Contiguous stereogenic quaternary carbons: A daunting challenge in natural products synthesis

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One element of structure that invariably increases the difficulty of a chemical synthesis is the presence in the target molecule of contiguous all-carbon quaternary stereocenters. This Perspective will examine the most useful transformations and strategies devised recently for directly assembling this structural unit.

The construction of complex organic molecules from simple chemicals is a multifaceted endeavor. Initially, a strategy must be devised that sequences chemical transformations, known or projected novel ones, in a way that could plausibly lead to the target structure. The number of steps and the yield of each transformation determine the efficiency of a successful synthesis. The structure and properties of the target molecule define the extent of the challenge. Although several metrics have been advanced to quantify the complexity of synthesis targets and, thus, the degree of difficulty involved, none is universally appropriate. Features of target structures that increase the challenge of a chemical synthesis include the following: (i) instability, either thermodynamic instability or lability in the presence of common reagents or solvents; (ii) the number of functional groups, particularly diverse ones displaying disparate reactivity; (iii) the density of these functional groups; (iv) the incidence of stereocenters; (v) the number and types of rings; and often (vi) the overall size of the molecule. Not captured in this list, yet of major importance in dictating the synthesis challenge, is the novelty of the molecule’s architecture. Of prime importance is the extent to which the various structural fragments of a molecule map onto the existing synthetic art. For example, 30 years ago acyclic chains rich in functionality presented an enormous hurdle for stereocontrolled chemical synthesis. Today, armed with the many transformations developed in the intervening years for stereocontrolled assembly of acyclic motifs, this challenge is a great deal less.

One element of structure that invariably increases the difficulty of a chemical synthesis is the presence in the target molecule of all-carbon quaternary stereocenters. The impediment to synthesis presented by such centers arises from the steric congestion imposed by the four attached carbons and the limited number of carbon—carbon bond-forming reactions that reliably assemble quaternary carbons. The challenge is exacerbated further when two all-carbon quaternary stereocenters are adjacent. Only in recent years have methods for constructing vicinal quaternary stereocenters been disclosed that deal with this challenge in a single stereoselective transformation. This Perspective will examine the most useful transformations and strategies devised for directly assembling contiguous quaternary carbon stereocenters. Our discussion will be limited to chemistry that has been verified by its use in the enantioselective total synthesis of natural products containing such stereocenters. The treatment is not meant to be exhaustive; in some cases, other excellent examples could just as well have been chosen.

Before proceeding we should briefly consider how Nature deals with this synthesis complexity. Quaternary carbon stereocenters, a common feature of terpenes and related natural products, are assembled biosynthetically by using carboxylation chemistry, either polyene cyclizations or cationic rearrangements. An illustrative example of the former is the enzyme-catalyzed cyclization of (S)-2,3-oxidosqualene (1) in various plant species to form dammaradienol (2) (Scheme 1; ref. 1).

Stimulated by the initial insight of Stork and Burghstahler (2) and Eschenmoser et al. (3) and the seminal systematic investigations of the Johnson school (4), biomimetic cascade cyclizations of acyclic precursors is now a deep-rooted synthesis strategy. We will look at two biomimetic total syntheses, from the laboratories of Corey and Heathcock, in which cascade cyclizations were used to forge contiguous quaternary carbon stereocenters. In both syntheses, structures of great complexity are assembled in a limited number of steps with excellent stereocontrol.

We begin with the enantioselective synthesis of dammarenediol II (3), a congener of dammaradienol (2), reported in 1996 by Corey and Lin (5). Their retrosynthetic analysis disassembled the three cyclohexane rings and the vicinal quaternary carbon centers of 3 to furnish polyene 4 (Scheme 2). The single stereocenter present in this triene epoxide will be exploited to organize the central cyclization event to correctly form five of the stereogenic centers in 3. Additionally, functionality is incorporated from the outset that will allow the cyclopentene D ring to be generated at a late stage of the synthesis by an aldol cyclization. Further retrosynthetic simplification of triene epoxide 4 reveals the dihydroxylated derivative 5 of (E,E)-farnesyl acetate.

The enantioselective total synthesis of dammarenediol II (3) begins with acetoxy diene diol 5, which is available in high enantiomeric purity by cinchona alkaloid-catalyzed terminal dihydroxyla- tion of (E,E)-farnesyl acetate (6, 7). After conversion of 5 to epoxy allylic bromide 6, this farnesol-derived fragment is combined with the lithium azaenolate of 7 to ultimately produce acylsilane 8. The tetrasubstituted enol ether is installed next by an innovative three-component coupling that forms the required Z configuration of the tetrasubstituted double bond with complete stereocontrol while concomitantly installing the remaining carbons of 3 (8). The central cationic tricyclization is realized upon treatment...
of triene epoxide 9 with methylaluminum dichloride at -95°C. Subsequent desilylation and cleavage of the dithiane group provides tricyclic diketone 10 in 42% overall yield. Protection of the A ring hydroxyl group, followed by acyl-catalyzed aldol cyclization, delivers tetracyclic intermediate 11, which is elaborated in three steps to dammarenediol II (3).

The power of biomimetic total synthesis strategies to expeditiously assemble intricate target structures is illustrated beautifully by the biomimetic total syntheses of *Daphniphyllum* alkaloids by Heathcock et al. (9–11). We will specifically look at the total synthesis of (-)-secodaphniphylline (12), first disclosed in 1990 (Scheme 3) (12). (-)-Secodaphniphylline (12) contains the entire C30 complement of squalene arrayed in two polycyclic units, a bicyclic ketal joined to a unique azapentacyclic moiety. The vastly different structural architectures of the *Daphniphyllum* alkaloids and dammarenes 2 and 3, which undoubtedly all arise biosynthetically from oxidized squalene precursors, illustrate the amazing chemical diversity that can be assembled in Nature from a single structural input.

The Heathcock group’s plan for assembling (-)-secodaphniphylline (12) is summarized in retrosynthetic format in Scheme 3. Introduction of an ester substituent at the α-position of 12 allows retro-Claisen disconnection of β-keto ester 13 to ketal and amine fragments 14 and 15. The strategic insight that the challenging pentacyclic core 15 could arise in a single transformation from a squalene derivative is the central element of this incisive synthesis plan.

Starting from enantiopure amide 16, the carbon framework necessary for the alkaloid portion of 12 is assembled by a convergent Michael addition–alkylation reaction to provide cyclopentane 17. After transformation of this intermediate to dienyl diol 18, the pivotal biomimetic sequence is initiated by sequential Swern oxidation and condensation of the resultant dialdehyde with NH3 to generate intermediate 19. In situ treatment of this bicyclic 2-azadiene with warm acetic acid promotes intramolecular aza-Diels–Alder reaction to form the contiguous quaternary carbon stereocenters of (-)-secodaphniphylline (12). The resultant unsaturated iminium ion 20 undergoes furtheraza-Prins cyclization to provide pentacyclic amine 21 in 77% overall yield from 18. Heathcock et al. (10) note that the mild conditions required to affect the cyclization cascade provide support for the hypothesis that this sequence mimics the biosynthesis of the *Daphniphyllum* alkaloids. Further elaboration of the side chain of 21, cross-Claisen condensation of this intermediate with bicyclic ketal ester 22, and subsequent decarboxylation ultimately provide (-)-secodaphniphylline (12).

As illustrated in the synthesis of (-)-secodaphniphylline (12), cycloaddition reactions can be extremely effective in constructing vicinal quaternary carbon arrays. The stereospecificity of pericyclic reactions and the retrosynthetic simplification gained by relating sp3 configuration to sp2 geometry make these transformations highly valuable in the synthesis of complex structures containing quaternary stereocenters. We will briefly consider two additional total syntheses that employ pericyclic reactions to assemble contiguous quaternary carbons.

The asymmetric total synthesis of (+)-maritimol (23), reported in 2000 by Deslongchamps and colleagues (13), utilizes a transannular Diels–Alder reaction to install the adjacent quaternary carbons present in this stemodane diterpenoid (14, 15). Their strategy is briefly outlined in Scheme 4. Retrosynthetic
disassembly of the D ring of 23 furnishes tricylic intermediate 24, which is envisaged to arise by transannular Diels–Alder cyclization of macrocycle 25. By introducing an ester side chain in 24, its progenitor, 25, simplifies to three relatively simple precursors 26–28. Disconnection of the two fused bonds of 24 to create a ring of more than seven members would not generally be considered strategic (16). What makes this approach effective is the efficient, convergent synthesis of the macrocycle developed by this group (17).

The transannular Diels–Alder approach elegantly addresses some of the pitfalls often encountered in using cycloaddition reactions to form quaternary centers. For example, the macrocyclic ring holds the diene in the productive s-cis conformation and organizes cycloaddition regioselectivity. This ring also restricts the cycloaddition to take place only by two plausible endo transition structures. Surprisingly, the favored process depicted in representation 25 is controlled solely by the remote nitrile substituent (18).

The total synthesis of (+)-maritimol (23) begins with Hagemann’s ester (29), which in two steps is transformed to tetrasubstituted alkene 30 (Scheme 4) (19). An (5)-N-amino-2-(methoxymethyl)pyrrolidine (SAMP) (20) hydrazone alkylation is used to introduce absolute chirality in the eight-step assembly of vinyl iodide 31. Transformation of the SAMP hydrazone of 31 to a nitrile, followed by Stille coupling with 27, macrocyclization, and adjustment of the C14 oxidation state provide macrocycle 25 in an additional six steps from 31. The pivotal transannular Diels–Alder cyclization occurs with concomitant decarboxylation upon heating 25 at 155°C in DMSO and water to produce tricyclic ketone 32 as a single stereoisomer in 86% yield. The remainder of the synthesis proceeds uneventfully by way of intermediates that previously had been used in a total synthesis of racemic maritimol (21). In this way, (+)-maritimol (23) is assembled in a convergent, enantioselective sequence with a longest linear branch of 22 steps.

The final pericyclic method we will discuss is a thio-Claisen rearrangement, which is used in an asymmetric total synthesis of (−)-trichodiene (33) (Scheme 5). Although relatively small and devoid of heteroatom functionality, this terpenoid presents a significant synthetic difficulty because its two rings are attached at vicinal quaternary carbon stereocenters. As a result of free rotation about the σ-bond joining the rings, relating the configuration of attached rings is difficult. This challenge is magnified when the attached carbons are both stereogenic and quaternary (22). As demonstrated in this total synthesis of (−)-trichodiene (33) by Lemieux and Meyers (23), sigmatropic rearrangements can be used profitably to deal with this challenge.

The strategy developed for preparing (−)-trichodiene (33) is depicted in Scheme 5. Retroaldol disconnection of 34, a known precursor to (±)-trichodiene (24), gives a keto aldehyde that would derive from thiolactam 35. The incorporation of thiolactam functionality provides the structural prerequisites, or retrons, for a thio-Claisen transform, simplifying the target to N,S-ketene acetal 36. Standard retrosynthetic simplification of 36 furnishes lactam 37 (25). In this asymmetric synthesis plan, the configuration of the chiral auxiliary ring (Aux*) controls the outcome of the sigmatropic rearrangement and hence the configuration of the contiguous stereogenic quaternary carbons.

This synthesis of (−)-trichodiene (33) begins by assembling thiolactam 38 in three steps from (S,S)-2-amino-1-phenylpropane-1,3-diol and 4-acetylbutanoic acid (25). Alkylation of 38 with allylic bromide 39 provides the thio-Claisen rearrangement substrate 40. At 90°C in dimethylformamide (DMF), this N,S-ketene acetal undergoes [3,3]-sigmatropic rearrangement to produce thiolactam 41 as a single diastereomer (26). However, because of the steric destabilization associated with joining two qua-
ternary carbons, product 41 is only slightly favored (36:64) in the apparent thermodynamic equilibrium set up between 40 and 41 under these conditions (27). After separating 41 and recycling recovered 40, a 60% combined yield of 41 is obtained. The oxazoline chiral auxiliary is then removed by reaction of 41 with Meerwein’s reagent, followed by reduction of thiomidate salt 42 with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich). Finally, hydrolysis of this product generates keto aldehyde 43, which undergoes in situ aldol condensation to provide enone 34 (24). This concise asymmetric total synthesis of (−)-trichodiene (33) is accomplished in nine steps from the bicyclic lactam 37.

Many successful methods for introducing contiguous quaternary stereocenters involve intramolecular transformations, such as those used in the total syntheses of (−)-secoaphidiphlyline, (+)-maritimmol, and (−)-trichodiene. Intramolecular tethering allows reacting partners to be precisely oriented for bond formation. However, the large entropic barrier to similar bimolecular reactions often precludes their success. Despite the extra difficulty involved in forming vicinal quaternary linkages by using intermolecular transformations, bimolecular coupling of prostereogenic nucleophiles with chiral electrophiles has been used effectively to assemble molecules containing adjacent stereogenic quaternary carbons.

We will first consider the total synthesis by Holton et al. (28) of aphidicolinone derivative (−)-45, an intermediate previously used in a total synthesis of racemic aphidicolin (Scheme 6) (29, 30). In this synthesis, a diastereoselective intermolecular Michael addition is used to form the two adjacent quaternary carbons of (−)-45. Related in structure to the stemodane diterpenoids, aphidicolin possesses four primary rings, eight stereocenters, and two contiguous stereogenic quaternary carbons, C9 and C10.

The synthesis planning of Holton et al. (28) begins with retrosynthetic disassembly of the C and D rings to provide keto lactone 46 (Scheme 6). At this point, two powerful disconnections are made that simplify 46 to three small building blocks. Specifically, retrosynthetic excision of carbons C6 and C7 from the B ring and cleavage of the α-bond joining the vicinal quaternary carbons reveals cyclohexenone 47, vinylmetal reagent 48, and chiral vinylic sulfone 49 as plausible precursors of 46. In the forward direction, sulfenyl butenolide 49 would be coupled with an enolate derivative of cyclohexenone 47 and the resulting adduct would be elaborated to a bicyclic dieneone by condensation with a vinyl organometallic reagent (31). A second Michael reaction, this time intramolecular, then would form ring B. This strategy divides the molecule into pieces of roughly equal complexity, allowing high convergence to be realized.

At an early stage of the synthesis of aphidicolinone derivative (−)-45, the pivotal combination of the lithium enolate of ( tert-butylidimethylsiloxy)-2-cyclohexenone (50) and (S),(+)-2-sulfenylbutenolide 49 is carried out (32). This union, which is organized most likely by chelation between the sulfenyl and enolate oxygens, produces a 7:1 mixture of diastereomeric adducts. The major isomer 51 could be isolated in pure form and good yield by recrystallization. The synthesis is operationally streamlined by incorporating this diastereoselective Michael addition into a telescoped sequence of transformations that produce keto lactone 54 in a single synthetic operation. For this purpose, 49 is added to the lithium dienolate of 50 in toluene at −78°C to generate 51, which is not isolated but instead directly reacts with vinyl lithium. Subsequent diol of the reaction with methanolic HF and addition of sodium methoxide remove the tert-butylidimethylsilyl (TBS) protecting group, induce dehydration to generate 53, and promote intramolecular Michael addition to form keto lactone 54 in 45% overall yield. Protodesulfenylations of 54 and lactone cleavage, followed by protecting group and oxidation state manipulation, produce aldehyde 55. In four additional steps, this intermediate is elaborated to the known aphidicolin precursor 45 (29). Starting with sulfenyl butenolide 49 and cyclohexenone 50, this insightful total synthesis plan delivers aphidicolinone 45, the precursor to aphidicolin (44), in a short sequence in which fewer than 10 intermediates had to be isolated and purified.

The total synthesis of (−)-idiospermuline (56), reported by our laboratory in 2003 (33), provides a second example of the use of a bimolecular reaction to simultaneously construct contiguous quaternary stereocenters (Scheme 7). Idiospermuline belongs to the poly-pyrroloindolino family of alkaloids, which are characterized by the connection of cyclotryptamine subunits at quaternary carbon centers. The linkage of two such fragments at their benzylic quaternary carbons generates a 3a,3a′-bispyrroloindolino moiety, which is always present in these alkaloids. Higher-order members of this alkaloid family, such as idiospermuline, contain additional cyclotryptamine subunits attached through their benzylic quaternary carbon stereocenters to position 7 of an existing pyrroloindolino fragment.

The synthesis plan we developed (33) to synthesize (−)-idiospermuline (56) is outlined in antithetic format in Scheme 7. Retrosynthetic disconnection of the flanking pyrroloindolino subunit furnishes unsymmetrical 3a,3a′-bispyrroloindolino 57 as a likely precursor of 56. Disassembly of the two aminal units of 57 and connection of the terminal carbons of the resulting β-aminoethyl frag-
ments leads to pentacyclic bisoxindole 58 as a plausible progenitor of bispyrrolidinoindoline 57. The unsymmetrical methylation pattern of idiospermuline, the requirement to differentiate the two peri positions (7 and 7') of 3a,3a'-bispyrrolidinoindoline intermediate 57, and the construction of the contiguous quaternary stereocenters are to be addressed early in the synthesis by combining in the forward direction a dienolate of a differentially protected dihydroisoindigo 59 with a chiral, tartrate-derived dielectrophile. In this pivotal step, the carbon—oxygen asymmetry of the dielectrophile regulates stereoselection in the formation of the contiguous quaternary stereocenters and concomitantly installs the four carbons necessary for fashioning the outer pyrrolidine rings of the 3a,3a'-bispyrrolidinoindoline moiety. Moreover, convergency in the synthesis is realized by late-stage installation of the third pyrrolidinoindoline subunit. The general features of this strategy were developed earlier during total syntheses of other higher-order polypyrrolidinoindoline alkaloids (34, 35).

The synthesis of (−)-idiospermuline (56) commenced by preparing unsymmetrically protected dihydroisoindigo 60 in four steps from isatin. Formation of the vicinal quaternary stereocenters is achieved by combining the lithium dienolate of 60 with enantiopure ditriflate 61, a union that could produce four distinct dialkylation products (36). Under optimum conditions, this crucial dialkylation reaction provided cyclohexane diol derivative 62 in 75% yield. For this conversion to take place in high yield, the initial bimolecular alkylation step must proceed with high stereoinduction and the subsequent intramolecular alkylation must take place by a transition structure in which the oxindole carbonyl and oxindole enolate oxygens are oriented away from each other (37). In 12 additional steps, 62 is elaborated to the iodo bispyrrolidinoindoline 63. Stille cross-coupling of 63 with α-stannyl-(E)-butenanalide 64 then provides heptacyclic intermediate 65. In the second key strategic step of the synthesis, catalyst-controlled Heck cyclization of 65 then provides oxindole 66 with a 6:1 diastereoselectivity (38). This intermediate is transformed to (−)-idiospermuline (56) in three additional steps. In this way, the total synthesis of idiospermuline is accomplished in 18 steps from dihydroisoindigo and ditriflate precursors 60 and 61.

The complex architecture of the polypyrrolidinoindoline alkaloids provides ample stimulus for the development of new methods for forming contiguous quaternary carbon stereocenters. A second method for constructing the 3a,3a'-vicinal quaternary carbon linkage present in these alkaloids was also developed in our laboratory (39). In this approach, a diastereoselective intramolecular Heck cyclization cascade is the key step. We will specifically consider the stereoecontrolled total synthesis of (−)-chimonanthine (67) reported in 1999 (39).

The general features of this plan are outlined in retrosynthetic format in Scheme 8. Employing disconnections similar to those used to address idiospermuline, the pyrrolidine rings of (−)-chimonanthine are disassembled and the carbons are rejoined to provide cyclohexene derivative 68. In this case, the quaternary carbon stereocenters are not disconnected by cleavage of two bonds of the cyclohexene ring; rather, the σ-bonds joining the aryl fragment of the spirooxindoles to the cyclohexene ring are retrosynthetically disconnected to
furnish cyclohexene dianilide 69 as a viable precursor. In the forward direction, a diastereoselective cascade Heck cyclization is seen constructing the requisite contiguous quaternary stereocenters of 68. As in the idiosyncratic synthesis, the chirality of the carbon—oxygen σ-bonds of the C2-symmetric cyclization precursor will control the configuration of the newly formed quaternary stereocenters. The synthesis of (−)-chimonanthine begins by assembling cyclohexene 70 in four steps from (R,R)-diethyl tartrate and succinic acid. In four additional steps, this intermediate is elaborated to cyclohexene dianilide 71. In a remarkably efficient and stereoselective reaction, cascade Heck cyclization of 71 with 10 mol% of (Ph3P)2PdCl2 as the pre-catalyst provides hexacyclic dioxindole azide substituents of 73 in 90% yield as a single stereoisomer. Oxidative cleavage of the cyclohexene ring of 73, installation of the remaining two nitrogen atoms, and oxidation state adjustment then give rise to pentacyclic intermediate 74. After reduction of the azide substituents of 74, dehydration to form the annals and methylation of the pyrrolidine rings provides (−)-chimonanthine (67). The central step in this synthesis is noteworthy, because it exemplifies the use of a catalytic reaction to generate contiguous stereogenic quaternary carbons (40).

Since its emergence as a recognized scientific discipline, many important developments in organic chemistry have been stimulated by the structures of natural products. In this Perspective, we have examined the chemistry that has been invented or developed recently for synthesizing one difficult structural motif encountered in natural products: contiguous stereogenic quaternary carbons. At present, only a limited number of chemical synthesis strategies have been devised for directly assembling this structural unit. Prominent among these are approaches that transform alkene geometry into the configuration of adjacent quaternary stereocenters, such as biomimetic polynye cyclizations, cycloaddition reactions, and sigmatropic rearrangements. Surprisingly few other methods have been developed to date. Two examples of intermolecular combination of enolate nucleophiles with electrophiles, in one case an sp2 electrophile and in the other an sp3 electrophile, have been described. In both, alkylation diastereoselectivity results from the union of a chiral electrophile with an achiral nucleophile. As diastereoselective alkylation reactions of this variety are in general extremely rare (41), related strategies wherein the nucleophile is the chiral reagent will surely prove useful for assembling contiguous stereogenic quaternary carbons. To date, only one diastereoselective catalytic reaction has been developed for forming this structural unit (39), and no catalytic asymmetric approach has been disclosed (40). In closing, we would emphasize that the extant chemistry for forming vicinal stereogenic quaternary carbons, although providing excellent solutions for the structures specifically addressed, will surely be found lacking when the target is even slightly different in structure. Until many additional new strategies and transformations are invented for constructing contiguous stereogenic centers in a sterecontrolled fashion, the chemical synthesis of this structural motif will remain a noteworthy challenge.

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