Transannulation Reactions in the Synthesis of Natural Products

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Abstract: An overview on the construction of polycyclic natural products by use of transannulation reactions across medium and large rings is presented.

1 Introduction

The construction of polycyclic natural products has been a lure for the synthetic chemist over many years, with great strides in their synthesis being made in the latter half of the 20th century. Many of the strategies employed involve the sequential synthesis of individual rings of fragments of the natural products followed by a unification step, or by the iterative annulation of one ring onto a pre-existing ring (Scheme 1). However, an alternative strategy which can be equally efficient, as well as aesthetically pleasing, is the use of transannulation reactions. This strategy requires the synthesis of a large or medium ring containing suitable functionality to allow for the formation of a bond (or bonds) across the ring to form two or more smaller ring systems (Scheme 1). All the major classes of natural products, such as steroids, terpenes, polyketides and alkaloids, have had members which have been synthesised using a transannulation reaction as the key step. The types of transannulation reactions that have been employed are also many, including aldol reactions, Diels–Alder reactions, anionic and cationic cyclisations, atom-transfer reactions and radical-mediated cyclisations. In this review, we focus on recent applications of transannulation reactions which have been used as key steps in the synthesis of natural products, but also include examples from the less-recent past if they were deemed particularly noteworthy or if they place a more recent piece of work in context. The exception to this is the section on transannular Diels–Alder reactions as an excellent review appeared on this topic in 2001,1 and so we cover only that which has been published since that time. This review is organised into the types of transannulation reactions used

Scheme 1 General strategies for the construction of polycyclic systems

1.1 Conclusions

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and then subdivided into the ring-size of the ring the reaction was performed upon.

2  Diels–Alder Cyclisations

Transannular Diels–Alder reactions are a powerful tool which enables the rapid increase in molecular complexity from a substantially less complex molecule. The power of this approach has been demonstrated by its many uses over the years in the synthesis of polycyclic natural products.

2.1  10-Membered Rings

Danishefsky exploited a remarkable oxidative dearomatisation–transannular Diels–Alder reaction in his synthesis of \((\pm)-11\text{--O-debenzylytashironin}\).\(^2\) Precursor 1 was synthesised in six steps from an appropriately functionalised arene and a vinyl stannane. When 1 was exposed to phenyliodine(III) diacetate (PIDA) it underwent smooth oxidative dearomatisation to give a mixture of both oxidised quinone monoketal 2 and Diels–Alder adduct 3. Heating this mixture in the microwave for four minutes gave Diels–Alder adduct 3 as the only isolable intermediate in 65% yield. Oxidation of 1 to the orthoquinone was followed by intramolecular formation of monoketal 2. This set up a 10-membered ring where the newly revealed cyclohexa-1,3-diene and allene are positioned to undergo Diels–Alder cyclisation, generating all four rings of the natural product in one pot (Scheme 2). Transannular Diels–Alder adduct 3 was taken on in eight steps to give the desired natural product \((\pm)-11\text{--O-debenzylytashironin}\).

![Scheme 2](image)

**Scheme 2**  Oxidative dearomatisation–transannular Diels–Alder reactions in the synthesis of the core of \((\pm)-11\text{--O-debenzylytashironin}\)

### Biographical Sketches

**Dr. Paul Clarke** began his career at the University of Bath where he obtained his BSc (Hons) in 1993. He remained at Bath to study the utility and mechanism of intramolecular dioxirane epoxidation reactions under the supervision of Dr. A. Armstrong. In 1996, he obtained his PhD and moved to Florida State University where he spent two years working with Professor R. A. Holton on the synthesis and functionalisation of taxane ring systems. In 1999, he returned to the UK to work on a carbenoid insertion approach to peptide synthesis with Professor C. J. Moody at the University of Exeter. In September 1999, he was appointed to the position of Lecturer in Organic Chemistry at the University of Nottingham. In January 2006, he moved to his current position of Senior Lecturer in Organic Chemistry at the University of York.

**Andrew Reeder** graduated from the University of Sheffield in 2005, after a three-month placement sponsored by Pfizer and his final year spent in the group of Professor I. Coldham. In 2006, he joined the group of Dr. Paul Clarke as a graduate student, at the University of York. His research is involved with the synthesis of the pinguisane-type sesquiterpenoids by use of a novel transannular alkylation of an enol by a carbon–carbon double bond.

**Joby Winn** was born in Castries, St Lucia in 1985. He is a graduate of the University of York and was awarded his MChem in 2007 before joining the Clarke group as a research student. His PhD work is focused on the development of novel transannulation strategies for the synthesis of the pinguisane-type sesquiterpenoid class of natural product.
2.2 12-Membered Rings

The transannular Diels–Alder reaction has also been applied to 12-membered rings: a study on the synthesis of the spinosyn A ring system by Roush and one on the tetracyclic core of the mangicols by Uemura. In the case of spinosyn A, a mixture of the two diastereomeric 12-membered rings 5 and 6 were formed in situ by the Claisen ring contraction of the 16-membered lactone 4. Once formed, the diastereomeric 12-membered rings underwent transannular Diels–Alder cyclisation at elevated temperatures, each via two diastereomeric transition states to yield the four diastereomeric tricyclic ring systems 7–10 (Scheme 3). This disappointing lack of stereoselectivity in the Claisen and Diels–Alder reactions was later overcome by conducting a thermal Diels–Alder reaction of 4 at 180 °C, which proceeded in a 46% yield, followed by a Claisen ring contraction of the resulting tricyclic 9-membered lactone, which gave 9 in 48% yield.

A greater degree of selectivity was achieved in the transannular cyclisation of a 12-membered ring reported by Uemura in a synthesis of the core of the mangicols. The 12-membered ring was constructed via an intramolecular Nozaki–Hiyama–Kishi reaction and furnished the two diastereomers 11 and 12, epimeric at C-3, in 14% and 62% yields respectively. Upon heating under reflux in toluene, 11 underwent a smooth transannular Diels–Alder cyclisation to give 13 quantitatively. When submitted to the same conditions, 12 cyclised to give a 1:1 mixture of 14 and 15 in 84% combined yield (Scheme 4).

Scheme 4  Transannular Diels–Alder reaction in the synthesis of the core of the mangicols

The selectivity of the Diels–Alder cyclisations can be accounted for by the energy differences in the conformations of the transition states. Product 13 is formed via an exo transition state, the competing endo transition state is substantially higher in energy due to a transannular interaction between H-11 and Me-15 as well as a 1,3-diaxial interaction between H-1 and OH-3. In the case of the cyclisation of 12, the exo transition state leading to 14 has an interaction between Me-5 and H-12 and a 1,3-diaxial interaction between H-1 and OH-3, while the endo transition state leading to 15 has a single, more severe, transannular interaction between H-11 and Me-15. Consequently, these transition states are the same in energy and thus lead to a 1:1 ratio of 14 and 15.

2.3 13-Membered Rings

A transannular inverse-electron-demand Diels–Alder cyclisation was used to construct the core of (±)-strychnine in a formal synthesis of the natural product. [3](1,3)Indolo[3][3,6]pyridazino[3]phane 16 was heated with N,N-diethylaniline and underwent Diels–Alder cyclisation followed by extrusion of molecular nitrogen to give 17, which was converted into 18, an intermediate in Rawal’s synthesis of strychnine, in two steps (Scheme 5).
A furanophane transannular Diels–Alder reaction has been used to form the core of (+)-anhydrochatancin.\textsuperscript{7} The 13-membered furanophane was made as a 2:1 \(Z/E\) mixture via ring-closing metathesis, and was separated by column chromatography. The ketone carbonyl was reduced with sodium borohydride to yield the Diels–Alder precursor 19. Upon heating to 115 °C in dimethylsulfoxide and water (2:1), 19 underwent a transannular Diels–Alder reaction to give 20 with 70\% conversion (Scheme 6).

Scheme 5  Inverse-electron-demand Diels–Alder cyclisation in the synthesis of (±)-strychnine

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Scheme 6  Furanophane transannular Diels–Alder cyclisation in the synthesis of (+)-anhydrochatancin

\[ \text{Scheme 6} \]

\[ \text{Furanophane transannular Diels–Alder cyclisation in the synthesis of (+)-anhydrochatancin} \]

2.4  15-Membered Rings

A tandem transannular Diels–Alder cyclisation across a 15-membered ring followed by a transannular aldol reaction across a 7-membered ring has led to an interesting approach to the ring systems of (+)-aphidicolin.\textsuperscript{8} The desired 15-membered ring 21 was synthesised by an intramolecular Stille reaction. When heated in a sealed tube to 250 °C in toluene with triethylamine, 21 underwent a transannular Diels–Alder reaction (presumably to give 22) which in turn, under the reaction conditions, underwent transannular aldol cyclisation to generate the desired aphidicolin ring system 23 in 77\% yield (Scheme 7).

Scheme 7  Tandem transannular Diels–Alder/aldol sequence for the construction of (+)-aphidicolin rings system

\[ \text{Scheme 7} \]

\[ \text{Tandem transannular Diels–Alder/aldol sequence for the construction of (+)-aphidicolin rings system} \]

Jacobsen has developed an oxazaborolidine-derived catalyst, 24, which promotes the enantioselective transannular Diels–Alder reaction across 15- and 16-membered rings.\textsuperscript{9} This methodology was used in the asymmetric synthesis of 11,12-diacetoxydrimane.\textsuperscript{9} Silyl-tethered macrocycle 25 was synthesised as a 3:6:1 \(E,E/E,Z\) mixture by ring-closing metathesis. When exposed to catalyst 24 (20 mol\%) in toluene for 20 hours, the \(E,E\)-configured macrocycle underwent transannular Diels–Alder cyclisation to furnish 26 in >20:1 dr and 83\% ee (Scheme 8). Decalin 26 was then converted into 11,12-diacetoxydrimane in a further five steps. Interestingly, studies on the use of this catalyst in other systems showed that it could reverse the preference for competing \textit{endo} transition states in methyl-substituted 15-membered lactones, over-riding the preference of the substrate to adopt a transition state conformation where the pendant methyl group was pseudo-equatorial.

Scheme 8  Asymmetric transannular Diels–Alder cyclisation

\[ \text{Scheme 8} \]

\[ \text{Asymmetric transannular Diels–Alder cyclisation} \]

2.5  16-Membered Rings

Shair has reported an elegant biomimetic synthesis of (–)-longithorone A that includes a key transannular Diels–Alder reaction of a quinone and a 1,3-diene across a 16-membered carbocycle.\textsuperscript{10} Compound 28 was synthesised by an intermolecular Diels–Alder ‘dimerisation’ which formed the central cyclohexene ring. The quinone was revealed by treatment with iodosylbenzene to afford the bisquinone which, while observed spectroscopically, was not isolated. This bisquinone underwent spontaneous transannular Diels–Alder cyclisation to afford (–)-longithorone A (29) in 90\% yield (Scheme 9).

Scheme 9  Tandem transannular Diels–Alder/aldol sequence for the construction of (+)-aphidicolin rings system

\[ \text{Scheme 9} \]

\[ \text{Tandem transannular Diels–Alder/aldol sequence for the construction of (+)-aphidicolin rings system} \]
2.6 19-Membered Rings

The pentacyclic core of the polyketide FR182877 was elegantly constructed by Sorensen in a biomimetic fashion via a tandem transannular Diels–Alder cyclisation across a 19-membered ring and transannular hetero-Diels–Alder cyclisation across a 12-membered ring. In this example, the cyclisation was initiated by the oxidative deselenylation of 30 with m-chloroperoxybenzoic acid. This underwent tandem transannular Diels–Alder/hetero-Diels–Alder at ambient temperatures in buffered chloroform over 24 hours to give 32, the pentacyclic core of FR182877. Conveniently, the reaction could be warmed to 40 °C for four hours to achieve the same result (Scheme 10).

Contemporaneously to these studies, Evans and co-workers reported a similar tandem transannular Diels–Alder/hetero-Diels–Alder approach to the core of FR182877. Evans, too, triggered his set of tandem transannular Diels–Alder reactions by the use of selenium reagents to install the unsaturated β-keto ester (Scheme 11). Evans noted that neither 34 nor the expected product of mono-transannular Diels–Alder cyclisation could be detected spectroscopically, implying that the transannular hetero-Diels–Alder reaction was much faster than the first Diels–Alder cyclisation.

2.7 22-Membered Rings

In a further report by Roush on the synthesis of spinosyn A, the tricyclic ring system was set up by sequential transannular Diels–Alder cycloaddition followed by a transannular Morita–Baylis–Hillman reaction. The reaction sequence was initiated by formation of the 22-membered macrocycle by means of a Horner–Wadsworth–Emmons cyclisation, which yielded the transannular Diels–Alder cyclisations in the synthesis of FR182877.
adduct 37 directly as a result of spontaneous transannular Diels–Alder cyclisation. It was rationalised that the correct transition state for cyclisation to the desired C-7–C-11 trans-fused ring system may be favoured by installation of a bromine at C-6. This should increase the steric interaction between the substituent at C-6 and the alkoxy group at C-9, thought to be present in the undesired transition state 40. Additionally, it was thought that the desired transition state would be reinforced by the macrocycle adopting a conformation where the C-21 ethyl group was pseudo-equatorial. In the end, this was shown to be the case, as the desired ring system was generated as the major isomer in 75% yield. Treatment of 37 with trimethylphosphine resulted in a transannular Morita–Baylis–Hillman reaction which afforded 38 in an 88% yield (Scheme 12).

3.1 8-Membered Rings

List has reported the synthesis of (+)-hirsutene using a trans-4-fluoroproline-catalysed transannular aldol reaction to set up the tricyclic carbon framework. The meso-cyclopentane-annulated diketone 42 was converted into the desired hydroxytriquinane 43 in 84% yield with an enantiomeric ratio of 98:2 (Scheme 13). Compound 43 was then taken on to (+)-hirsutene in 65% yield over three steps. List proposed that transition state 44 accounted for the observed selectivity, which is in line with their general transition state model for enantioselective intermolecular organocatalytic aldol reactions.

A transannular aldol reaction across an 8-membered ring has also been used as the key step in the total synthesis of (−)-merrilactone A. This key reaction depended upon deprotonation of the 8-membered ring of 45 occurring at C-9 rather than at C-3. However, this was in theory complicated by the fact that 45 could exist in either a chair-boat or boat-chair conformation. In the chair-boat conformation, deprotonation at C-3 would lead to the energetically higher trans-enolate, and so it was rationalised that deprotonation would occur from the desired C-9. However, in the competing boat-chair conformation, it would be deprotonation of C-9 which would lead to the energetically higher trans-enolate, therefore favouring deprotonation at the undesired C-3 position. To obviate this problem, a bulky 2,6-ditrifluoromethylbenzyl group was used to hinder deprotonation of C-3 from the boat-chair conformation. Deprotonation did then occur at C-9 from the chair-boat conformation, thereby leading to an enolate in the chair-boat conformation which was destabilised by a 1,3 diaxial interaction between the axial CH₂OR group and the enolate ONa. Relief of this interaction was gained by a change in conformation to the boat-boat conforma-

3 Aldol Cyclisations

The aldol reaction is one of the most important and most used reactions in organic synthesis. It usually manifests itself in the form of either an intermolecular coupling reaction or as a cyclisation strategy. Recently, however, there have been several reports of the aldol reaction being used in a transannular fashion to create bicyclic systems from larger monocyclic precursors. This application of the venerable reaction further extends its scope and its uses.
3.2 22-Membered Rings

A key biomimetic transannular aldol reaction was used in the final stages of Evans’ synthesis of (+)-miyakolide. Reduction of the nitrogen–oxygen bond in isoxazole gave β-keto enamine. This was hydrolysed to the enol form of the β-diketone which cyclised onto the carbonyl group across the ring to give the β-hydroxycyclohexanone; transannular hemiketal formation followed in the same pot and generated, the desired ring system of the natural product (Scheme 15).

4 Anionic Cyclisations

In addition to the aldol reaction, other anion-driven reactions have been used in a transannular fashion for the construction of the polycyclic cores of a wide range of natural products. These reactions include Michael reactions, S_N2-type reactions, vinylogous ‘aldol-type’ reactions and organometallic cyclisations onto carbon–carbon double or triple bonds.
A transannular Michael reaction across an 8-membered ring was reported by Magnus in his investigations towards a synthesis of paclitaxel.\textsuperscript{18} Treatment of 58 with 1,5-di-azabicyclo[5.4.0]undec-5-ene in toluene under reflux resulted in $\beta$-elimination of the oxo-bridge to give 59. Compound 59 underwent enolate formation to give the anti-Bredt enolate 60 which then cyclised in a transannular fashion onto the $\alpha,\beta$-unsaturated lactone to give 61 (Scheme 18).

### 4.2 10-Membered Rings

A cyclisation of an amine across a cis-decalin onto an epoxide was used to synthesise the supposed structure of a constituent of the New Brunswick cranberry leaf.\textsuperscript{19} Tri-fluoroacetamide 62 was hydrolysed with potassium carbonate in methanol and the resulting anion cyclised onto the epoxide on the other ring (Scheme 19). The alcohol 63 was then dehydrated to furnish the target structure.

### 4.3 12-Membered Rings

The bicyclo[7.3.0]dodecane core of the enediyne anticancer agent N1999A2 was synthesised by a transannular cyclisation of a vinyl lithium onto an alkyne across a 12-membered ring.\textsuperscript{20} This transformation required some optimisation: substrate 64 was stirred in a 1:1 mixture of tetrahydrofuran and toluene in the presence of 4 Å molecular sieves at 23 °C for 15 minutes, before the tertiary alcohol was deprotonated with a 1 M solution of lithium hexamethyldisilazide in tetrahydrofuran. The solution of alkoxide was then treated with four equivalents of a 1.7 M solution of tert-butyllithium in pentane at $-78$ °C, followed by immediate quenching with a solution of acetic acid in tetrahydrofuran after less than three seconds. This provided the desired bicyclo[7.3.0]dodecane ring system 65 in 30–40% yield (Scheme 20).
5 Pericyclic Reactions

There have been several recent examples of transannular non-Diels–Alder pericyclic reactions being used in the construction of natural product fragments. These reactions include Cope rearrangements and photochemical as well as higher-order cycloaddition reactions. The more notable examples are discussed here.

5.1 10-Membered Rings

The key step in a total synthesis of (+)-arteannium M involved a tandem oxy-Cope/transannular ene reaction.21 1,2-Divinylcarbinol 66 was synthesised in one step from (+)-limonene and heated with 1,5-diazabicyclo[5.4.0]undec-5-ene in toluene at 220 °C to give 69 as the only detectable product. An oxy-Cope reaction generated enol 67 which tautomerised to the keto form 68-A. The product arises from conformation 68-B, which the authors rationalise as being lower in energy as the alkyl chain is in a pseudo-equatorial position, thus favouring the formation of 69 from the ene reaction (Scheme 21).

Ascorbic acid derivatives have been shown to undergo transannular [2+2]-photocycloaddition reactions to give highly substituted cyclobutane-containing compounds.22 Compounds of the general type 70 were prepared by olefin metathesis using Grubbs’ first-generation catalyst and then irradiated at 254 nm at 5 °C in dilute solutions of either dichloromethane or acetonitrile. This yielded the substituted cyclobutane structures 71 and 72 in good yields and modest selectivities (Scheme 22).

5.2 12-Membered Rings

Pattenden and co-workers have reported an elegant biomimetic synthesis of (+)-intricarene (76) by use of a transannular [5+2] cycloaddition of an oxidopyrylium ion.23 They hypothesised that (+)-intricarene may arise from another natural product (–)-bipinnatin J (73) and then developed conditions for its conversion into (+)-intricarene (76), by oxidative expansion of the furan with vanadyl acetylacetonate and tert-butyl hydroperoxide, then acylation to give 74, followed by elimination with 1,5-diazabicyclo[5.4.0]undec-5-ene under reflux to form the oxidopyrylium species 75, which underwent the desired biomimetic [5+2] cycloaddition to generate 76 in an unoptimised 10% yield (Scheme 23).

A stereocontrolled transannular nitrone cycloaddition has been used to construct the spirocyclic core of pinnaic acid.24 Tridecanolide 77 was synthesised via ring-closing metathesis as a 4:1 E/Z mixture and this was treated with p-toluenesulfonic acid which resulted in the formation of hydroxylamine 78. The latter underwent spontaneous intramolecular condensation to form nitrone 79 as a 4:1 mixture of E and Z isomers. After removal of the minor Z isomer (E)-79 was heated in toluene to generate a single product which was identified as the cycloadduct 80.
Methanolation of the lactone and reduction of the nitrogen–oxygen bond revealed 81, the core of pinnaic acid. The authors rationalise that only one diastereomer is formed as the macrocycle is too small to allow the nitrone oxygen to pass through the ring, and hence the transannular cycloaddition can only occur from the rear face of the double bond, as shown (Scheme 24).

Scheme 24 Transannular nitrone cycloaddition in the synthesis of the pinnaic acid core

5.3 14-Membered Rings

The oxabicyclo[3.2.1]octene ABCD ring systems of the cortistatins were constructed in the first example of a transannular [4+3]-cycloaddition reaction.25 When furanoallene 82 was treated with palladium(II) acetate in the presence of lithium bromide, the desired ring system 83 was isolated in 37% yield. The authors suggested that the likely mechanism for the formation of 83 involved palladium(II) activation of the allene and formation of palladium π-allyl system 84, followed by nucleophilic attack of the furan on the palladium π-allyl system. The stereochemistry of the product is consistent with a compact transition state with an endo-tether 84-TS (Scheme 25).

6 Cationic Cyclisations

The biosyntheses of many terpene or steroidal natural products have been shown to proceed via the intermediacy of carbocations. Synthetic chemists have been inspired by this and have sought to develop chemical methods in the laboratory to mimic those processes found in nature. To this end, there have been many elegant reports in which the key step in the synthesis involves a transannular reaction of a carbocation or other cationic intermediate.

Scheme 25 Transannular [4+3] cycloaddition in the synthesis of the cortistatin ring systems

6.1 8-Membered Rings

The 1980s witnessed several groups competing in the area of sesquiterpene synthesis using a key transannular cyclisation across an 8-membered ring onto a carbocation. Pattenden targeted the synthesis of Δ^8(9)-capnellene26 and (±)-pentalene,27 while Ohtsuka et al. focused on pentalenolactones E and F.28 Both strategies involved a cationic cyclisation across a suitably functionalised bicyclo[6.3.0]undecene of the type illustrated in Scheme 26. Treatment of either 85 or 86 with boron trifluoride–diethyl ether complex generated three new products, the major one, 87, was shown to have the structure of Δ^8(9)-capnellene. All three products 87, 88 and 89 presumably arise from the same carbocation 91, formed by the transannular cyclisation of 90. In a similar vein, (±)-pentalene 93 was constructed from 92 via a transannular cyclisation onto carbocation 94 (Scheme 27). Interestingly, another product, 96, was also isolated. Pattenden suggested that it was
formed by the formation of the alternative carbocation 95 and subsequent rearrangements (Scheme 27).

(±)-Anatoxin A and several analogues were constructed by selenocyclisation of a carbamate nitrogen across a cyclooctene ring (Scheme 28).29 The authors had investigated several methods to activate the alkene, including palladium(II) chloride, palladium(II) acetate and rhodium(III) chloride; however, the only products isolated were from alkene isomerisation. Alkene isomerisation to the anatoxin A ring system was required after cyclisation and, using the knowledge gained from their earlier studies, this was achieved by use of rhodium(III) chloride in ethanol.

Scheme 28 Transannular selenocyclisation in the synthesis of (±)-anatoxin A

The cores of the cladiellin (eunicellin) family of marine natural products were constructed by some novel transannular rearrangement chemistry initiated by the formation of selenonium ion 101 and subsequent formation of oxonium ion 102 (Scheme 29).30 It was found that the course of the reaction was affected by the nature of the counterion. When chloride was used, the reaction followed path a, with chloride attacking the oxonium ion at the most electrophilic site, which is α to the carbonyl group, leading to 103. However, with the less nucleophilic trifluoroacetate as the counterion, the acetate of 102 participates and attacks the oxonium ion at the proximal position, through path b. Upon hydrolysis, 105 is formed from 104, and undergoes a transannular hemiketalisation to form 106, the core of sclerophytin B.

6.2 9-Membered Rings

Paquette noted a number of interesting carbocation-mediated transannulation reactions in his work towards a synthesis of the taxane ring system.31 The acid-catalysed addition of methanol to 107 led exclusively to 108: the double bond underwent a transannular cyclisation onto the carbonyl group opposite, to generate the cyclopentene-containing compound 108 (Scheme 30). This paper also contained several other examples of both cationic and anionic transannular cyclisations across 9-membered rings.

Fukuyama employed a transannular Mannich reaction in the synthesis of (–)-strychnine.32 Removal of the N-nosyl protecting group of 109 was followed by intramolecular formation of the iminium from the now-free amine and the aldehyde. The iminium ion underwent smooth attack...
by the indole to generate 110, the pentacyclic core of (–)-strychnine, in 84% yield over the two steps (Scheme 31).

Clarke and co-workers reported a transannular iodonium ion cyclisation followed by a transannular lactonisation which formed 114 and 115, the DEF-ring systems of both hexacyclic acid and FR182877 respectively. The initial transannular cyclisation was assumed to generate an iodonium ion which was trapped by the carbonyl group to form an oxocarbenium ion. This could then either be attacked by acetic acid to form the hexacyclic acid ring system 112, or lose a proton to form the enol ether present in the FR182877 ring system 113 (Scheme 32). The compounds could be separated and carried forward independently to form the DEF-ring systems of the natural products. Interestingly, when the reaction was run in chloroform as solvent, a mixture of iodolactones 116 and 117 was formed, and when diethyl ether was used, bicyclic furan 118 was formed. It would seem that 118 was formed by iodonium cyclisation via the tert-butyldimethylsilyl ether, which liberated a tert-butyldimethylsilyl cation which in turn caused the removal of the tert-butyld ester and subsequent decarboxylation. As these products arose from cyclisations onto different diastereomeric iodonium ions (either α- or β-) through different conformations (112/113 via β-iodonium ion in a boat-boat conformation, 116/117 via α-iodonium ion in a chair-chair conformation and 118 via an α-iodonium ion in a boat-boat conformation) the authors proposed that the different solvents in some way stabilised the different iodonium ions and thus led to the different products.

In studies towards the synthesis of the pinguisane-type sesquiterpenoids, the same group reported a novel transannular attack of an enol onto a double bond promoted by tetrafluoroboric acid (Scheme 33). Enolisation at the correct site was ensured by lactone formation, which not only made the α-position of the β-keto ester a bridgehead position but also orientated the enolisable carbon–hydrogen bond to be aligned with the C=O π* orbital. Enolisation and simultaneous protonation of the double bond in 120 was achieved with tetrafluoroboric acid; transannular cyclisation occurred to give, after methanolysis, compound 122, the bicyclo[4.3.0]nonane ring system of the pinguisane-type sesquiterpenoids.

### 6.3 10-Membered Rings

In their studies on the reactivity of the heliangolides, Bellido and co-workers reported several transannular cat-ionic cyclisations that produced decalin ring systems. Transannular attack of the double bond in an SN2 manner on the carbon–oxygen bond of the lactone accounts for the formation of the decalin products 124 and 125, the cis and trans ring junctions can easily be accounted for by the two most stable conformations of the 10-membered ring 123 (Scheme 34). When epoxide 126 was treated with p-toluenesulfonic acid, the epoxide was opened to form the tertiary carbocation which was trapped by the double bond on the opposite side of the ring; this new tertiary carbocation was then itself trapped by the pendant hydroxy group to give the epoxy-decalin 127 (Scheme 34).

A transannular cyclisation and ring contraction was reported as a strategy for the synthesis of oxygen-bridged terpenoids. Crude 128 was treated with trimethylsilyl chloride and sodium iodide to promote an α-ketol rearrangement; in this process, migration of the C-9–C-10 bond to the C-1 carbonyl generated the alkoxide, which then underwent a transannular cyclisation onto the epoxide, producing 129 in 83% yield (Scheme 35).
Transannular cyclisations have also been used in the synthesis of isoquinoline alkaloids. The authors rationalised that protonation of the vinyl silane occurred to the silicon and hence the carbocation formed in the α-position was trapped in a transannular fashion by the amide nitrogen. They proposed that the more usual formation of a β-carbocation was disfavoured due to the proximity of the amide carbonyl group (Scheme 36).

Scheme 36  Transannular cyclisation in the formation of isoquinoline alkaloids

6.4 11-Membered Rings

A series of powerful tandem transannular cyclisations were used in the synthesis of the kopsia alkaloid ring systems. It was found that treatment of 132 with a powerful electrophile, such as triflic anhydride, generated the iminium ion 133, which underwent a transannular Mannich reaction to give 135 after loss of a proton. Iminium ion 136 was then generated under the reaction conditions and this was trapped via a vinylogous Mannich reaction to give final iminium ion 138, which was formed by loss of a proton and elimination of PhO from 137, was trapped by trimethylsilyl cyanide and generated the desired ring system of the kopsia alkaloids 139 in one pot and in 68% yield (Scheme 37).

Scheme 37  Tandem transannular cyclisations in the synthesis of the kopsia alkaloid ring systems

6.5 12-Membered Rings

Examples of transannular cyclisation across a 12-membered ring have been key in two of the reported syntheses of apicularen A. Rizzacasa developed an Amberlyst-15 promoted 6-endo-trig cyclisation to form the tetrahydropyran-4-one. It was found that either of the two C-13 diastereomeric alcohols 140 could be used, as this centre epimerised under the reaction conditions to a greater than 10:1 ratio in favour of the epimer required for completion of the synthesis of 141 (Scheme 38). A mercury(II) trifluoroacetate mediated cyclisation was used to install the tetrahydropyran ring of 143 in Maier’s synthesis of the same molecule (Scheme 38). However, ring opening of the mercurial intermediate was a problem in the reductive demercuration of 143 and so it was necessary to change the solvent from dichloromethane to tetrahydrofuran and perform the reduction with lithium borohydride in order to obviate this.

6.6 13-Membered Rings

A number of transannular cyclisations of the lathyrane diterpenes have been reported. The dienol 145, formed by the proton-catalysed opening of the cyclopropyl ring in
144, undergoes a transannular Nazarov-like cyclisation onto the carbon bearing the tertiary acetate to give tricyclic 146 (Scheme 39). Other triggers found to be effective for initiating transannular cascades in these systems included ytterbium(III) trifluoromethanesulfonate. When epoxide 147 was treated with ytterbium(III) trifluoromethanesulfonate in methanol, addition of methanol opened up the cyclopropane ring to generate dienyl acetate 149, which underwent transannular cyclisation to the epoxide to give cation 150. The fate of cation 150 was shown to include products which derived from H-12 migration to C-11 followed by transannular trapping of the new allyl cation by the primary hydroxy to give 151, as well as loss of a proton and transannular SN2¢ attack of the primary hydroxy on the allylic acetate to give 152 (Scheme 40).

Scheme 39  Transannular cyclisations of the lathyrane diterpenes

Scheme 40  Further transannular cyclisations of the lathyrane diterpenes

these cyclisations mimic the biosynthetic cationic cyclisations, but oftentimes they can be used to form carbon–carbon bonds in substrates where cationic reactions would be inappropriate.

7.1 8-Membered Rings

Curran reported a transannular radical cyclisation across an 8-membered ring in his synthesis of (±)-modhephene and (±)-epi-modhephene.42 Thermolysis of 153 at 80 °C generated a secondary radical which underwent a transannular 5-exo-trig cyclisation to form a primary radical, which in turn cyclised in a transannular 5-exo manner onto the appropriately positioned vinyl group to form, after trapping, 154 (Scheme 41).

Scheme 41  Tandem transannular radical cyclisations in the synthesis of (±)-modhephene

7  Radical Cyclisations

The high reactivity and functional group tolerance of radicals has meant that they have been exploited in a wide range of transannular cyclisation reactions. Sometimes
An alternative transannular radical cyclisation approach to modhephene was reported by Pattenden. In this route, thioester 156 was treated with tributyltin hydride and 2,2'-azobisisobutyronitrile in hot benzene and the tricyclic core 158 was isolated in 59% yield. The reaction proceeded via the transannular cyclisation of an acyl radical onto the remote double bond, followed by attack of the newly generated radical back onto the ketene in 157 in a 5-exo-dig manner (Scheme 42).

Scheme 42  Pattenden’s synthesis of (+)-modhephene

The hirsutene ring systems were synthesised via a radical cyclisation across a cyclooctene ring. When 159 was heated with di-tert-butyl peroxide in a sealed tube for three hours, 160 and 161 were formed in a 2.8:1 ratio and in 90% yield based on recovered starting material (Scheme 43). The authors rationalised the cis-anti-cis stereochemistry of the tricyclic ring system 161 to have formed as a result of the steric bulk of the dithiolane ring increasing the energy difference between the transition states leading to the syn and anti cyclisation products, compared to the case where the radical formed is unsubstituted, to such an extent that only anti-161 is formed.

Scheme 43  Transannular radical cyclisations in the synthesis of the hirsutene ring system

A formal synthesis of (+)-platensimycin was achieved where one of the rings of the molecule’s core was synthesised by a transannular cyclisation. Monothioacetal 162 was treated with tributyltin hydride and 2,2'-azobisisobutyronitrile to form the radical which cyclised onto the cyclohexene double bond. The product of the cyclisation was then treated with aqueous hydrochloric acid to remove the acetal protecting group and reveal 163 in 57% yield (Scheme 44). The product of reduction of the monothioacetal was also isolated in 18% yield.

Scheme 44  Construction of the platensimycin core via radical cyclisation

7.2  9-Membered Rings

Transannular cyclisation of the epoxycaryophyllenes to form tricyclo[6.3.0.02,5]undecanes has been catalysed by titanium(III). The titanium(III) reagent was formed by the in situ reduction of bis(cyclopentadienyl)titanium(IV) dichloride by manganese dust. This new titanium(III) reagent reduced the tertiary carbon–oxygen bond of the epoxide 164 to give a radical which was positioned to cyclise onto the exocyclic double bond across the ring. The formation of two diastereomers of the product can be rationalised by cyclisation via one of two different conformations of the 9-membered ring. Boat-boat conformation 165 cyclises to produce diastereomer 166, while chair-boat conformation 168 cyclises to form 166 (Scheme 45).

Scheme 45  Radical cyclisations of the epoxycaryophyllenes

The unusual cis-anti-cis-anti-cis steroid stereochemistry was constructed by a radical cyclisation protocol, where the cyclisation to form the CD rings was a transannular radical cyclisation across a 9-membered ring. The cascade was initiated by the 6-endo cyclisation of an acyl radical, which led to 170 via a 9-endo-trig cyclisation. Radical 170 was then poised for a transannular cyclisation onto the double bond to form a single steroidal system, 171, in 45% yield (Scheme 46).

7.3  10-Membered Rings

The laurenene ring system which contains a stereogenic quaternary carbon has been synthesised by transannular
radical cyclisations. Pattenden combined a radical Grob fragmentation with a transannular cyclisation in his approach (Scheme 47).\(^{48}\) Alcohol 172 was treated with phenyliodine(III) diacetate in the presence of iodine while being irradiated with a sunlamp and was converted in one pot into 174 in 58% yield, presumably via a transannular cyclisation of radical 173 and then a 5-exo cyclisation onto the adjacent vinyl group.

Scheme 47 Synthesis of the laurenene ring system

7.4 11-Membered Rings

Malacria used a tandem radical cyclisation across an 11-membered ring to construct the core of the linear triquinanes.\(^{49}\) Formation of the triquinane 180 arises from sequential radical cyclisations. Initially, the 5-exo-dig cyclisation of the α-silyl radical 176 gave vinyl radical 177, which in turn underwent transannular 5-exo-trig cyclisation to 179 and then further transannular 5-exo-trig cyclisation. Tamao oxidation revealed 180 in 45% yield and as a single diastereomer (Scheme 48). Interestingly β-fragmentation of 179 gave rise to side product 181 in 12% yield and as a 2:1 mixture of diastereomers.

The same group used this strategy for the synthesis of epi-illudol.\(^{50}\) In this instance, cyclisation of the α-silyl radical generated a vinyl radical which cyclised in a transannular 4-exo-trig fashion and was followed by a 5-endo-trig cyclisation to generate 183 (Scheme 49).

Scheme 49 Radical cyclisations in the synthesis of epi-illudol

generated both 185, as a mixture of two diastereomers in 25% yield, and 186, the product of reduction after the initial macrocyclisation in, 20% yield (Scheme 50). The reduction product of 184 was also isolated in 30% yield.

7.6 12-Membered Rings

The cembranoid natural product (±)-7,8-epoxy-4-basmen-6-one was constructed via the use of a transannular cyclisation across a 14-membered ring.\(^{52}\) Initially, a 5-exo-trig cyclisation onto the isolated double bond generated the first 5-membered ring. The resultant radical was then poised to cyclise onto the allene again to generate a mixture of 189 and 190 (Scheme 51). The product mixture could be converted into predominately 189 by further treatment with thiophenol and 2,2′-azobisisobutyronitrile under irradiation.
8 Miscellaneous Transannular Reactions

The following do not fall into any of the above categories for transannular reactions, and so have been grouped together in this the final section of the review.

8.1 8-Membered Rings

An ‘exocyclic’ transannular cycloaddition of methylencyclopropanes 191 promoted by either nickel(0) or palladium(0) resulted in the formation of propellane structures 193 in excellent yields. It was discovered that Pd(0)–PPh₃, generated from bis(triphenylphosphine)palladium(II) dichloride and diisobutylaluminium hydride gave the best results (Scheme 52). The reaction was, unlike its intermolecular counterpart, entirely regioselective. The authors also found that the reaction was very substrate-dependent, and when an additional methyl group was added to the cyclooctane ring adjacent to the methylencyclopropane, the reaction shut down completely.

8.2 9-Membered Rings

The synthesis of (+)-saxitoxin was completed with the aid of a transannular oxidative cyclisation of a 9-membered cyclic guanidine. It was found that the optimum conditions for the formation of 195 over undesired 196 or uncyclised 197 included the use of a mixture of osmium(III) chloride, Oxone®, and sodium carbonate. This gave the products in a ratio of 12:1:1 (195/196/197) and an overall yield of 62% (Scheme 53). Compound 195 was taken forward to complete the total synthesis in a further two steps. The authors postulated that the key oxidative cyclisation reaction proceeded by the formation of an Os(V)=O species and that the pendant guanidine unit has a role as a base to promote the selective elimination from the C-4 centre.

8.3 11-Membered Rings

A transannular platinum(II) chloride catalysed cycloisomerisation has led to the construction of the tricyclic cores of natural products such as anastreptene and myliol (Scheme 54). It was proposed that the key oxidative cyclisation reaction proceeded by the formation of an Os(V)=O species and that the pendant guanidine unit has a role as a base to promote the selective elimination from the C-4 centre.
ether, presumably arising from a hydride shift to form the isomeric oxocarbenium ion which could then undergo isomerisation to a platinitacarbene species and cyclopropanation to give 203 in 55% yield.

Scheme 54 Platinum(II) chloride catalysed transannular cycloisomerisation

9 Conclusions

It is clear that the nature and scope of transannular reactions can provide synthetic chemists with a powerful and efficient strategy for the formation of complex polycyclic ring systems and this has been demonstrated many times in the literature. Particularly effective are transannular cycloaddition reactions such as the Diels–Alder reaction and methods for polycycle construction. This synthetic utility has been to great effect in the construction of many natural products. However, rivaling the use of the Diels–Alder reaction and isomerisation to a platinacarbene species and cyclopropa-ether, presumably arising from a hydride shift to form the isomeric oxocarbenium ion which could then undergo isomerisation to a platinitacarbene species and cyclopropanation to give 203 in 55% yield.

Scheme 54 Platinum(II) chloride catalysed transannular cycloisomerisation

9 Conclusions

It is clear that the nature and scope of transannular reactions can provide synthetic chemists with a powerful and efficient strategy for the formation of complex polycyclic ring systems and this has been demonstrated many times in the literature. Particularly effective are transannular cycloaddition reactions such as the Diels–Alder reaction and this has been to great effect in the construction of many natural products. However, rivaling the use of the Diels–Alder reaction is the use of cationic and radical-based methods for polycycle construction. This synthetic utility coupled with the aesthetic value of transannulation reactions will ensure that this is a vibrant subject of study for many years to come.

References


