Synthesis of Tetrahydrolipstatin

Significance: Tetrahydrolipstatin (Xenical®) is a pancreatic lipase inhibitor that is marketed as a treatment for obesity. The eleven-step small-scale synthesis depicted (31% overall yield) features the regioselective carbonylation of the cis-epoxide using the bimetallic [Lewis acid]+[Co(CO)₄]⁻ catalyst J to give the trans-β-lactone.

Comment: Seven diastereoisomers of tetrahydrolipstatin were also prepared by this epoxide carbonylation route. Attempts to synthesize epoxide via the direct DCC coupling of N-formyl-L-leucine occurred with appreciable amounts of epimerization.

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**Significance:** A-type procyanidins are oligomeric catechins that feature a dioxabicyclo[3.3.1]-nonane core constituted of two catechin units. Suzuki and co-workers report the first, high yielding, stereoselective synthesis of (+)-procyanidin A2. Their synthetic strategy relies on the highly selective annulation of an ethylenedioxy-bridged flavan with a nucleophilic flavan unit.

**Comment:** Electrophilic flavan G was treated with BF3·OEt2 in presence of selectively protected flavan unit D to afford the bicyclic compound H regioselectively, stereoselectively, and in high yield. The synthesis of the targeted molecule was completed by silyl deprotection followed by bromine and benzyl group removal.
Total Synthesis of (+)-Cavicularin

Significance: (+)-Cavicularin, isolated from the liverwort Cavicularia densa, is a chiral cyclophane natural product. Because of its unusual molecular structure, several total syntheses have been reported to date. Zhao and Beaudry report a conceptually different approach, which relies on an intramolecular enantioselective pyrone Diels–Alder reaction with subsequent CO₂ extrusion to generate the aromatic A ring of the natural product.

Comment: The synthesis commences with a remarkably selective one-pot three-component Suzuki cross-coupling between dibromide B and boronic esters A and C. Coupling product D was further advanced to α-hydroxy pyrone E. In the presence of cinchona alkaloid F, this material underwent the desired Diels–Alder reaction to yield intermediate G, which immediately eliminated CO₂ and phenylsulfinic acid to generate H as a single regioisomer. Finally, reduction and protecting group removal yielded (+)-cavicularin in 7.3% overall yield.
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Macrocyclic Protease Inhibitors with Reduced Peptide Character
Angew. Chem. Int. Ed. 2014, 53, 7828–7831.

Synthesis of Macrocyclic Protease Inhibitors

**Significance:** Protease substrates and inhibitors adopt a β-strand conformation on active site binding. Abell and co-workers have shown that a pyrrole can be used to replace two amino acids of a peptide to generate a macrocycle that retains the required geometry for active site binding.

**Comment:** Six macrocycles were synthesized and screened against three cysteine proteases (μ-calpain, cathepsin L and cathepsin M) and two serine proteases (α-chymotrypsin and human leukocyte elastase). An X-ray structure of macrocycle M bound to α-chymotrypsin was obtained.
Synthesis of Sitagliptin

**Significance:** The key step in a new synthesis of Sitagliptin® entails selective formation of the Schiff base (R,R)-C derived from the benzophenone (R)-A and the β-amino acid rac-B. The resultant nickel(II) complex (R,R)-C was obtained in 68% yield and with dr = 98:2. One recrystallization from EtOH gave the enantiopure complex. The auxiliary (R)-A was recovered in 96% yield. The authors explain this is an example of kinetic resolution, though the information presented may also be compatible with a thermodynamically driven epimerization.

**Comment:** Sixteen examples of the auxiliary-assisted epimerization of β-aryl-, β-heteroaryl and β-alkyl-substituted β-amino acids are provided with yields typically being ≥75% and dr ≥ 97:3. A significant development in the optimization of the chiral auxiliary A was the discovery that the presence of water in the formation of the nickel(II) complex had a detrimental effect on the reaction progress. The three chlorine substituents were also significant contributors to the performance of the auxiliary.
**Synthesis of Hydroxyphthioceranic Acid**

**Significance:** A novel synthetic route towards hydroxyphthioceranic acid, a constituent of the major cell-wall lipid of virulent human *Mycobacterium tuberculosis*, is reported. After the preceding work by the groups of Minnaard and Schneider in 2013 (both 34 steps in total), it is the third successful total synthesis of this natural product. By following a distinct strategy which is heavily based on a methodology developed by the Aggarwal group, the target was reached in only 17 steps.

**Comment:** The key element of this work is the development of a protodeboronation protocol for pinacol boronic esters, which in conjunction with the previously reported lithiation–borylation procedure, leads to a new methodology for traceless one-pot C–C bond formation. Clever tactical use of lithiation–borylation, lithiation–borylation–oxidation, and lithiation–borylation–protodeboronation methodologies led to a very efficient overall strategy.

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Total Syntheses of Spirooliganones A and B

Significance: In 2013, spirooliganones A and B were isolated from the roots of *Illicium oligandrum*, which have been used in traditional Chinese folk medicine for the treatment of rheumatoid arthritis. Xie and co-workers report the first syntheses of (–)-spirooliganones A and B.

Comment: A one-pot Knoevenagel condensation/hetero-Diels–Alder reaction gave a mixture of C17 epimers A and B, which were further elaborated, through a seven-step sequence, including a late-stage oxidative dearomatization, to give spirooliganones A and B.
Syntheses of Spirooliganones A and B

Significance: It was previously proposed that spirooliganones A and B are produced via a biogenetic pathway involving a hetero-Diels–Alder reaction of a monoterpenoid and (–)-sabinene. Based on this hypothesis, Tong and co-workers report their approach to the spirooliganones (see L. Wei, M. Xiao, Z. Xie Org. Lett. 2014, 16, 2784; Synfacts 2014, 10, 1009 for the first and closely related syntheses by Xie and co-workers).

Comment: Heating a mixture of resorcinol derivative A and (–)-sabinene resulted in a 1:1 mixture of C17 epimers C via a Claisen rearrangement/hetero-Diels–Alder reaction. After asymmetric dihydroxylation, the resulting diastereomers were separated and transformed into spirooliganones A and B.
**Synthesis of Gracilamine**

**Significance:** Gracilamine is a member of the *Amaryllidaceae* alkaloid family. Several members of this family show a range of interesting biological properties such as antiviral and antitumor activity as well as acetylcholinesterase inhibition. Isolated in 2005, gracilamine’s biological activities have not been investigated because of its scarcity. The authors describe the second total synthesis of this complex alkaloid, thereby providing additional support for its stereochemical configuration.

**Comment:** Substrate A was synthesized in seven steps in 33% yield. A key photo-Nazarov reaction followed by deprotection and mesylation afforded B in 67% yield. Subsequent Saegusa oxidation led to D and C in 60% and 18% yield, respectively. The undesired isomer C could be transformed back into B by treatment with hydrochloric acid and sodium iodide in acetone. A three-step sequence led to E, which was converted into F by condensation with hydroxylamine and subsequent reduction as a favorable 5:1 mixture of diastereomers. F was converted into H by a Mannich reaction. Final reduction using sodium borohydride afforded gracilamine in 82% yield.

**Key words**
- gracilamine
- amaryllidaceae alkaloids
- photo-Nazarov cyclization
- Mannich reaction
**Synthesis of Paroxetine**

**Significance:** Paroxetine (Paxil®) is a selective serotonin reuptake inhibitor that is widely prescribed for the treatment of anxiety and depression. The synthesis of racemic paroxetine depicted features a diastereocoupling cobalt-catalyzed sp<sup>3</sup>–sp<sup>2</sup> cross-coupling reaction of 4-fluorophenylmagnesium bromide (F) with the bromopiperidine E.

**Comment:** The diastereocoupling to the thermodynamically more stable trans-4-aryl-piperidine trans-G is due to the configurational lability of a radical intermediate. Fe(acac)<sub>3</sub> in combination with TMEDA and HMTA also catalyzes the cross-coupling reaction, but in low yield. A mechanism for the cross-coupling reaction is proposed.
**Synthesis of (–)-Crinipellin A**

**Significance:** The crinipellin diterpenoids are the only known examples of tetraquinane natural products. Their unique skeleton, comprised of four fused cyclopentane rings and including up to eight contiguous stereocenters, makes them formidable synthetic targets. Despite their structural complexity and promising biological profiles, only a single total synthesis has been reported in the 25 years since their isolation (crinipellin B: E. Piers, J. Renaud *J. Org. Chem.* 1993, 58, 11).

In an impressive display of their tandem cycloaddition methodology, utilizing trimethylenemethane diyls, Lee and co-workers demonstrate the highly efficient and selective construction of three cyclopentane rings in a single step and in excellent yield for their synthesis of (–)-crinipellin A.

**Comment:** Enantiopure cyclopentanone A was advanced to cyclization precursor F in 12 steps with high yield, setting the stage for the key cyclization cascade. Base-mediated formation of the corresponding diazoalkane allowed for a 1,3-dipolar cycloaddition with the allene to afford G. Nitrogen extrusion to generate trimethylenemethane diradical H then led to a second cyclization event with the exomethylene group, forging the complete tetraquinane skeleton in I. Unfortunately, α-hydroxylation at C9 afforded the undesired epimer K, but the problem was creatively solved by oxidation, reversible sulfoximine anion addition to the C8-ketone, and hydroxyl-directed reduction. Construction of the epoxynone and silyl ether deprotection finally afforded (–)-crinipellin A.
A New Cobalt–Salen Catalyst for Asymmetric Cyclopropanation. Synthesis of the Serotonin–Norepinephrine Repuptake [sic!] Inhibitor (+)-Synosutine

**Org. Lett. 2014, 16, 3880–3883.**

**Synthesis of Synosutine via Asymmetric Cyclopropanation**

![Chemical Structures and Reactions](Insert Image Here)

**Significance:** A new cobalt–salen complex C based on a chiral cis-2,5-diaminobicyclo[2.2.2]-octane scaffold, together with potassium thioacetate as a promoter, catalyzes the reaction of 1,1-disubstituted alkenes with ethyl diazoacetate to give cyclopropanes with high diastereo- and enantioselectivity. Fifteen examples of the reaction are reported. A mechanism and rationale for the stereochemistry of the cyclopropanation are presented.

**Comment:** Synosutine is a prospective antidepressant that is a dual inhibitor of serotonin and norepinephrine transporters. For a previous asymmetric synthesis of synosutine and related analogues based on the Charette cyclopropanation of an allylic alcohol, see: J. D. White et al. *J. Med. Chem.* 2009, 52, 5872.