Synthesis of Spirocyclic Compounds

Introduction

The name "Spirocyclane" was first introduced by Baeyer in 1900.[1] Spirocyclic structures are found in wide range of natural compounds isolated from various sources.[2-8] The complexity of these ring structures is represented by the quaternary carbon center and two fused rings. Stereoselective methodologies in constructing the spirocenter[9] have allowed for the total syntheses of many spirocenter-containing natural compounds over the years.

Synthetic Methodologies

The construction of the spirocyclics can be roughly categorized into alkylation, rearrangement, cycloaddition and cleavage of bridged systems. The intramolecular alkylation on the quaternary carbon is one of the most common methods in constructing spirocenters. The alkylation can either take place as a direct substitution or as a 1,4-addition (Fig. 1). Iwata and co-workers[10] have reported the stereoselective synthesis of spiro[5.5]undecane systems using Lewis-acid promoted spiroannulation of *bis*-acetals. A tandem reaction involving yamine was used by Ficini and co-workers[11] during the synthesis of the acoradiene. Spiroannulation *via* intramolecular 1,4-addition has also been shown for the synthesis of the core structure of alkaloid Manzamine A.[12]

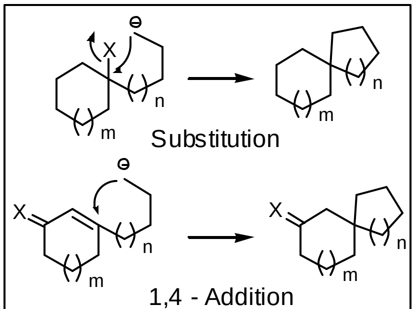


Figure 1. Alkylation Methods

Rearrangement reactions have also found wide application in the syntheses of spirocenters, due to their ability to form multiple stereocenters in one step. For example a vinylcyclopropanol/ vinycyclobutanol rearrangements (Fig. 2)[13,14] has also been reported for the synthesis of spirocycles by Trost's lab. This methodology has been successfully applied to the synthesis of spiro systems containing medium to large-size rings with controlled stereochemistry. The diastereoselectivity of this rearrangement can be explained by an extended transition state,[15] analogous to the enolates. The combination of Prins cyclization followed a Pinacol rearrangement, which has been used in the synthesis of five-membered rings,[16,17] has also been applied to the synthesis of spiro[4.5]decan-5-ones by Overman and co-workers (Fig. 3).[18]

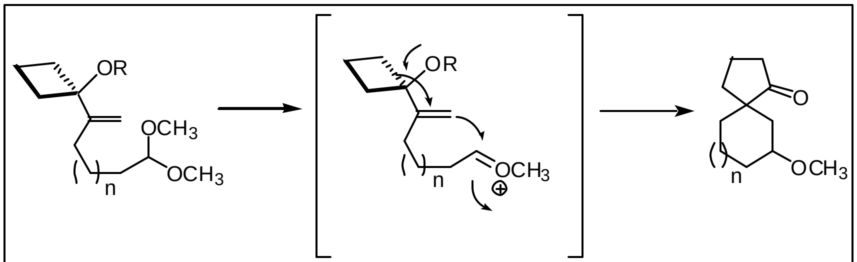


Figure 2. Vinylcyclopropane/vinylcyclobutane Rearrangement

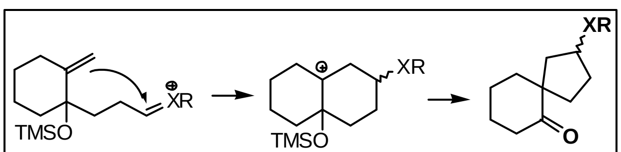
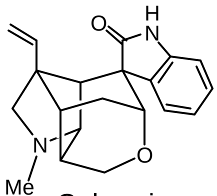


Figure 3. Prins-Pinacol Spiroannulation

Gelsemine

Gelesmine (Fig. 4) was found to be the major component of the alkaloids in *Gelsemium sempervirens*, and its structure was elucidated independently by X-ray crystallography[19] and NMR[2] in 1959. Its unique hexacyclic cage and spiro-oxindole structures attracted many synthetic studies. In 1994 Johnson and co-worker[20] reported a total synthesis of gelsemine in the racemic form. A radical cyclolization[21] was used to construct the spiro-oxindole center. However, the poor stereoselectivity of the cyclization step yielded only 22% of desired epimer during the key step. In the same year, Speckamp's lab[22] published another total synthesis of gelsemine with improved stereoselectivity during the formation of key spiro-oxindole compound through an intramolecular Heck reaction.[23] The only synthesis with complete control over the formation of spiro-oxindole center was achieved by Fukuyama's lab (Fig. 4).[24] The spirocenter was constructed in the early stage of the synthesis through a Cope-like divinyl-propane rearrangement.[25]



Gelsemine

Figure 4.

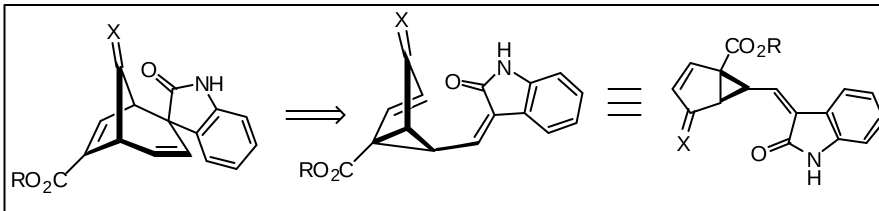
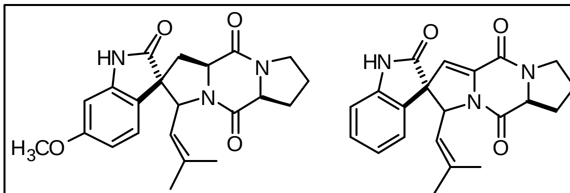


Figure 5. Fukuyama's Retrosynthesis of Gelsemine

Spirotryprostatins

Spirotryprostatin A and B, are members of the diketopiperazine alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*.[3,4] The key spiro-oxindole center of Spirotryprostatin A was synthesized in Danishefsky's lab via a Pinacole-type rearrangement.[26,27] Williams' achieved the syntheses of both antipodes of spirotryprostatin B by forming the core pyrrolidine ring through an asymmetric [1,3]-dipolar cycloaddition. In another recent synthesis of spirotryprostatin B, Overman[28] successfully utilized an asymmetric Heck insertion followed by trapping of η^3-allylpalladium intermediate by nitrogen nucleophiles.



Spirotryprostatin A Spirotryprostatin B

Figure 6

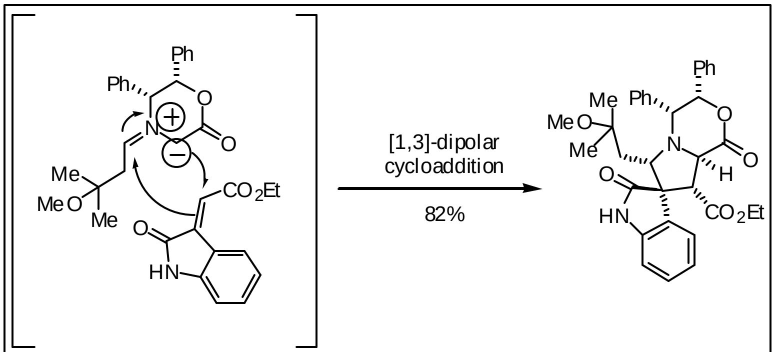
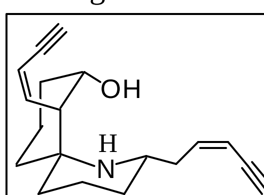


Figure 7. Williams' 1,3 Dipolar Cycloaddition Approach

(-)-Histrionicotoxin

(-)-Histrionicotoxin is one of the first members of unusual spiropiperidine-containing alkaloids. It was isolated from the brightly colored poison-dart frog *Dendrobates histrionicus* found in South America countries.[6] (-)-Histrionicotoxin and its analogues have attracted considerable pharmacological interest as noncompetitive inhibitors of the nicotinic acetylcholine receptor and as probes to study neuromuscular signal transmission.[29,30] Many effort towards the synthesis of (-)-histrionicotoxin and the simpler perhydrohistrionicotoxin have been reported,[31] not only due to its novel spiropiperidine structure but also due to its ever-diminishing supply from the natural sources. Since Kishi's[32] first total synthesis of racemic histrionicotoxins, several new routes have been published with the focus on the introduction of the spiropiperidine



(-)-Histrionicotoxin

Figure 8.

center. Stork's approach[33] utilized an intramolecular alkylation method. An "allylic expoxide cyclization" [34] was utilized to form the cyclohexane ring. A recently published total synthesis of (-)-histrionicotoxin by Holmes and co-workers[35] formed the spiropiperidine core from a [3+2] cycloaddition, followed by cleavage of the strained N-O bond.

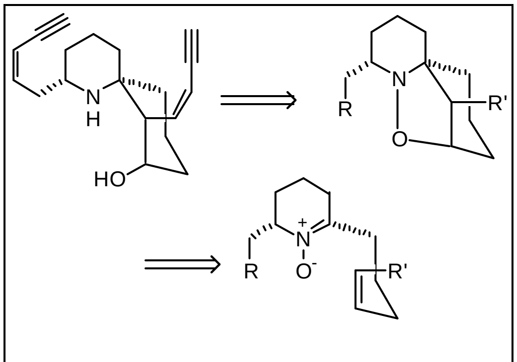


Figure 9. Homles' [3+2] Cycloaddition

Ginkgolide B

Ginkgo biloba, termed the "living fossil" by Darwin, has ancestors dating back to 230 million years.[36,37] Extracts of *Ginkgo biloba* have been used as herbal medicines for 5000 years in China and Japan to treat a variety of conditions, such as coughs, asthma, and circulatory disorders, and is currently undergoing clinical evaluation for treatment of dementia.[38,39] Since the structure of Ginkgolide B (Fig. 10) was first elucidated in 1967,[7,8,40] many synthetic efforts have been directed toward the total synthesis of this complex molecule. So far, only two successful total syntheses of the racemic form have been reported.[41,42] The structural complexity rises from Ginkgolide B's six rings, eleven stereogenic centers, ten oxygenated carbons, and four contiguous fully substituted carbons, including a spirocenter. During Corey and co-works and total synthesis of Ginkgolide B, the spirocenter was constructed through an intramolecular alkylation of acetal. Crimmins and co-workers approach to the formation spirocenter is an intramolecular [2+2] photocyclization[43] followed by regioselective cleavage of the cyclobutane ring.

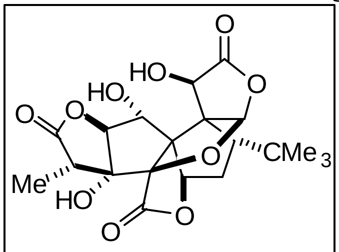


Figure 10.

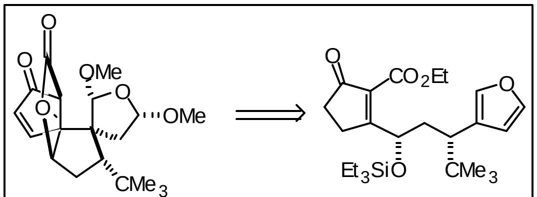


Figure 11. Crimmins' [2+2} Approach

Besides methodology mentioned in this seminar, some other novel ways have also emerged through the years, such as ring closing metathesis,[44,45] intramolecular condensation,[46] ene reaction[47] and some other metal catalyzed reactions.[48-50] With the ongoing discovery of new natural compound containing spirocenters, the synthesis of these structures will remain an active area of research.

References

(1) Baeyer, A. "Systematik und Nomenclatur Bicyclischer Kohlenwasserstoffe" *Ber. dtsch. chem. Ges.* **1900**, *33*, 3771-3775.

(2) Conroy, H.; Chakrabarti, J. K. "Nuclear magnetic resonance spectra of gelsemine derivatives. Structure and biogenesis of the alkaloid gelsemine" *Tetrahedron* **1959**, *4*, 6-13.

(3) Cui, C. B.; Kakeya, H.; Osada, H. "Novel mammalian cell cycle inhibitors, spirotryprostatins A and B, produced by Aspergillus fumigatus, which inhibit mammalian cell cycle at G2/M phase" *Tetrahedron* **1996**, *52*, 12651-12666.

(4) Cui, C. B.; Kakeya, H.; Osada, H. "Spirotryprostatin B, a novel mammalian cell cycle inhibitor produced by Aspergillus fumigatus" *J. Antibiot.* **1996**, *49*, 832-835.
(5) Cui, C. B.; Kakeya, H.; Osada, H. "Novel mammalian cell cycle inhibitors, cyclotryprostatins A-D, produced by Aspergillus fumigatus, which inhibit mammalian cell cycle at G2/M phase" *Tetrahedron* **1997**, *53*, 59-72.
(6) Daly, J. W.; Karle, I.; Myers, C.; Tokuyama, T.; Waters, J. A.; Witkop, B. "Histrionicotoxins. Roentgen-ray analysis of the novel allenic and acetylenic spiroalkaloids isolated from a Colombian frog, Denrobates histrionicus" *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870-1875.
(7) Okabe, K. J.; Yamada, K.; Yamamura, S.; Takasa, S. J. "Ginkgolides" *J. Chem. Soc. C* **1967**, *21*, 2201-2206.
(8) Sakabe, N.; Takada, S.; Okabe, K. J. "Structure of ginkgolide A, a novel diterpenoid trilactone" *J. Chem. Soc., Chem. Commun.* **1967**, *6*, 259-261.
(9) Sannigrahi, M. "Stereocontrolled synthesis of spirocyclics" *Tetrahedron* **1999**, *55*, 9007-9071.
(10) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Iwata, C. "A Novel and Stereoselective Spiroannelation - a Facile Access to Aphidicolane and Stemodane B/C/D-Ring Systems" *Tetrahedron Lett.* **1994**, *35*, 4125-4128.
(11) Ficini, J.; Revial, G.; Genet, J. P. "Acylation of ynamines by enol lactones: a new method of stereoselective spiroannulation." *Tetrahedron Lett.* **1981**, *22*, 629-632.
(12) Brands, K. M. J.; DiMichele, L. M. "An efficient and stereoselective construction of the core structure of the manzamines via an intramolecular Michael reaction" *Tetrahedron Lett.* **1998**, *39*, 1677-1680.
(13) Trost, B. M.; Lee, D. C. "Cyclization Terminators - Vinylcyclopropanol as a Composite Functional-Group" *J. Am. Chem. Soc.* **1988**, *110*, 6556-6558.
(14) Trost, B. M.; Chen, D. W. C. "Vinylcyclobutanols: A composite functional group?" *J. Am. Chem. Soc.* **1996**, *118*, 12541-12554.
(15) Murata, S.; Suzuke, M.; Noyori, R. "Trialkylsilyl triflates. 5. A stereoselective aldol-type condensation of enol silyl ethers and acetals catalyzed by trimethylsilyl trifluoromethanesulfonate" *J. Am. Chem. Soc.* **1980**, *102*, 3248-3249.
(16) Overman, L. E. "New reactions for forming heterocycles and their use in natural products synthesis" *Aldrichim. Acta* **1995**, *28*, 107-120.
(17) Overman, L. E. "Charge as a Key Component in Reaction Design - the Invention of Cationic Cyclization Reactions of Importance in Synthesis" *Accounts Chem. Res.* **1992**, *25*, 352-359.
(18) Minor, K. P.; Overman, L. E. "Prins-pinacol spiroannulations" *Tetrahedron* **1997**, *53*, 8927-8940.
(19) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. "X-ray analysis of the structure of gelsemine hydrohalides" *Tetrahedron Lett.* **1959**, *4*, 1-5.
(20) Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. "A Total Synthesis of Gelsemine - Synthesis of a Key Tetracyclic Intermediate" *J. Chem. Soc.-Chem. Commun.* **1994**, 763-764.
(21) Wender, P. A.; Cooper, C. B. "The Photochemistry of 1-Alkenylbenzotriazoles - Methodology for the Synthesis of Indoles" *Tetrahedron* **1986**, *42*, 2985-2991.
(22) Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. "The Total Synthesis of (+/-)-Gelsemine" *J. Chem. Soc.-Chem. Commun.* **1994**, 767-768.
(23) Madin, A.; Overman, L. E. "Controlling Stereoselection in Intramolecular Heck Reactions by Tailoring the Palladium Catalyst" *Tetrahedron Lett.* **1992**, *33*, 4859-4862.
(24) Fukuyama, T.; Liu, G. "Stereocontrolled total synthesis of (+/-)-gelsemine" *Pure Appl. Chem.* **1997**, *69*, 501-505.
(25) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. R. "Divinylcyclopropane-cycloheptadiene rearrangement" *Org. React.* **1992**, *41*, 1-133.
(26) von Nussbaum, F.; Danishefsky, S. J. "A rapid total synthesis of spirotryprostatin B: Proof of its relative and absolute stereochemistry" *Angew. Chem.-Int. Edit.* **2000**, *39*, 2175-+.
(27) Edmondson, S. D.; Danishefsky, S. J. "The total synthesis of spirotryprostatin A" *Angew. Chem.-Int. Edit.* **1998**, *37*, 1138-1140.

(28) Overman, L. E.; Rosen, M. D. "Total synthesis of (-)-spirotryprostatin B and three stereoisomers" *Angew. Chem.-Int. Edit.* **2000**, *39*, 4596-4598.

(29) Gessner, W.; Takahashi, K.; Witkop, B.; Brossi, A.; Albuquerque, E. X. "Probes for a Regulatory Site on the Nicotinic Acetylcholine Receptor-Channel - Synthesis of (+/-)-7-Debutylperhydrohistrionicotoxin, (+--)-2-Depentyl-7- Debutylperhydrohistrionicotoxin, and Their Analogs" *Helv. Chim. Acta* **1985**, *68*, 49-55.

(30) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. "Total Synthesis and Electro-Physiological Properties of Natural (-)-Perhydrohistrionicotoxin, Its Unnatural (+)-Antipode and Their 2-Depentyl Analogs" *Helv. Chim. Acta* **1982**, *65*, 252-261.

(31) Tanner, D.; Hagberg, L. "A convergent enantioselective total synthesis of (-)- perhydrohistrionicotoxin with an intramolecular imino ene-type reaction as a key step" *Tetrahedron* **1998**, *54*, 7907-7918.

(32) Carey, S. C.; Aratani, M.; Kishi, Y. "A Total Synthesis of D,1-Histrionicotoxin" *Tetrahedron Lett.* **1985**, *26*, 5887-5890.

(33) Stork, G.; Zhao, K. "Total Syntheses of (-)-Histrionicotoxin and (-)- Histrionicotoxin-235a" *J. Am. Chem. Soc.* **1990**, *112*, 5875-5876.

(34) Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. "The Allylic Epoxide Cyclization - a Method for the Control of Regiochemistry and Stereochemistry in Cyclohexane Systems" *J. Am. Chem. Soc.* **1990**, *112*, 1661-1663.

(35) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. "Synthesis of (-)-histrionicotoxin by a tandem process" *J. Am. Chem. Soc.* **1999**, *121*, 4900-4901.

(36) van Beek, T. A.; Bombardelli, E.; Morazzoni, P.; Peterlongo, F. "Ginkgo biloba L" *Fitoterapia* **1998**, *69*, 195-244.

(37) Major, R. T. "Ginkgo, the most ancient living tree" *Science* **1967**, *157*, 1270-1273.

(38) Ernst, E.; Pittler, M. H. "Ginkgo biloba for dementia - A systematic review of double- blind, placebo-controlled trials" *Clin. Drug Invest.* **1999**, *17*, 301-308.

(39) LeBars, P. L.; Katz, M. M.; Berman, N.; Itil, T. M.; Freedman, A. M.; Schatzberg, A. F. "A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia" *JAMA-J. Am. Med. Assoc.* **1997**, *278*, 1327-1332.

(40) Nakanishi, K. "The ginkgolides" *Pure Appl. Chem.* **1967**, *14*, 89-113.

(41) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, J. N. "Total Synthesis of (+/-)-Ginkgolide-B" *J. Am. Chem. Soc.* **1988**, *110*, 649-651.

(42) Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. "Total synthesis of (+/-)-ginkgolide B" *J. Am. Chem. Soc.* **1999**, *121*, 10249-10250.

(43) Crimmins, M. T.; Thomas, J. B. "Intramolecular Enone-Furan Photocycloadditions - Studies toward the Synthesis of Ginkgolide-a and Ginkgolide-B" *Tetrahedron Lett.* **1989**, *30*, 5997-6000.

(44) Aburel, P. S.; Romming, C.; Ma, K. B.; Undheim, K. "Synthesis of alpha-hydroxy and alpha-oxospiranes through ruthenium(II)-catalyzed ring-closing metathesis" *J. Chem. Soc.-Perkin Trans. 1* **2001**, 1458-1472.

(45) Wright, D. L.; Schulte, J. P.; Page, M. A. "An imine addition/ring-closing metathesis approach to the spirocyclic core of halichlorine and pinnaic acid" *Org. Lett.* **2000**, *2*, 1847-1850.

(46) Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. "First synthesis of cytotoxic 8,9-secokaurene diterpenoids. An enantioselective route to (-)-O-methylshikoccin and (+)-O-methylepoxyshikoccin" *J. Am. Chem. Soc.* **1997**, *119*, 9662-9671.

(47) Oppolzer, W.; Mahalanabis, K. K.; Battig, K. "A flexible stereoselective synthesis of the spirosesquiterpenes (±)-b-acorenol, (±)-b-acoradiene, (±)-acorenone B and (±)-acorenone via an intramolecular ene reaction" *Helv. Chim. Acta* **1977**, *60*, 2388-2401.

(48) Tanaka, M.; Takahashi, M.; Sakamoto, E.; Imai, M.; Matsui, A.; Fujio, M.; Funakoshi, K.; Sakai, K.; Suemune, H. "Enantio- and diastereoselective construction of 4,9- dimethylspiro 4.4 nonane-2,7-dione using Rh-catalyzed asymmetric cyclization" *Tetrahedron* **2001**, *57*, 1197-1204.

(49) Takahashi, M.; Tanaka, M.; Sakamoto, E.; Imai, M.; Matsui, A.; Funakoshi, K.; Sakai, K.; Suemune, H. "Application of Rh-catalyzed cyclization for the construction of three consecutive chiral carbons in 4,9-dimethylspiro 4.4 nonane-2,7-dione" *Tetrahedron Lett.* **2000**, *41*, 7879-7883.
(50) Kondakov, D. Y.; Wang, S.; Negishi, E. "Titanium-catalyzed cascade carboalumination of 2-alkyl-substituted dienes and related trienes" *Tetrahedron Lett.* **1996**, *37*, 3803-3806.