoms for an $^{\circ}I$=24. Bis Madelung cyclization of this material nicely affords bis indole **51**. The loss of two oxygen heteroatoms in the expelled water is counterbalanced by the formation of two new doubly stereogenic indole rings with an extra common (hetero)aromatic substitution, so $\Delta^{\circ}I$=+3 for this process. Rhodium catalyzed decomposition of the protected diazotetramic acid **53** presumably initially affords cyclopropane adduct **54** which suffers isomerization to a new bisindole–tetramic acid **55**. Dehydrative aromatization of this substrate gives the key arene fused lactam **56** which has $\Delta^{\circ}I$=+2 via formation of a new arene ring bearing two additional substituents (AR=8). If one includes the diazo moiety in $\sum^{\circ}I$ of the two starting materials, the overall transformation (**51**+**53**→**56**) results in a net change of intricacy factors of zero because of the loss of dinitrogen ($^{\circ}I$=4). Counting dinitrogen as a desired co-product along with **54** from the reaction of **51** and **53** then gives $\Delta^{\circ}I$=+4. Alternatively, since the diazo moiety is prepared from intermediate **52** by reaction with tosylazide, it is equally acceptable to consider the diazo function as overhead. Using the latter method, the increase in intricacy calculation from **51** and **52**, also results in $\Delta^{\circ}I$=+4 for the genesis of desymmetrized lactam **56**.

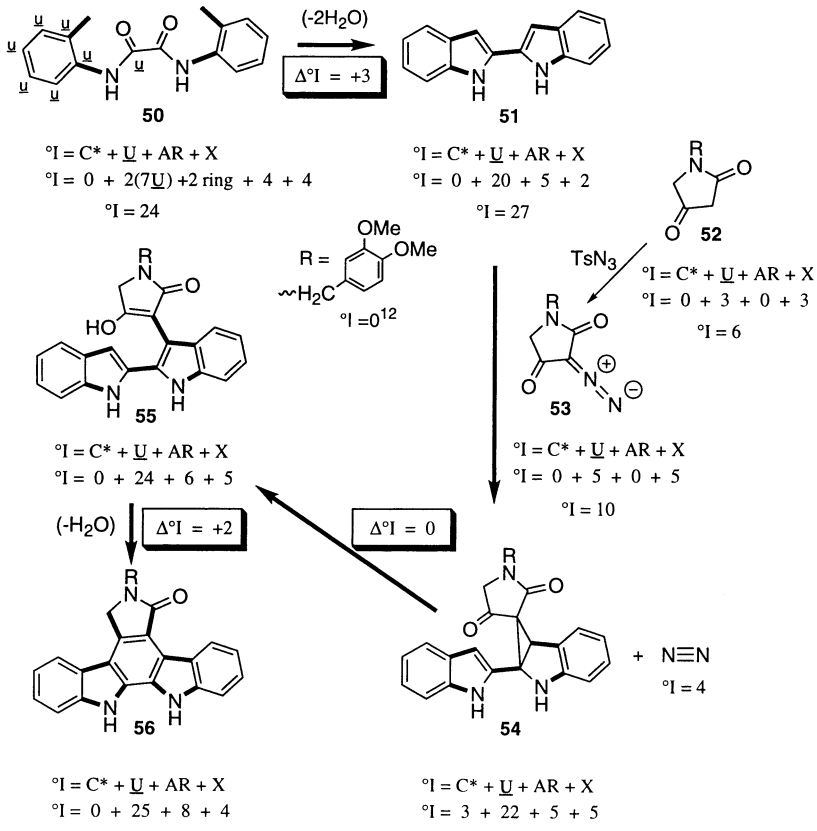
11. The synthesis blueprint

The outline of a complete synthesis is called the *synthesis blueprint* and includes the structures of all starting materials, the target, and includes the $^{\circ}I$ values for each. The number of operations, yields, as well as the IQ, and EQ are also presented in compact form. Such blueprints should not occupy journal space, but are easily provided as supplementary internet information. The SB will result in substantial timesavings for those who wish to compare partial or total syntheses. The synthetic blueprint for the Wood K252a synthesis[26] is shown in Eq. (20).

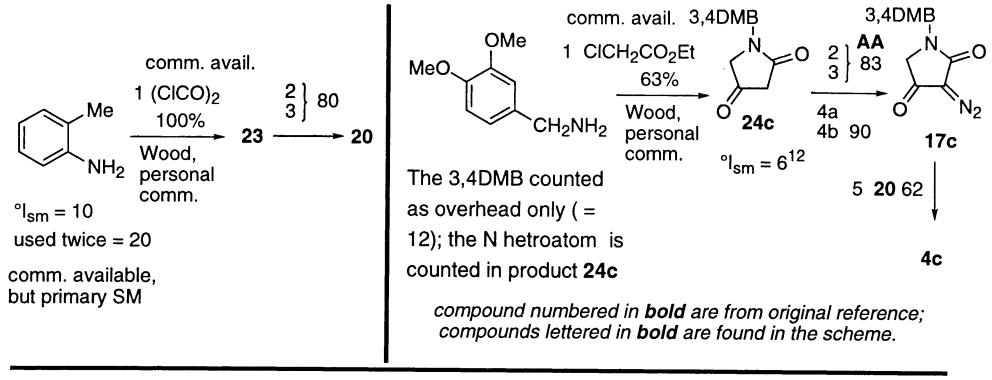
The two oxygens of the oxaloyl chloride precursor are not counted in the $\sum^{\circ}I_{sm}$ calculation because the material is commercially available. While the toluidine is commercially available, the high degree of intricacy of all aromatic starting materials must be counted in order not to skew the calculation. Moreover, toluidine is the primary starting material and would be counted for that reason alone. The protected tetramic acid **24c** contributes to the $\sum^{\circ}I_{sm}$ calculation but neither the ethyl acetoacetate nor the tosyl azide is included. The 3,4DMB moiety is ignored since this material is both commercially available and only used as a protecting group; therefore, its arene moiety is not incorporated into the structure (but is still considered to be overhead).

12. The intricacy–efficiency product

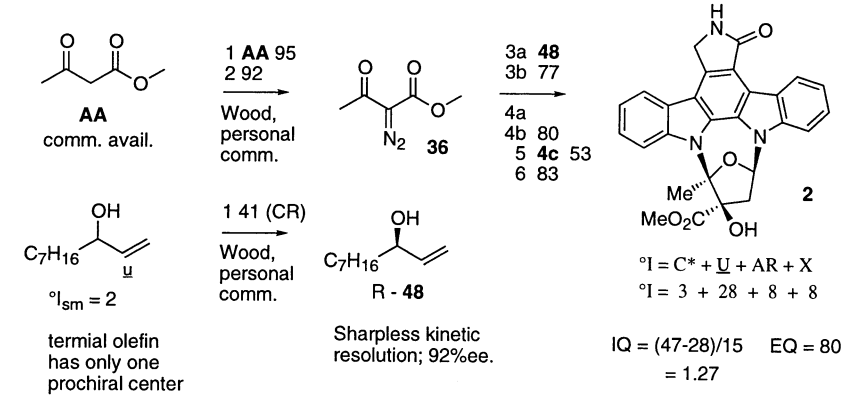
A third indication of the 'quality' of an organic synthesis can be derived from the product of IQ and EQ. This number, termed the intricacy–efficiency product ($I{\cdot}E$), is akin to 'slugging percentage' in baseball.[21] Table 1 lists the data


(-2H2O)
ΔºI = +3
50
51
ºI = C* + U + AR + X
ºI = 0 + 2(7U) +2 ring + 4 + 4
ºI = 24
ºI = C* + U + AR + X
ºI = 0 + 20 + 5 + 2
ºI = 27
52
TsN3
ºI = C* + U + AR + X
ºI = 0 + 3 + 0 + 3
ºI = 6
R = OMe OMe
~H2C
ºI =0[12]
55
53
ºI = C* + U + AR + X
ºI = 0 + 24 + 6 + 5
ºI = C* + U + AR + X
ºI = 0 + 5 + 0 + 5
ºI = 10
(-H2O)
ΔºI = +2
ΔºI = 0
56
54
+ N≡N
ºI = 4
ºI = C* + U + AR + X
ºI = 0 + 25 + 8 + 4
ºI = C* + U + AR + X
ºI = 3 + 22 + 5 + 5

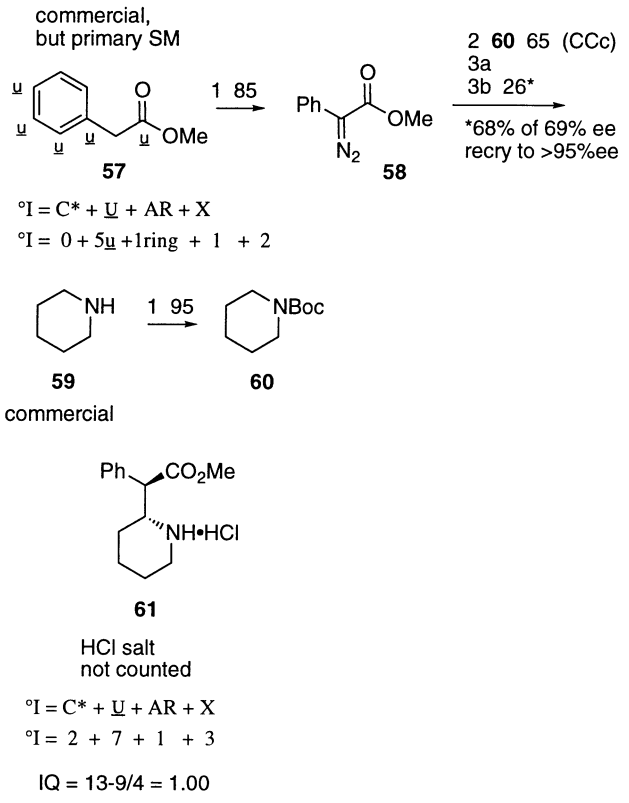
(19)


comm. avail.
1 (ClCO)2
100%
Wood, personal comm.
2 3 } 80
23
20
Me
NH2
ºIsm = 10
used twice = 20
comm. available, but primary SM
comm. avail. 3,4DMB
1 ClCH2CO2Et
63%
Wood, personal comm.
24c
ºIsm = 6[12]
2 3 AA 83
4a 4b 90
17c
5 20 62
4c
OMe
MeO
CH2NH2
The 3,4DMB counted as overhead only (= 12); the N hetroatom is counted in product 24c
compound numbered in bold are from original reference;
compounds lettered in bold are found in the scheme.

(20)


AA
comm. avail.
1 AA 95
2 92
Wood, personal comm.
36
3a 48
3b 77
4a
4b 80
5 4c 53
6 83
2
Me
MeO2C
OH
ºI = C* + U + AR + X
ºI = 3 + 28 + 8 + 8
IQ = (47-28)/15 EQ = 80
= 1.27
OH
C7H16
ºIsm = 2
termial olefin has only one prochiral center
1 41 (CR)
Wood, personal comm.
R - 48
Sharpless kinetic resolution; 92%ee.

obtained from analysis of 40 total syntheses and includes the *I·E* value, but it must be stressed that in the case of this many-variable study, the *I·E* value is not intended to provide an accurate measure of the relative standing of either the individual PI's or their syntheses. Nevertheless, it is asserted that a head-to-head comparison of a number of different approaches to the *same target* or a *cumulative I·E over a 5–10 year period* would indeed provide a meaningful comparison of synthetic strategies or the individuals who devise them.



(21)

13. °*I* and the quest for an ideal synthesis

The design and testing of new strategies having the potential to efficiently generate high °*I* factors can help to stimulate the evolution of organic synthesis. A successful example of such a strategy is seen in the synthesis of the childhood antipsychotic agent methyl phenidate **61** (Ritilin™). An enantiopure Rhodium [II] catalyst is used to achieve enantioselective C–H functionalization of Boc-piperidine **60**, providing a beautiful and efficient synthesis of the active (*R*,*R*) enantiomer. This outstanding chemistry was independently disclosed by the groups of Winkler and Davies[33] (Eq. (21)). Product **61** is comprised of 2 stereocenters and 6 unsaturations (°*I*=8). Although **57** bears no chiral centers, its °*I* value must be subtracted from the degree of difficulty of the target since it bears the arene (and is the primary starting material). Calculation generates an IQ value of 1.0; with the key asymmetric carbenoid insertion and removal of the Boc protecting group constituting two of the four total operations.

14. Syntheses included in the dataset

Armed with the previously described formulas, we surveyed a collection of total syntheses of enantiopure targets in order to determine a typical range of values for IQ, EQ, and *I·E*. The dataset initially comprised more than 100 syntheses published in 1996 or later. This set was first surveyed for IQ values, which exhibited values of from <0.1 to 1.83. In an attempt to secure a varied and representative array, it was decided to include no more than one synthesis per principal investigator. For similar reasons, no more than one synthesis per given target was included in Table 1.[22] Once it became apparent that wide variability in IQ existed, it was decided to limit inclusion to the 40 syntheses with the largest IQ scores. It is important to reiterate that these 40 syntheses are the *top 40% of the original set of molecules surveyed.*

15. Conclusions

Based upon above analysis, the current state-of-the-art of organic syntheses provides an impressive benchmark for the planning of new syntheses. Once one has accounted for the intricacy features supplied by the starting materials, it requires an average of only ~1.33 synthetic operations (IQ = 0.75) to create each of the remaining intricacy factors (1/IQ). Therefore, it would seem to be reasonable to suggest that one should strive to *design a synthetic plan which has fewer than two net operations for per intricacy factor* required (i.e. a projected IQ > 0.5). The craftsmanship of organic chemists is also at a very high level, with an average yield per operation of ~80% (EQ = 79).

The increase in intricacy (Δ°*I*) method is mathematically unforgiving of chemistry which increases the number of operations without concomitant expansion in the complexity of the substrate; examples include protection/deprotection, functional group interconversion, and introduction/removal of auxiliaries.

One must be cautious in application of the Δ°*I* method. This simple protocol stresses the *creation* of stereocenters, rings, and unsaturations. Therefore, even outstanding syntheses which incorporate segments with numerous preexisting stereocenters obtained from chiral pool starting material will not generate high IQ scores.[4] Specific examples include the synthesis of saccharides and peptides.

Acknowledgements

The author wishes to thank Dr D. Lantrip for his multivarient analysis of the initial dataset.

Appendix A. Supplemental materials available

Synthetic Blueprints of all 40 total syntheses shown in Table 1 are available from the author's research archives at: http://fox6.chem.purdue.edu/Public/intricacy.pdf

Table 1. The top 40

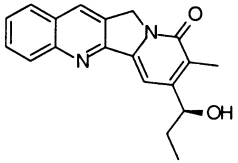
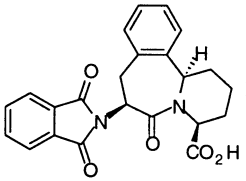
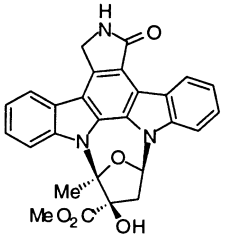
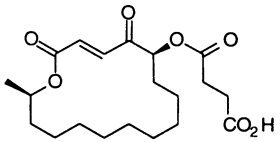
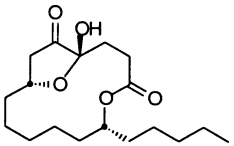
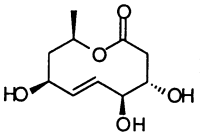
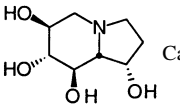
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t-\sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I*·*E*	Refs.	Year
1	 U-106305	CR	25	22	12	1.83	72	1320	23	1996
2	 Mappicine	CR	27	15	11	1.36	82	1118	24	1998
3	 MDL 28,726	CCb/Csm	31	9	6	1.50	73	1095	25	1999
4	 K252a	CR	47	19	15	1.27	80	1013	26	1997
5	 A26771B	CCc/Csm	16	10	9	1.11	76	844	27	2000
6	 Ricinelaidic Acid	CCc	12	8	8	1.00	82	820	28	1997
7	 Decarestrictine D	Csm/CCc	13	9	10	0.90	84	756	29	1998
8	 Castanospermine	CA/CCc	12	9	9	1.00	75	750	30	1999

Table 1. (*continued*)

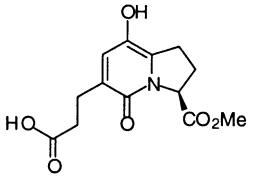
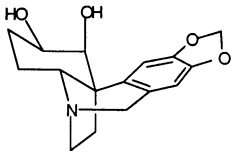
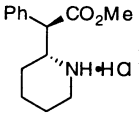
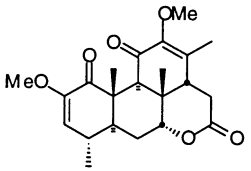
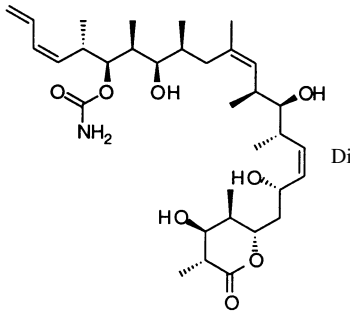
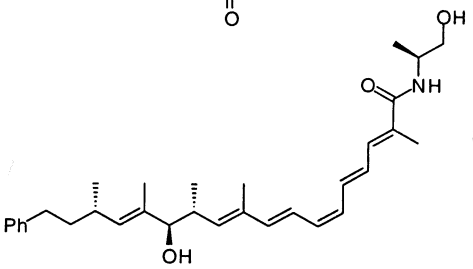
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t - \sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I·E*	Refs.	Year
9	 A58365A	Csm	17	9	11	0.82	90	736	31	1999
10	 Amabiline	Csm	24	6	7	0.86	85	729	32	1998
11	 Methyl Phenidate	CCc	13	4	4	1.00	68	680	33	1999
12	 Quassin	Csm	24	17	23	0.74	86	636	34	1998
13	 Discodermolide	Csm	32	27	37	0.73	87	635	35	2000
14	 Stipiamide	CA	26	14	16	0.88	71	621	36	1997

Table 1. (*continued*)

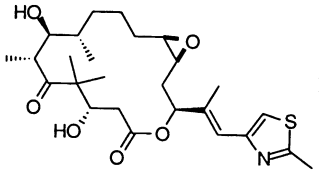
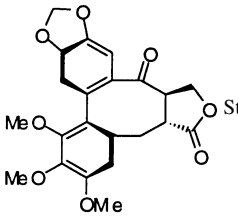
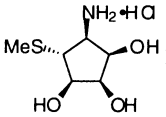
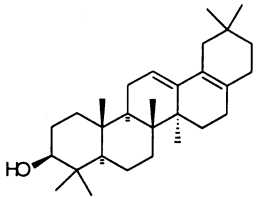
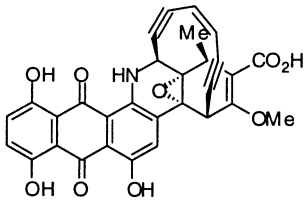
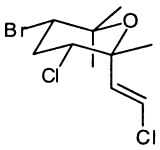
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t-\sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I·E*	Refs.	Year
15	 Epothiolone A	CR/CA	26	17	20	0.85	73	621	37	1997
16	 Steganone	CA	41	12	16	0.75	79	593	38	2000
17	 Mannostatin A	CCb	11	7	10	0.70	83	581	39	1998
18	 Aegiceradienol	CCc	16	10	13	0.77	75	577	40	1999
19	 Dynemicin A	CA	49	27	38	0.71	80	568	41	1997
20	 Aplysiapyranoid C	CR	10	7	10	0.70	79	553	42	1998

Table 1. (*continued*)

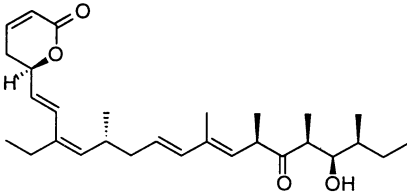
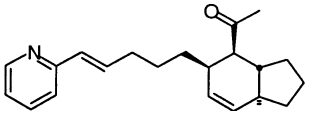
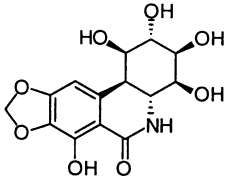
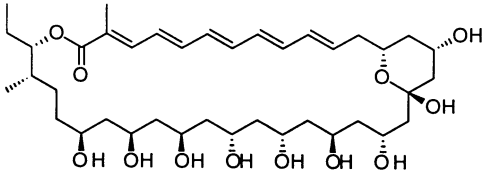
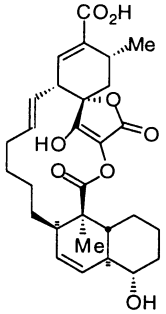
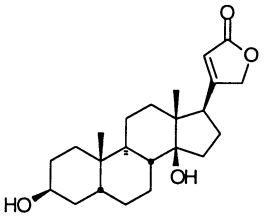
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t - \sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I·E*	Refs.	Year
21	 Callystatin A	Csm/CA	23	16	25	0.64	85	544	43	1998
22	 Isopulo'upone	CCc	20	11	19	0.58	86	498	44	1997
23	 Pancratistatin	CR	31	11	19	0.58	82	475	45	1998
24	 Roflamycoin	Csm/CCc	35	24	38	0.63	75	474	46	1997
25	 Chlorothricolide	CR/CA	32	19	34	0.56	84	469	47	1998
26	 Digitoxigenin	CCc	20	14	25	0.56	81	454	48	1996

Table 1. (*continued*)

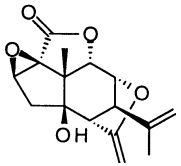
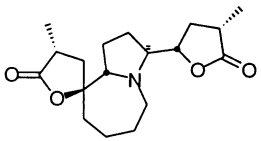
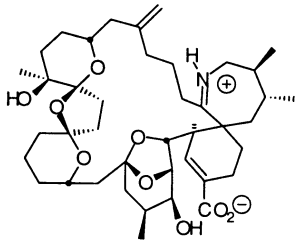
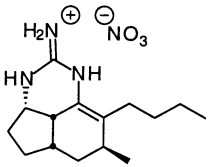
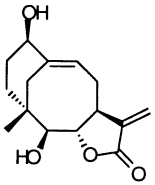
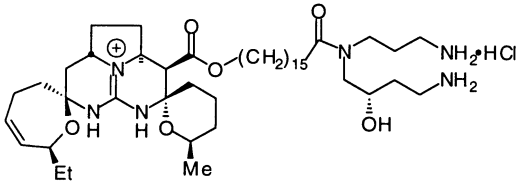
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t-\sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I·E*	Refs.	Year
27	 Picrotoxinin	Csm	20	13	22	0.59	76	449	49	1999
28	 Croomine	Csm	17	6	10	0.60	74	444	50	1999
29	 Pinnatoxin A	CR/CA	36	31	60	0.52	82	424	51	1998
30	 Ptilocaulin	CA	13	8	11	0.73	77	423	52	1996
31	 Deoxycrispolide	CR	16	11	19	0.58	71	411	53	1996
32	 Isocrambescidin 800	Csm/CCc	30	13	28	0.46	87	404	54	1999

Table 1. (*continued*)

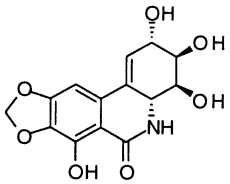
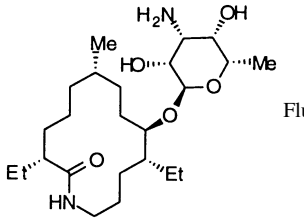
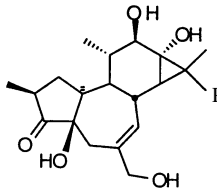
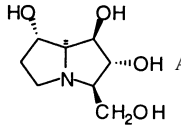
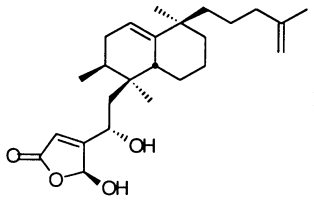
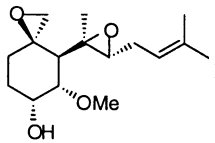
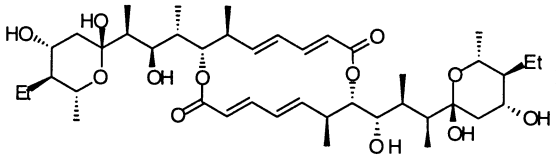
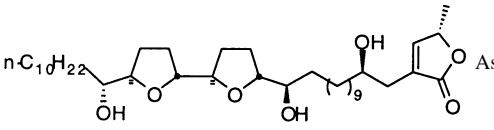
Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t - \sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I·E*	Refs.	Year
33	 Narciclasine	CCb	30	7	11	0.64	62	395	55	1999
34	 Fluvirucin B1	CCc/CR	19	12	24	0.50	76	380	56	1997
35	 Phorbol	CA	22	15	34	0.44	82	362	57	1997
36	 Australine	Csm	12	6	15	0.40	86	344	58	1998
37	 Dysidiolide	CA	19	8	20	0.40	84	336	59	1998
38	 Fumagillol	Csm	15	7	18	0.39	82	319	60	1999

Table 1. (*continued*)

Rank	Target	Strategy[a]	$^{\circ}I_t$	$^{\circ}I_t-\sum^{\circ}I_{sm}$	#ops	IQ	EQ	*I*·*E*	Refs.	Year
39	 Elaiolide	Csm	21.5	11.5	34	0.34	82	277	61	1999
40	 Asimicin	Csm/CR	21	7	22	0.32	84	267	62	1997
Avg(s)			23	13	19	0.75	79	585	–	1998

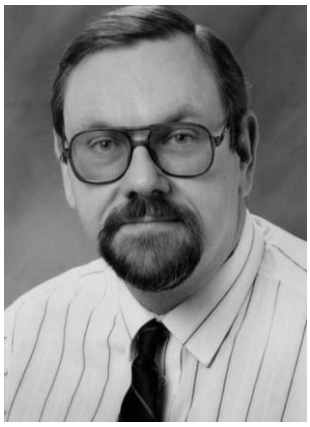
[a] Csm=Chiral starting material; CR=chiral reagent; CA=chiral auxiliary; CCc=chiral chemical catalyst; CCb=chiral biological catalyst.

References

1. Seoane, C. *Aldrichim. Acta* **1989**, *22*, 41–46.
2. For an insightful discussion of modern organic synthesis see: Snieckus, V. *Med. Res. Rev.* **1999**, *19*, 342.
3. Service, R. F. *Science* **1999**, *285*, 6/9/99, 184; for a reply by Djerassi see: *Science*, **1999**, *285*, 9/6/99, 835.
4. This analysis and the formulas derived therefrom place a high premium on the creation of stereocenters, rings, and unsaturations. By comparison, the chiron approach of Hanessian more highly values incorporation of preexisting stereocenters obtained from chiral pool starting material. For an excellent comparative discussion of the chiron approach see: Hanessian, S. *Pure Appl. Chem.* **1993**, *65*, 1189.
5. As noted by a reviewer, the specific objective of a given synthesis may not simply be the most efficient generation of the target. Unambiguous structure proof, analog production, or commercial synthesis will impose additional and differing constraints upon the chemist responsible for synthetic planning. Thus, simple application of the guidelines developed in this paper may not do justice to a synthesis that strongly focuses on one of the aforementioned goals.
6. (a) Corey, E. J. *Pure. Appl. Chem.* **1967**, *14*, 19–37. (b) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Peterson, G. *J. Am. Chem. Soc.* **1975**, *97*, 6116–6124. (c) Corey, E. J.; Long, A. K.; Rubenstein, S. D. *Science* **1985**, *228*, 408–418. (d) Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111–133.
7. (a) Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3599–3601. (b) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801–5803. (c) Bertz, S. H. *Chem. Commun.* **1984**, 218–219. (d) Bertz, S. H. *Chem. Commun.* **1986**, 1627–1628. (e) Bertz, S. H.; Sommer, T. J. *Chem. Commun.* **1997**, 2409.
8. (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439–5450. (b) Hendrickson, J. B.; Grier, D. L.; Toczko, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5228–5238.
9. Jorgensen, W. L.; Laird, E. R.; Gushurst, A. J.; Fleischer, J. M.; Gothe, S. A.; Helson, H. E.; Paderes, G. D.; Sinclair, S. *Pure Appl. Chem.* **1990**, *62*, 1921–2932.
10. Long, A. K.; Kappos, J. C. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 915.
11. Whitlock, W. H. *J. Org. Chem.* **1998**, *63*, 7982–7989.
12. Sugihara, T.; Coperet, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E.-I. *J. Am. Chem. Soc.* **1994**, *126*, 9723–9724.
13. Alves, G. B. C.; Lopes, R. S. C.; Lopes, C. C.; Snieckus, V. *Synthesis* **1999**, 1875–1877.
14. (a) Keck, G. E.; Webb, II, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3173–3177. (b) Keck, G. E.; Webb, II, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 39171.
15. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35–62.
16. Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328–9329.
17. (a) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 2135–2139. (b) Müller, G. H.; Lang, A.; Seithel, D. R.; Waldmann, H. *Chem. Eur. J.* **1998**, *4*, 2513–2522. (c) Smith, III, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468–10477.
18. It is noted that in combinatorial syntheses divergent strategies are essential. Thus, it would not be appropriate to use the convergency guideline in judging the efficiency of production of a library of compounds.
19. Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
20. For an important discussion of environmental factors with respect to green syntheses, see: (a) Sheldon, R. A. *Chem. Ind.* **1990**, 212. (b) Sheldon, R. A. *Chem. Tech.* **1994**, 38. (c) Sheldon, R. A. *Chem. Ind.* **1997**, 12.
21. In baseball, batting average is defined as hits/official times at bat; multiplying this number by total bases/hit gives the total bases/official at bats, which is defined as the slugging percentage. The *I·E* value is defined as the IQ×EQ×1000. The factor of 10^3 is simply to give a number in the hundreds so that it is easily distinguished from EQ.
22. This criterion was strictly followed, but in three instances, exceptionally similar strategies were undertaken by pairs of research groups. The parallel studies can be found in the references provided.
23. (a) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327–10328. (b) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608–8615.
24. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **1998**, *120*, 1218–1222.
25. Henton, D. R.; Barton, K. P.; Clouse, R. C.; DesJardin, M. A.; Donaldson, R. E.; Fetner, N. J.; Goralski, C. T.; Heinrich, G. P.; Hoops, J. F.; Keaten, R. T.; McConnell, J. R.; Nitz, M. A.; Stolz-Dunn, S. K. *Org. Proc. Res. Dev.* **1999**, *3*, 241–247.
26. Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641–9651.
27. Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612–615.
28. Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.
29. Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421–4424.
30. Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056.
31. Straub, C. S.; Padwa, A. *Org. Lett.* **1999**, *1*, 83–85.
32. Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607–3617.
33. (a) Ivy, J. M.; Axten, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6511–6512. (b) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510.
34. Shing, T. K. M.; Jiang, Q.; Mak, T. C. W. *J. Org. Chem.* **1998**, *63*, 2056–2057.
35. Smith, III, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.
36. Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327–2328.
37. Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166–168.
38. Monovich, L. G.; Le Huérou, Y.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52–57.
39. Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072–6076.
40. Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.
41. Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.
42. Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982–2987.

43. (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085. (b) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349–2352.
44. Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786–787.
45. Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509–15524.
46. Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058–2059.
47. Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419.
48. Stork, G.; West, F.; Lee, H. Y.; Isaacs, R. C. A.; Manabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10660–10661.
49. Trost, B.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131–6141.
50. Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990–6997.
51. McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648.
52. Cossy, J.; BouzBouz, S. *Tetrahedron Lett.* **1996**, *37*, 5091–5094.
53. Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620–5633.
54. (a) Coffey, D. S.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **2000**, *122*, 4904. (b) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893.
55. Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077–3080.
56. Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.
57. Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898.
58. White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360.
59. Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228–229.
60. Taber, D. F.; Christos, T. E.; Rheingold, A. L.; Guzel, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589–5590.
61. Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19–22.
62. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989–5995.

Biographical sketch



Phil Fuchs was born (1945) and raised near Milwaukee, WI. During his high school career, he participated in the building of a small research laboratory including all the physical, plumbing, and electrical facilities. He and his partner, Richard Pariza, initiated their organic training by repeating various literature and organic synthesis preparations. A number of these products were sold to Aldrich as well as being advertised on the back cover of JACS and marketed commercially under the Willow Brook Laboratory trademark. Fuchs then attended the University of Wisconsin, Madison, obtaining a BS in 1968 after doing undergraduate research with H. W. Whitlock and subsequently received the first PhD awarded from the laboratory of Edwin Vedejs (1971). Two years of postdoctoral study with E. J. Corey at Harvard led to his being accepted as an Assistant Professor at Purdue University in 1973. He was awarded Eli Lilly and Sloan fellowships early in his career and was promoted to full professor in 1982. He served as consultant for both Pfizer and Lilly, and has been selected four times by the undergraduate students as one of the 'top ten teachers' in the School of Science at Purdue. This far, he has graduated 47 PhD students and has published around 200 papers in the area of synthetic methods and total synthesis.