Chem. Soc. Rev., 1988, **17**, 111—133

ROBERT ROBINSON LECTURE*

Retrosynthetic Thinking—Essentials and Examples

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1 Introduction

The ability of chemists to synthesize organic compounds has evolved through a number of discernible stages over the past 160 years in a progression which is marked historically by ascendance to a new and qualitatively higher level of sophistication at intervals of roughly 20 years. One clear sign of this advance is the achievement in a particular period of syntheses which are conceptually more complex and technically well beyond those realized in the preceding stage.[1]

The vigorous development of organic synthesis over the past decades is due in no small part to the earlier contributions of Sir Robert Robinson, a pioneer in 20th century synthesis. His insights into the relation between chemical structure, reactivity, and reaction pathways and his application of mechanistic thinking to synthesis spearheaded the advance during his active period (1910—1950) and helped set the course of modern synthesis.[2] Also of great importance was his introduction of elegant new synthetic processes and reaction sequences, for example the famous Robinson annulation, which provided an early model and inspired subsequent generations of chemists toward the rational discovery of useful new synthetic methods. A. J. Birch wrote of Robinson, 'His great assets in the general area of synthesis were his "feel" for mechanism and his prodigious memory for published work.'[3] Robinson's genius surely also included a penetrating intellect and the ability to associate previously disparate facts in a highly original but logical way.

Robert Robinson was giant in the field of chemistry. It is a great honour and privilege to present this article in his memory.

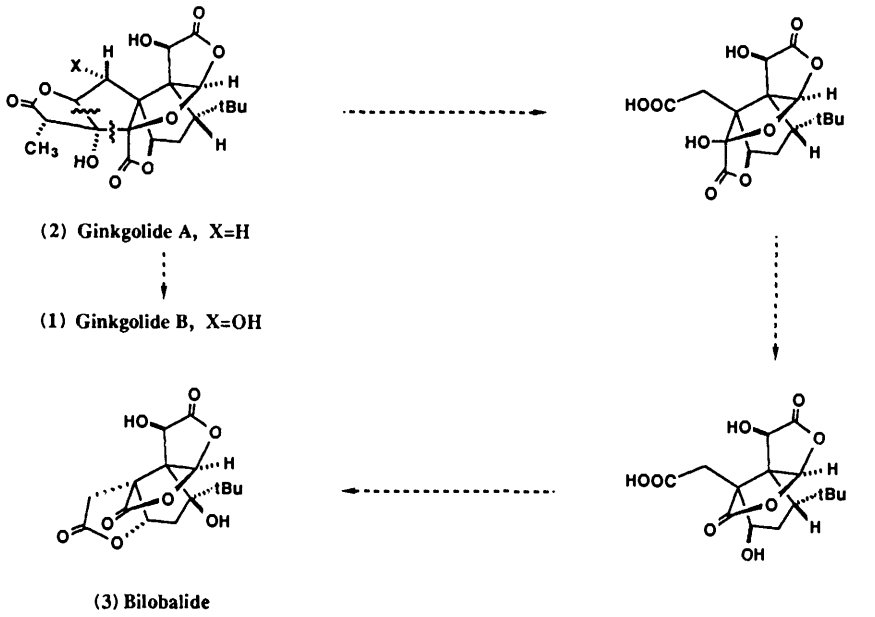
This paper outlines the fundamentals of retrosynthetic thinking and illustrates the application of the method to the synthesis of three interesting organic compounds, (1)—(3), which occur in the ginkgo tree, *Ginkgo biloba*. The C_{20}

* Presented at the Annual Chemical Congress of the Royal Society of Chemistry, University of Kent at Canterbury, on 12 April 1988.

[1] One indicator of the ever-increasing sophistication of organic synthesis is the survey of I. Fleming, 'Selected Organic Syntheses', Wiley-Interscience, 1973.

[2] A. R. Todd and J. W. Cornforth, 'Robert Robinson', *Biograph. Mem. Fellows R. Soc.*, 1976, **22**, 415.

[3] A. J. Birch, 'Sir Robert Robinson: A Contemporary Historical Assessment and a Personal Memoir', *J. Proc. R. Soc. N. S. Wales*, 1976, **109**, 151.



Scheme 1 *Structural relationship between ginkgolide A and bilobalide*

ginkgolide, ginkgolide B (1),[4] is a powerful antagonist of platelet activating factor and of great interest as a therapeutic agent.[5] The C_{15} ginkgolide, bilobalide (3),[6] is structurally related to ginkgolides A[4] and B and may derive from the common precursor ginkgolide A (2) (Scheme 1). Ginkgolide A displays strong insect antifeedant activity. The synthesis of the ginkgolides represents a formidable challenge to the synthetic chemist, unmet for more than two decades.

2 Essentials of Retrosynthetic Analysis

Retrosynthetic (or 'antithetic') analysis is a problem-solving technique for transforming the structure of a 'synthetic target' (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a 'transform', the exact reverse of a synthetic 'reaction', to a target structure. Each structure derived antithetically from a TGT then itself becomes a TGT for further

[4] (*a*) N. Sakabe, S. Takada, and K. Okabe, *J. Chem. Soc., Chem. Commun.*, 1967, 259; (*b*) K. Okabe, S. Yamada, S. Yamamura, and S. Takada, *J. Chem. Soc. C.*, 1967, 2201; (*c*) K. Nakanishi, *Pure Appl. Chem.*, 1967, **14**, 89.

[5] (*a*) P. Braquet, *Drugs of the Future*, 1987, **12**, 643; (*b*) P. Braquet and J. J. Godfroid, *Trends Pharmacol. Sci.*, 1986, 7, 397; (*c*) P. J. Barnes and K. F. Chung, *ibid.*, 1987, **8**, 285; (*d*) B. Max, *ibid.*, 1987, **8**, 290.

[6] K. Nakanishi, K. Habaguchi, Y. Nakadaira, M. C. Woods, M. Maruyama, R. T. Major, M. Allauddin, A. R. Patel, K. Weinges, and W. Bähr, *J. Am. Chem. Soc.*, 1971, **93**, 3544.

analysis. In order for a transform to operate on a target structure to generate a synthetic predecessor the requisite structural subunit or 'retron'[7] for that transform must be present in the target. The 'retron' for Diels–Alder reaction, for instance, is a six-membered ring containing a π-bond and it is this structural subunit which represents the minimal 'keying' element for transform function.

The logical and systematic application of retrosynthetic analysis depends on the use of higher level strategies to guide the selection of transforms. The *general* strategies which are available for devising retrosynthetic pathways fall into several classes including the following.[7,8]

1. Transform-based strategies—for example long range search or look-ahead to apply a powerfully simplifying transform (or a tactical combination of simplifying transforms) to a TGT with certain appropriate keying features.[9] Usually the retron required for application of a powerful transform is not present in a complex TGT and a number of antithetic steps (subgoals) are needed to establish it.
2. Structure-goal strategies—for example directed at the structure of a potential intermediate or potential starting material. Such a goal (S-goal) greatly narrows a retrosynthetic search and allows the application of bidirectional search techniques.[7,10,11] This is the oldest and most traditional of all synthetic strategies, and long the dominant strategy. The modification of a limited substructural region of a molecule, for example to accommodate the retron for some powerfully simplifying transform, leads to a substructure goal (SS-goal) which can provide the same kind of guidance as an S-goal.
3. Topological strategies—for example the identification of one or more individual bond disconnections or correlated bond-pair disconnections as strategic.[12] Topological strategies may also lead to the recognition of a key substructure for disassembly or to the use of rearrangment transforms.
4. Stereochemical strategies—general strategies which remove stereocentres and stereorelationships under stereocontrol.[7] Such stereocontrol can arise from transform-mechanism control or substrate control. In the case of the former the retron for a particular transform contains critical stereochemical information (absolute or relative) on one or more stereocentres. Stereochemical strategies may also dictate the retention of certain stereocentre(s) during retrosynthetic processing or the joining of atoms in three-dimensional proximity.

[7] E. J. Corey, A. K. Long, and S. D. Rubenstein, *Science*, 1985, **228**, 408.

[8] These strategies have been described previously in connection with the computer-assisted analysis of synthetic problems and the interactive program, LHASA, which is designed to emulate the problem solving techniques used by chemists. In turn, the LHASA project has been of great value in the development of new and general ways of thinking about synthesis.

[9] (*a*) E. J. Corey, W. J. Howe, and D. A. Pensak, *J. Am. Chem. Soc.*, 1974, **96**, 7724; (*b*) E. J. Corey, A. P. Johnson, and A. K. Long, *J. Org. Chem.*, 1980, **45**, 2051; (*c*) E. J. Corey, A. K. Long, J. Mulzer, H. W. Orf, A. P. Johnson, and A. P. Hewett, *J. Chem. Inf. Comp. Sci.*, 1980, **20**, 221.

[10] E. J. Corey, *Quart. Rev. Chem. Soc.*, 1971, **25**, 455.

[11] S. Hanessian, 'Total Synthesis of Natural Products: The Chiron Approach', Pergamon Press, Oxford, 1983.

[12] E. J. Corey, W. J. Howe, H. W. Orf, D. A. Pensak, and G. Petersson, *J. Am. Chem. Soc.*, 1975, **97**, 6116.

5. Functional group based strategies.[13] The retrosynthetic reduction of molecular complexity involving functional groups (FGs) as keying structural subunits encompasses many important general problem-solving tactics. Single FGs or pairs of FGs (and the interconnecting atom path) can (as retrons) key directly the disconnection of a TGT skeleton to form simpler molecules. In addition FGs can signal the application of transforms which replace functional groups by hydrogen (FG removal in the retrosynthetic direction, clearly a simplifying process) or change the reactivity of FGs (corresponding to FG protection, activation, or interchange in the synthetic direction). Functional group interchange (FGI) is a commonly used tactic for generating from a TGT retrons which allow the application of simplifying transforms.[13] FGs frequently key transforms which stereoselectively remove stereocentres or break topologically strategic bonds so that in effect they play a role in the other types of retrosynthetic strategies. Functional groups also may key the stereochemically dictated joining of proximate atoms to form rings in the retrosynthetic direction.[14]
6. 'Other' types of strategies. The recognition of substructural units within a TGT which represent major obstacles to synthesis often provides major strategic input. Certain other strategies result from the requirements of a particular problem, for example economic requirements or a requirement that several related target structures be synthesized from a common intermediate. A TGT which resists retrosynthetic simplification may require that new chemical methodology be developed for a synthesis and thus suggest a line of research leading to the invention of new chemical processes. The recognition of obstacles to synthesis provides a stimulus for the discovery of such novel processes. One important human problem-solving strategy is the application of 'imagination' or 'intelligent use of a chain of hypotheses' to guide the search for an effective line of retrosynthetic analysis. This inductive problem-solving dimension has been described in somewhat different terms previously.[15,16]

'The synthetic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of synthesis, but they are very real and extremely important. Further, it must be emphasized that intellectual processes such as the recognition and use of *retrons and* synthons require considerable ability and knowledge; here, too, genius and originality find ample opportunity for expression.

The proposition can be advanced that many of the most distinguished synthetic studies have entailed a balance between two different research philo-

[13] E. J. Corey, R. D. Cramer III, and W. J. Howe, *J. Am. Chem. Soc.*, 1972, **94**, 440.
[14] E. J. Corey and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1976, **98**, 203.
[15] E. J. Corey, *Pure Appl. Chem.*, 1967, **14**, 30. The italicized words have been added to this quotation to clarify the original meaning since the word 'synthon' has now come to be used to mean synthetic 'building block' rather than retrosynthetic fragmentation structures.
[16] For an entirely different discussion of 'strategy in synthesis' see P. Deslongchamps, *Aldrichchimica Acta*, 1984, 17, 59.

> sophies, one embodying the ideal of a deductive analysis based on known methodology and current theory, and the other emphasizing innovation and even speculation. The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations whenever it presents a clear challenge to the creativity, originality, and imagination of the expert in synthesis.'[15]

Certain strategies not mentioned above relate to the question of optimization of a synthetic design *after* a set of pathways has been generated antithetically. Such strategies are used to determine the optimum ordering of synthetic steps, the use of protection or activation steps (or the avoidance of same),[17] or the determination of alternate or bypass paths for problematic segments of the ex-TGT tree of intermediates.

Systematic and rigorous retrosynthetic analysis is the *broad principle* of synthetic problem solving under which the various types of strategies which are delineated above take their place. Another overarching strategy of great importance is the use *concurrently* of as many independent strategies as possible to guide the search for retrosynthetic pathways.[7] *In general the greater the number of strategies which are used in parallel to develop a line of analysis, the easier the analysis and the simpler the emerging synthetic plan is likely to be.*

During the past 20 years retrosynthetic thinking has permeated all areas of organic synthesis and, together with new methods and processes for molecular construction, has significantly enhanced the field. It is no longer possible to teach the subject of organic synthesis effectively without the extensive use of retrosynthetic concepts and thinking, as expressed previously.[7]

> 'These achievements (syntheses of the 1945—1960 period) provided the impetus for further developments, which led to a great improvement in the power and elegance of synthetic planning. In the 1960s, general problem-solving strategies and methods that could be applied to the analysis of any complex synthetic problem were explicitly formulated, and the underlying principles of synthesis were defined in a way that made synthetic planning more logical, more systematic, and easier. The insights so gained had an impact on the teaching of organic synthesis as well as its practice. Even in the 1950s, synthesis was taught by the presentation of a series of illustrative (and generally unrelated) examples of actual syntheses. Chemists who learned synthesis in this inductive manner approached each problem in an *ad hoc* way. The intuitive search for clues to the solution of the problem at hand was not guided by effective and consciously applied general problem-solving techniques.'[7]

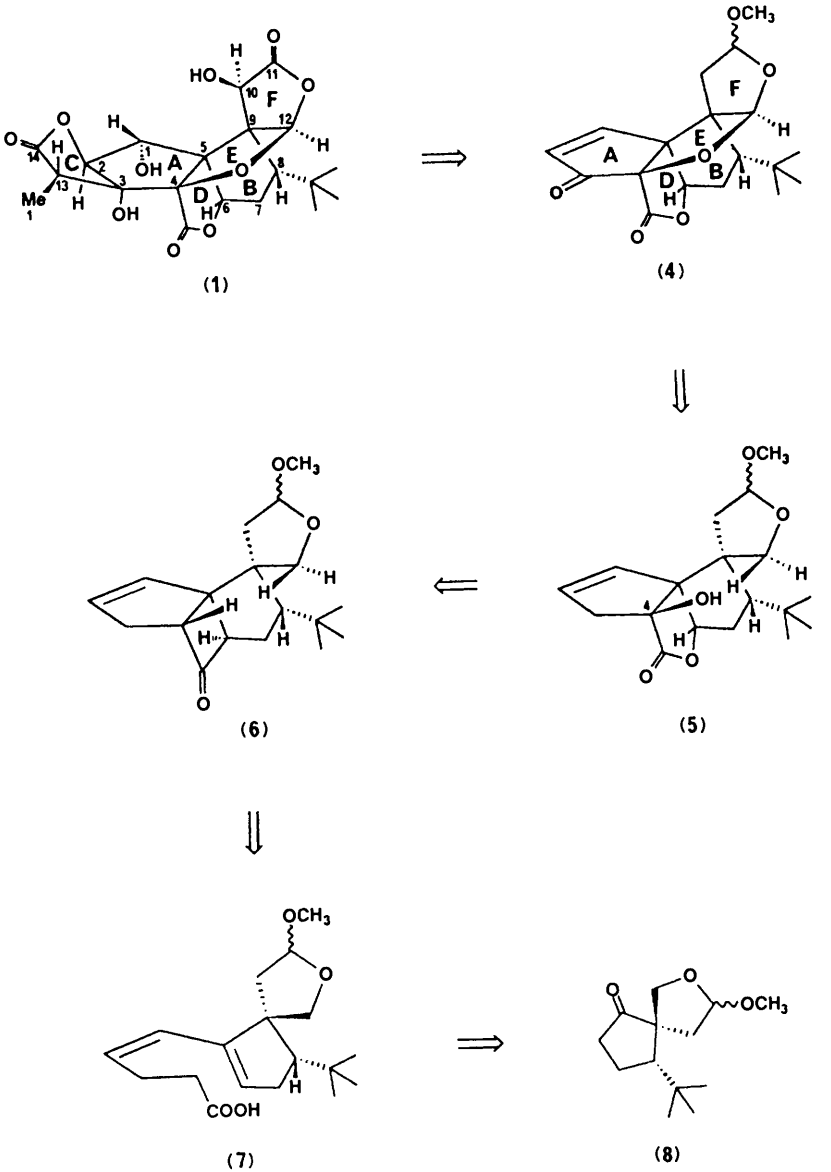
[17] (*a*) E. J. Corey, H. W. Orf, and D. A. Pensak, *J. Am. Chem. Soc.*, 1976, **98**, 210; (*b*) E. J. Corey, A. K. Long, T. W. Greene, and J. W. Miller, *J. Org. Chem.*, 1985, **50**, 1920.

3 Retrosynthetic Analysis Exemplified

A. Synthesis of Ginkgolides A and B.—The basic ideas of retrosynthetic analysis become much more tangible when illustrated by specific applications. The problem of synthesis of complex *polycyclic* molecules such as the ginkgolides provides an especially useful testing ground since these molecules combine functional, topological, and stereochemical complexity at high density. Also, it is not obvious from inspection of the structures of the ginkgolides which starting materials (achiral or chiral) are appropriate for molecular construction. The concurrent use of several different types of retrosynthetic strategies is essential because antithetic processing of these TGTs in an opportunistic way would lead to an enormous number and variety of synthetic possibilities, most being of dubious value.

Retrosynthetic analysis of the ginkgolide B structure (1) was carried out by the concurrent use of several different strategies to guide the antithetic search. One particular retrosynthetic path toward which there was strong strategic convergence is outlined in abbreviated form in Scheme 2. For brevity several retrosynthetic steps (transforms) are combined in each of the retrosynthetic changes shown. This line of analysis was selected for experimental study and the validity of the general plan was demonstrated by successful execution of the synthesis. Nonetheless, it is important to make clear at this point that several of the individual steps and countless procedural details of the synthesis had to be developed by experimentation.

1. From the category of transform-based strategies a number of useful guides emerged. For example, the hydroxy lactonization transform and the aldol transform can be applied directly (in that order) to the A/C ring portion of (1) with consequent reduction in the number of stereocentres (by four), rings (by one), skeletal carbons (by three), functionality, and chemical reactivity level. The application of two simplifying transforms in *tactical combination* is directly signalled because the retron for the first is present in the TGT and transform application produces the retron for the next transform to operate. The molecular simplification which results is considerable.
2. The above notwithstanding, in a practical sense it is necessary to remove the possible interference of the α-hydroxy carbonyl FG pair of the F ring in (1) before the simplifying Tfs cited above can be applied. Thus, from the category of FG-based strategies a less reactive precursor or 'equivalent' of the α-hydroxy carbonyl FG pair must first be generated. It is not uncommon that such retrosynthetic changes in FG reactivity must be made before application of the 'goal' transform for simplification even though the retron for the latter may be present in the TGT. This situation also exemplifies the enforced concurrent use of transform-based and FG-based strategies. Retrons for the direct removal of ring F are absent.
3. Another reason for removing ring C at the earliest retrosynthetic stage is the identification of ring B for preservation (origin ring) during retrosynthetic disconnection, based on its carbocyclic nature and its substitution by a large substituent at a stereocentre which is a strong candidate as an *ab initio*



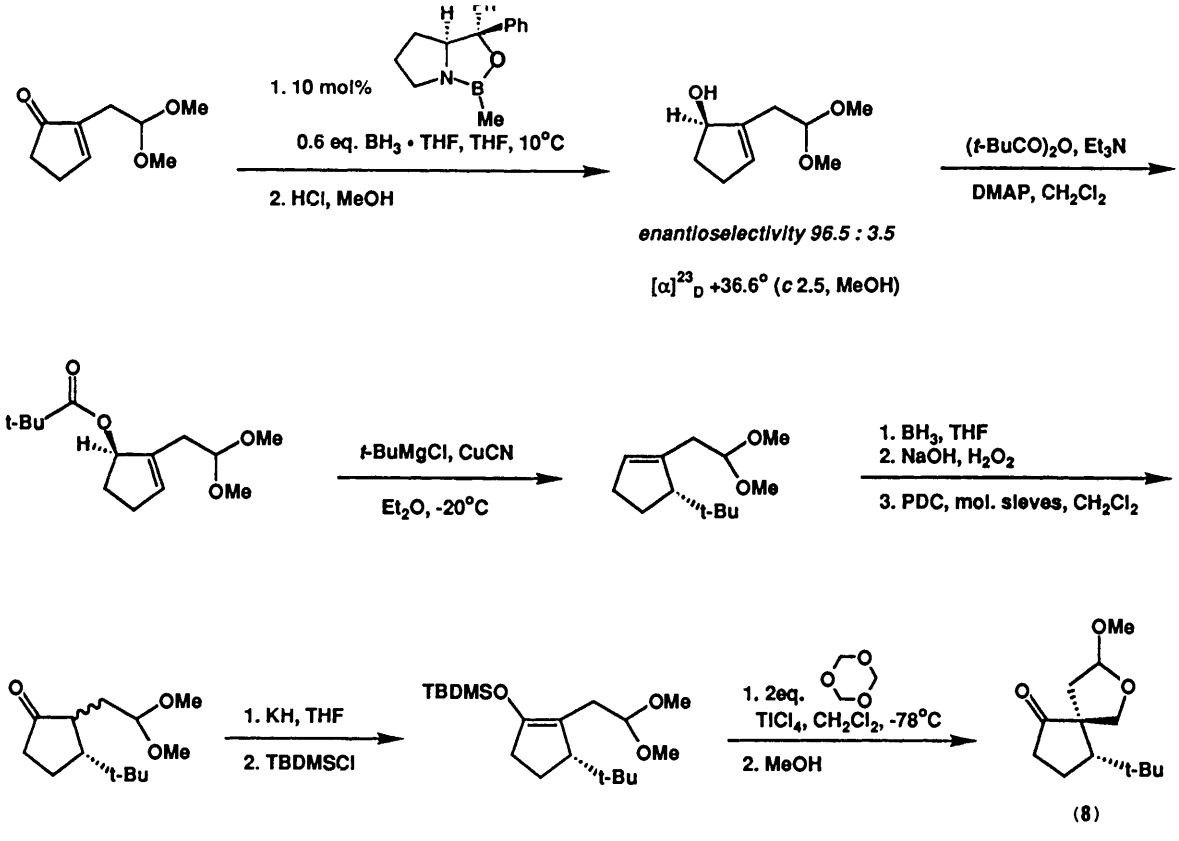
Scheme 2

controller of stereochemical elaboration. The t-butyl-bearing stereocentre at C(8) can potentially direct the development of the adjacent C(9) and then the C(5) and C(6) stereocentres on the B ring. This stereochemical strategy converges with purely topological and FG-based (reactivity) strategies which also argue for the origin status of ring B in (1).

4. After the generation of precursor (4) from (1) it is quite clear that ring B is the best candidate as origin ring in this structure as well as in (1). The A ring in (4) lacks any qualification as a possible origin ring.
5. The C–O bonds within ring E of (4) are strategic for disconnection. They are in the maximally fused ring [12] of (4) (fused to rings A, B, D, and F) and also *exo* to three rings. They are termed *exendo* or more specifically *hetexendo* bonds (since a C-heteroatom bond is involved [12]). Transforms exist for sequentially disconnecting one or both of these *hetexendo* bonds. However, because of possible functional group reactivity interference with the valid use of these transforms, it is advisable to remove retrosynthetically the keto function on ring A of (4) prior to cleavage of ring E. Retrosynthetic precursors such as (5) or the 4-deoxy analogue result.
6. Precursor 4-deoxy-(5) is also suggested by the application to (4) or (1) of key transform-based strategies which are aimed at ring disconnections. Among the key ring-transforms whose retrons map partially on to structures (1) and (4) are some which are capable of simultaneous disconnection of a pair of *exendo* bonds vicinal to the primary ring. These transforms correspond to internal cycloaddition transforms. One such specific transform is the ketene–olefin internal cycloaddition transform [18] in tactical combination with the Baeyer–Villiger transform. Another is the recently developed [19] internal carbolactonization (Mn^{III}-mediated) transform. Antithetic multistep search to apply these transforms to either (1) or (4) leads (with disconnection rings C and E or ring E, respectively) to precursor (7).
7. Strategic bond and FG-keyed strategies suggest disconnection of (7) to form precursor (8).

The steps for the synthesis of (8) and for its conversion into ginkgolide B (1) will now be considered. The initial synthetic studies which led to the synthesis of (±)-(1) have recently been described [20] as has a modification which leads enantioselectively to the naturally occurring and chiral form of (1).[21] Only the latter route will be outlined here. Scheme 3 records the enantioselective synthesis of spiro-ketone (8) from 2-(2,2-dimethoxyethyl)cyclopenten-1-one. A key step in this transformation was the highly selective borane reduction of the starting cyclopentenone catalysed by the chiral oxazaborolidine derived from (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine and methylboronic acid.[21] For this and numerous other cases, this process is outstanding because of the high enantioselectivity which can be achieved

[18] E. J. Corey, M. C. Desai, and T. A. Engler, *J. Am. Chem. Soc.*, 1985, **107**, 4339.
[19] E. J. Corey and M.-c. Kang, *J. Am. Chem. Soc.*, 1984, **106**, 5384.
[20] E. J. Corey, M.-c. Kang, M. C. Desai, A. K. Ghosh, and I. N. Houpis, *J. Am. Chem. Soc.*, 1988, **110**, 649.
[21] E. J. Corey and A. V. Gavai, *Tetrahedron Lett.*, 1988, **29**, 3201.


1. 10 mol%
0.6 eq. BH3 • THF, THF, 10°C
2. HCl, MeOH
enantioselectivity 96.5 : 3.5
[α]23D +36.6° (c 2.5, MeOH)
(t-BuCO)2O, Et3N
DMAP, CH2Cl2
t-BuMgCl, CuCN
Et2O, -20°C
1. BH3, THF
2. NaOH, H2O2
3. PDC, mol. sieves, CH2Cl2
1. KH, THF
2. TBDMSCl
1. 2eq.
TiCl4, CH2Cl2, -78°C
2. MeOH
(8)

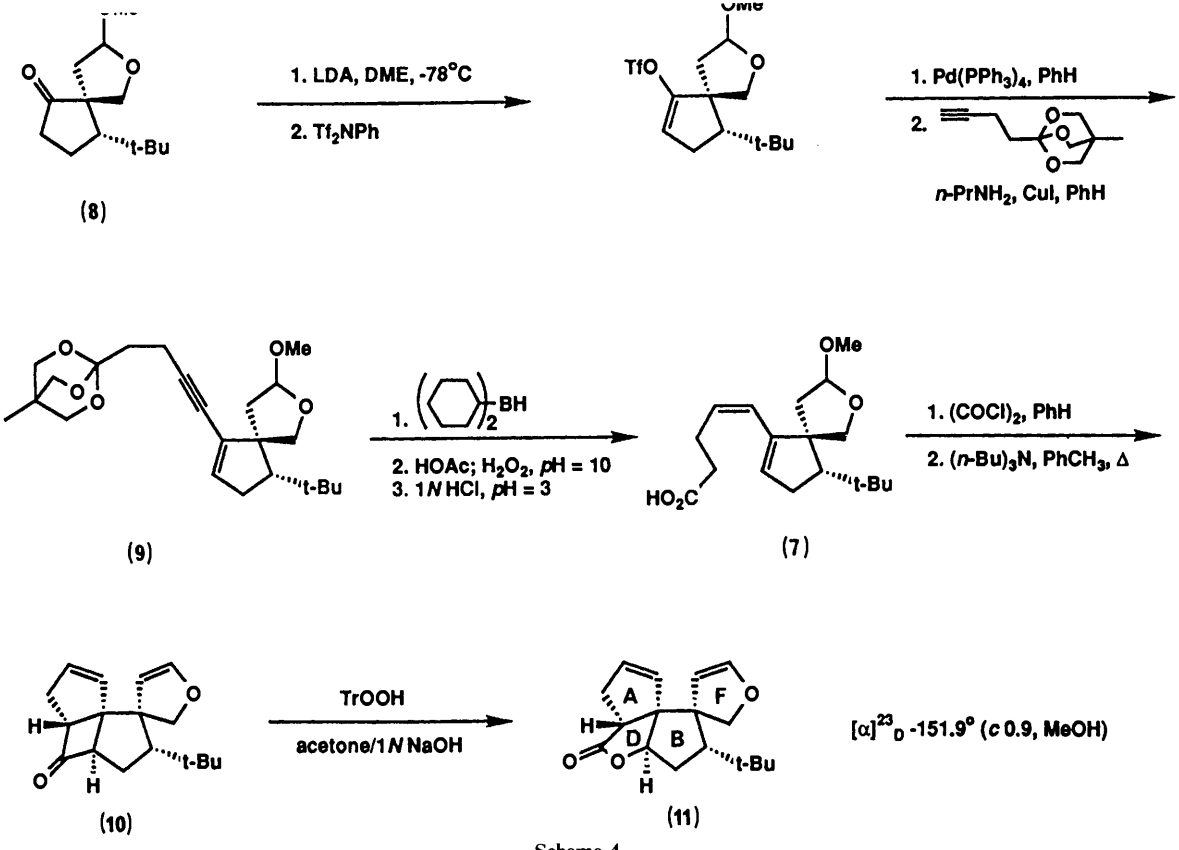
Scheme 3

and the predictability of the absolute configuration of the product.[22–24] This methodology for enzyme-like, catalytic enantioselective reduction provides an excellent route to chiral allylic alcohols, which as a class are enormously useful as starting materials for the construction of complex chiral organic molecules.[25] The all-important introduction of the t-butyl group at the primary synthetic stereocentre was achieved by stereoselective *anti* S_N2' displacement[26] with t-butylmagnesium chloride and 2—3 mole % of cuprous cyanide as reagent. The effectiveness of the origin stereocentre and its t-butyl substituent as a controller for the stereoselective generation of new stereocentres was demonstrated by the remainder of the sequence shown in Scheme 3 which led specifically to the required diastereomeric spiro-ketone (8).

Scheme 4 summarizes the reaction sequence used for the attachment of two rings (A and D) to the ketone (8). The enol triflate of (8) underwent efficient palladium(0)-catalysed cross coupling[27] with the ortho-ester of 2-pentynoic acid to form (9) which was reduced and deprotected to give diene-acid (7), one of the key retrosynthetic structures shown in Scheme 2. Conversion of (7) into the corresponding acid chloride and slow addition of the latter to a solution of tertiary amine in toluene at reflux resulted in ketene formation and subsequent internal addition[27] to form stereospecifically tetracyclic ketone (10). Elimination of methanol from the 1-methoxy-tetrahydrofuran subunit also occurred under the reaction conditions, evidently promoted to the trialkylammonium chloride present in the reaction mixture. *Selective* Baeyer–Villiger ring expansion could be accomplished using alkaline trityl hydroperoxide (but not HOO^- or Bu^tOO^-)[20] as reagent to produce tetracyclic lactone (11) in 82% yield and 100% enantiomeric purity after recrystallization.[21]

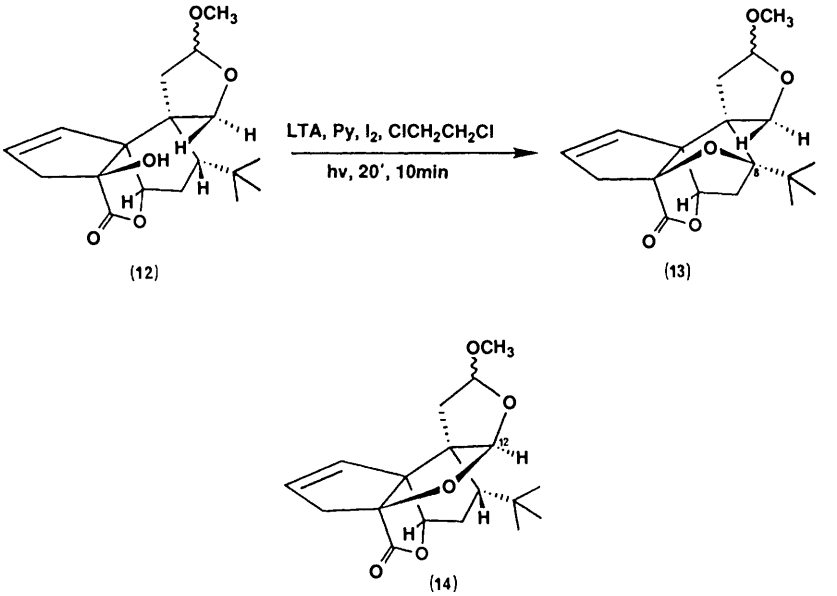
Lactone (11) was readily α-oxygenated by the Davis method[28] and combined with methanol under acid catalysis to form α-hydroxy-lactone (12), a potential substrate for the generation of the E ring (Scheme 5). Reaction of (12) with lead tetraacetate and iodine proceeded rapidly and cleanly to afford not the desired pentacycle (14), but the isomeric ring-closure product (13) as shown in Scheme 5.[20] Although the formation of (13) was not useful as a synthetic step, it did provide confirmation of the stereochemistry of the intermediates (10) and (11). The introduction of the two C–O linkages required for intermediate (4) was accomplished successfully as indicated in Schemes 6 and 7. The need for multistep sequences to achieve the conversion (11) → (4) is an indication of a considerable gap which still exists in the methodology for the selective oxygenation of organic compounds.

[22] E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551.
[23] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.
[24] E. J. Corey, S. Shibata, and R. K. Bakshi, *J. Org. Chem.*, 1988, **53**, 2861.
[25] For example, total synthesis of forskolin; see E. J. Corey, P. D. S. Jardine, and J. C. Rohloff, *J. Am. Chem. Soc.*, 1988, **110**, 3672; *Tetrahedron Lett.*, 1988, in press.
[26] See, E. J. Corey and N. Boaz, *Tetrahedron Lett.*, 1984, **25**, 3063 and refs. cited therein.
[27] See, E. J. Corey, M. C. Desai, and T. Engler, *J. Am. Chem. Soc.*, 1985, **107**, 4339.
[28] (*a*) F. A. Davis and O. D. Stringer, *J. Org. Chem.*, 1982, **47**, 1774; (*b*) F. A. Davis, L. C. Vishwakarma, J. M. Billmers, and J. Finn, *J. Org. Chem.*, 1984, **49**, 3241.

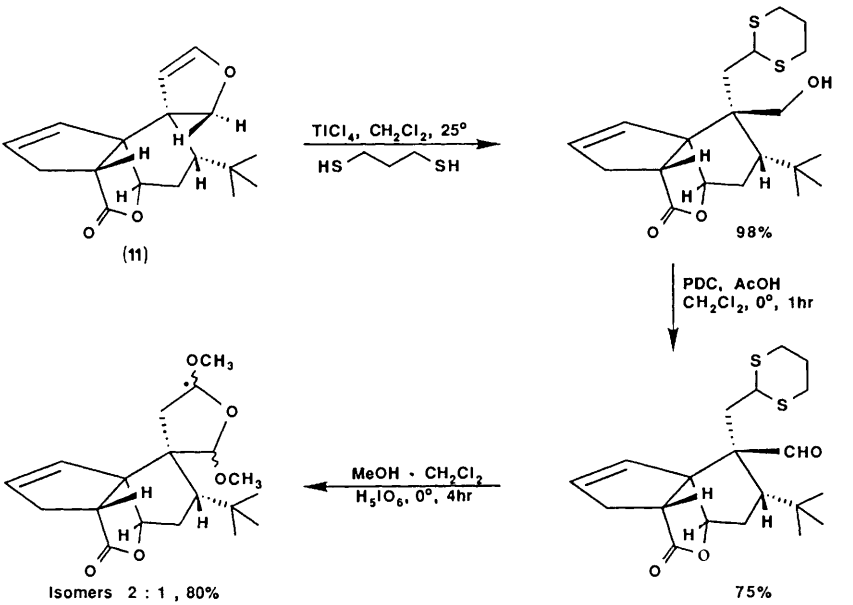


(8) (9) (7) (10) (11)

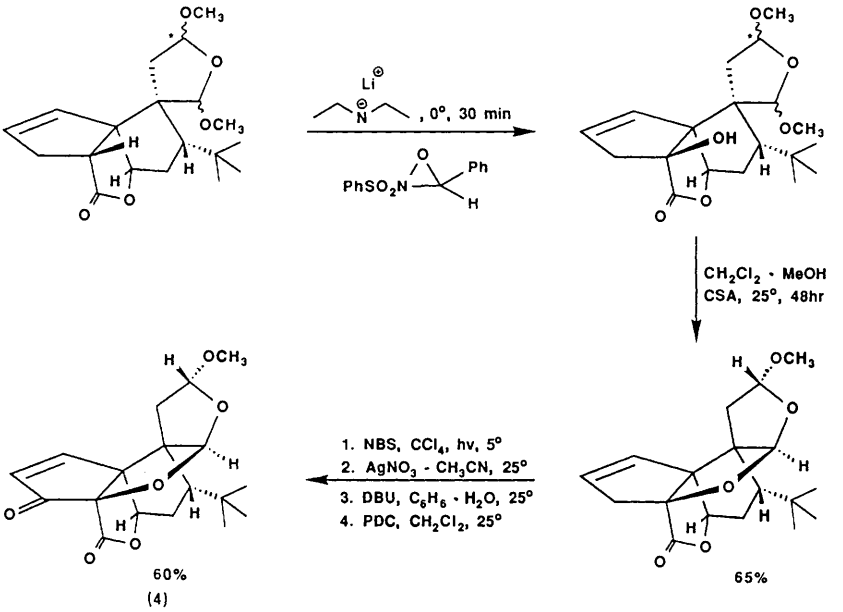
Scheme 4



Scheme 5



Scheme 6

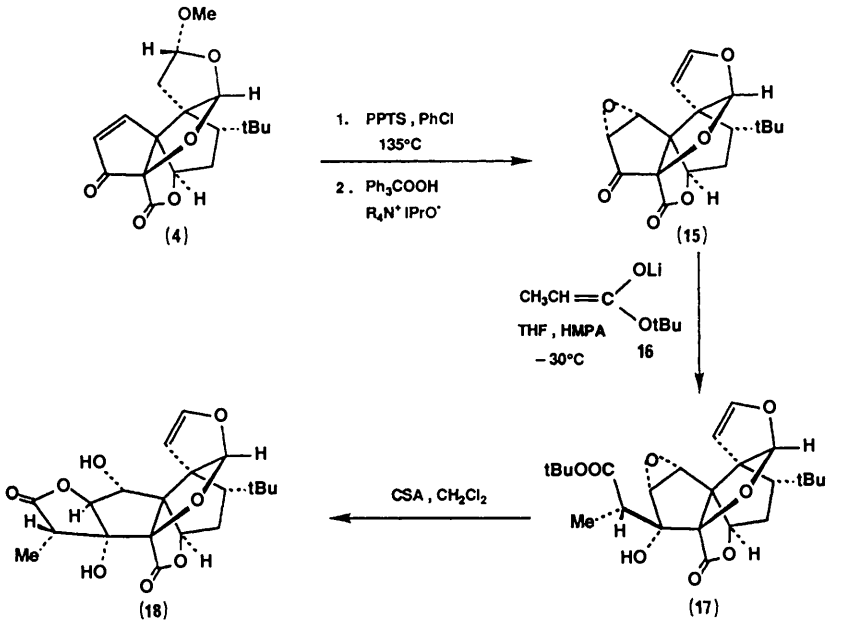


Scheme 7

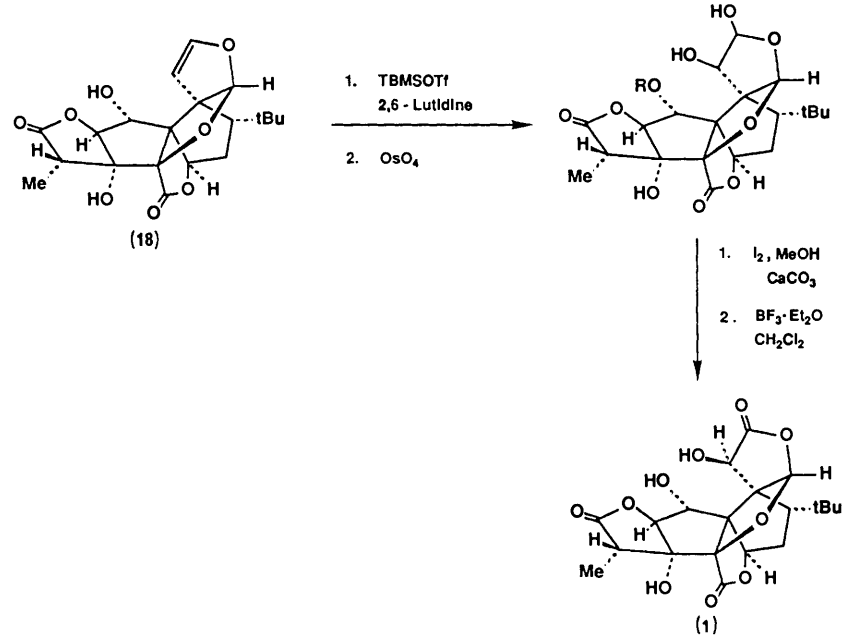
The completion of the synthesis of ginkgolide B is shown in Schemes 8 and 9. A very critical (and in fact experimentally difficult) part of the synthesis was the attachment of ring C. As is often the case a straightforward retrosynthetic change (1) ⇒ (4) corresponded to a highly challenging segment of the laboratory synthesis. Of the many conceivable processes for the attachment of ring C only one could be demonstrated experimentally, and then only under carefully defined conditions. Elimination of methanol and alkaline epoxidation of (4) afforded epoxy-ketone (15) stereospecifically. Reaction of (15) with lithiated t-butyl propionate (16) in tetrahydrofuran–hexamethylphosphoric triamide (HMPA) produced (17) stereoselectively. The use of HMPA, the presence of a 1,2-epoxy function, the trigonal centres at C(10) and C(11), and the reaction temperature of −30 °C *are all crucial* to the success of this aldol process. Reaction of enone (4) with the lithium enolate of t-butyl propionate at −78 °C leads *selectively to the opposite mode of attack at C(3)* (bottom face, *trans* to ring E). Camphor 10-sulphonic acid catalysed the lactonization of (17) to give (18) which was converted into ginkgolide B in four steps as outlined in Scheme 9.[20]

The hexacyclic lactone (18) was also transformed into ginkgolide A as indicated in Scheme 10.[29] Transformation of (18) to the imidazolethiocarbonyl derivative (19) and subsequent reaction with tri-n-butyltin hydride gave (20) which was

[29] E. J. Corey and A. K. Ghosh, *Tetrahedron Lett.*, 1988, **29**, 3205.



Scheme 8



Scheme 9

hydroxylated and oxidized to the α-hydroxy lactone (21). The 9-*epi* configuration was inverted by an oxidation–reduction sequence to produce ginkgolide A. It is noteworthy that the reactions of silylated (18) and (20) with osmium tetroxide show opposite stereoselectivities. Ginkgolide A was also synthesized from ginkgolide B using the analogous C(1) deoxygenation process.[29]

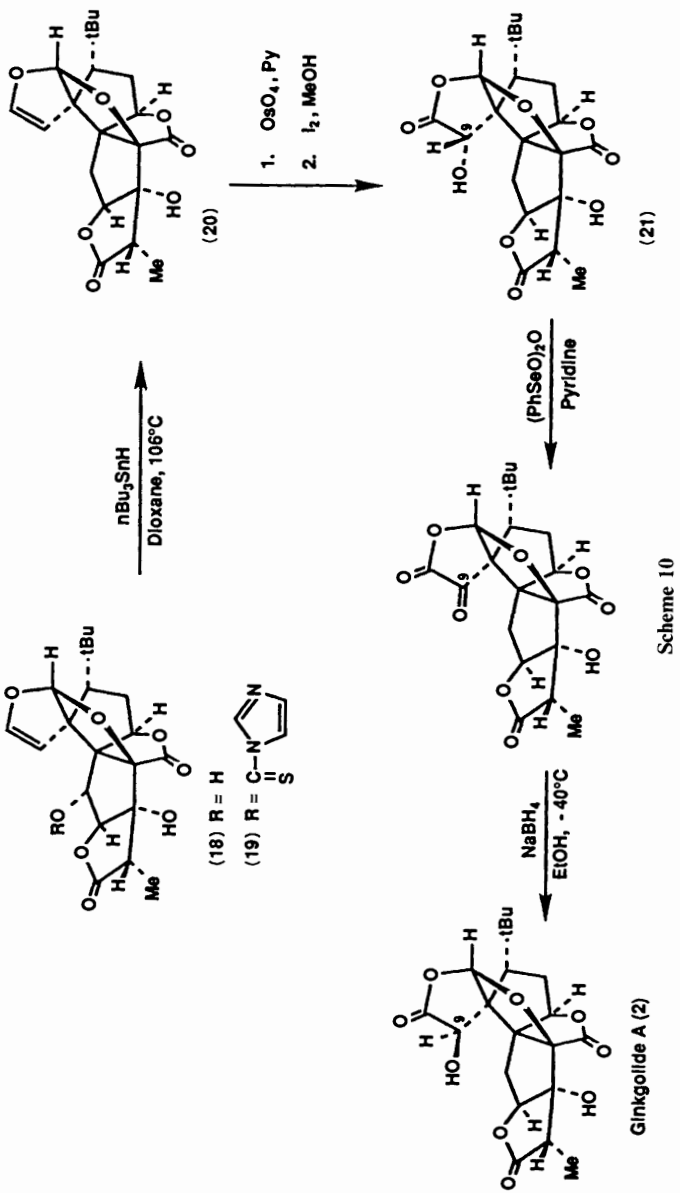
B. Synthesis of Bilobalide.—Although the structures of the C_{20} ginkgolides, A and B, and bilobalide (3) are clearly related to one another, retrosynthetic analysis of structure (3) produces completely different pathways for synthesis. The presence of only one carbocyclic ring in (3) and the types of carbon substituents on that ring drastically change the nature of the appropriate strategies (transform-based, topological, stereochemical, and FG-based). Another difference is the occurrence on the t-butyl-bearing ring carbon of (3) of a hydroxyl function which independently affects the stereochemical and FG-related strategies to be considered. The abbreviated retrosynthetic plan shown in Scheme 11 illustrates these points.

The synthetic introduction of a t-butylcarbinol subunit at C(1) by conventional chemical processes poses several non-trivial problems. For example, the reaction of t-butyllithium with sterically screened cyclopentanones or even cyclopentanone itself does not lead to efficient 1,2-carbonyl addition, but to other reaction modes stemming from α-deprotonation. Other t-butyl metalloids are either unreactive or similar in behaviour to t-butyllithium. The t-butylcarbinol grouping also is a likely source of interference with a number of possible synthetic constructions. Thus, the recognition of the obstacles to synthesis associated with the t-butylcarbinol subunit provides strategic guidance, since it suggests the use of specific approaches, for instance that the t-butyl group be introduced *before* the oxygen atom at C(1). The first retrosynthetic change shown in Scheme 11 (which actually corresponds to several individual transforms) includes a functional group interchange (FGI) step which replaces the hydroxyl at C(1) by a 1,2-double bond. In addition the α-hydroxy-lactone unit at C(6)/C(7) is replaced by a less reactive equivalent such that the D ring of (3) is modified to the 2-methoxytetrahydrofuran system.

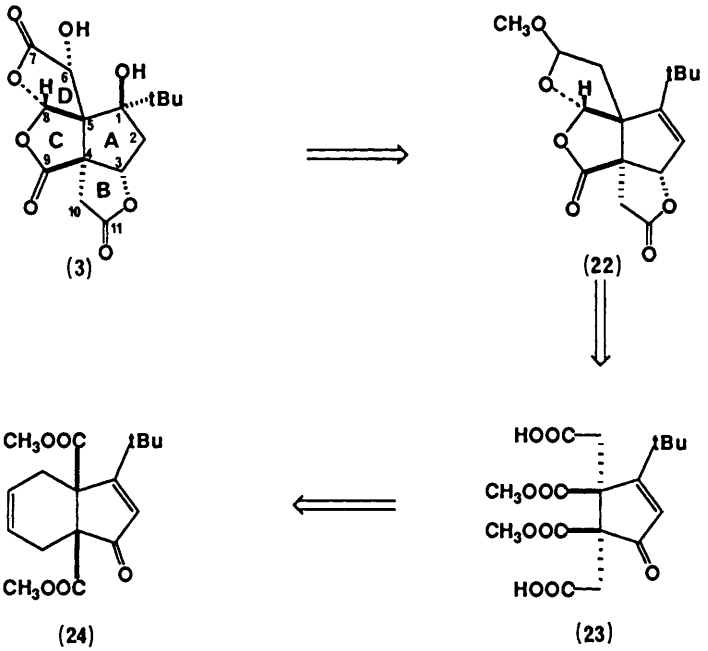
The deoxygenation at C(6) is also suggested by stereotopological and FG-based strategies. Topologically the presence of two functionalized two-carbon appendages on adjacent atoms [C(4) and C(5)] of ring A suggests the application of an appendage-connection strategy[14]—all the more because these appendages are *cis* to one another on ring A and can be made identical by retrosynthetic removal of the hydroxyl at C(6).

The two one-carbon appendages at C(4) and C(5) are also *cis* to one another and convertible into identical groups by redox FGI. Thus, the parallel application of these well-known strategies guides the retrosynthetic conversion of (3) successively into (22) and (23). Application of the connective FG-pair transform[14] C=C oxidative cleavage to (23) produces the bicyclic keto-diester (24).

Although intermediate (24) has the full retron for application of the Diels–Alder transform, one of the precursors generated from (24) by that transform is the super-reactive 2,3-dimethoxycarbonyl-4-t-butylcyclopentadienone. Although the synthesis of this substance might be possible, it would probably be highly reactive in


1. OsO4, Py
2. I2, MeOH
(20)
(21)
nBu3SnH
Dioxane, 106°C
(PhSeO)2O
Pyridine
NaBH4
EtOH, - 40°C
(18) R = H
(19) R = C(=S)N1C=CN=C1
Ginkgolide A (2)

Scheme 10



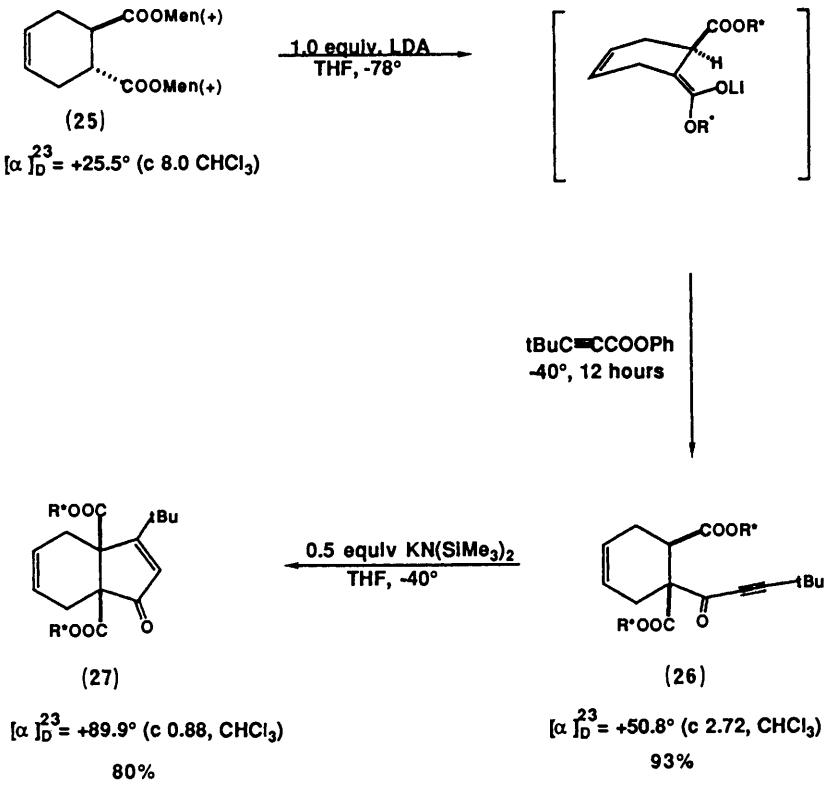
Scheme 11

Diels–Alder dimerization and, hence, did not seem to be an outstanding candidate for the synthesis of (24). Fortunately, another plan for the synthesis of (24) was developed which was more interesting conceptually and which also had the potential to produce (24) enantioselectively.

Another possible problem with the retrosynthetic plan shown in Scheme 11 is associated with the generation of intermediate (23) which, though possessing a symmetrical subunit for further processing and eventual disconnection, contains duplicate FGs which have to be differentiated in the course of the synthesis. While such FG redundancy potentially can invalidate a synthetic approach, in this instance it poses no real problem since the FG placement and reactivities of (23) allow a straightforward synthetic differentiation. The retrosynthetic analysis outlined in Scheme 11, in fact, provided the basis of a successful enantioselective synthesis of (3) which will now be described briefly.[30,31]

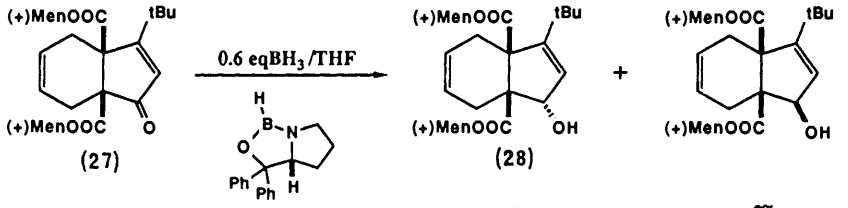
Reaction of the (+)-menthol diester of fumaric acid with butadiene and diisobutylaluminum chloride in 1:1 hexane–methylene chloride produced the (*R,R*)-Diels–Alder adduct[32] (obtained in 85% yield in pure form after chromatography)

[30] E. J. Corey and W.-g. Su, *J. Am. Chem. Soc.*, 1987, **109**, 7534 [synthesis of (±)-bilobalide].
[31] E. J. Corey and W.-g. Su, *Tetrahedron Lett.*, 1988, **29**, 3423 (enantioselective synthesis of the naturally occurring form of bilobalide).
[32] K. Furuta, K. Iwanaga, and H. Yamamoto, *Tetrahedron Lett.*, 1986, **27**, 4507.



Scheme 12

with a diastereoselectivity of 43:1 (Scheme 12, R* = menthyl). Mono-deprotonation of (25) and reaction with phenyl 3-t-butylpropiolate afforded the Claisen product (26) which underwent base-promoted cyclization to form (27), the dimenthyl ester corresponding to (24). The mechanism of this interesting cyclization has been discussed.[31] The conversion of (27) into (24) was unsuccessful and so (27) was utilized directly in the synthesis. Although reduction of the methyl ester ketone (24) with sodium borohydride produced the desired allylic alcohol (HO and $COOCH_3$ *trans*),[30] the corresponding reaction with the bismenthyl ester followed the opposite stereochemical course (Scheme 13).[31] Fortunately, borane reduction catalysed by the (*R*)-oxazaborolidine shown in Scheme 13 led to the desired allylic alcohol (28) (as predicted) with 23:1 diastereoselectively. The transformation of (27) into (28) is an interesting example of the enzyme-like power of chiral oxazaborolidines to overcome a strong intrinsic stereochemical bias of a substrate in carbonyl reduction. Despite considerable experimentation with a variety of



	45%	2%
$NaBH_4$/methanol	0%	85%
Na/iPrOH-Toluene	30%	25%

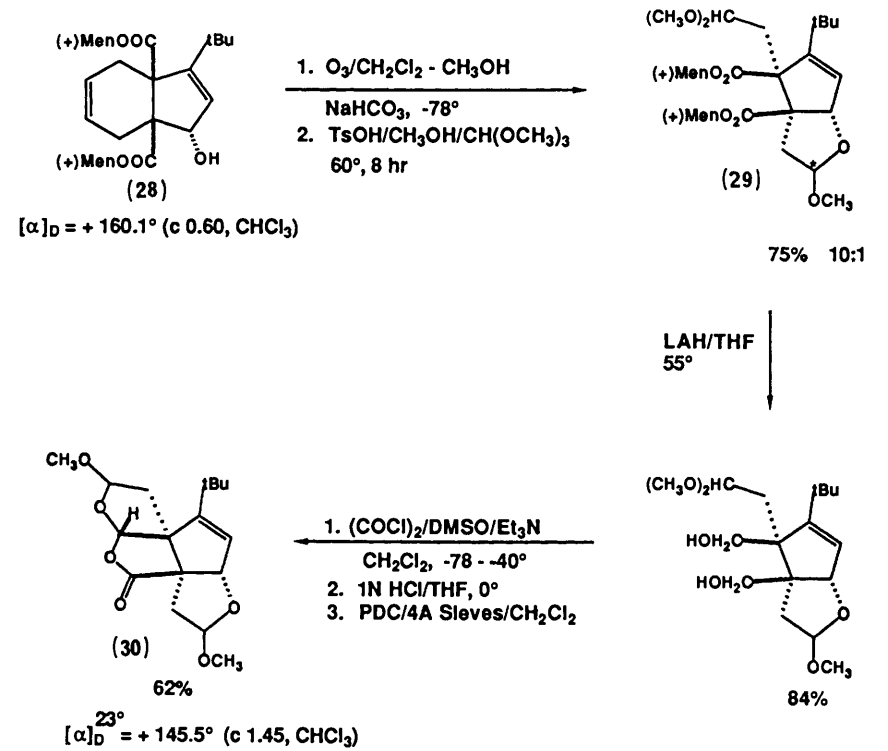
(no reduction with borane-THF, SmI_2, $Zn(BH_4)_2$)

Scheme 13

reducing agents, no other method for the stereoselective synthesis of (28) from (27) could be found.

The allylic hydroxyl function provided a key for distinguishing between like substituents on the five-membered ring. Ozonolysis of (28) followed by treatment with acid afforded the bicyclic diester (29) as shown in Scheme 14. Differentiation of the two ester functions and generation of the ring system of bilobalide was effected in four steps which gave (30) as indicated in this Scheme.

Exposure of (30) to potassium hydroxide resulted in an interesting cleavage of the 7-acetal function to form (31), clearly by a sequence involving γ-lactone hydrolysis and temporary cleavage of ring D to a dialdehyde–carboxylate intermediate (not shown) (Scheme 15). Reaction of (31) with methanesulphonyl chloride–triethylamine afforded an unusually stable (and isolable) 2-chlorotetrahydrofuran derivative which underwent base-promoted elimination to produce dihydrofuran (32). Treatment of (32) with peroxy-3,5-dinitrobenzoic acid unexpectedly proceeded more rapidly at the C(1)–C(2) double bond (t-butyl substituted) than at the 6,7-double bond (vinyl ether). Therefore, (32) was converted into the bis-epoxide (33) using an excess of peracid. The D ring epoxide unit in (33) was also unusually stable for a 2,3-epoxytetrahydrofuran, as evidenced by the fact that (33) could be chromatographed over silica gel at 23 °C. It would seem that the stabilities of the chloride of (31), the dihydrofuran unit in (32), and the 2,3-epoxytetrahydrofuran unit in (33) are all a consequence of the electron-withdrawing carboxylate substituent at C(8) which reduces strongly the electron



Scheme 14

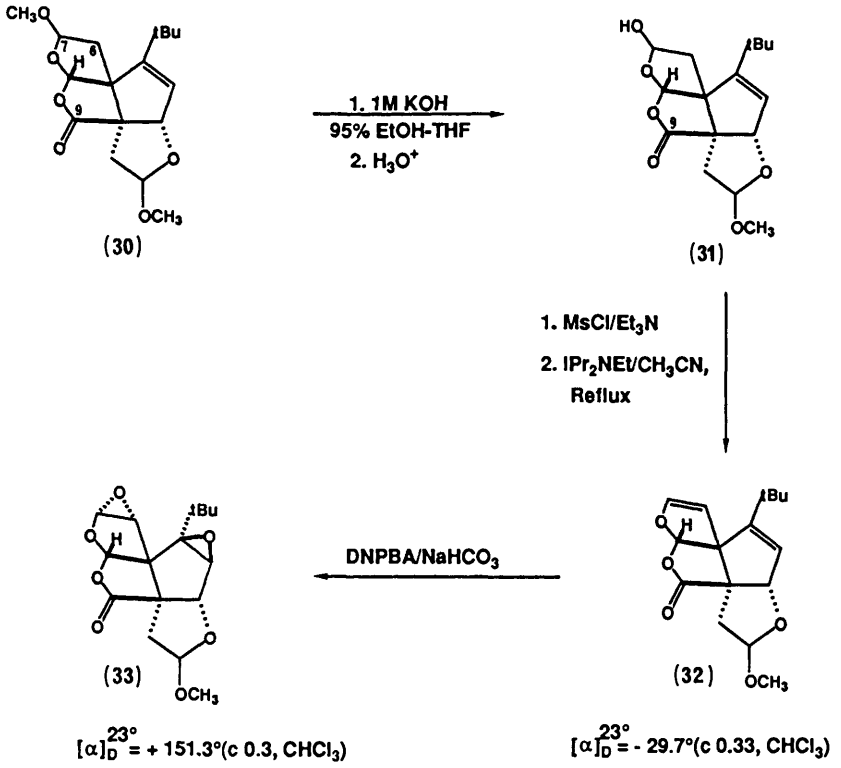
density about the second oxygen at C(8). Establishment of the ring B lactone function and the ring D α-oxylactone unit was next accomplished using the selective reactions outlined in Scheme 16 which converted bis-epoxide (33) into the mono-epoxide-trilactone (34).

The synthesis of bilobalide from (34) was completed by the steps shown in Scheme 17. Various attempts to cleave the 1,2-epoxide function in (34) with attachment of hydrogen at C(2) were unsuccessful. Consequently, (34) was deoxygenated to (35) in a novel way by heating with triethylsilane. Hydroxylation of the 1,2-double bond of (35) proceeded stereospecifically and the resulting diol was deoxygenated as shown [30,33] to give, after deacetylation, synthetic bilobalide.

4 Epilogue

This article has outlined some of the essential ideas behind the retrosynthetic approach to the planning of organic syntheses, and their application specifically to syntheses of (1), (2), and (3). For several reasons one hopes that the subject matter

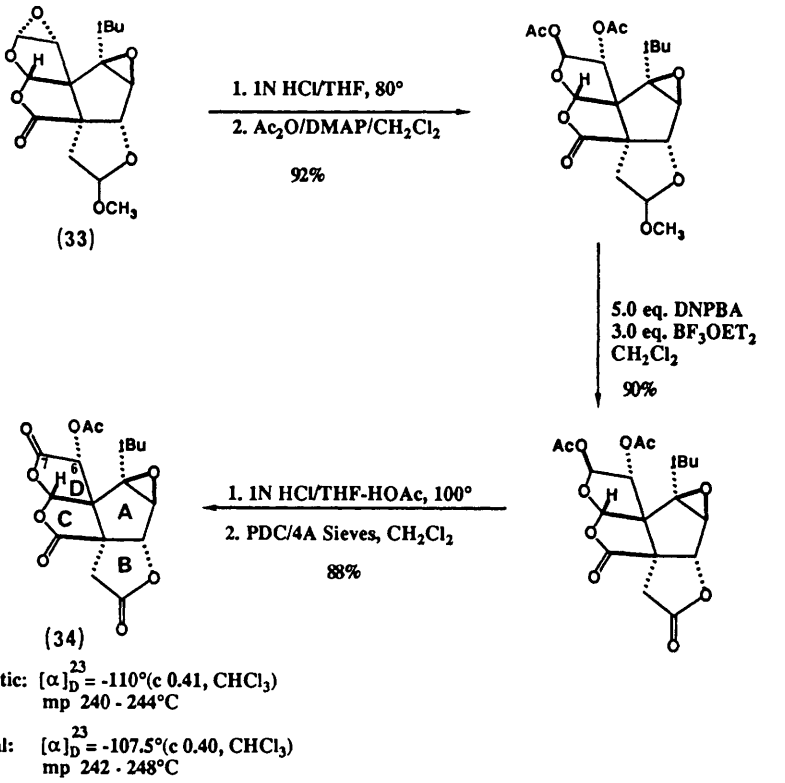
[33] S. C. Dolan and J. MacMillan *J. Chem. Soc., Chem Commun.*, 1985, 1588.



Scheme 15

will be of interest to a broad range of chemists and students of chemistry. First of all, it provides a snapshot of contemporary organic synthesis for comparison with the past, or with events of the future as the science makes its way toward the close of the twentieth century, a period of enormous progress. Second, the emphasis on the logic underlying synthesis is intended to reflect the conceptual nature and beauty of modern synthesis and the value of the continuing study of its intellectual foundations. And last, although chemistry is a science of vast scope and countless specialties, it has no real boundaries and many of its activities (including synthesis) interact in a synergistic way.

Some aspects of organic synthesis have not changed since the era of Sir Robert Robinson. The laboratory execution of a multistep synthetic sequence is still an arduous task requiring time, ability, and effort. Although it is now much easier to analyse complex synthetic problems under retrosynthetic and strategic guidance,

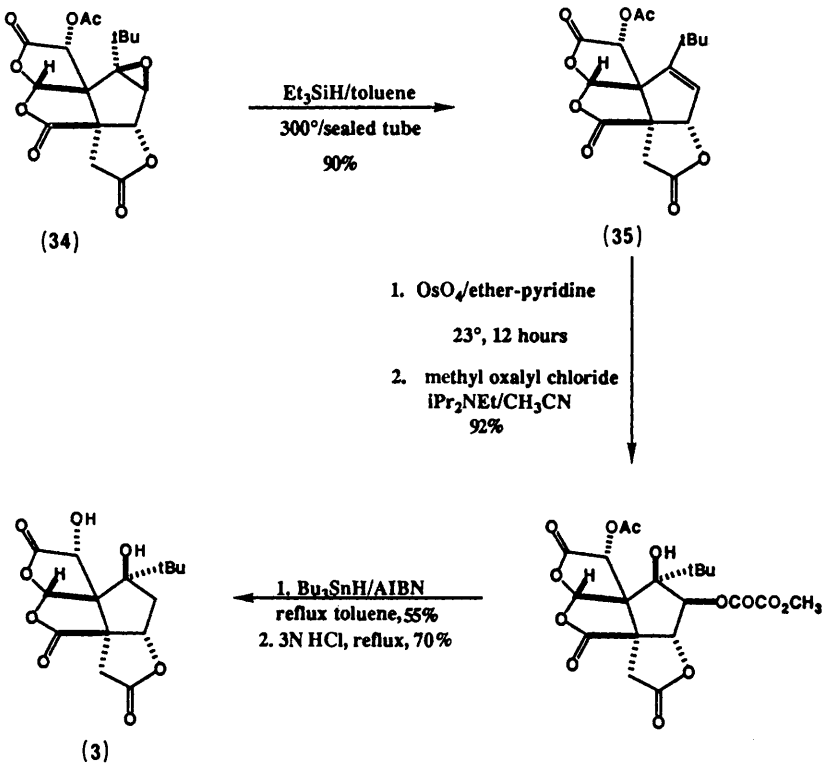


Synthetic: $[\alpha]_D^{23} = -110°$(c 0.41, $CHCl_3$)
mp 240 - 244°C

Natural: $[\alpha]_D^{23} = -107.5°$(c 0.40, $CHCl_3$)
mp 242 - 248°C

Scheme 16

and although organic chemists now have at their disposal powerful new tools for analysis and separation of molecules, determining suitable conditions and optimum procedures for synthetic processes ('making reactions work') is as much of a challenge today as it ever has been. Experienced synthetic organic chemists are keenly aware of this fact and also of the many large gaps which exist in synthetic methodology. It is only through continued vigorous effort at the frontiers of synthesis that such deficiencies will be appreciated and remedied. Because of this fact and also the obvious importance of synthesis to human well-being, for example as the primary tool in the development of new therapeutic agents, it might appear that all are agreed on the need for a high degree of activity in synthesis for the foreseeable future. Not so. There are now, as there have been for many years, savants and prophets (including more than a few chemists), who proclaim that organic synthesis is a mature field with limited possibilities for future discovery. In truth, as Sir Robert Robinson would have appreciated, the frontiers and the



Scheme 17

progress of organic synthesis are limited only by the creative abilities and the vision of those who work in the field. Organic synthesis is the essence of organic chemistry, just as organic chemistry is the fundamental language of life.

Acknowledgement. It is with much pleasure and gratitude that I acknowledge my collaborators in the successful syntheses of ginkgolide B, ginkgolide A, and bilobalide which are described herein. These individuals are Myung-chol Kang, Manoj Desai, Arun Ghosh, Ioannis Houpis, Weiguo Su, and Ashvinikumar Gavai. I am also deeply indebted to the U.S. National Institutes of Health, the U.S. National Science Foundation, and Pfizer Inc. for generous financial support over the years.