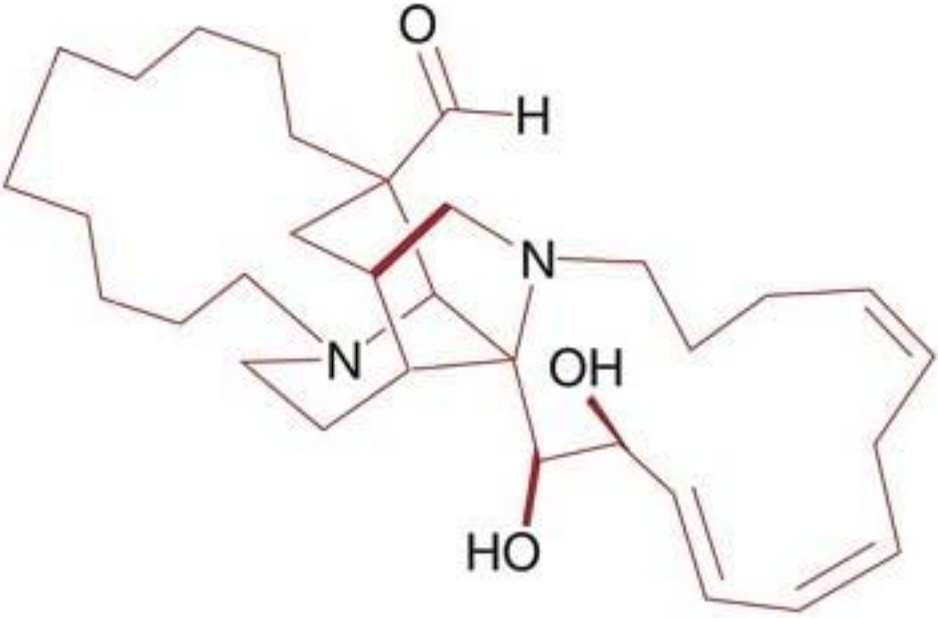
Organic Synthesis

State of the Art 2005–2007



DOUGLASS F. TABER

WILEY

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State of the Art 2005–2007

Douglass F. Taber
University of Delaware
Newark, DE

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Preface

Several years ago, I was approached about updating Rich Larock's valuable compendium of organic transformations. As I contempated that task, it became clear to me that what the organic synthesis community needed more was a real-time overview of current developments. With the able assistance of Reto Mueller, webmaster of www.organic-chemistry.org, I started writing weekly Organic Highlights columns. These soon developed into mini-reviews of areas of current interest in organic synthesis. The Highlights columns provide in-depth coverage of new developments across the field. Some topics, such as asymmetric organocatalysis and C-H functionalization, are often mentioned in the scientific press. Other topics, such as new methods for C-C bond construction, receive little popular notice, but are at least as important.

There was still the problem of information retrieval. To this end, Wiley was persuaded to publish the first two years of the Highlights columns in book form, *Organic Synthesis: State of the Art 2003-2005,* with author and transformation indices. This volume continues that series, with cumulative indices. With both volumes in hand, one can at a glance be up to date on a particular topic. For many recent advances, including organocatalysis, this level of search provides a comprehensive overview of the field. To make in-depth review more convenient, each of the weekly columns is still up on the web, with links to the original journal articles.

I often consult these volumes myself in my day-to-day work of teaching and research. These two volumes together (and the later biennial volumes that will follow) are a valuable resource that should be on the bookshelf of every practicing organic synthesis chemist.

DOUGLASS F. TABER

Newark, DE
March 1, 2008

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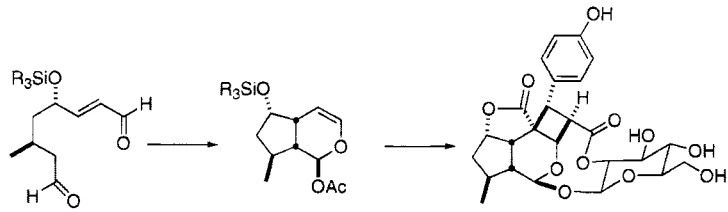
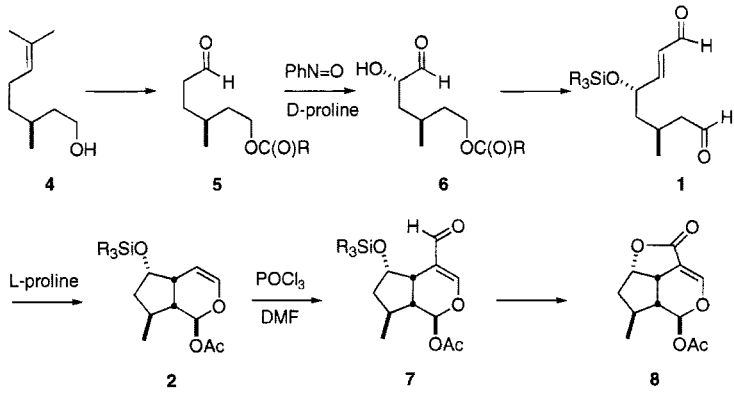
Synthesis of (-)-Littoralisone

January 2, 2006

The loss of mental function associated with aging is thought to be due at least in part to the degradation of neurite connections between neurons. Natural products such as (-)-littoralisone **3** that promote neurite outgrowth in cell culture are therefore interesting lead compounds for pharmaceutical discovery. The synthesis of **3** recently reported (*J. Am. Chem. Soc.* **2005**, *127*, 3696) by David W. C. MacMillan of Caltech uses organocatalysis to assemble **1**, to control the relative configuration of the ring system of **2**, and to assemble the glucose component of **3**.

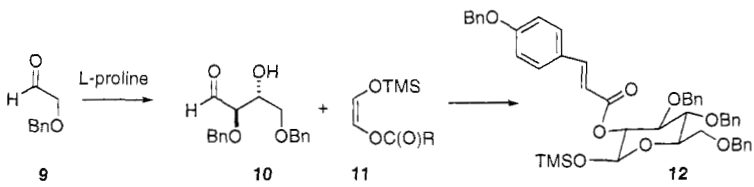


The preparation of **1** began with commercial enantiomerically-pure citronellol **4**. Ozonolysis of the ester delivered the aldehyde **5**, which was hydroxylated with high diastereocontrol (enantiocontrol), using the proline-catalyzed procedure developed by MacMillan (LINK: Organic Highlights 26 January 2004). Protection and homologation of **6** then gave **1**.



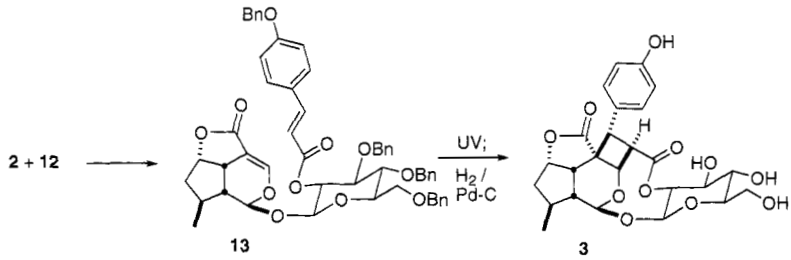
With most catalysts the dialdehyde **1** cyclized predominantly to the trans-fused product. With the correct enantiomer of the organocatalyst, however, the cyclization could be directed toward the desired cis-fused **2**. Vilsmeier homologation of the electron-rich alkene followed by oxidation and lactonization then delivered **8.**

A glucose derivative such as **12** would usually be prepared over several protection and deprotection steps from a commercially-available form of glucose. The authors took a different approach, using the method for protected glucose synthesis they have developed (LINK: Organic Highlights 21 March 2005). Thus, proline-catalyzed dimerization of **9** gave **10**, which after condensation with **11** and benzylation gave **12**.



9 **10** **11** **12**

Condensation of **12** with **8** gave the exo glycoside **13**. Brief exposure of **13** to 350 nm irradiation followed by debenzylation then gave **3**. It is interesting to note that the photocyclization of **13** proceeded slowly even under ambient laboratory light, suggesting that this step in the biosynthesis of **3** need not be enzyme-mediated.



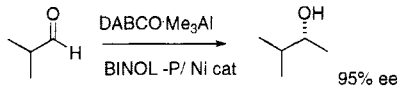
13 **3**

Enantiocontrolled Construction of Oxygenated and Animated Sterogenic Centers

January 9, 2006

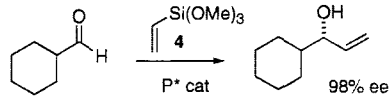
Asymmetric synthesis depends substantially on the enantiocontrolled construction of oxygenated and aminated stereogenic centers.

One of the more exciting developments of recent years has been the development of enantioselective dialkyl zinc addition to aldehydes. These reagents are, however, challenging to handle. Simon Woodward of the University of Nottingham has now shown (*Angew. Chem. Int. Ed.* **2005**, *44*, 2232) that complexation with DABCO converts readily-available trialkylaluminum reagents such as **1** to attentuated donors. BINOL-mediated additions of these reagents to aldehydes proceed with high enantiomeric excess.



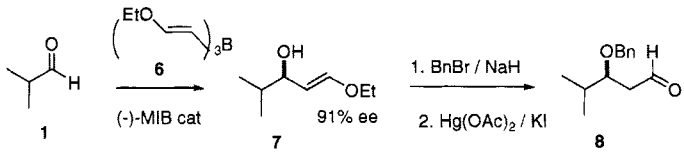
1 **2**

Motomu Kanai and Masakatsu Shibasaki of the University of Tokyo have reported (*J. Am. Chem. Soc.* **2005**, *127*, 4138) another family of easily-prepared nucleophiles, the alkenyl siloxanes. The catalyst for the addition is an enantiomerically-pure phosphine.



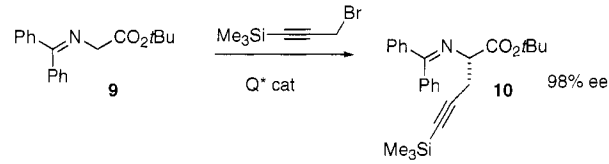
3 **5**

Patrick J. Walsh of the University of Pennsylvania has described (*Organic Lett.* **2005**, *7*, 1729) a complementary source of vinyl nucleophiles, based on alkenyl transfer from boranes such as **6**. The product **7** can be protected, then hydrolyzed to the aldehyde.

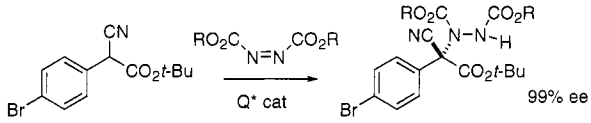


1 **7** **8**

Phase-transfer alkylation of the benzophenone imine of glycine ester remains a workhorse for the synthesis of α-amino acids. Merritt B. Andrus of Brigham Young University has developed (*Tetrahedron Lett.* **2005**, *46*, 3839) an improved dihydrocinchodine catalyst that delivers very good ee's.

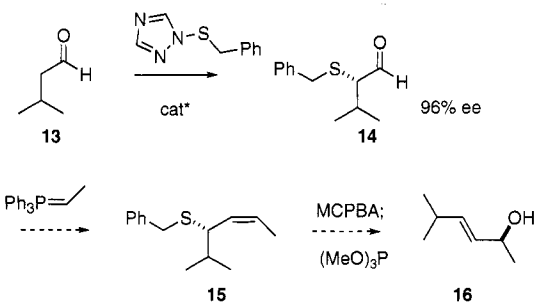


Another way to form a C-N bond is to directly aminate an enolate. Li Deng of Brandeis University has reported (*Organic Lett.* **2005**, *7*, 167) the remarkable observation that aryl cyanoacetates such as **11** can be aminated with high enantioselectivity to form the quaternary centers, again by using a quinine-derived organocatalyst.



11 **12**

Another asymmetric transformation with intriguing potential is the enantioselective sulfenylation of aldehydes reported (*Angew. Chem. Int. Ed.* **2005**, *44*, 794) by Karl Anker Jørgensen of Aarhus University. Using a proline-derived organocatalyst, ternary centers are formed with high enantiomeric excess. This new availability of sulfides such as **14** raises the intriguing question of whether the aldehyde could be homologated without epimerization. If **15** could be prepared with high geometric and enantiomeric purity, Evans-Mislow rearrangement of the derived sulfoxide should deliver **16** also with high geometric and enantiomeric purity. The net transformation would be an interesting homologation of the aldehyde **13**.



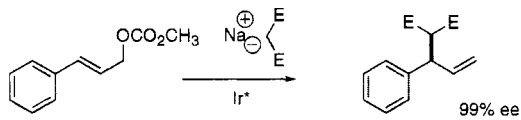
13 **14** **15** **16**

Catalytic Enantioselective Construction of Alkylated Stereogenic Centers

January 16, 2006

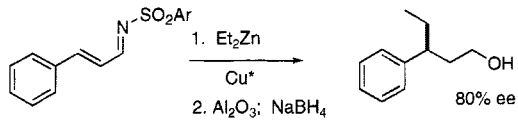
There are several strategies now available for the catalytic enantioselective construction of oxygenated and aminated stereogenic centers. Catalytic processes for the enantioselective construction of *alkylated* stereogenic centers are just starting to appear. In general, investigators have approached this problem by reacting a prochiral electrophile with a chiral catalyst and a nucleophile. There are three variables that are useful to consider: the nucleophile, the catalyst, and the substituent(s) at the reacting center.

One of the first such reactions to be reduced to practice was the addition of malonate to cinnamyl carbonate **1**. The current state of the art is illustrated by a recent contribution (*Organic Lett.* **2005**, *7*, 1621) from Alexandre Alexakis at the University of Geneva, in which the Ir catalyst was further optimized. The coupling proceeded with 98:2 regioselectivity in the desired sense.



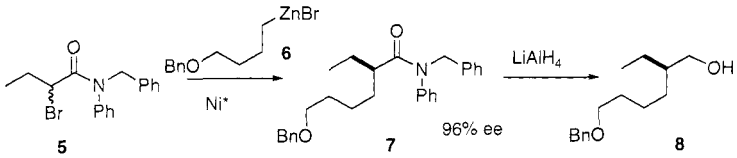
1 **2**

In general, *aryl* substituted stereogenic centers such as that of **2** are the easiest to form with high enantioselectivity. Thus, when Kiyoshi Tomioka and co-workers of Kyoto University investigated (*J. Org. Chem.* **2005**, *70*, 297) the conjugate addition of dialkyl zinc reagents to α,β-unsaturated aldehydes, they began with substrates such as **3**. They found that when the aldehyde was replaced by a sterically-demanding sulfonyl imine, Cu*-mediated conjugate addition was efficient. They chose to analyze the intermediate enantiomerically-enriched aldehyde as the corresponding alcohol **4**. The ee's are modest by current standards.

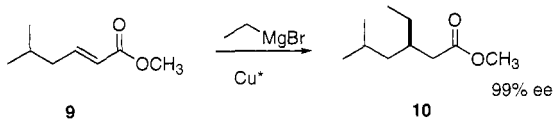


3 **4**

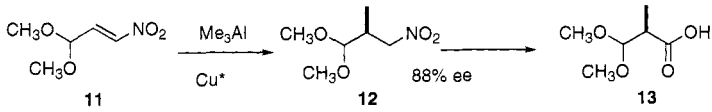
Alkyl zinc halides are more readily available than dialkyl zincs. Gregory C. Fu of MIT recently described (*J. Am. Chem. Soc.* **2005**, *127*, 4594) the Ni*-mediated coupling of such reagents to racemic α-bromoamides such as **5**, to give the highly enantiomerically-enriched products such as **7**. This is the functional equivalent of catalytic enantioselective alkylation of the amide enolate. The amide **7** is easily reduced to the primary alcohol **8**. The authors note that the alkyl zinc halides must be freshly prepared – a commercial reagent did not work.



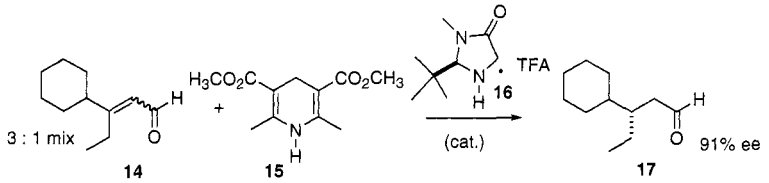
Conjugate addition is complementary to α-alkylation. Ben L. Feringa of the University of Groningen has described (*Angew. Chem. Int. Ed.* **2005**, *44*, 2752) the catalytic enantioselective addition of Grignard reagents to α,β-unsaturated esters such as **9**. This procedure works well with a wide range of esters and Grignard reagents.



Some trialkyl aluminum reagents are commercially available. Alexandre Alexakis of the University of Geneva has also reported (*Tetrahedron Lett.* **2005**, *46*, 1529) the conjugate addition of Me_3Al to nitro alkenes such as **11**. The product nitro compounds can be converted into acids without racemization. Carreira previously [link: Highlights June 20, 2005] has shown that nitro compounds such as **12** can also be converted into the corresponding nitriles without epimerization.



One could imagine that alkylated stereogenic centers could also be constructed by the enantioselective reduction of trisubstituted alkenes. David W. C. MacMillan of Caltech has now (*J. Am. Chem. Soc.* **2005**, *127*, 32) reduced this to practice. Using Hantsch ester **15** and an organocatalyst, geometric mixtures of α,β-unsaturated aldehydes such as **14** are reduced with remarkable enantiomeric excess.

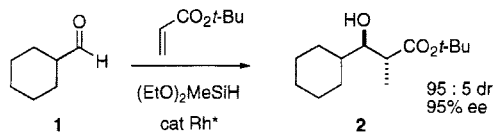


Catalytic Enantioselective Aldol/Mannich Reactions Leading to Extended Arrays of Stereogenic Centers

January 23, 2006

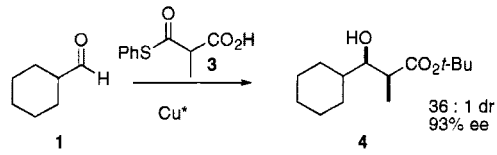
There are several strategies now available for the catalytic construction of isolated oxygenated and aminated stereogenic centers in high enantiomeric excess (Organic Chem Highlights **2006**, Jan. 9). Processes for the catalytic enantioselective construction of extended arrays of aminated, oxygenated and alkylated stereogenic centers have also been developed (for the previous treatment of this topic, see Organic Chem Highlights **2005**, June 27).

The enantioselective element can be complexed with the nucleophile, with the acceptor, or both. A powerful approach is to use the chiral ligand sphere around a catalytic transition metal as the controlling element. Hisao Nishiyama of Nagoya University has recently (*J. Am. Chem. Soc.* **2005**, *127*, 6972) developed such an approach. Silane-mediated reduction of an unsaturated ester in the presence of an aldehyde and a chiral Rh catalyst delivered the anti aldol product **2** in high diastereoselectivity and enantioselectivity.



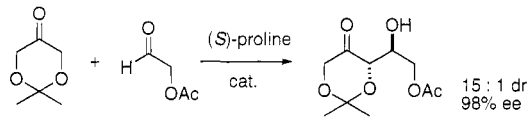
1 2

In a complementary approach, Matthew D. Shair of Harvard University has found (*J. Am. Chem. Soc.* **2005**, *127*, 7284) that Cu*-catalyzed decarboxylation of malonate thioesters such as **3** in the presence of an aldehyde led to the *syn* aldol product **4** in high diastereoselectivity and enantioselectivity.



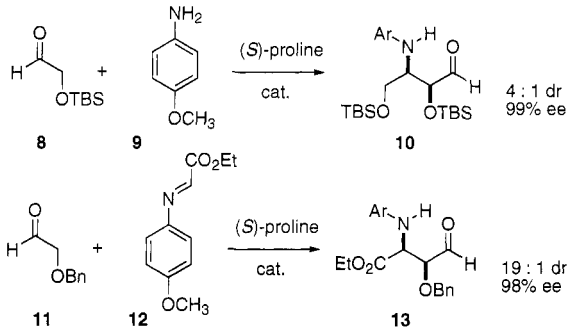
1 4

Enantomerically-pure secondary amines can condense with reactive ketones to make enantiomerically-pure enamines. Essentially simultaneously, Dieters Enders at the RTWH, Aachen, (*Angew. Chem. Int. Ed.* **2005**, *44*, 1210) and Carlos F. Barbas III at Scripps (*Organic Lett.* **2005**, *7*, 1383) described the highly diastereoselective proline-catalyzed condensation of the acetonide **5** of dihydroxy acetone with aldehydes such as **6** to give the differentially-protected anti aldol product **7** in high ee.



5 6 7

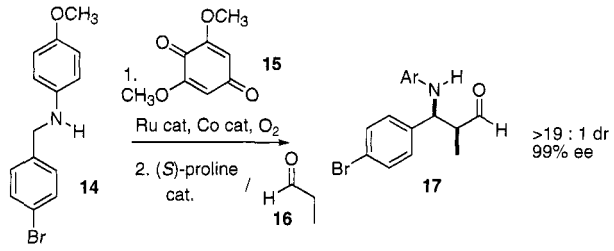
In a remarkable series of three papers, Armando Córdova of Stockholm University has expanded on the proline-mediated condensation of activated aldehydes such as **8**. In the first paper (*Tetrahedron Lett.* **2005**, *46*, 2839), enantioselective Mannich reaction is described. Homocondensation with an aryl amine **9** gave the four-carbon array **10** in high ee. Condensation with other activated imines such as **12** also proceeded efficiently.



8 9 10

11 12 13

In the following paper (*Tetrahedron Lett.* **2005**, *46*, 3363), Professor Córdova reported that condensations such as **5** with **6** (above) proceed more quickly and in higher yield and ee when a small quantity of water is deliberately added to the reaction mixture. He also reported the proline-catalyzed Mannich condensation of **5**. In the final paper of the series, (*Tetrahedron Lett.* **2005**, *46*, 3965), co-authored by Jan E. Bäckvall, Professor Córdova reported oxidation of benzylic amines such as **14** to the imine, with subsequent *in situ* Mannich condensation with **16** to give **17**.



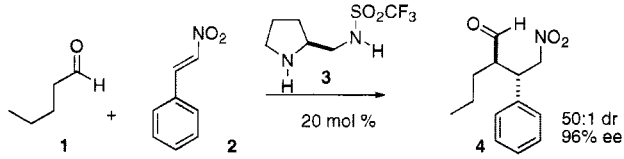
14 17

Alternative Strategies for the Construction of Extended Arrays of Stereogenic Centers

January 30, 2006

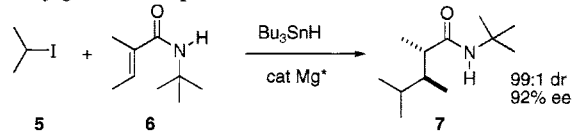
Last week (OHL 2006 Jan 23), aldol and Mannich-based strategies for the catalytic enantioselective construction of extended arrays of aminated, oxygenated and alkylated stereogenic centers were reviewed. This week, the focus is on alternative strategies for the construction of extended arrays of stereogenic centers.

Organocatalysts have been used to effect transformations that might not have been expected to be practical. Wei Wang of the University of New Mexico has reported (*Angew. Chem. Int. Ed.* **2005**, *44*, 1369) that the sulfonamide **3** mediates the enantioselective Michael addition of aldehydes to nitrostyrene derivatives, with impressive stereocontrol.



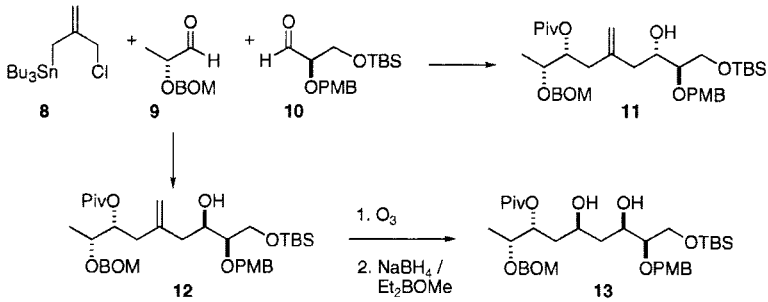
1 2 3 4

Even free radical reactions can be carried out with high diastereoselectivity. Mukund P. Sibi of North Dakota State University has demonstrated (*J. Am. Chem. Soc.* **2005**, *127*, 2390) that reduction of an iodide **5** in the presence a catalytic amount of an enantiomerically-pure Lewis acidic Mg complex delivers the conjugate addition product **7** with remarkable control of *both* centers.



5 6 7

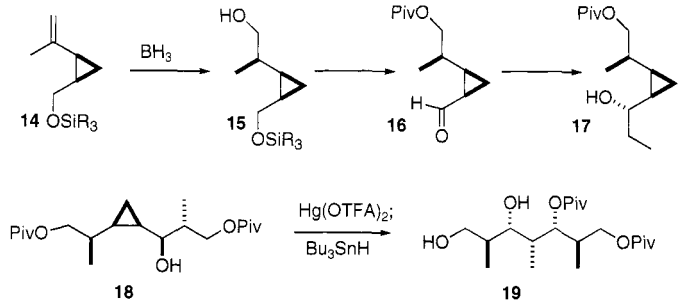
The stereocontrolled assembly of more extended arrays is also important. Gary E. Keck of the University of Utah has designed (*J. Org. Chem.* **2005**, *70*, 2543) the linchpin chlorostannane **8**.



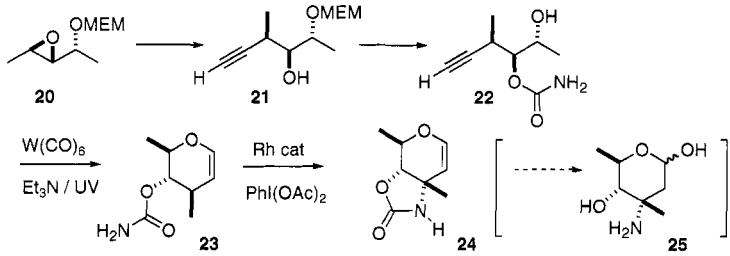
8 9 10 11 12 13

Sequential condensation of **8** with **9** and then with **10** could be directed toward either **11** (BF_3 OEt_2) or **12** ($MgBr_2$). Ozonolysis of **12** followed by OH-directed reduction gave **13**, a key intermediate toward the total synthesis of bryostatin.

Janine Cossy of ESPCI, Paris has also developed (*Tetrahedron* **2005**, *61*, 7632) an approach to extended arrays of stereogenic centers. Cis alkenyl cyclopropanes such as **14**, readily available in high enantiomeric purity, undergo hydroboration with substantial diastereocontrol. Organometallic addition to the derived aldehyde **16** also proceeds with high diastereoselectivity. All of this is of interest because the hydroxy cyclopropanes are opened under oxymercuration conditions, to give, with clean pivaloyl transfer, the stereopentad **19**. Although in this application the C-Hg was replaced by C-H, to yield a methyl group, there are many other ways to functionalize the intermediate organomercurial.



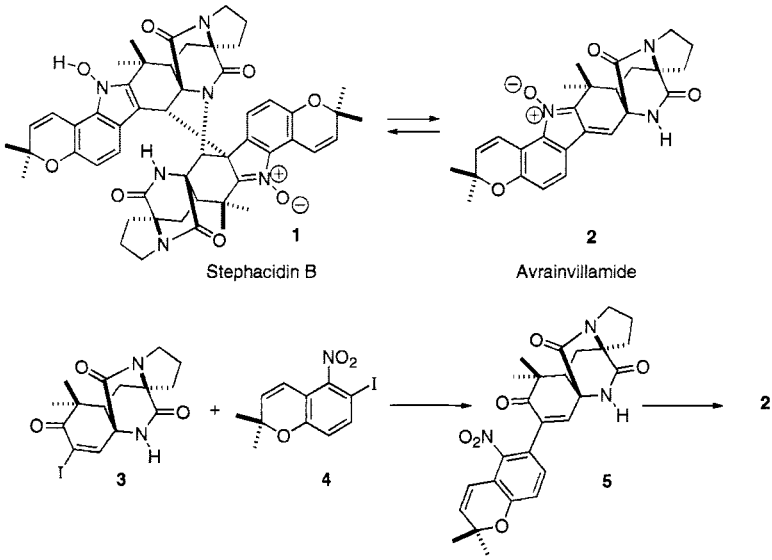
The recent (*Organic Lett.* **2005**, *7*, 1785) synthesis of D-saccharosamine **25** by Kathlyn A. Parker of SUNY Stony Brook is a showcase for the power of organometallic reagents in stereocontrolled organic synthesis. The starting material **20** was prepared by Sharpless epoxidation. Acetylide opening was highly regioselective, to give **21**. After protecting group exchange, tungsten-mediated cyclization of **22** gave **23**. Dubois cyclization of **23** proceeded selectively *away* from the ether methine, to give the protected D-saccharosamine **24**.



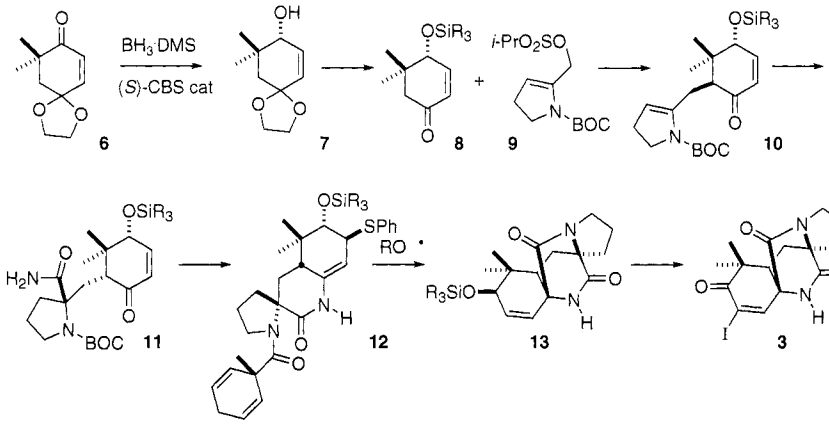
Synthesis of (-)-Avrainvillamide and (+)-Stephacidin B

February 6, 2006

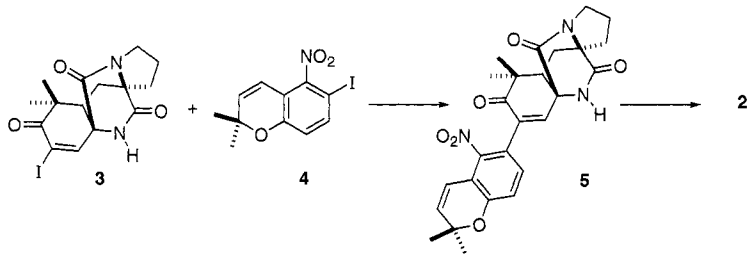
The dimeric alkaloid stephacidin B **1** was recently isolated from a fungus culture. The "monomer" avrainvillamide **2** had previously been described. Andrew G. Myers of Harvard University has reported (*J. Am. Chem. Soc.* **2005**, *127*, 5342) the enantioselective total synthesis of **2**, and the dimerization of **2** to **1**. The key intermediate in the synthesis was the tetracyclic amide **3**.



The absolute configuration of the target natural products was set by enantioselective reduction of the enone **6**. Usually, catalytic Itsuno-Corey reduction of cyclohexenones without an α-substituent is not selective. In this case, advantage was taken of that lack of induction from the alkene side, with the steric bulk on the other side of the ketone directing the reduction. Alkylation of **8** with **9** proceeded to give the expected axial product **10**. Cyanation proceeded with remarkable diastereocontrol, to give, after epimerization and hydrolysis, the amide **11**. Conjugate addition of thiophenol followed by spontaneous cyclization and dehydration led to the amide **12**. With the phenylthio enamide in place, the stage was set for the elegant final cyclization: hydrogen atom abstraction from the dihydroaromatic followed by fragmentation delivered the formamide radical, that cyclized efficiently to give the tetracyle **13**. Oxidation and iodination of the enone then gave **3**.



Ullman coupling of **3** with the aryl iodide **4** to give **5** proved to be more effective than the alternative coupling with the areneboronic acid. Reduction of **5** with activated zinc powder converted the nitro group to the N-OH, which spontaneously cyclized to the nitrone **2**. While **2** so preparared gave a ^{13}C spectrum that was congruent with that of natural avrainvillamide, authentic material was not available, so a direct comparison could not be made.

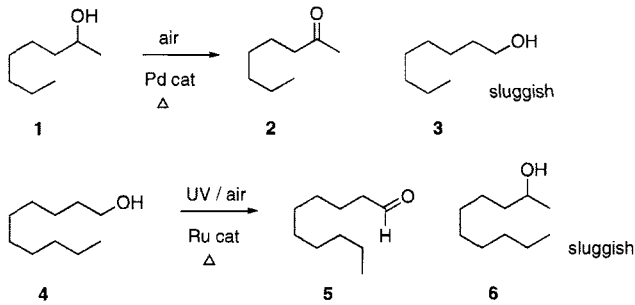


In Et_3N and CH_3CN, **2** spontaneously dimerized to **1**. As **2** is levorotatory (-35°) and **1** is dextrorotatory (91°), this ready interconversion of the monomer and the dimer will make it difficult to assign the absolute configuration of either natural product solely by comparison of rotations.

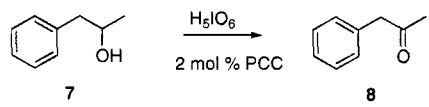
Best Synthetic Methods: Oxidation

February 13, 2006

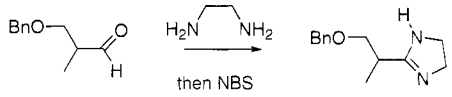
Classsically, stoichiometric oxidants have been used to convert alcohols into aldehydes and ketones. A practical alternative is to use air oxidation, with a transition metal catalyst. Usually, a secondary alcohol such as **1** is oxidized much more readily than is a primary alcohol such as **3**, as illustrated by the work (*Organic Lett.* **2005**, *7*, 1077) of Jaiwook Park of Pohang University of Science and Technology in Korea. Tsutomu Katsuki of Kyushu University has developed (*Tetrahedron Lett.* **2005**, *46*, 783) a complementary approach, based on UV activation of a Ru complex, that directs the oxidation specifically to *primary* alcohols such as **4**.



Despite the difficulties associated with the disposal of chromium waste, stoichiometric chromium oxidants are still commonly used in organic synthesis. One of the more popular is pyridinium chlorochromate (PCC). Mo Hunsen of Kenyon College in Ohio has developed a way around this difficulty (*Tetrahedron Lett.* **2005**, *46*, 1651), using the PCC catalytically, with stoichiometric periodic acid. The alcohol **7**, sometimes troublesome to oxidize, responded smoothly.



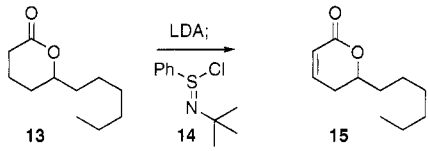
The carboxylic acid oxidation state can take many forms. The transformation of aldehydes such as **9** to the 2-dihydroimidazole **10**, reported (*Tetrahedron Lett.* **2005**, *46*, 2197) by Yasuyuki Kita of Osaka University is formally the conversion of the aldehyde to the acid oxidation state. The procedure works well for both aliphatic and aromatic aldehydes. Remarkably, Shlomo Rozen of Tel Aviv University has shown (*Organic Lett.* **2005**, *7*, 2177) that an azide such as **11** is oxidized smoothly to the corresponding nitrile **12**. This is an example of conversion from the alcohol to the acid oxidation state.



9 **10**

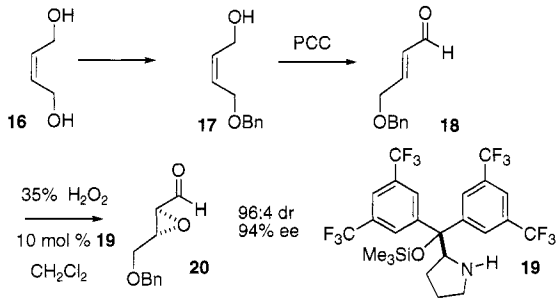
11 **12**

Several years ago, Teruaki Mukaiyama introduced the now commercially-available sulfinimidoyl chloride **14** as a reagent for converting ketone enolates to enones. Jun-ichi Matsuo of the Kitasato Institute, Kanagawa, has extended (*Tetrahedron Lett.* **2005**, *46*, 407) this oxidation to esters, thioesters, amides, lactams, and lactones such as **13**.



13 **14** **15**

For more than two decades, Sharpless asymmetric epoxidation of allyic alcohols has been the workhorse for enantioselective synthesis. Karl Anker Jørgensen of Aarhus University, Denmark, has devised (*J. Am. Chem. Soc.* **2005**, *127*, 6964) what appears to be a practical competitor, the enantioselective epoxidation of α,β-unsaturated aldehydes such as **18** using the proline-derived organocatalyst **19**. The (*E*)-aldehyde **18** is easily prepared from the inexpensive butenediol **16**.

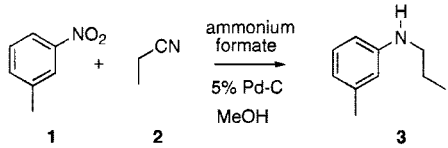


16 **17** **18** **20** **19**

Best Synthetic Methods: Reduction

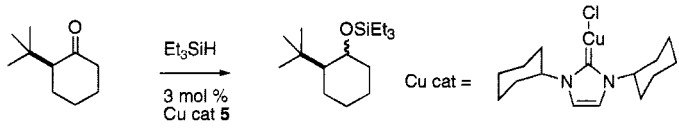
February 20, 2006

Aryl amines are common constituents of pharmaceuticals, so there has been a great deal of interest in their preparation, e.g by Pd- or Cu-mediated amination of aryl halides. Multi-step procedures for monoalkylation of amino arenes have also been developed. Richard A. Hudson of the University of Toledo, OH, has put forward (*Organic Lett.* **2005**, *7*, 471) a complementary approach, the mono N-alkylation of nitrobenzenes such as **1** by reduction in the presence of a nitrile **2**. Another way of seeing this transformation is as the mono-N-arylation of the primary amine derived by reduction of the nitrile **2**, using the nitroaromatic **1** as the source of the arene. The nitroaromatic **1** can be replaced in these transformations by the corresponding primary aniline.



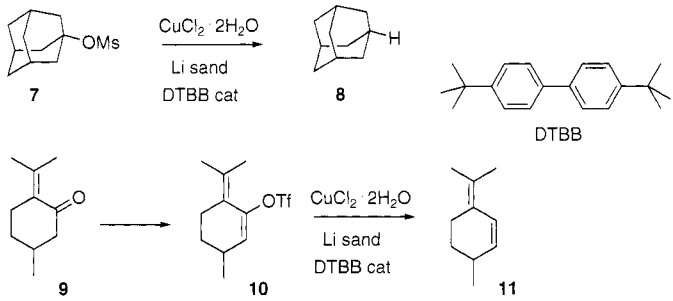
1 **2** **3**

Ketones such as **4** can be converted to the silyl ether **6** by reduction followed by protection. Previous catalysts for the alternative one step procedure, direct hydrosilylation, have often failed with more hindered ketones. Steven P. Nolan of the University of New Orleans has now (*J. Org. Chem.* **2005**, *70*, 4784) developed a robust Cu carbene complex **5** that effectively catalyzes the reductive silylation of even very hindered ketones.



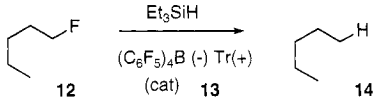
4 **6** **5**

Alcohol deoxygenation is usually carried out by free radical reduction. Alternatively, hydride reagents can be used to reduce some sulfonates. Gabriel Radivoy of the Universidad Nacional del Sur, Argentina, and Miguel Yus of the Universidad de Alicante have found (*Tetrahedron* **2005**, *61*, 3859) that low-valent copper smoothly mediates the reduction of primary, secondary, and tertiary mesylates including **7**. This reagent combination will also reduce enol sulfonates such as **10**, leaving the alkene or diene intact.



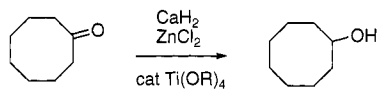
7 8 9 10 11

Carbon-fluorine bonds are resistant to direct reduction. Oleg V. Ozerov of Brandeis University has taken (*J. Am. Chem. Soc.* **2005**, *127*, 2852) an alternative approach to this problem, setting up a catalytic cycle that is initiated by trityl cation, **13**. Hydride abstraction from Et_3SiH by the trityl cation gives $Et_3Si(+)$, that then extracts F from **12**. The transient or incipient carbocation so produced abstracts a hydride from Et_3SiH, regenerating $Et_3Si(+)$ and so continuing the catalytic cycle. Aryl C-F and benzylic C-F bonds are also reduced smoothly.

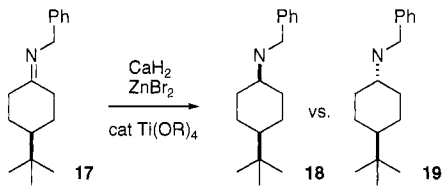


12 13 14

Commonly, the inexpensive CaH_2 is used as a drying agent. Sentaro Okamoto of Kanagawa University, Yokohama, has found (*Tetrahedron Lett.* **2005**, *46*, 1667) that in the presence of a stoichiometric amount of ZnX_2 and a catalytic amount of Lewis acid, ketones such as **15** are readily reduced to the corresponding alcohol, and imines such as **17** are reduced to the amine. The reduction of the cyclic imine **17** itself was not reported, but it is included here because the stereochemical outcome is of substantial importance. While there are many ways to reduce the imine of a cyclic ketone to the axial amine **18**, there is as yet no general way to reduce it to the equatorial amine **19**.



15 16



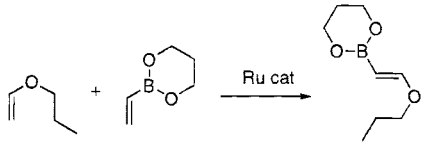
17 18 19

Selective Reactions of Alkenes

February 27, 2006

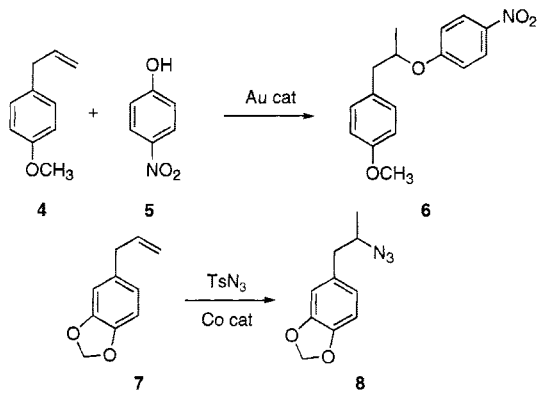
Alkenes are among the least expensive of organic functional groups. They are easily incorporated into a growing molecule, and are stable to many of the reagents that transform other functionality. Conversely, it is possible to activate alkenes in the presence of other organic functional groups.

The power of this approach is illustrated by the Ru-catalyzed transborylation of alkenes reported (*Chem. Comm.* **2005**, 663) by Bogdan Marciniec of Adam Mickiewicz University, Poznan. This is not a metathesis reaction, but a transfer of the boryl group from one alkene to the other. The products such as **3** are useful building blocks for further coupling.



1 **2** **3**

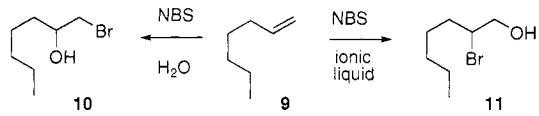
Although hydroboration is well developed as a protocol for the anti-Markovnikov hydration of an alkene, there has not been a comparable environmentally friendly method for Markovnikov functionalization. Now, two such methods have appeared. Chuan He of the University of Chicago has found (*J. Am. Chem. Soc.* **2005**, *127*, 6966) a Au catalyst that mediates the addition of phenols and of carboxylic acids to alkenes. In a related development, Erick M. Carreira of ETH, Zurich has developed (*J. Am. Chem. Soc.* **2005**, *127*, 8294) a Co catalyst that mediates the transformation of an alkene such as **7** to the secondary azide **8**.



4 **5** **6**

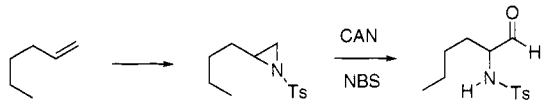
7 **8**

The bromohydroxylation of a terminal alkene such as **9** usually proceeds to give the primary bromide **10**. J.S. Yadav of the Indian Institute of Chemical Technology, Hyderabad has now observed (*Tetrahedron Lett.* **2005**, *46*, 3569) that in an ionic liquid, halohydrin formation proceeds with the opposite regioselectivity, leading to **11** as the dominant product.



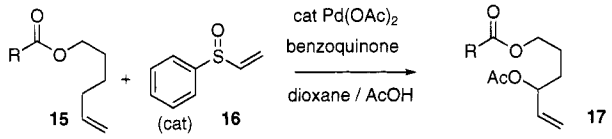
10 **9** **11**

Aziridines such as **13**, both racemic and enantiomerically-enriched, are readily prepared from the corresponding alkene. K. Rama Rao of the Indian Institute of Chemical Technology, Hyderabad, has found (*Tetrahedron Lett.* **2005**, *46*, 4111) that a combination of N-bromosuccinimide and ceric ammonium nitrate in CH_3CN/H_2O converts the aziridine **13** to the protected α-amino aldehyde **14**. A key question, as yet unanswered, is whether the enantiomeric excess of **13** would be maintained through the oxidation.

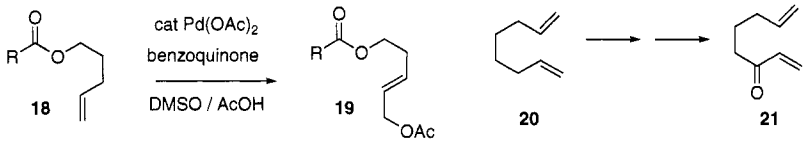


12 **13** **14**

Monosubstituted alkenes such as **15** are among the least expensive of organic functional groups. M. Christina White, now at the University of Illinois, has been developing conditions for specific Pd-catalyzed allylic oxidation of such alkenes. Two products are possible, the branched isomer such as **17** and the linear isomer **19**. Professor White has found that in the presence of a catalytic amount of the sulfoxide **16** (*J. Am. Chem. Soc.* **2005**, *127*, 6970) the branched isomer is dominant, while in the presence of DMSO (*Organic Lett.* **2007**, *7*, 223) the product is linear. Internal alkenes are not affected. Among many other applications, one can imagine using such an oxidation to convert the inexpensive butadiene dimer **20** into the valuable bis-annulation synthon **21**.



15 (cat) **16** **17**

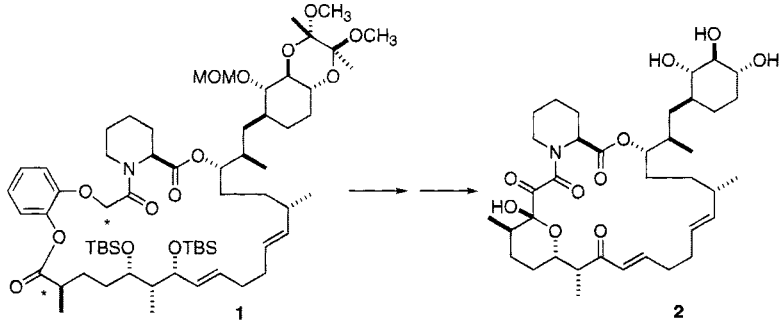


18 **19** **20** **21**

Synthesis of the Potent FBBP12 Ligand Antascomicin B

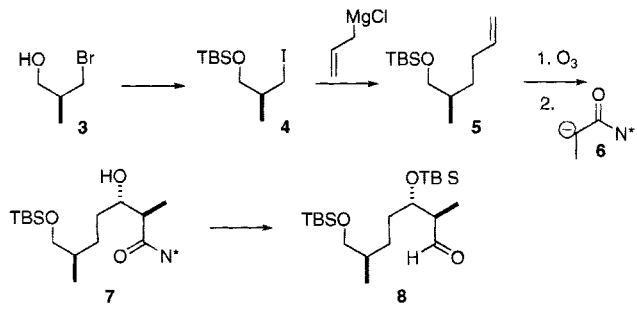
March 6, 2006

The FK binding protein ligands that suppress the immune response, such as FK506 and rapamycin, have been thoroughly studied. FKBP ligands have also been shown to promote the regrowth of damaged neurons, both peripherally and in the central nervous system. To differentiate these two disparate activities, it is important to develop potent FKBP ligands that are not immune suppressive. The antascomicins, represented by antascomicin B **2**, are such a class of natural products. Steven V. Ley of the University of Cambridge has described (*Angew. Chem. Int. Ed.* **2005**, *44*, 2732) an elegant synthesis of **2**, the key step of which was the ring-contracting transannular Dieckmann cyclization of **1**.



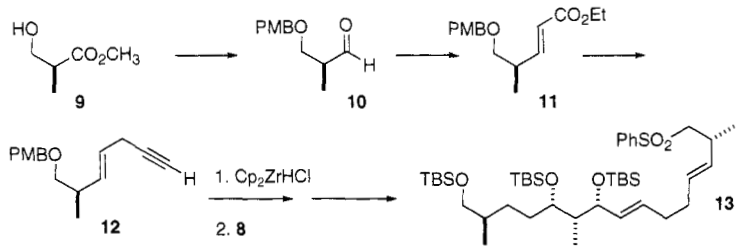
1 **2**

The enantiomerically-pure fragments **8**, **12** and **17** were coupled to prepare the macrolide **1**. The preparation of **8** started with the commercially-available enantiomerically-pure bromide **3**. Protection and halide exchange set the stage for homologation with allylmagnesium chloride. Ozonolysis followed by condensation with the acyl oxazolidinone **6** set the last two stereogenic centers of **8**.

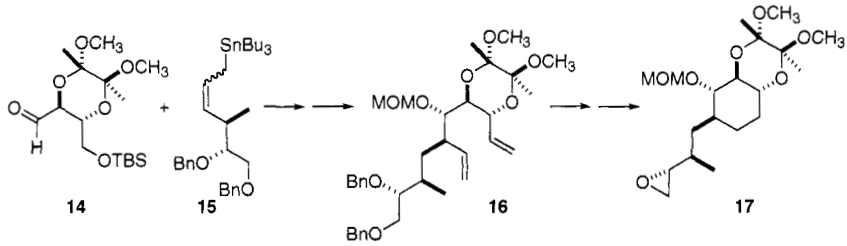


3 **4** **5** **6** **7** **8**

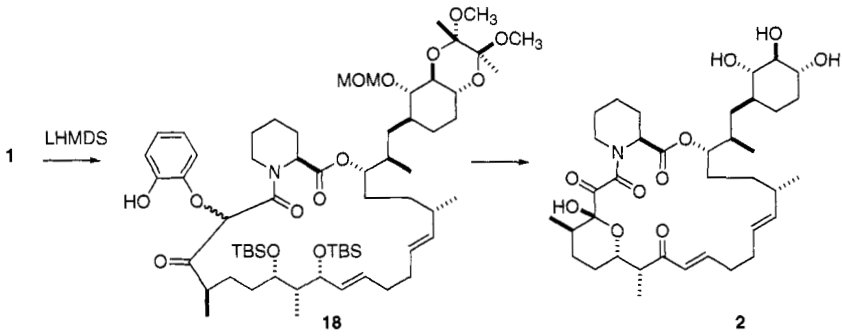
The starting point for **12** was the commercially-available enantiomerically-pure Roche ester **9**. Protection, reduction and oxidation gave **10**, which was homologated to the ester **11**. Reduction to the allylic alcohol followed by conversion to the chloride and coupling with TMS acetylene led to **12**. Addition to **8** of the alkenyl zirconium derived from **12** then gave **13**.



Professor Ley used his elegant tartrate method to assemble the carbocyclic fragment **17**. Condensation of two inexpensive components, dimethyl *D*-tartrate and biacetyl, followed by reduction and monoprotection delivered the aldehyde **14**. Diastereoselective addition of the allyl stannane **15** led to diene **16**, setting the stage for cyclization with the Grubbs second-generation Ru catalyst.



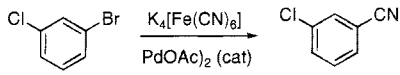
The sulfone anion derived from **13** added smoothly to **17**, to give, after reduction and acylation, the ester **1**. The templating effect of the arene ring of **1** facilitated macrolide formation. The Dieckmann cyclization then could proceed via a 6-membered ring transition state, leading to the ring-contracted product **18**. In addition to establishing the β-keto amide, this cyclization left residual oxygenation at the α-carbon, allowing direct elaboration of the 1,2,3-tricarbonyl system of **2**.



Best Synthetic Methods: Carbon-Carbon Bond Formation

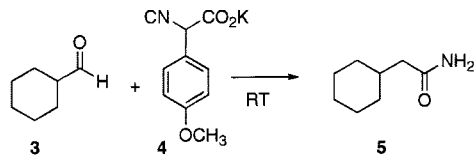
March 13, 2006

Carbon-carbon bond formation is central to organic synthesis. In the ideal, a homologation method will start with a common functional group, and proceed under mild conditions using non-toxic reagents. These standards are exemplified by the conversion of aryl bromides to nitriles reported (*J. Org. Chem.* **2005**, *70*, 1508) by Steven A. Weissman of Merck Rahway. Note that this reaction proceeds without supporting phosphine ligands for the Pd catalyst.



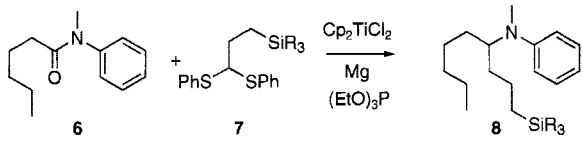
1 **2**

Jieping Zhu of the Insitut de Chimie at Gif-sur-Yvette has developed (*J. Am. Chem. Soc.* **2005**, *127*, 6926) an elegant procedure for the one-carbon homologation of aldehydes and ketones to the corresponding amide. The most efficient alternatives would have taken at least three steps.



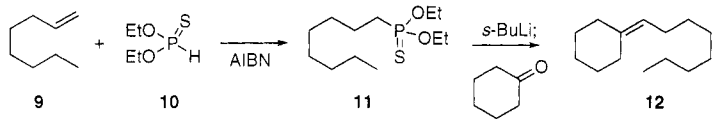
3 **4** **5**

Takeshi Takeda of the Tokyo University of Agriculture and Technology has found (*Tetrahedron Lett.* **2005**, *46*, 3157) that an N-aryl amide such as **6** can be efficiently homologated to the corresponding amines by Ti-mediated reductive condensation with a thioacetal.



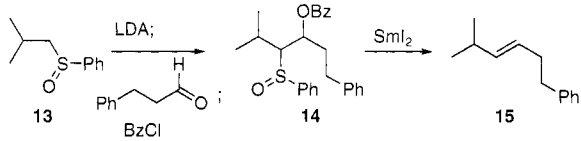
6 **7** **8**

The Wittig reaction, a staple of organic synthesis, is far from atom efficient. Andrew F. Parsons of the University of York has created (*Organic. Lett.* **2005**, *7*, 1597) a promising alternative. Free radical addition of diethyl thiophosphite to a terminal alkene proceeds smoothly. The product phosphonothioate **11** is readily deprotonated with *s*-BuLi, and the resulting anion condenses smoothly with ketones to give alkenes.



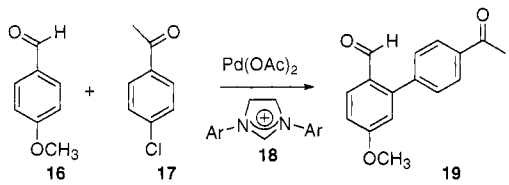
9 10 11 12

Sulfoxides can also be used to homologate aldehydes and ketones. István Markó of the Université Catholique de Louvain has described (*Organic Lett.* **2005**, *7*, 2373) an optimized procedure based on SmI_2 reduction of the benzoylated adduct. As with Julia-Lythgoe homologation, the products from aldehydes are predominantly *E*.



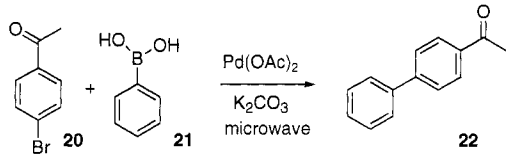
13 14 15

Transition metal catalyzed *o*-activation of aromatic C-H bonds has become a practical method for organic synthesis. In a recent advance, Bekir Çetinkaya of Ege University, Turkey has found (*Tetrahedron Lett.* **2005**, *46*, 2273) that the imidazolium ligand **18** activates the Pd sufficiently that even aryl chlorides can be used to *o*-arylate benzaldehydes. Aryl bromides lead to the doubly arylated products.



16 17 18 19

Nicholas E. Leadbetter of the University of Connecticut recently reported a "Pd-free" Suzuki coupling. He has now (*J. Org. Chem.* **2005**, *70*, 161) found that these reactions were indeed Pd catalyzed – the commercial Na_2CO_3 used in the reactions was found to contain 20 to 50 *parts per billion* Pd. Indeed, the couplings did not proceed with Pd-free K_2CO_3, but worked smoothly on addition of 100 ppb $Pd(OAc)_2$. This corresponds to a turnover number of 1,250,000.



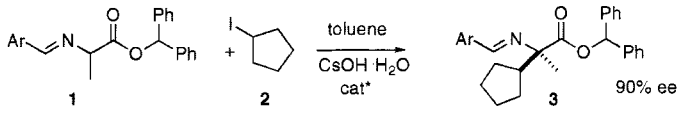
20 21 22

Enantioselective Construction of Quaternary Centers

March 20, 2006

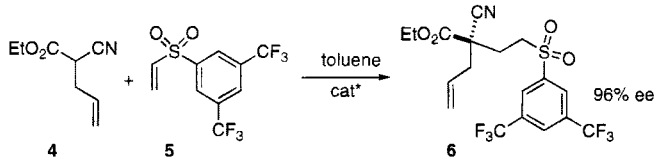
Enantiodefined quaternary centers are common in physiologically-active natural products. They are much less common in pharmaceuticals, since such centers have been so difficult to prepare. With the development of new catalytic methods for the enantioselective construction of quaternary centers, the cost of such centers is dropping.

Keiji Maruoka of Kyoto University has developed highly selective catalysts for the alkylation of protected glycine anions. He has now shown (*J. Am. Chem. Soc.* **2005**, *127*, 5073) that in addition, the alkylated amino esters such as **1** themselves can be alkylated with high enantiocontrol, to give the α-quaternary amino acid esters such as **3**.



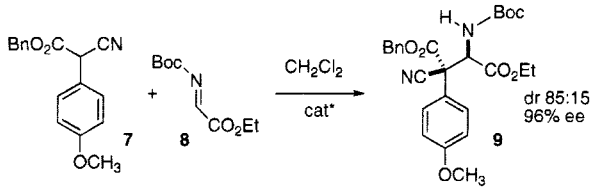
1 2 3

Using quinine-derived catalysts, Li Deng of Brandeis University has achieved (*J. Am. Chem. Soc.* **2005**, *127*, 8948) remarkable enantiomeric excesses with Michael additions to establish quaternary centers. The α-R group on the cyanoacetate **4** can be alkyl or aryl. With aryl, the phenyl sulfones work well as acceptors. With alkyl, the more active acceptor **5** gives higher ee's. Note that the cyano group of **6** can be selectively hydrated to the primary amide and inverted, delivering the α-quaternary amino acid ester.



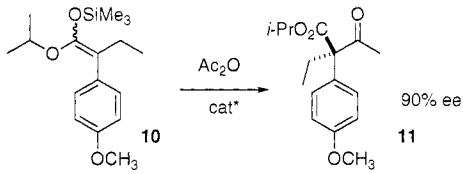
4 5 6

Karl Anker Jørgensen of Aarhus University has developed (*Angew. Chem. Int. Ed.* **2005**, *44*, 2896) quinine-based catalysts that effect enantioselective addition of an α-aryl cyanoacetate **7** to a glyoxylate imine **8**, setting not just one, but two stereogenic centers.

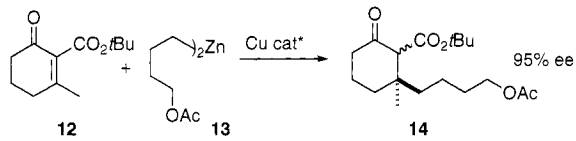


7 8 9

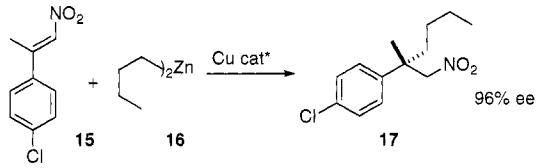
Gregory C. Fu of MIT has devised (*J. Am. Chem. Soc.* **2005**, *127*, 5604) a ferrocene-based catalyst that effects enantioselective acylation of a ketene silyl acetal such as **10**. Both cyclic and acyclic silyl acetals are acetylated with high ee.



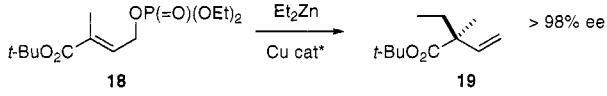
Amir Hoveyda of Boston College has reported three enantioselective dialkylzinc-based approaches to quaternary centers, using as a catalyst Cu bound to an oligopeptide designed for the particular purpose. Although tetrasubsituted acceptors such as **12** can be sluggish, he has found (*J. Am. Chem. Soc.* **2005**, *127*, 14988) that with the appropriately designed ligand, addition proceeds smoothly, and with high ee.



Professor Hoveyda has shown (*J. Am. Chem. Soc.* **2005**, *127*, 4584) that conjugate addition to β, β-disubstituted nitroalkenes can also proceed with high ee. The product nitro alkanes can easily be carried on to amines, nitriles, or carboxylic acids.



Professor Hoveyda has also reported (*Organic. Lett.* **2005**, *7*, 1255) an improved procedure for the S_N2' displacement of an allylic leaving group to generate a chiral quaternary center. The ee's are a little higher with the *t*-butyl ester than with the ethyl ester.

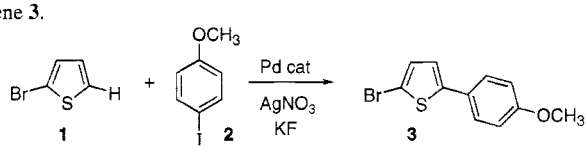


Pd-Mediated Arylation of Aromatic and Heteroaromatic Rings

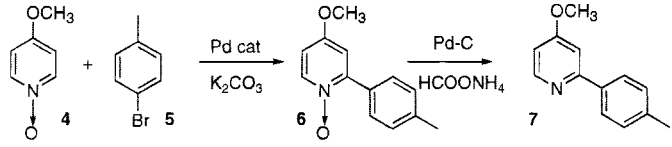
March 27, 2006

Usually, aryl-aryl bonds are formed by the coupling of two *functionalized* aromatic carbons. Having *both* of the aromatic carbons functionalized is not always necessary. It is sometimes possible to directly arylate an aromatic ring, replacing a C-H bond with a C-C bond.

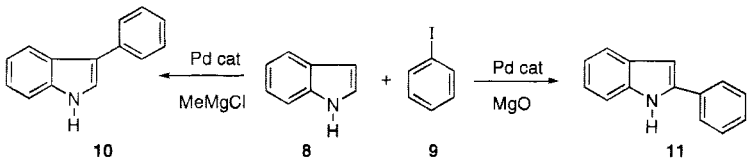
The *intermolecular* arylation works particularly well with electron rich heteroaromatics. For instance, Atsunori Mori of the Tokyo Institute of Technology has shown (*Organic Lett.* **2005**, *7*, 5083) that bromothiophene **1** couples with aryl iodides such as **2** under Pd catalysis to give the arylated thiophene **3**.



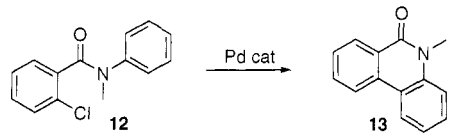
Pyridines themselves are not sufficiently reactive, but Keith Fagnou of the University of Ottawa has found (*J. Am. Chem. Soc.* **2005**, *127*, 18020) that the corresponding N-oxides couple efficiently. The product N-oxides are easily hydrogenated to deliver the substituted pyridine **7**. In a competition experiment, the 4-nitropyridine oxide was shown to be more reactive than the 4-methoxy pyridine oxide.



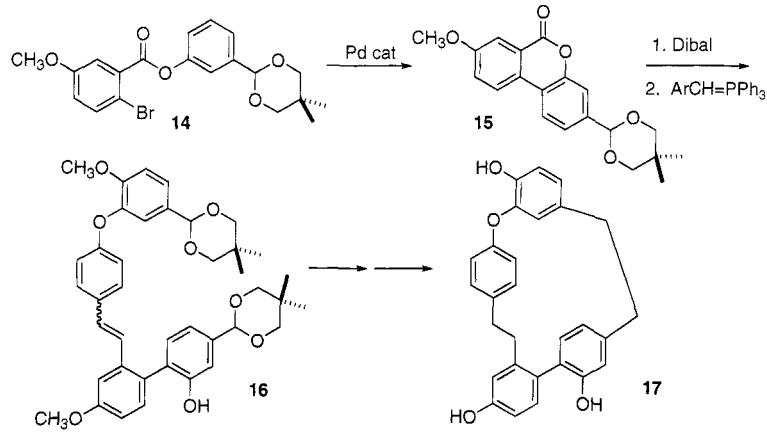
Dalibor Sames of Columbia University has developed conditions (*J. Am. Chem. Soc.* **2005**, *127*, 8050) for the direct arylation of indoles. By modulating the reaction conditions, arylation can be directed either towards C-2, to give **10**, or toward C-3, to give **11**. Note that although three related papers from the group were recently withdrawn (*J. Am. Chem. Soc.* **2006**, *128*, 3102), the work cited here was not affected.



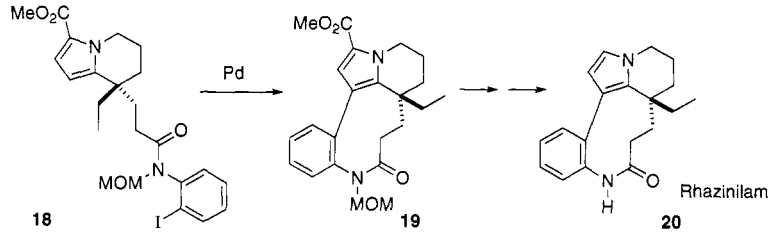
Professor Fagnou has also demonstrated (*Organic Lett.* **2005**, *7*, 1857) the design of Pd catalysts that activate even aryl chlorides for cyclization. Carbocycles, cyclic ethers and amines, and lactams such as **13** are formed efficiently in this intramolecular reaction.



Direct intramolecular arylation is a method for specific homologation. In the course of a total synthesis (*Angew. Chem. Int. Ed.* **2005**, *44*, 3899) of riccardin C **17**, David C. Harrowven of the University of Southampton constructed the ester **14**. Pd-mediated cyclization proceeded with a modest (5:2) preference for the para product **15**.



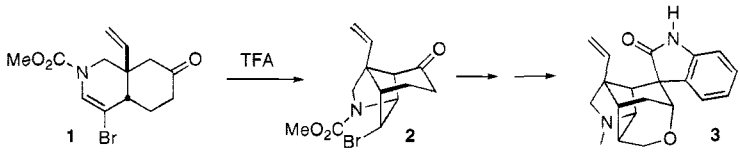
Direct arylation can also be used for the construction of larger rings. Dirk Trauner of the University of California at Berkeley employed (*Organic Lett.* **2005**, *7*, 5207) Pd-mediated cyclization of **18** to **19** as the key step in the synthesis of rhazinilam **20**.



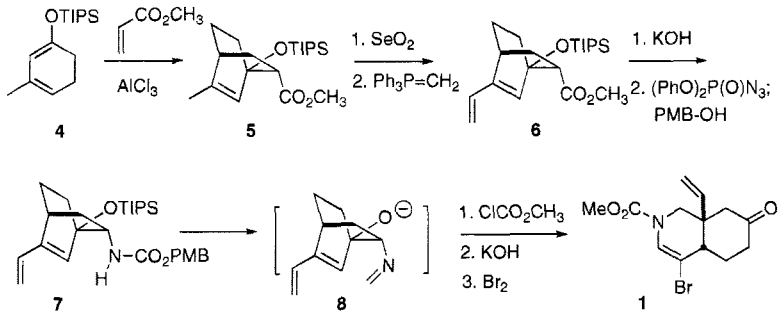
The Overman Route to Gelsemine

April 3, 2006

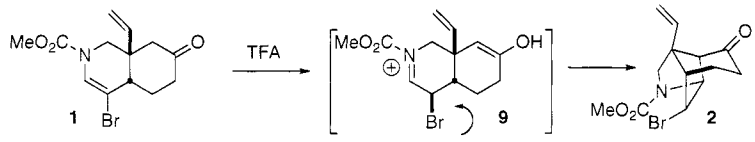
Gelsemine **3** has no particular biological activity that recommends it, but its challenging architecture has been a motivation to a generation of organic synthesis chemists. Larry E. Overman of the University of California at Irvine has described (*J. Am. Chem. Soc.* **2005**, *127*, 18046, 18054) his total synthesis of gelsemine, the key step of which was the acid-mediated cyclization of **1** to **2**.



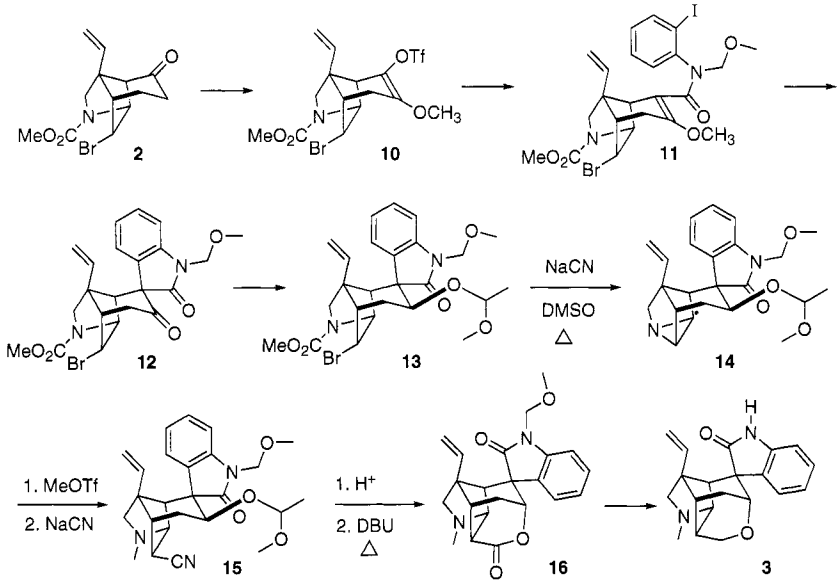
The synthesis of **1** started with the preparation of the diene **4** from 3-methyl anisole. Diels-Alder cycloaddition with methyl acrylate gave the endo adduct **7**. The methyl group was converted to the vinyl group of the natural product by allylic oxidation followed by methylenation. Hydrolysis followed by inversion and trapping with *p*-methoxybenzyl alcohol gave the protected amine **7**. This underwent smooth aza-oxy-Cope rearrangement, to give, after protection and bromination, the ketone **1**.



The acid-mediated cyclization of **1** to **2** proceeds by way of the protonated enol **9**. It seems likely that kinetic protonation at the indicated carbon would have led to the other diastereomer of the bromide. With that diastereomer, however, the Br would be inside in the transition state leading to cyclization. That may slow down the cyclization sufficiently that epimerization can intervene, leading to the more easily cyclized diastereomer **9** and thus to **2**.



There were several problems to solve in the conversion of **2** to **3**. The key step was the intramolecular Heck cyclization of **11** to **12**. There was some concern that such a cyclization would not proceed with a tetrasubstituted alkene. In fact, Moriarty methoxylation of the ketone **2** followed by generation of the enol triflate delivered **10**. Pd-mediated carbonylation followed by coupling with *o*-iodoaniline and protection gave **11**, which underwent smooth intramolecular Heck cyclization, to give, after hydrolysis, predominantly the unnatural diastereomer **12**.



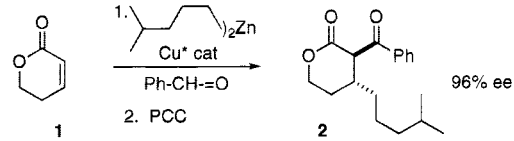
The completion of the synthesis, including the addition of the last carbon, proved elusive. Early on, it was found to be important to reduce and protect the 1,3-dicarbonyl system, to give the equatorial ether **13**. Attempted displacement to introduce the last carbon led instead to the aziridine **14**. Taking advantage of this, the aziridine was quaternized, then opened at the less-hindered secondary site. Deprotection followed by warming with base led, via retro-aldol epimerization of two stereogenic centers, to the long-sought lactone **16**. Deprotection followed by reduction of the lactone then gave **3**.

Stereoselective Construction of Oxygen Heterocycles

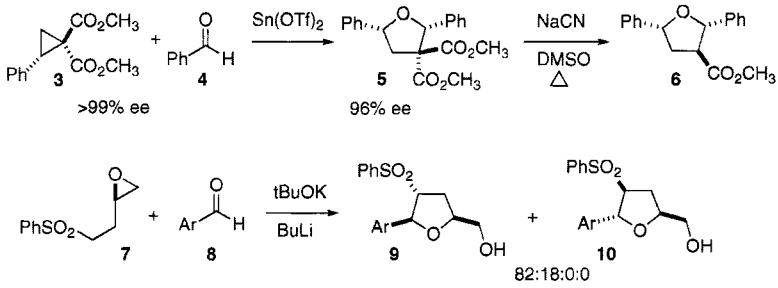
April 10, 2006

Nitrogen heterocycles, because of their relative ease of preparation, have dominated pharmaceutical discovery. Improved methods for the diastereoselective and enantioselective construction of oxygen heterocycles have now made these much more readily available.

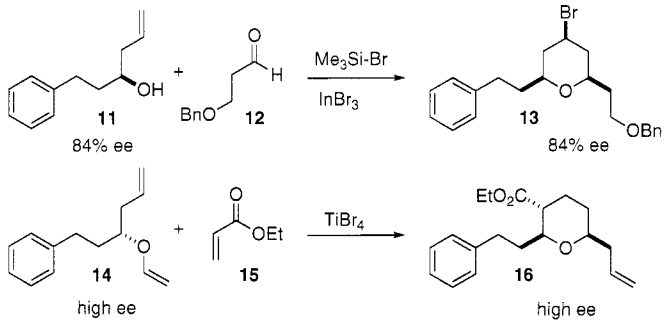
Unsaturated lactones such as **1** and its five-membered ring analogue are inexpensive. Attempts at enantioselective conjugate addition to these very reactive receptors have been plagued by low material recovery. Amir H. Hoveyda of Boston College speculated (*Angew. Chem. Int. Ed.* **2005**, *44*, 5306) that the problem lay with the reactivity of the intermediate lactone enolate. He included a trapping aldehyde in the reaction mixture, and found that product ee was outstanding, and the mass balance was substantially improved.



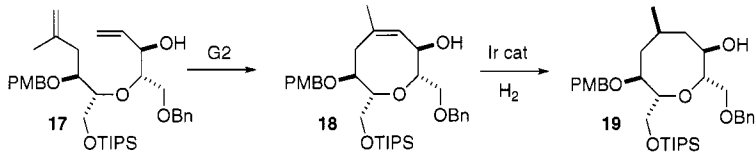
Many methods have been developed for the stereocontrolled synthesis of five- and six-membered ethers using S_N2 displacement. Even more interesting are recent observations of high stereoselectivity where that might not have been expected. Jeffrey S. Johnson of the University of North Carolina has found (*J. Am. Chem. Soc.* **2005**, *127*, 16014) that the opening of the activated cyclopropane **3** proceeds via an incipient carbocation, that is trapped by the nonbonding electrons of the aldehyde **4** with nearly perfect inversion, leading to **5**. Even more striking is the coupling of **7** and **8** to give predominantly **9**, reported (*Org. Lett.* **2005**, *7*, 2945) by Mieczyslaw Makosza of the Polish Academy of Sciences, Warsaw. Apparently, the initial aldol condensation is reversible, as demonstrated by crossover experiments with an isolated intermediate put back into the reaction. Of the four diastereomeric aldol products, only two do the intramolecular epoxide opening, one significantly more rapidly than the other. The absolute configuration of **9** and of **10** is set by the absolute configuration of the starting epoxide **8**.



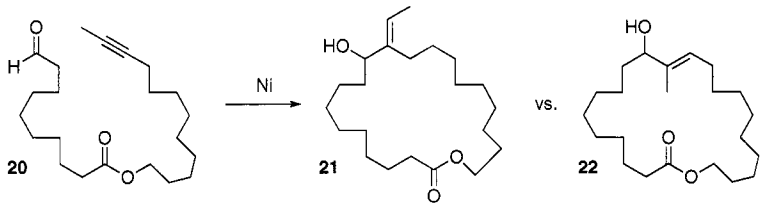
The Prins cyclization has become a workhorse of six-membered cyclic ether construction. Teck-Peng Loh of Nanyang Technological University, Singapore, observed (*Org. Lett.* **2005**, *7*, 4491) that allyl adducts such as **11** tended to racemize before cyclizing. Use of $InBr_3$ as the catalyst suppressed racemization, delivering **13** in high ee. In related work, Scott D. Rychnovsky of the University of California, Irvine has reported (*J. Am. Chem. Soc.* **2005**, *127*, 16044) an elegant Mukaiyama-Michael cascade protocol. The formation of **16** proceeds with inversion of absolute configuration, but maintains the enantiomeric purity of the starting ether **14**.



As illustrated by the recent work (*Org. Lett.* **2005**, *7*, 4033) of Michael T. Crimmins of the University of North Carolina, medium rings can often be formed efficiently by Grubbs metathesis. With the proper choice of catalyst, **18** can be hydrogenated to either diastereomer of **19**.



Attempted formation of larger rings often leads to unwanted polymer formation. John Montgomery, now at the University of Michigan, has shown (*J. Am. Chem. Soc.* **2005**, *127*, 13156) that with the proper Ni catalyst, even large rings can be formed efficiently. Remarkably, with the proper choice of reaction conditions, the cyclization can be directed to either **21** or **22**.

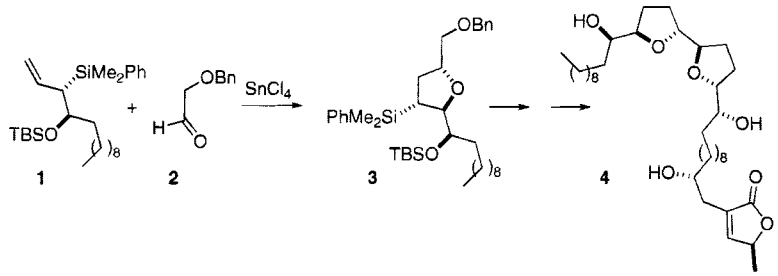


Enantioselective Construction of Naturally-Occurring Cyclic Ethers

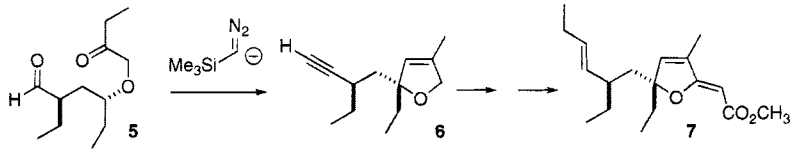
April 17, 2006

Powerful methods for the stereocontrolled construction of cyclic ethers have recently been developed, enabling the synthesis of a variety of complex natural products.

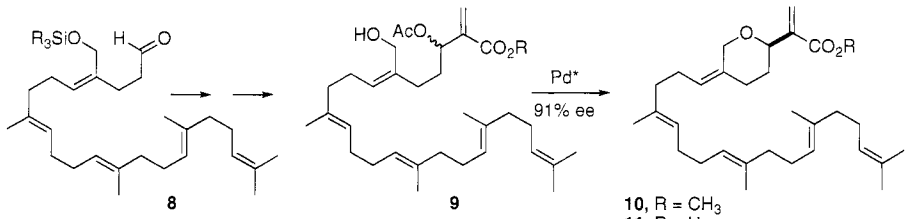
Many of the Annonaceous acetogenins, represented by asimicin **4**, exhibit powerful and selective cytotoxicity against human malignant cell lines. William R. Roush, now at Scripps Florida, has developed (*J. Am. Chem. Soc.* **2005**, *127*, 10818) a method for the stereocontrolled construction of trisubstituted tetrahydrofurans such as **3**, based on the condensation of enantiomerically-pure allyl silanes such as **1** with aldehydes. It is particularly elegant that by the choice of Lewis acid, the combination of **1** and **2** can be directed cleanly to either the trans product **3** or the cis diastereomer. This condensation was applied twice in the synthesis of asimicin **4**.



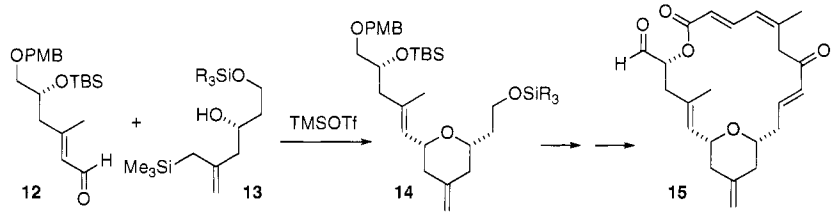
The ester **7** is representative of several closely-related natural products isolated from the Caribbean sponge *Plakortis halichondroides*. The central challenge in the synthesis of **7** is the stereocontrolled assembly of the quaternary center. Susumu Ohira of the Okayama University of Science has put forward (*Tetrahedron Lett.* **2005**, *46*, 7483) an elegant solution to this problem, based on the cyclization of the ketone **5**. Using the lithium salt of TMS diazomethane, the ketone and the aldehyde are each converted into the corresponding alkylidene carbene. The alkylidene carbene from the aldehyde spontaneously rearranges into the terminal alkyne. The carbene derived from the ketone effects concerted intramolecular C-H insertion into the proximal ternary center of **5**, establishing the quaternary center of **6** and thus of **7**.



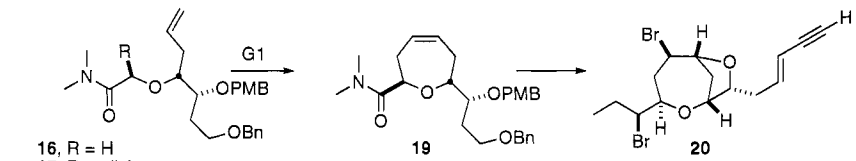
Barry M. Trost of Stanford University has extensively developed Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) as a tool for organic synthesis. The power of this method is illustrated by the enantioselective synthesis (*J. Am. Chem. Soc.* **2005**, *127*, 7014) of the gastrulation inhibitor (+)-hippospongic acid A **11**. The Baylis-Hillman adduct **9** is racemic, but the enantiomerically-pure Pd complex converts it into **10** in high ee.



As illustrated in the synthesis of (+)-dactylolide reported (*Org. Lett.* **2005**, *7*, 3053) by Gary E. Keck of the University of Utah, 2,6-dialkyl tetrahydropyran derivatives can be prepared with high diastereocontrol under equilibrating conditions. The secondary alcohol of **13** sets the relative and absolute configuration of **14**. Both **12** and **13** were prepared using the catalytic enantioselective allyl stannane addition developed by Professor Keck.



In the course (*J. Org. Chem.* **2005**, *70*, 8723) of a synthesis of (-)-isoprelaurefucin **20**, a metabolite of *Laurencia nipponica*, Deukjoon Kim of Seoul National University took advantage of remarkable diastereoselectivity in the alkylation of the chelated lithium enolate derived from **16**. Allylation proceeded in a 10:1 diastereomeric ratio, to give **17**, and prenylation proceeded in a 15:1 ratio, to give **18**. Exposure of **18** to the first generation Grubbs catalyst delivered **19**.

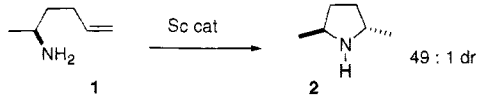


Stereoselective Construction of Nitrogen Heterocycles

April 24, 2006

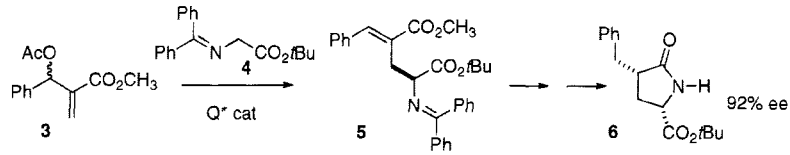
Nitrogen heterocycles are the basis of many essential pharmaceuticals, and of many physiologically-active natural products. There is a continuing interest in the development of new methods for the construction of nitrogen heterocycles with control of relative and of absolute configuration.

Tom Livinghouse of Montana State University has developed (*Organic Lett.* **2005**, *7*, 4391) new Sc-based catalyst systems for intramolecular hydroamination. As illustrated for the conversion of **1** to **2**, the Sc-based catalysts can effect cyclization with high diastereocontrol. Catalysts based on Zr (*Chem. Commun.* **2005**, 5205) are also effective, but so far show low diastereoselectivity.



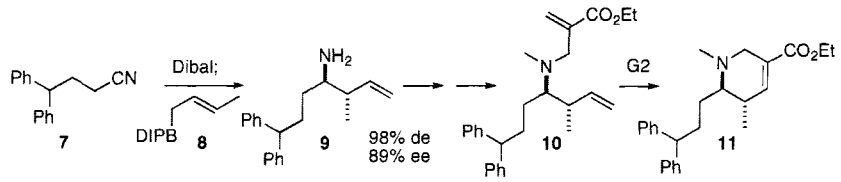
1 **2**

P. Veeraraghavan Ramachandran of Purdue University has shown (*J. Am. Chem. Soc.* **2005**, *127*, 13450) that a catalyst derived from the *Cinchona* alkaloids mediates the phase transfer Michael addition to **3** with high enantio- and geometric control, giving **5**. On deprotection and reduction, **5** is converted to **6** with high diastereocontrol.



3 **5** **6**

Professor Ramachandran has also (*J. Org. Chem.* **2005**, *70*, 7911) taken advantage of the diastereo- and enantioselective addition of (-)-*B*-crotyldiisopinocampheylborane **8** to imines developed earlier by the H.C. Brown group. Alkylation of the amine **9** with a Baylis-Hillman adduct followed by cyclization with the second-generation Grubbs catalyst delivers the dehydropiperidine ester **11**.

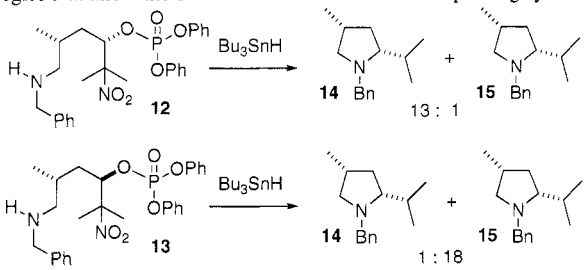


7

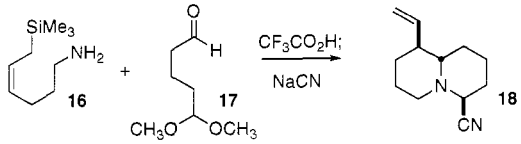
Usually, one would expect that intramolecular trapping of a carbocation would proceed with little diastereocontrol. David Crich of the University of Illinois at Chicago has observed (*J. Am. Chem. Soc.* **2005**, *127*, 9924) that the radical cations derived from the reduction of **7** and **8** cyclize predominantly

with inversion of absolute configuration. The radical cation intermediate is apparently a contact ion pair, with one face blocked by the departing phosphate.

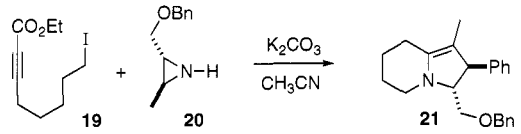
Strategies that allow the controlled construction of multiple ring systems are also important.



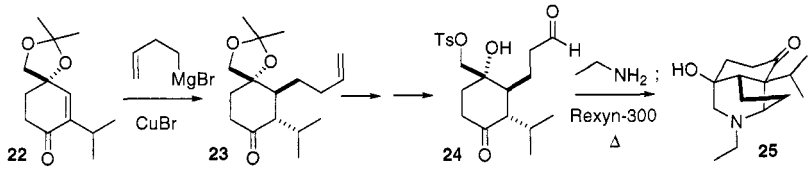
Stephen F. Martin of the University of Texas has developed (*Organic Lett.* **2005**, *7*, 2031) a family of allyl silane reagents, represented by **16**. Condensation with the protected dialdehyde **17** leads to the bicyclic amine **18** as a single diastereomer.



Many methods have been developed for the diastereoselective and enantioselective construction of aziridines. Dawei Ma of the Shanghai Institute of Organic Chemistry has devised conditions (*Organic Lett.* **2005**, *7*, 5545) for the condensation of aziridines with alkynyl esters such as **19**. Ring opening and cyclization proceed with double inversion, to give **21**.



The intramolecular Mannich condensation has been a workhorse of alkaloid construction. Douglass F. Taber of the University of Delaware found (*J. Org. Chem.* **2005**, *70*, 8739) that the strong acid-strong base ion exchange resin Rexyn-300® was effective in pushing a reluctant intramolecular Mannich condensation to completion.

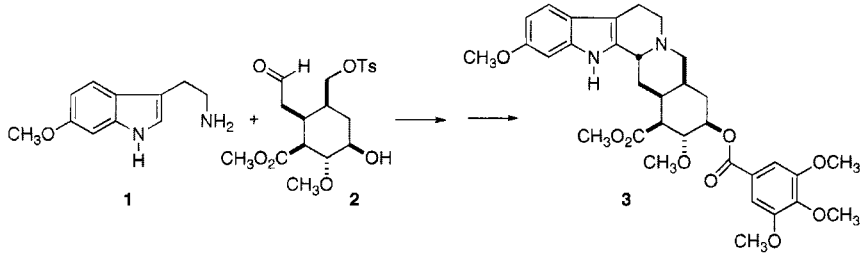


The Stork Synthesis of (-)-Reserpine

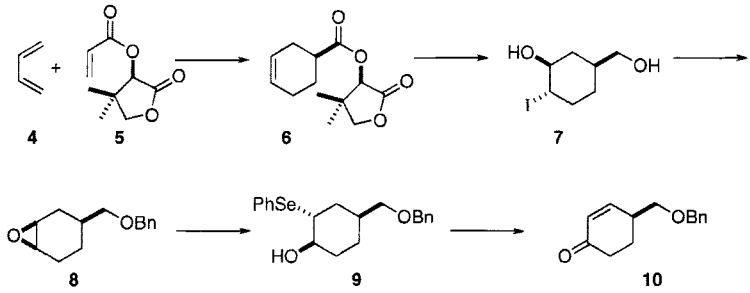
May 1, 2006

The history of reserpine **3**, isolated from the Indian shrub *Rauwolfia serpentina*, is storied. The anxiolytic activity of reserpine, the first tranquilizer, pointed the way to the development by Hoffmann-LaRoche of the blockbuster drugs Librium and Valium.

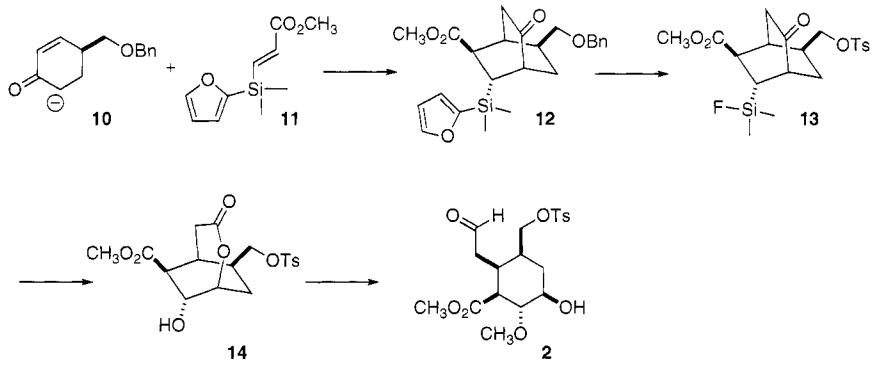
The spectacular first total synthesis of reserpine was achieved by R.B. Woodward in 1956. Several alternative approaches have been been published since that time. The most recent (*J. Am. Chem. Soc.* **2005**, *127*, 16255), by Gilbert Stork of Columbia University, centering on the aldehyde tosylate **2**, illustrates the power of chiral induction for the kinetic establishment of distal stereocenters. Condensation of **2** with 6-methoxytryptamine **1** led to reserpine **3**.



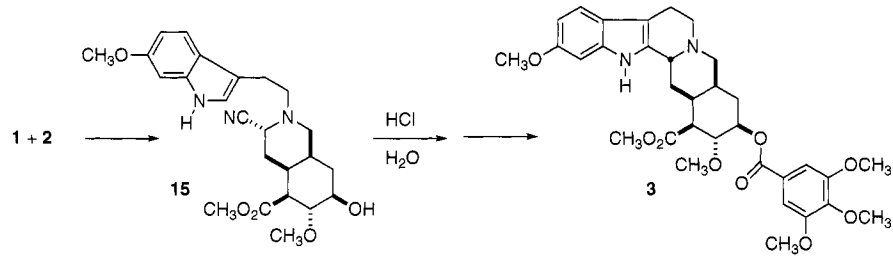
The preparation of **2** started with the previously-reported enantioselective addition of acrylate to butadiene, to give the acid **6**. Iodolactone formation followed by reduction gave the diol **7**. Under the conditions of benzyl ether formation, the iodohydrin cyclized to the epoxide, giving **8**. Phenyl selenide added to **8** to give the expected diaxial product **9**, which on oxidation gave **10** in high enantiomeric excess.



The key reaction in the assembly of **2** was the addition of the kinetic lithium enolate of **10** to the silyl acrylate **11** to give **12**. This reaction is seen as involving two sequential Michael additions, but the stereochemical outcome is the same as would be expected from a concerted Diels-Alder cycloaddition. Exposure to TBAF converted the furyl silane to the fluorosilane, which was debenzylated and carried on to the tosylate **13**. On exposure to two equivalents of hydrogen peroxide, the ketone underwent Baeyer-Villiger oxidation with high regioselectivity. The silane was also oxidized, delivering **14**. Methylation followed by Dibal reduction then gave **2**.



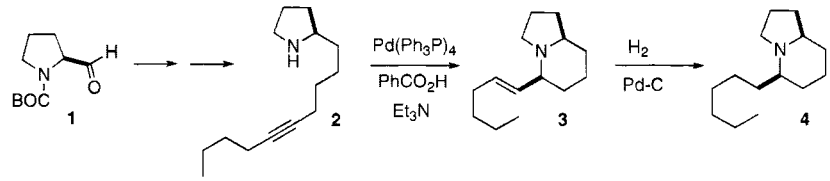
An additional stereogenic center is created when **1** and **2** are combined. Initial attempts to carry out the condensation gave the wrong stereochemical outcome, as Pictet-Spengler condensation preceded tosylate displacement. To work around this problem, **1** and **2** were combined in the presence of cyanide ion, to give **15**. Heating of **15** gave cyclization, but again to the wrong diastereomer, perhaps because in the intermediate ion pair from cyanide ionization, the cyanide ion was blocking one face of the intermediate cation. Fortunately, on stirring at room temperature in aqueous HCl, **15** did cyclize to the correct diastereomer, providing, after acylation, reserpine **3**.



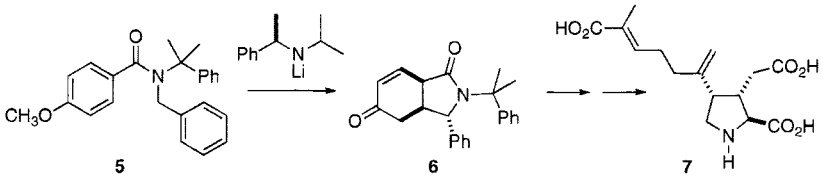
Stereocontrolled Construction of Azacyclic Natural Products

May 8, 2006

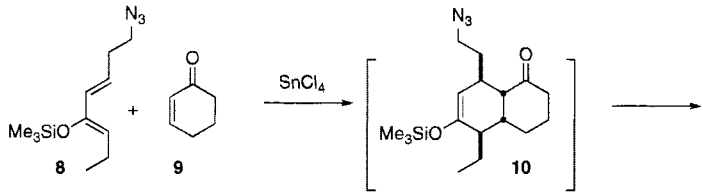
Yoshinori Yamamoto of Tohoku University has pioneered the Pd-catalyzed intramolecular hydroamination of alkynes. He has now demonstrated (*Tetrahedron Lett.* **2005**, *46*, 2101) that such cylizations can proceed with high diastereocontrol. Exposure of **2** to the reaction conditions they have developed delivered **3** as a single diastereomer. Hydrogenation converted **3** into the Dendrobatid alkaloid indolizidine 209D **4**.

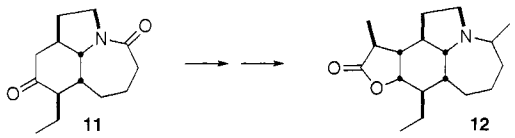


Four years ago, Jonathan Clayden of Manchester University reported the powerful cyclization of **5** to the bicyclic **6** in high enantiomeric excesss (86% ee, > 99% ee after recrystallization). He has now (*J. Am. Chem. Soc.* **2005**, *127*, 2412) described the conversion of **6** into the neuroexcitatory alkaloid isodomoic acid C **7**.



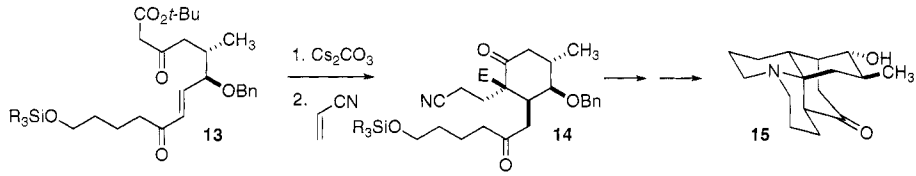
One of the most powerful methods developed in recent years for the construction of polyazacyclic systems is the tandem Diels-Alder/azide insertion protocol introduced by Jeff Aubé of the University of Kansas. Professor Aubé recently reported (*J. Am. Chem. Soc.* **2005**, *127*, 15712) a short stereocontrolled synthesis of the *Stemona* alkaloid (±)-stenine **12** using this approach.





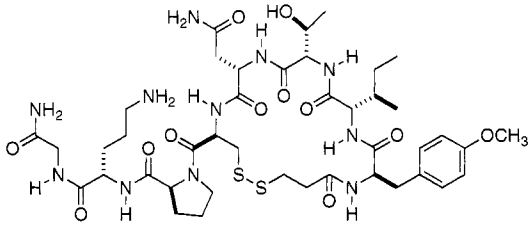
11 12

David A. Evans of Harvard University has reported (*Angew. Chem. Int. Ed.* **2005**, *44*, 6038) an even more spectacular cascade cyclization. Exposure of the linear precursor **13** to base followed by acrylonitrile led, by two highly diastereoselective Michael additions, to **14**. Reduction followed by hydrolysis and decarboxylation delivered the *Lycopodium* alkaloid clavolonine **15**.

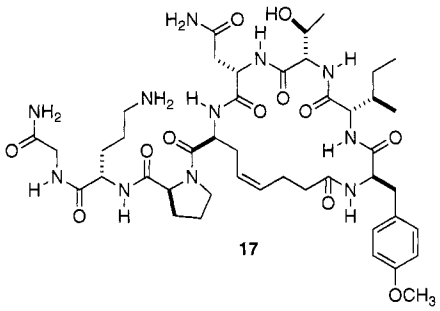


13 14 15

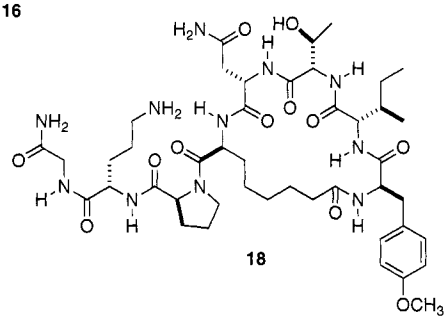
Atosiban **16** is an antagonist of the delivery-inducing cyclic peptide oxytocin that has been approved in Europe for the treatment of premature labor. John C. Vederas of the University of Alberta has used (*J. Org. Chem.* **2005**, *70*, 7799) ring-closing metathesis to prepare the carba analogues **17** and **18**, and found that they are active. The saturated analogue **18** also has a longer placental halflife than does **16**.



16



17



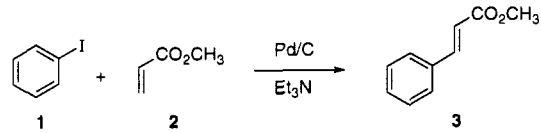
18

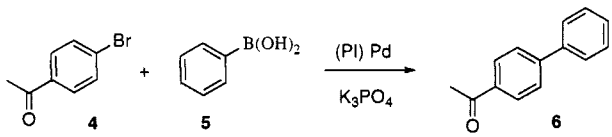
Preparation of Benzene Derivatives

May 15, 2006

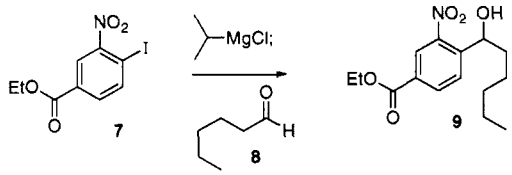
Two of the most common methods for homologating an aryl halide are the Heck reaction (**1** → **3**) and the Suzuki reaction (**4** → **6**). Shriniwas D. Samant of the University of Mumbai has reported (*Tetrahedron Lett.* **2005**, *46*, 2483) optimization of the conversion of **1** to **3** using Pd/C as the catalyst, at room temperature with ultrasound acceleration. The reaction proceeded most efficiently using NMP as the solvent, and Et_3N as the base.

For the Suzuki coupling of **4** plus **5** to give **6**, Shū Kobayashi of the University of Tokyo has been investigating (*Organic Lett.* **2005**, *7*, 4831) polymer-incarcerated (PI) Pd. There is no need for added ligand, as the incarcerating polymer includes triaryl phosphines. The Pd did not leach at all into the reaction solution, so it could be used multiple times with no diminution in yield.



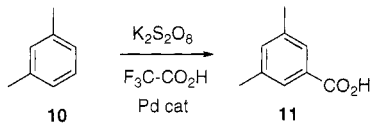


Nitro-substituted organometallics are notoriously difficult to prepare. Paul Knochel of the University of Munich has now shown (*J. Org. Chem.* **2005**, *70*, 2445) that the method his group developed for halide exchange works well even with nitro iodides such as **7**.



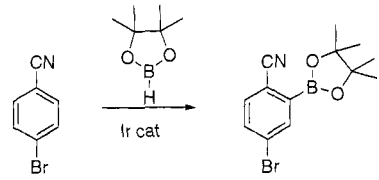
There is growing interest in methods for the direct functionalization of C-H bonds, including aromatic C-H bonds. Kyoko Nozaki of the University of Tokyo has found (*Tetrahedron Lett.* **2005**, *46*,

959) that the previously-reported Pd-mediated carboxylation of benzene derivatives proceeds much more efficiently in the presence of a phosphenium salt. Steric effects are pronounced, so homologation of **10** gives predominantly **11**.



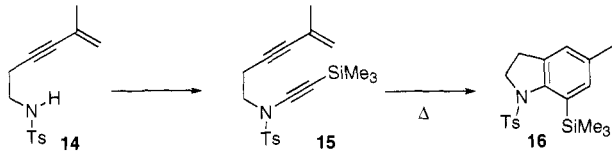
10 **11**

Functional groups can direct the metal-mediated C-H activation. Milton R. Smith III of Michigan State University found (*J. Am. Chem. Soc.* **2005**, *127*, 10539) that the cyano group is a particularly powerful director of *ortho* metalation and functionalization.



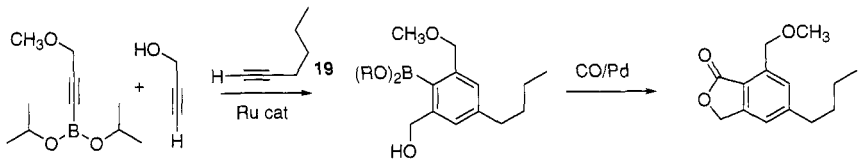
12 **13**

More highly substituted benzene derivatives can be constructed by intramolecular bond formation. Rick L. Danheiser of MIT has shown (*J. Am. Chem. Soc.* **2005**, *127*, 5776) that the thermal cyclization of ynamides with conjugated enynes proceeds smoothly.



14 **15** **16**

It is also possible to bring the ring components into proximity with a *temporary* tether. Yoshihiko Yamamoto of Nagoya University has developed (*J. Am. Chem. Soc.* **2005**, *127*, 9625) a boron tether that serves well. The product arylboronates such as **20** can then be further functionalized, as illustrated by carbonylation of **20** to give the phthalide **21**. The alcohol **18** can be replaced by an enantiomerically-pure secondary propargyl alcohol, leading to the enantiomerically-pure secondary phthalide.

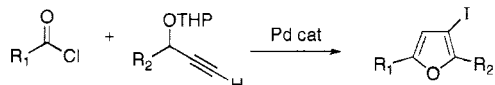


17 **18** **20** **21**

Preparation of Heteroaromatics

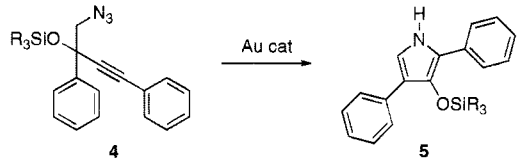
May 22, 2006

Thomas J. J. Müller of the Universität Heidelberg has reported (*Chem. Commun.* **2005**, 2581) a powerful method for the assembly of highly substituted furans, Pd-mediated condensation of an acid chloride **1** with a propargylic ether **2**. Depending on the halide used in the work-up, either chloro or iodofurans are prepared. The reaction works well for R_2 = H, opening access to rare 2,4-disubstituted furans.



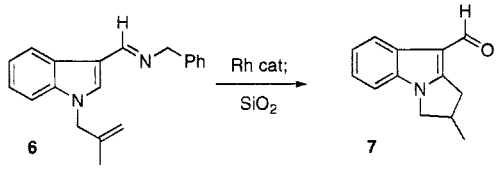
1 **2** **3**

F. Dean Toste of the University of California, Berkeley, has found (*J. Am. Chem. Soc.* **2005**, *127*, 11260) that exposure of an alkynyl azide such as **4** to an Au catalyst leads to intramolecular Schmidt reaction, to deliver the substituted pyrrole. In the case of **4**, the rearrangement proceeds with concomitant migration of the siloxy group, to give **5**. Alkyl-substituted alkynyl azides and alkynyl azides without the silyloxy groups also rearrange efficiently.



4 **5**

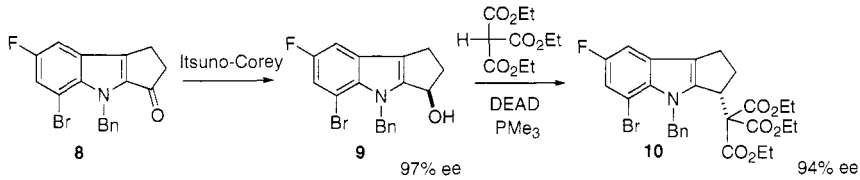
Robert G. Bergman and Jonathan A. Ellman of the University of California, Berkeley, have developed (*J. Org. Chem.* 2005, 70, 6775) a C-H activation-based method for the intramolecular alkylation of an aromatic ring. Applied to the indole **6**, this leads to the tricyclic indole **7**. The procedure works well with pyrroles also, as well as with benzene derivatives.



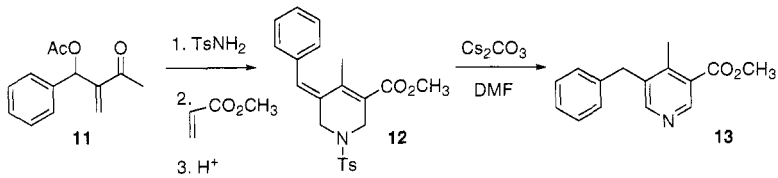
6 **7**

Michael C. Hillier of the Merck Process group in Rahway, NJ was faced (*J. Org. Chem.* **2005**, *70*, 8385) with the challenge of preparing the indole **10** in enantiomerically-pure form. Itsuno-Corey reduction of the ketone **8** worked well, but subsequent Mitsunobu coupling to give **10** led to substantial

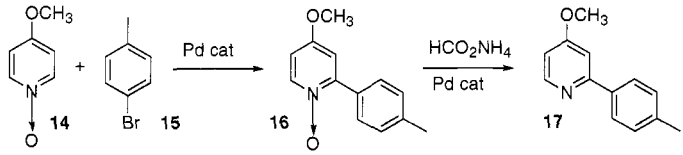
racemization. The authors eventually found that use of PMe_3 allowed nearly perfect inversion in the conversion of **9** to **10**.



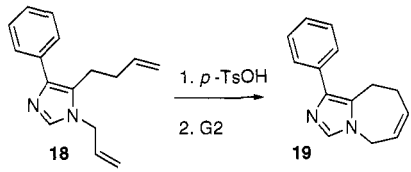
Highly substituted pyridines are often most easily prepared by total synthesis. Jae Nyoung Kim of Chonnam National University, Gwangju has developed (*Tetrahedron Lett.* **2005**, *46*, 8799) a new route to pyridines such as **13**, based on the addition of tosyl amide to Baylis-Hillman adducts such as **11**.



Keith Fagnou of the University of Ottawa has found (*J. Am. Chem. Soc.* **2005**, *127*, 18020) that transition metal-mediated C-H functionalization also works efficiently with pyridine N-oxides. An aryl halide such as **15** couples directly with **14** under Pd catalysis to give **16**. The product N-oxide is easily reduced to the pyridine **17**.



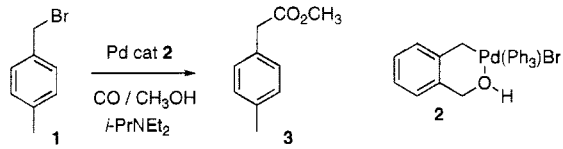
The Grubbs second - generation alkene metathesis catalyst ("G2") is compatible with many organic functional groups. It cannot be used, however, with basic amines. As illustrated by the efficient cyclization of **18** to **19** reported (*Organic Lett.* **2005**, *7*, 3183) by Vijaya Gracias of Abbott Laboratories, Abbott Park, IL, a simple solution to this problems is to pre-treat the amine with a stoichiometric amount of acid.



Preparation and Reactions of Carboxylic Acids, Esters and Amides

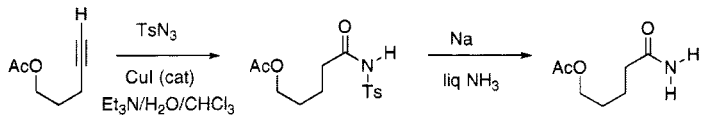
May 29, 2006

W. Edward Lendsell and Peter N. Preston of Herriot-Watt University, Edinburgh, have developed (*Tetrahedron Lett.* **2005**, *46*, 8695) a new family of Pd catalysts, exemplified by the complex **2**. These catalysts efficiently (1 mol %) mediate homologation of benzylic halides such as **1** to the corresponding methyl esters at low temperature (35 °C) and modest CO overpressure (3.45 bar).



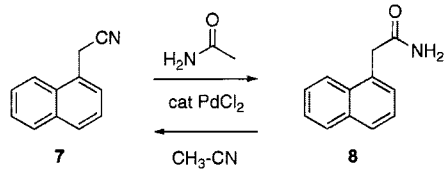
1 **3** **2**

Sukbok Chang of KAIST, Daejon, Korea has uncovered (*J. Am. Chem. Soc.* **2005**, *127*, 16046) a truly remarkable reaction, the hydrative conversion of a terminal alkyne such as **4** to the N-sulfonyl amide **5**. The free amide **6** can be released by dissolving metal reduction. It is likely that **5** could be N-alkylated efficiently, including under Mitsunobu conditions. The sulfonyl amide **5** may also behave like a Weinreb amide, allowing efficient coupling with organometallic nucleophiles to form the corresponding ketones.



4 **5** **6**

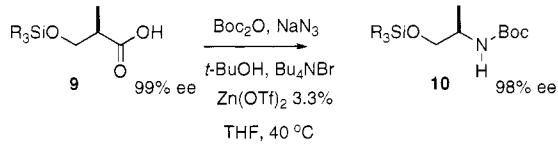
Another remarkable set of transformations has been reported (*Organic Lett.* **2005**, *7*, 5237) by Sonia I. Maffioli of Vicuron Pharmaceuticals, Gerenzano, Italy. Exposure of a nitrile **7** to a catalytic amount (as little as 0.5 mol %) of $PdCl_2$ ($Pd(OAc)_2$ served equally well) in the presence of acetamide led to the primary amide **8**. Conversely, the same catalyst in the presence of acetonitrile converts the primary amide **8** to the nitrile **7**. These reactions run at or slightly above ambient temperature.



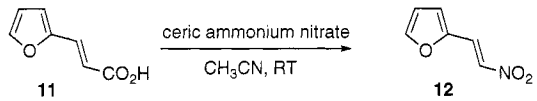
7 **8**

The one-carbon degradation of carboxylic acids is often used to install amines, converting the C-CO_2H bond into a C-N bond. Hélène Lebel of the Université de Montréal has developed (*Organic Lett.*

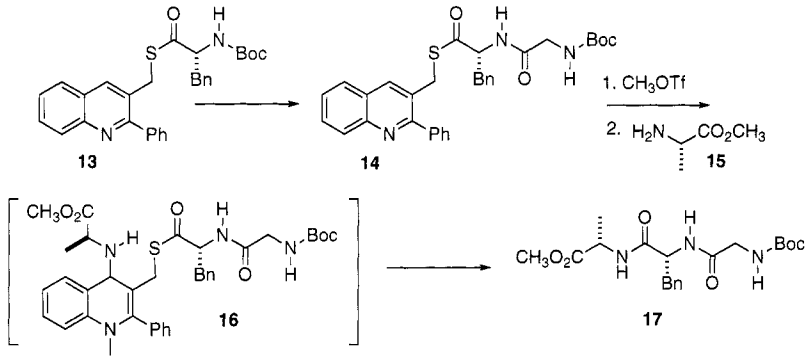
2005, *7*, 4107) a one-pot procedure leading directly to the N-Boc protected amine **10**. Of the several catalysts investigated for this transformation, $Zn(OTf)_2$ gave by far the best results.



J. Madhusudana Rao of the Indian Institute of Chemical Technology, Hyderabad, has developed (*Tetrahedron* Lett. **2005**, *46*, 8141) a simple protocol for the one-carbon degradation of an α,β-unsaturated carboxylic acid such as **11** to the corresponding nitro alkene **12**. The other examples given were also β-aryl or β-heteroaryl substituted. It will be interesting to learn whether or not this transformation can be extended to aliphatic and alicyclic α,β-unsaturated carboxylic acids, as well as to α,β-unsaturated carboxylic acids such as **11** having additional substituents on the alkene.



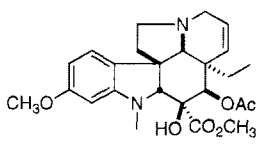
There have been several noteworthy advances in esterification (Kazuaki Ishihara, *J. Am. Chem. Soc.* **2005**, *127*, 4168), ester hydrolysis (K. C. Nicolaou, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378), and amide bond formation (Zbigniew J. Kaminski and Anna Maria Papini, *J. Am. Chem. Soc.* **2005**, *127*, 16912). Of these, the most striking is the quinoline thio ester **13** developed (*J. Am. Chem. Soc.* **2005**, *127*, 15668) by Vincent Levacher of the Université de Rouen. The thioester is robust enough to stand up under normal Boc removal and peptide forming conditions, to give **14**. N-Alkylation with Me triflate then activates the quinoline for addition by the free amine of **17**, leading to intramolecular acylation and eventual release of the tripeptide **17**. If such intramolecular acylation is effective with longer chain oligopeptides, this simple quinoline platform could enable the preparation of proteins by total synthesis.



The Boger Route to (-)-Vindoline

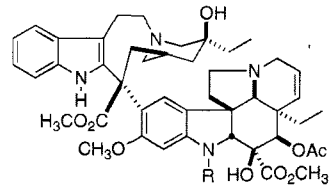
June 5, 2006

The *Vinca*-derived vinblastine **2a** and vincristine **2b** are still mainstays of cancer chemotherapy. The more complex half of these dimeric alkaloids, vindoline **1**, has in the past presented a formidable challenge for total synthesis. Dale L. Boger of Scripps, La Jolla has developed (*Organic Lett.* **2005**, *7*, 4539) a strikingly simple solution to this problem, based on sequential cycloaddition.



1

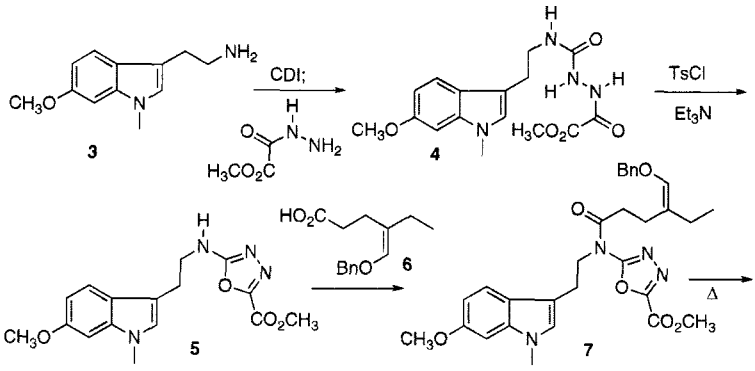
(-)-Vindoline



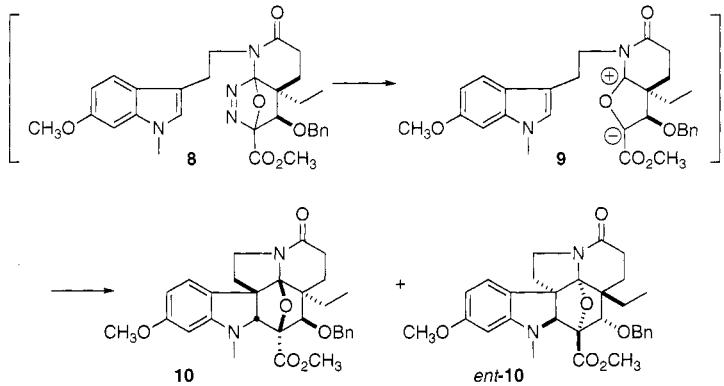
2a, R = CH_3 Vinblastine

2b, R= CH=O Vincristine

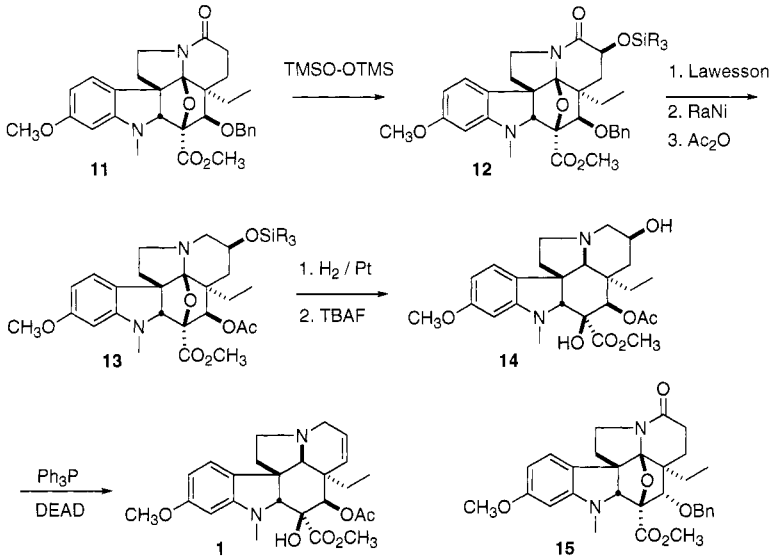
The starting point for the synthesis was N-methyl 6-methoxytryptamine **3**, an improved preparation of which is described by the authors. This was extended to **4**, which was then cyclized to **5**, and acylated with **6** to give **7**. On heating, **7** cyclized to **8**, which lost N_2 to give the zwitterion **9**. Addition of the intermediate **9** to the indole then gave **10**. In one reaction, the entire ring system of vindoline, appropriately oxygenated, was assembled! The precursor **7** was flat, so it offered no opportunity for chiral synthesis. Fortunately, **10** and *ent*-**10** proved to be very easy to resolve by chiral chromatography.



3 **4** **5** **6** **7**



To complete the synthesis, the δ-lactam **11** was oxygenated to **12**. Conditions for desulfurization of the derived thiolactam also effected debenzylation, to give, after acetylation, the ether **13**. Pt-mediated hydrogenolysis gave **14**, which was dehydrated to vindoline **1**.

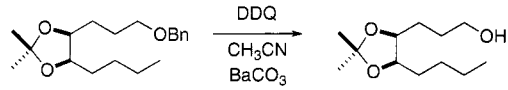


A complementary synthetic route, based on the *E* isomer of **6**, and so leading through the ether **15**, is also described. Although slightly longer, this approach was about as efficient as the route via **11**.

Protection of C-O and C-N

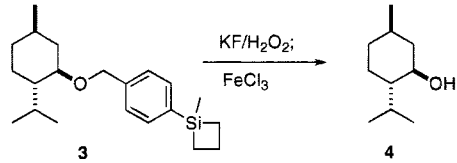
June 12, 2006

Although excellent books are available on organic functional group protection, there is still room for improvement. The DDQ cleavage of a benzyl ether is a classic transformation, yet it has not always been reliable. Kazunobu Toshima of Keio University has recently (*Tetrahedron Lett.* **2005**, *46*, 7307) found that the efficiency of the deprotection, e.g. conversion of **1** to **2**, is substantially improved if the reaction is exposed to long wavelenth UV. With acid sensitive substrates, yields are improved by the inclusion of insoluble $BaCO_3$. The previously observed variability in this deprotection may be due to differences in ambient laboratory lighting.



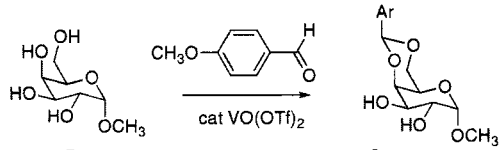
1 **2**

One way to avoid the difficulties of benzyl deprotection has been to use the more easily oxidized *p*-methoxybenzyl (PMB) group. Gregory B. Dudley of Florida State University has developed (*Tetrahedron Lett.* **2005**, *46*, 3283) a group that is orthogonal to *p*-methoxy benzyl, based on a *p*-siletanyl group (PSB). Mild conditions convert **3** to the *p*-hydroxybenzyl ether, which is removed very quickly with $FeCl_3$. In competition experiments, deprotection of PMB could be carried out in the presence of PSB, and the deprotection of PSB could be carried out in the presence of PMB.



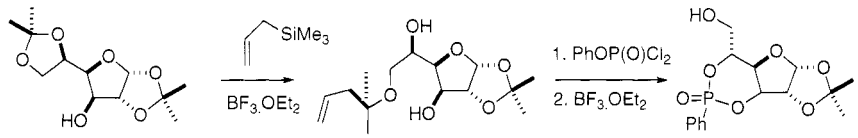
3 **4**

Protection of 1,2- and 1,3-diols is also important. Chien-Tien Chen of National Taiwan Normal University and Chung-Cheng Lin of the Academia Sinica, Taipei have found (*Organic Lett.* **2005**, *7*, 3343) that arylidene protection can be effected by direct condensation of an aromatic aldehyde with the diol (e.g. **5**) in the presence of catalytic vanadyl triflate. This observation will make arylidene protection, especially with less common aryl groups, more readily available.



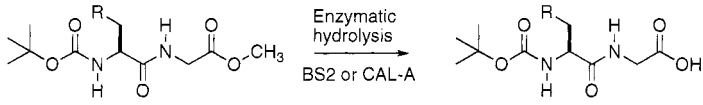
5 **6**

Fernando Sartillo-Piscil of the Universidad Autónoma de Puebla, Mexico, has uncovered (*J. Org. Chem.* **2005**, *70*, 7107) a new protocol for the selective deprotection of 1,2-diols. Exposure of **7** to allyltrimethyl silane in the presence of $BF_3.Et_2O$ yields the monoadduct **8**. After phosphorylation, the alcohol protecting group is readily removed by exposure to $BF_3.Et_2O$, to deliver **9**.



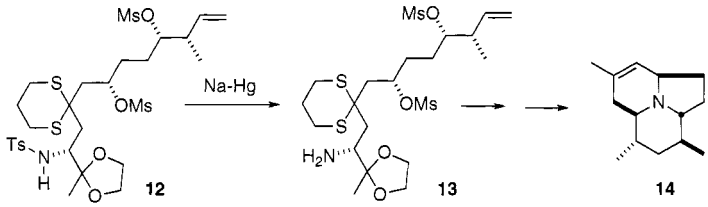
7 **8** **9**

Ester hydrolysis can present difficulties if there are sensitive functional groups elsewhere in the molecule. Uwe T. Bornscheuer of Greifswald University and George Kokotos of the University of Athens have found (*J. Org. Chem.* **2005**, *70*, 3737, 8730) that some readily-available enzymes can remove *t*-butyl, methyl and benzyl esters, in the presence of amine protecting groups such as Boc, Z, and Fmoc.



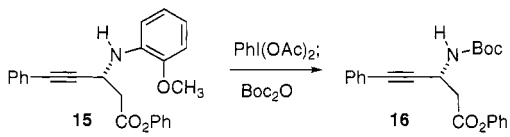
10 **11**

There is a widespread perception that the N-tosyl group is difficult to remove. In fact, it is often easily removed reductively. In the course of a synthesis of the Dendrobatid alkaloid 205B **14**, Amos B. Smith III of the University of Pennsylvania demonstrated (*Organic Lett.* **2005**, *7*, 3247) that the N-tosyl group could be reductively removed under conditions that did not affect two other organosulfur functional groups, mesylate and dithiane.



12 **13** **14**

The 4-methoxyphenyl N-protecting group has often resisted efficient oxidative removal (*J. Org. Chem.* **2005**, *70*, 10592). Marc L. Snapper and Amir H. Hoveyda of Boston College have now shown (*Organic Lett.* **2005**, *7*, 2711) that the alternative 2-methoxyphenyl N-protecting group can be removed cleanly by exposure to iodosobenzene diacetate.



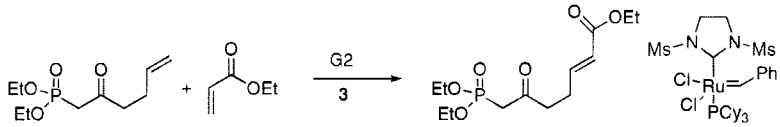
15 **16**

New Catalysts and Strategies for Alkene Metathesis

June 19, 2006

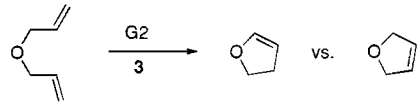
Alkene metathesis ("Grubbs Reaction") is now well-developed as a synthetic method. Still, there is a continuing effort to develop more efficient catalysts, and to extend the range of substrates that will participate efficiently.

William V. Murray of Johnson & Johnson, Raritan, NJ (*J. Org. Chem.* **2005**, *70*, 9636) and Sally-Ann Poulsen of Griffith University, Brisbane (*Tetrahedron Lett.* **2005**, *46*, 7389) independently reported that intramolecular alkene metathesis can be conveniently carried out under microwave irradiation. The cross metathesis of **1** and **2** to give **4** using the Grubbs second generation catalyst **3** required 24 hours at room temperature, or two hours in refluxing CH_2Cl_2. On microwave irradiation in a sealed vial, the reaction was complete in 15 minutes. Rapid heating of the reaction vessel in a conventional heating bath gave the same result, so there does not appear to be any special rate enhancement from the microwave, but it may offer a convenience in process development.



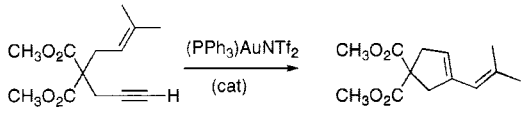
1 **2** **4** **3**

Alkene migration in the starting material and/or the product can be a serious issue with the Grubbs reaction. Robert H. Grubbs of Caltech (*J. Am. Chem. Soc.* **2005**, *127*, 17160) reported that exposure of the diene **5** to G2 alone led mainly to **6**. If 10 mol % of benzoquinone, or even better 2,6-dichloro or tetrafluorobenzoquinone, was included, the reaction delivered the simple metathesis product **7**. Note that both **6** and **7** could potentially be useful. Joachim H. G. Steinke of Imperial College, London and Ramón Vilar of the Institute of Chemical Research of Catalonia (*J. Org. Chem.* **2005**, *70*, 8235) have found that monophenyl phosphoesters also suppress alkene migration.



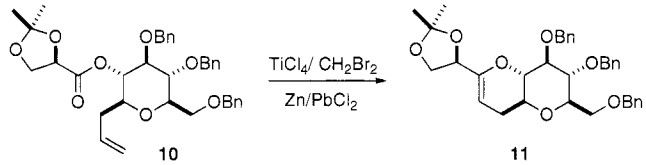
5 **6** **7**

Alkene metathesis is not limited to Ru catalysts. Fabien Gagosz of the Ecole Polytechnique, Palaiseau found (*Organic Lett.* **2005**, *7*, 4133) that an Au catalyst smoothly effected the metathesis cyclization of the ene yne substrate **8** to **9**.



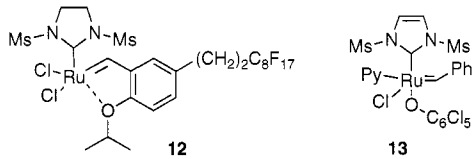
8 **9**

Esters can also participate in metathesis. In the course of establishing synthetic routes to the ladder polyether marine toxins, Jon D. Ranier of the University of Utah found (*Tetrahedron Lett.* **2005**, *46*, 7209) that the Takai-Utimoto stoichiometric Ti reagent effected direct conversion of alkenyl esters such as **10** into cyclic enol ethers such as **11**.



10 **11**

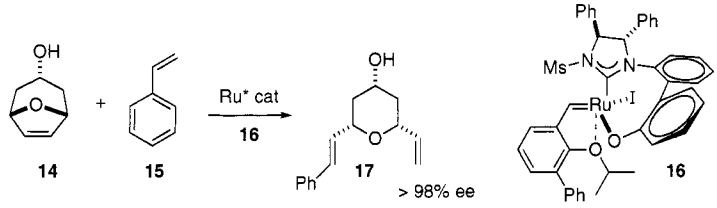
Three interesting new families of Ru catalysts have been developed. Dennis P. Curran of the University of Pittsburgh has reported (*J. Org. Chem.* **2005**, *70*, 1636) light fluorous Grubbs-Hoveyda catalysts such as **12**. Either alone or supported on fluorous silica gel, these catalysts are easily removed from the reaction mixture when the metathesis is complete. This minimizes Ru contamination of the product. The fluorous Ru catalyst can also be reused.



12 **13**

Deryn E. Fogg of the University of Ottawa has created (*J. Am. Chem.* Soc. **2005**, *127*, 11882) a new family of phenoxide-substituted Ru complexes, illustrated by **13**. The pyridine ligand is labile, so these catalysts are fast. They also appear to be more robust than G2, allowing lower catalyst loadings. It is particularly important that these aryloxide catalysts have a high affinity for silica gel. A single chromatography led to organic products containing less than 100 ppm Ru.

Amir H. Hoveyda of Boston College has developed a series of chiral Ru catalysts. The most recent entry (*J. Am. Chem. Soc.* **2005**, *127*, 6877) is the easily prepared **16**, that draws its chirality from the inexpensive diphenylethylenediamine. Exposure of prochiral **14** to an excess of styrene **15** in the presence of 5 mol % of the catalyst **16** for 30 min at room temperature delivered the cyclic ether **17** in 89% isolated yield and high ee.



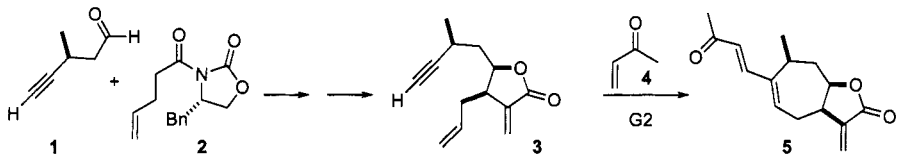
14 **15** **17** > 98% ee **16**

Creative Applications of Alkene and Alkyne Metathesis in Total Synthesis: (+)-8-epi-Xanthatin, (+)-Longicin, Latrunculin A, and Garsubellin A

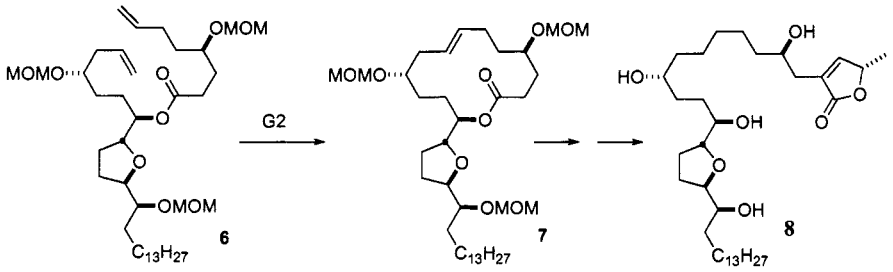
June 26, 2006

Alkene and alkyne metathesis, well-developed synthetic methods, are now often employed in natural product synthesis. The total syntheses outlined here are noteworthy for their creative application of these reactions.

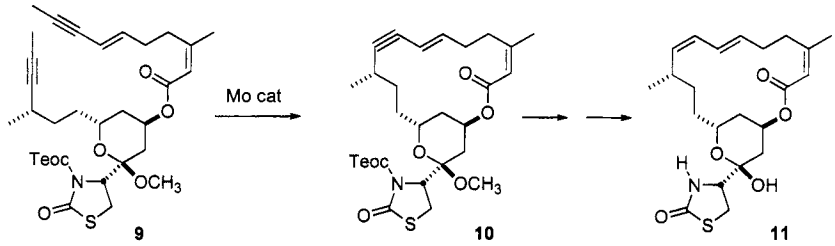
The sesquiterpene (+)-8-*epi*-xanthatin **5**, isolated from the aerial parts of the genus *Xanthium*, has been shown to inhibit the in vitro proliferation of several cultured human tumor cell lines. Stephen F. Martin of the University of Texas has described (*Organic Lett.* **2005**, *7*, 4621) a succinct assembly of **5**, starting with the addition of the enolate of **2** to the aldehyde **1**. The key step in the synthesis is the domino intramolecular metathesis – intermolecular metathesis, using the second-generation Grubbs catalyst, that converts **3** into **5**.



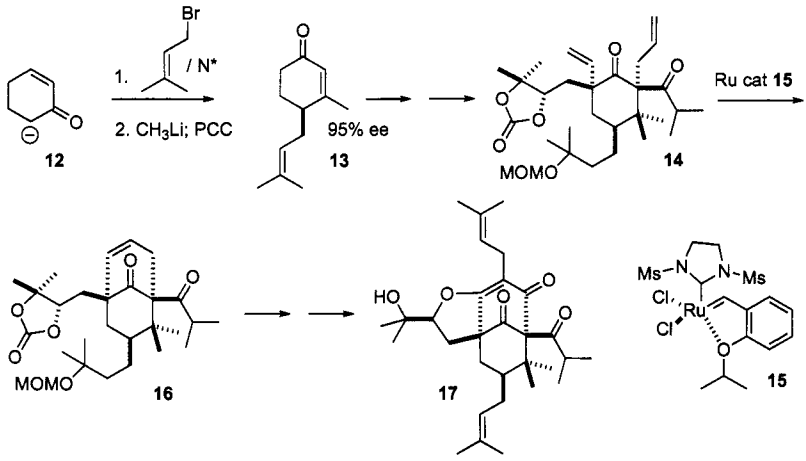
The *Annonacea* acetogenin (+)-longicin **8** is spectacularly more toxic toward malignant cells than toward normal cells. Stephen Hanessian has recently (*Organic Lett.* **2005**, *7*, 3989) reported the first total synthesis of **8**. The assembly of the carbon skeleton of **8** was accomplished expeditiously by convergent esterification of a tetrahydrofuran precursor with the enantiomerically-pure alkoxy acid to give **6**, followed by alkene metathesis to give **7**. It is striking that macrolide formation, once considered one of the most technically challenging of all organic synthesis transformations, can now be used for routine homologation.



Exposure of cultured cells in vitro to latrunculin A **11** leads to disruption of the actin cytoskeleton. The total synthesis of **11** by Alois Fürstner of the Max-Planck-Institut, Mülheim (*Angew. Chem. Int. Ed.* **2005**, *44*, 3462) addressed whether alkyne metathesis could be carried out in the presence of two reactive alkenes, one of which was also easily reducible. In fact, the cyclization of **9** to **10** proceeded efficiently. Partial hydrogenation of **10** then delivered the *Z*, *E*-diene of **11**.



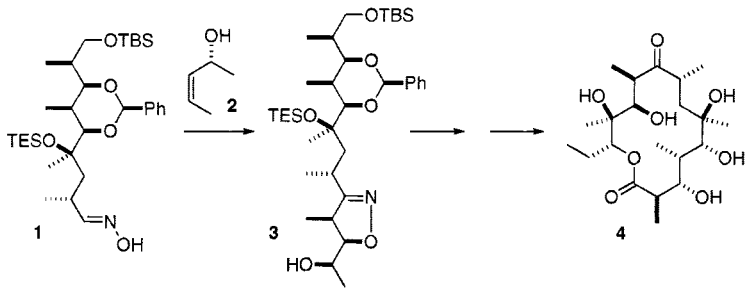
The polyprenylated phloroglucin garsubellin A **17**, an inducer of choline acetyltransferase, presents many synthetic challenges, from the easily-hydrolyzed nonenolizable tricarbonyl system to the three quaternary centers of the central cyclohexanone ring. The synthesis reported (*J. Am. Chem. Soc.* **2005**, *127*, 14200) by Motomu Kanai and Masakatsu Shibasaki of the University of Tokyo used as a key step the cyclization of **14** to **16**. The catalyst of choice in this case was the Hoveyda Ru complex **15**. Although the synthesis was carried to completion in the racemic series, the authors did demonstrate that alkylation of the enolate **12** of cyclohexenone using the elegant chiral amine procedure developed by the late Kenji Koga delivered the starting enone **13** in high ee.



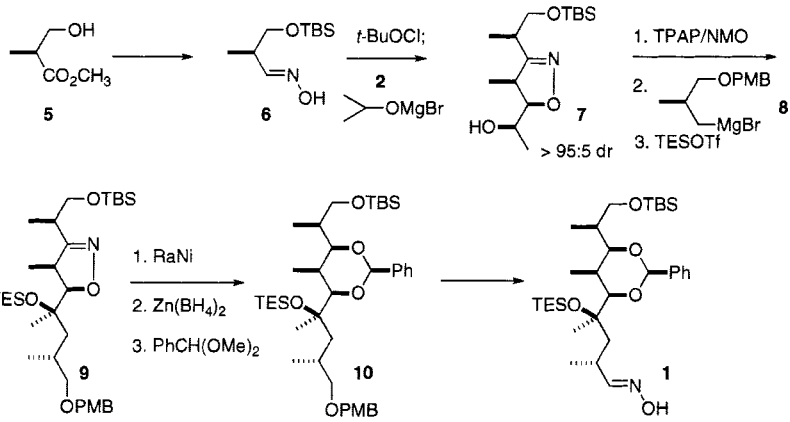
Synthesis of Erythronolide A

July 3, 2006

Erythronolide A **4**, with its array of ten stereogenic centers, is the parent of several classic antibiotics, including erythromycin. The key step in the total synthesis of **4** recently reported (*Angew. Chem. Int. Ed.* **2005**, *44*, 4036) by Erick M. Carreira of the ETH Hönggerberg is the activation of **1** and subsequent diastereoselective 1,3-dipolar cycloaddition to **2** to give **3**.



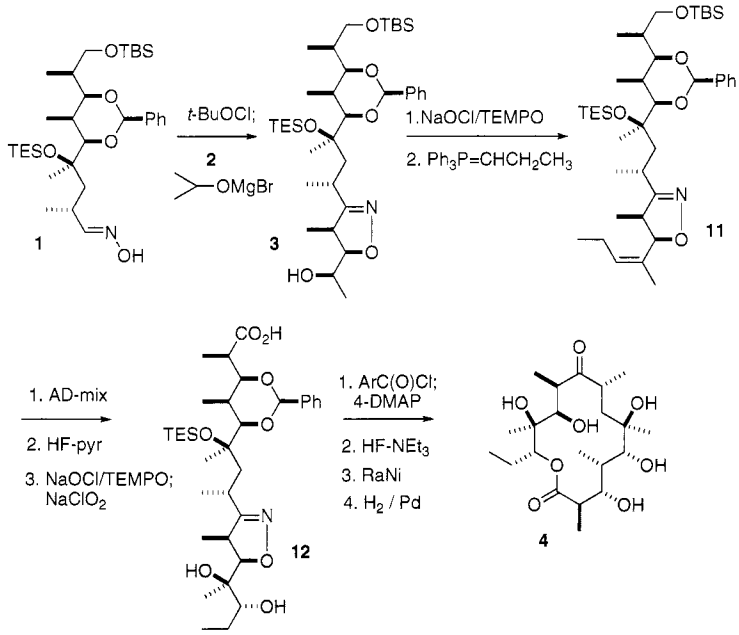
The synthesis of **1** started with two simple chirons, the alcohol **2**, prepared by Noyori reduction of the acetylenic ketone followed by semi-hydrogenation, and the inexpensive (< one euro/gram) Roche alcohol **5**. Functional group manipulation led to **6**, which underwent smooth Mg-mediated cycloaddition to the enantiomerically-pure alcohol **2**, to give **7**. Addition of the Grignard reagent **8**, also derived from the Roche ester **5**, to the derived methyl ketone also proceeded with high diastereocontrol,



to give the tertiary alcohol. Reduction of **9** and subsequent hydrolysis liberated the hydroxy ketone,

which was reduced selectively to the syn diol. It is a tribute to the stability of tertiary triethylsilyl ethers that the TES protecting group put on at this stage survived all the way to the end of the synthesis.

While the diastereoselectivity of 1,3-dipolar cycloaddition was well-precedented in simpler systems, it was not clear that the diastereoselectivity would be maintained with such a complex substrate as **1**. In fact, addition to **2** proceeded with > 99:1 dr. Wittig homologation of the derived methyl ketone proceeded with remarkable (33:1) geometric control, setting the stage for asymmetric dihydroxylation to put in place the last two stereocenters.



Controlled desilylation of **11** followed by selective oxidation delivered the seco acid **12**. It had previously been shown by others that some cyclic protecting groups facilitate macrolactone formation, while others do not. Fortunately, the two cyclic protecting groups of **12** served well, and the macrolactonization proceeded efficiently. Protecting group removal and reductive unmasking of the hydroxy ketone then delivered erythronolide A **4**.

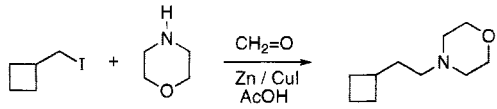
Overall, this elegant synthesis is a showcase for the iterative use of the 1,3-dipolar cycloaddition of enantiomercially-pure allylic alcohols for the preparation of extended arrays of acyclic stereogenic centers.

Best Synthetic Methods: C-C Bond Formation

July 10, 2006

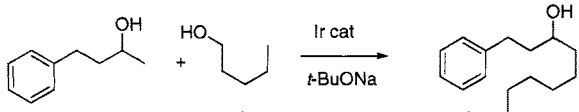
Carbon-carbon bond formation is the fundamental transformation of organic synthesis. Several new procedures have been put forward that offer advantages of selectivity and economy.

Lothar W. Bieber of the Universidade Federal de Pernambuco, Recife, Brazil, has reported (*Tetrahedron Lett.* **2005**, *46*, 7601) the one-carbon aminoalkylation of alkyl halides such as **1** using Zn and acetic acid. Remarkably, aqueous formaldehyde works efficiently in the reaction.



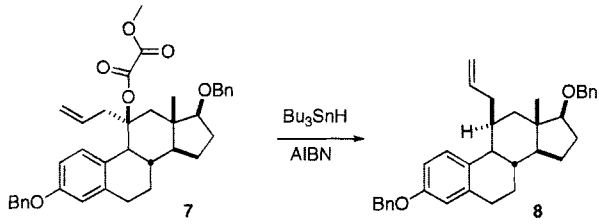
2 **3**

The telescoping of several synthetic steps offers substantial advantages on scale. Ken-ichi Fujita and Ryohei Yamaguchi of Kyoto University have developed (*Organic Lett.* **2005**, *7*, 4017) an Ir catalyst that mediates the condensation of a secondary alcohol such as **4** with a primary alcohol such as **5**. The overall transformation must include six steps: oxidation of each alcohol, aldol condensation, dehydration, reduction of the alkene, and reduction of the ketone.



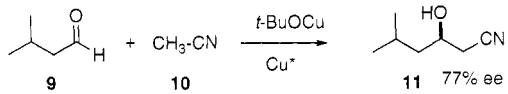
4 **5** **6**

One might think that ternary alkyl centers such as that of **8** would be formed by nucleophilic substitution. Jean-Claude Blazejewski of the Université de Versailles has described (*J. Org. Chem.* **2005**, *70*, 8907) an alternative approach, free radical reduction of the corresponding tertiary alcohol. Equatorial H atom addition sets the relative configuration of the pendant alkyl group. With radical-stabilizing substituents, an increasing proportion of the equatorial alkyl group is observed.



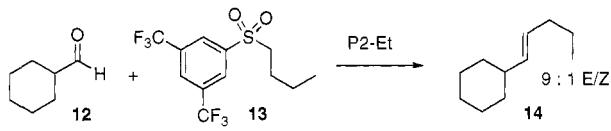
7 **8**

The anion of acetonitrile **10** adds efficiently to aldehydes and ketones. Simultaneously, Oleg. V. Ozerov of Brandeis University (*Chem Commun.* **2005**, 4450) and Masakatsu Shibasaki of the University of Tokyo (*Chem Commun.* **2005**, 3600) reported that this addition can be carried out using sub-stoichiometric DBU and a transition metal catalyst. Later, Professor Shibasaki and his colleague Motomu Kanai found (*Organic Lett.* **2005**, *7*, 3757) that the use of a chiral Cu catalyst led to the adduct with useful ee.



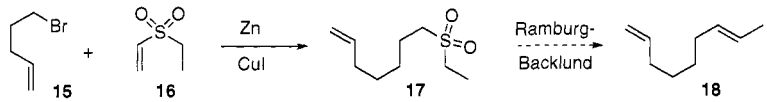
9 **10** **11** 77% ee

The Julia olefination using heteroaryl sulfones has been developed extensively over the past several years. Carmen Nájera of the Universidad de Alicante has now established (*J. Org. Chem.* **2005**, *70*, 6404) that electron-withdrawing arene sulfones such as **13** in conjunction with phosphazene bases also work well.



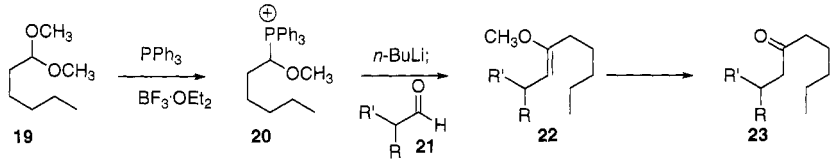
12 **13** **14**

Matthew M. Zhao of Merck Process, Rahway, has found (*J. Org. Chem.* **2005**, *70*, 6944) that Zn/Cu mediates the addition of halides to unsaturated sulfones such as **16**. Unsaturated sulfonates work well also. Note that Ramburg-Backlund contraction of the sulfone **17** would give the alkene **18**.



15 **16** **17** **18**

Steven D. Burke of the University of Wisconsin reports (*J. Org. Chem.* **2005**, *70*, 9382) a simple procedure for the homologation of an aldehyde such as **21** to the ketone **23**. The phosphonium salt **20** was readily prepared from the acetal. The key to this approach was to convert **20** to the phosphorane at -40 °C.



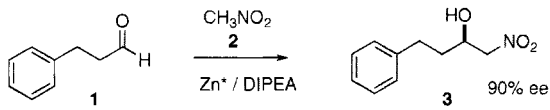
19 **20** **21** **22** **23**

Catalytic Enantioselective Homologation of Aldehydes to Alcohols and Amines

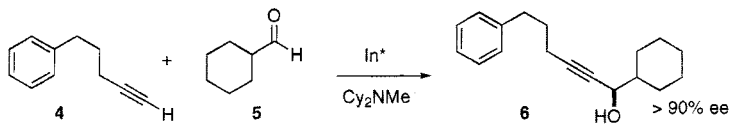
July 17, 2006

Convergent coupling of a nucleophile with an aldehyde ideally will proceed with high enantioselectivity, while at the same time allowing the attachment of a usefully functionalized fragment. Several recently-reported aldehyde homologations are particularly noteworthy.

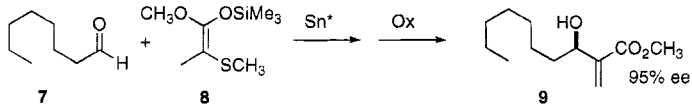
One of the simplest of functionalized nucleophiles is nitromethane **2**. Claudio Palomo of the Universidad del País Vasco has found (*Angew. Chem. Int. Ed.* **2005**, *44*, 3881) that a Lewis acid and an amine base together mediate the enantioselective addition of nitromethane to an aldehyde **1** (Henry reaction) to give the alcohol **3**.



The enantioselective addition of an alkyne **4** to an aldehyde **5** has become a workhorse of organic synthesis. Masakatsu Shibasaka of the University of Tokyo has developed (*J.Am. Chem. Soc.* **2005**, *127*, 13760) an indium-based protocol for this addition.

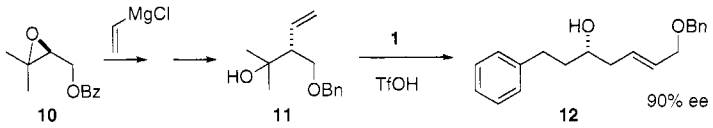


Isamu Shiina of the Tokyo University of Science has devised (*J. Org. Chem.* **2005**, *70*, 8103) an enantioselective procedure for the three-carbon homologation of an aldehyde **7** to give, after oxidation of the initial adduct, the unsaturated ester **9** ("Baylis-Hillman reaction). Note that this transformation should work equally well with esters bearing longer sidechains than **8**.



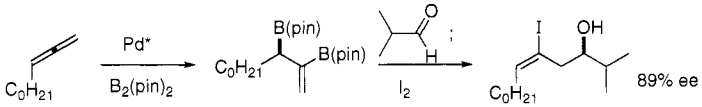
Acid-catalyzed allyl transfer is an efficient method for adding an allylic "anion" to an aldehyde with control of regioselectivity, geometry and absolute configuration. Junzo Nokami of the Okayama University of Science has introduced (*Organic Lett.* **2005**, *7*, 2957) a new route to substituted allyl donors, based on alkenyl addition to **10**, prepared by Sharpless asymmetric epoxidation. The ee of **12** is

the same as the ee of **10**. It might be possible to devise a derivative of **10** or of **11** that could be recrystallized to higher ee.



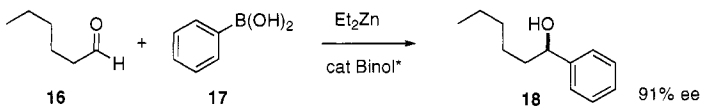
10 11 12

One of the most powerful methods for catalytic enantioselective aldehyde homologation ever developed is the catalytic asymmetric allene diboration approach reported (*Organic Lett.* **2005**, *7*, 5505) by James P. Morken, now at Boston College. Sequential reaction of **14** with an aldehyde and then with another electrophile leads to highly functionalized, stereodefined products such as **15**.



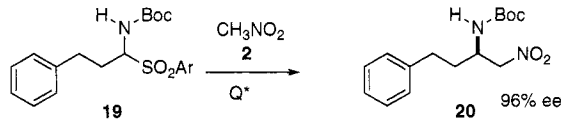
13 14 15

The catalytic enantioselective adddition of an aryl nucleophiles to aldehydes has been difficult to achieve. Katsuji Ito of the Fukuoka University of Education and Tsutomu Katsuki of Kyushu University have reported (*Tetrahedron* Lett. **2005**, *46*, 6083) a general solution to this problem, using an areneboronic acid activated by Et_2Zn in presence of a catalytic amount of a binol derivative.



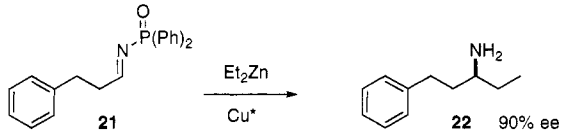
16 17 18

Alkyl imines do not react with nucleophiles such as **14**, so more electrophilic imine equivalents have been developed. Independently, Raquel P. Herrera and Luca Bernardi of the Università di Bologna (*Angew. Chem. Int. Ed.* **2005**, *44*, 7975) and Professor Palomo (*J. Am. Chem. Soc.* **2005**, *127*, 17622) have described the use of α-sulfonyl amine derivatives such as **19**. Adddition of nitromethane in the presence of a chiral quaternary ammonium salt delivered the aza-Henry product **20**.



19 20

The multicomponent condensation created by André Charette of the Université de Montreal (*J. Org. Chem.* **2005**, *70*, 10864) is particularly convenient. Exposure of the phosphonyl imine **21**, prepared in situ, to a dialkyl zinc in the presence of a chiral Cu catalyst gives, after workup, the unprotected primary amine **22** in high ee.

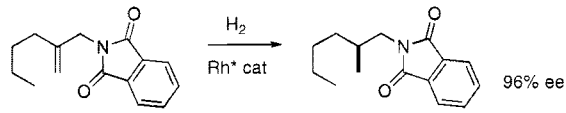


21 22

Catalytic Enantioselective Construction of Alkylated Stereogenic Centers

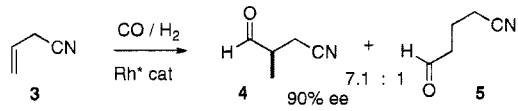
July 24, 2006

One of the simplest ways to construct alkylated ternary centers is enantioselective catalytic hydrogenation. Xumu Zhang of Pennsylvania State University has devised (*Angew. Chem. Int. Ed.* **2005**, *44*, 4933) a chiral Rh catalyst that reduces allyl phthalimides such as **1** with high ee. This appears to be a general method for preparing β-methyl chiral amines.



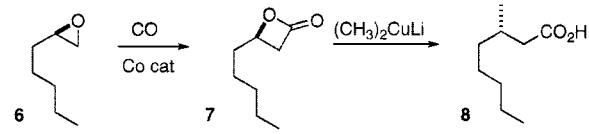
1 **2**

Hydroformylation homologates an alkene such as **3** into either the branched product **4** or the linear product **5**. Jerzy Klosin of Dow Chemical, Midland, MI has developed (*Angew. Chem. Int. Ed.* **2005**, *44*, 5834) a chiral Rh catalyst that converts **3** into **4** with high selectivity and high ee.



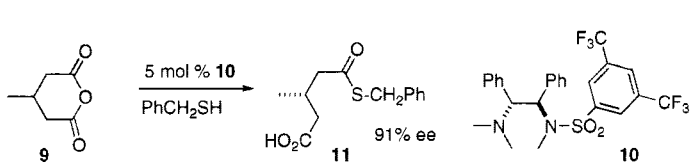
3 **4** **5**

Epoxides such as **6** are now readily available using the Jacobsen kinetic resolution. Geoffrey W. Coates of Cornell University has prepared (*J. Am. Chem. Soc.* **2005**, *127*, 11426) a Co catalyst that efficiently carbonylates such epoxides, leading to the β-lactone **7**. β-Lactones such as **7** are known to react with lithium dialkyl cuprates with clean inversion at the secondary center.



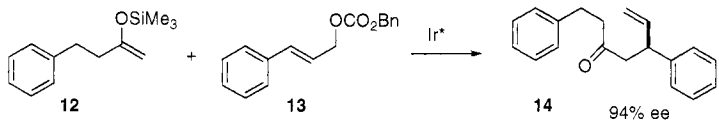
6 **7** **8**

Stereogenic centers can also be established by desymmetrization of prochiral anhydrides such as **9**. Yoshimitsu Nagao of the University of Tokushima has found (*Angew. Chem. Int. Ed.* **2005**, *44*, 5838) that the organocatalyst **10** effects the opening of **9** with high enantioselectivity. Note that thioesters such as **11** are cleanly homologated to the corresponding ketones with Fe-catalyzed Grignard reagents.

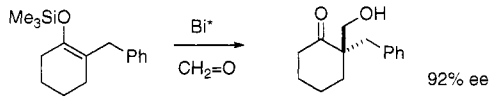


9 **11** **10**

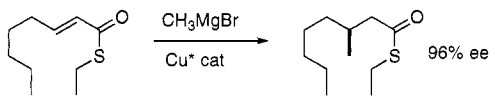
Control of absolute configuration in the alkylation of acyclic ketone enolates has been a long-standing problem in organic synthesis. John F. Hartwig of Yale University has reported (*J. Am. Chem. Soc.* **2005**, *127*, 17192) an Ir catalyst that mediates enantioselective bond formation between silyl enol ethers such as **12** of methyl ketones, and allylic carbonates. Barry M. Trost of Stanford University has described (*J. Am. Chem. Soc.* **2005**, *127*, 17180) a complementary approach.



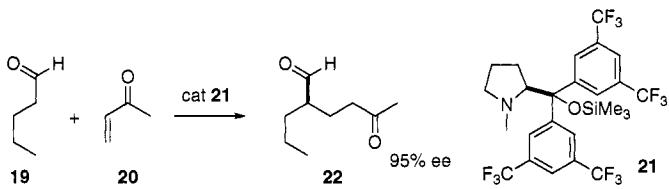
Shu Kobayashi of the University of Tokyo has reported (*Organic Lett.* **2005**, *7*, 4729) the remarkable aldol condensation of both cyclic (e.g. **15**) and acyclic ketone silyl enol ethers with aqueous formaldehyde. With a chiral bismuth catalyst, the homologation proceeds at room temperature in good yield and high ee.



The most active area of investigation has been enantioselective conjugate addition. In a particularly important development, Adriaan J. Minnaard and Ben L. Feringa of the University of Groningen have shown (*J. Am. Chem. Soc.* **2005**, *127*, 9966) that while α,β-unsaturated esters are mediocre substrates for Cu-catalyzed conjugate addition, the corresponding α,β-unsaturated thioesters work well.



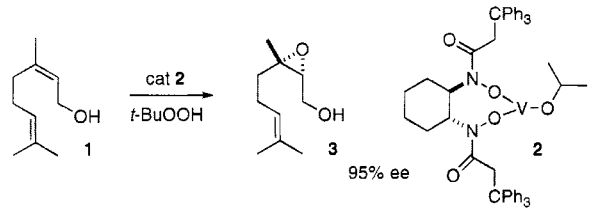
Another advance that will be of general utility is the organocatalyst-mediated chiral conjugate addition of aldehydes such as **19** to enones such as **20**, developed independently by Karl Anker Jorgensen of Aarhus University (*J. Am. Chem. Soc.* **2005**, *127*, 18296), by Yujiro Hayashi of Tokyo University of Science (*Angew. Chem. Int. Ed.* **2005**, *44*, 4212) and by Samuel H. Gellman of the University of Wisconsin (*J. Am. Chem. Soc.* **2005**, *127*, 11598; *Organic Lett.* **2005**, *7*, 4253).



Enantioselective Construction of Arrays of Stereogenic Centers

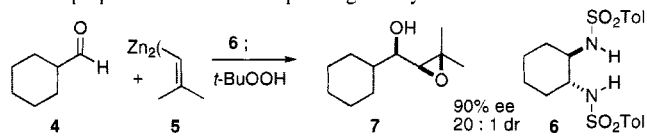
July 31, 2006

Sharpless asymmetric epoxidation has long been a workhorse of enantioselective synthesis. The SAE protocol, however, gives only mediocre ee's with cis allylic alcohols such as nerol **1**. Hisashi Yamamoto of the University of Chicago has devised an alternative procedure (*Angew. Chem. Int. Ed.* **2005**, *44*, 4389), based on the bis N-hydroxyamide **2**. This gives high ee's with a variety of substituted allylic alcohols, including **1**.



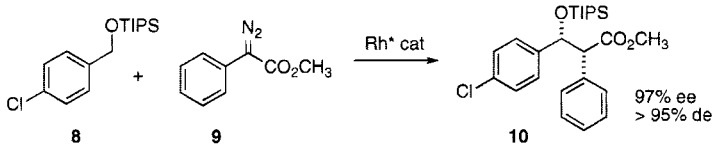
1 3 2

In a related development (*J. Am. Chem. Soc.* **2005**, *127*, 14668), Patrick J. Walsh of the University of Pennsylvania has added alkenyl zincs such as **5** to aldehydes such as **4** in the presence of the chiral ligand **6**. Oxygenation in situ of the resulting zinc alkoxide delivers the epoxy alcohol **7** in high ee. The alkenyl zincs are prepared from the corresponding alkenyl bromides with Li and $ZnBr_2$.



4 5 7 6

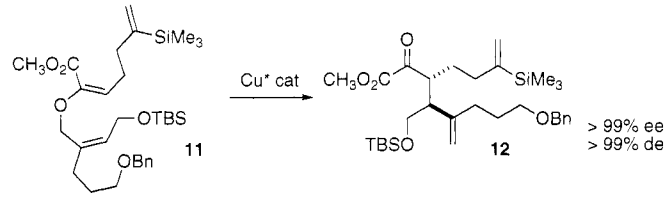
Arrays of stereogenic centers are often assembled by aldol condensation. Huw M.L. Davies of the University at Buffalo has put forward (*J. Org. Chem.* **2005**, *70*, 10737) an alternative. Enantioselective Rh-mediated insertion of the carbene derived from **9** into the benzylic C-H of **8** gives the "protected aldol" product **10** in high ee.



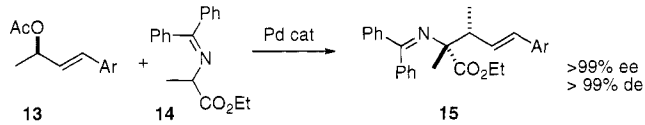
8 9 10

The Claisen rearrangement is a powerful method for assembling adjacent alkylated stereogenic centers. Martin Hiersemann of the Technische Universität Dresden has shown (*Organic Lett.* **2005**, *7*, 5705) that a chiral Cu catalyst mediates the conversion of **11** to **12**. The α-keto ester **12** so prepared was a single enantiomer of a single diasteromer. A limitation on this approach is the necessity of preparing

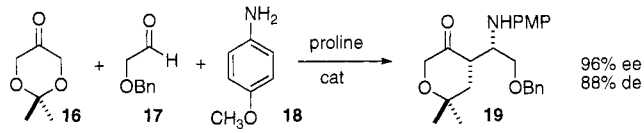
the stereodefined enol ether starting material. Joseph M. Ready of UT Southwestern Medical Center has reported (*Organic Lett.* **2005**, *7*, 5681) an effective procedure for preparing such ethers.



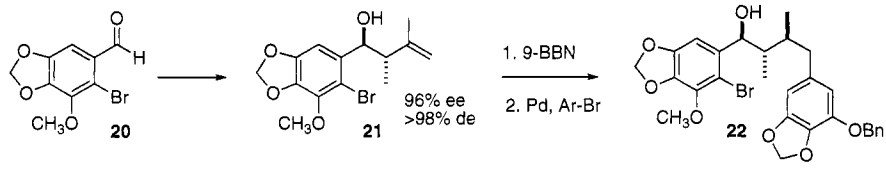
Enantiomerically pure allylic acetates such as **13** are easily prepared. Motoi Kawatsura of Tottori University has devised conditions (*Tetrahedron Lett.* **2005**, *46*, 6663) for coupling **13** with **14** with very high regio- and diastereocontrol.



Aldol reactions of **16** have been extensively reported. Bernhard Westermann of the Institute of Plant Biochemistry in Halle (*Angew. Chem. Int. Ed.* **2005**, *44*, 4077) and Dieter Enders of RWTH Aachen (*Angew. Chem. Int. Ed.* **2005**, *44*, 4079) have now independently shown that the Mannich condensation can also be successful. James C. Anderson of the University of Nottingham (*J. Org. Chem.* **2005**, *70*, 5665), Ming-Hua Xu and Guo-Qiang Lin of the Shanghai Institute of Organic Chemistry (*J. Am. Chem. Soc.* **2005**, *127*, 11956) and Scott E. Schaus of Boston University (*J. Am. Chem. Soc.* **2005**, *127*, 11256) have also reported significant progress with catalytic enantioselective Mannich reactions.



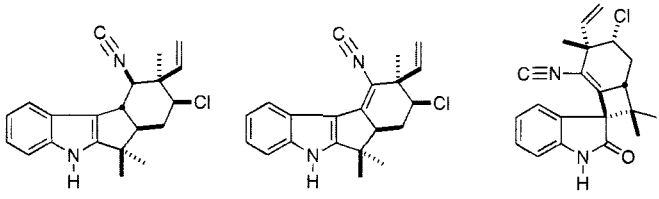
Strategies for the assembly of more extended arrays of stereogenic centers are also important. Robert S. Coleman of The Ohio State University found (*J. Org. Chem.* **2005**, *70*, 8932) that the best results for the homologation of **20** were achieved using the protocol developed by James L. Leighton of Columbia University. Diastereoselective hydroboration then led to **22**. In another development, William R. Roush of Scripps Florida has reported (*Org. Lett.* **2005**, *7*, 3941) further applications of his linchpin strategy for the assembly of arrays of stereogenic centers.



Adventures in Complex Indole Synthesis: (-)-Fischerindole I, (+)-Fischerindole G and (+)-Weltwitindolinone A

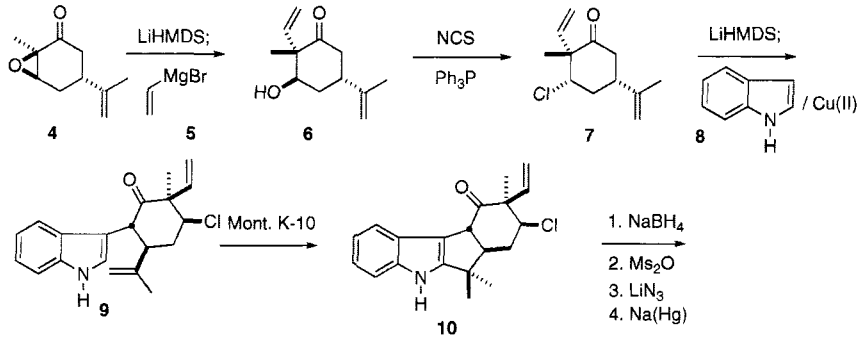
August 7, 2006

Phil S. Baran of Scripps La Jolla has described (*J. Am. Chem. Soc.* **2005**, *127*, 15394) an elegant entry to the complex indole-derived natural products (-)-fischerindole G **1**, (+)-fischerindole I **2** and (+)-weltwitindolinone A **3**.

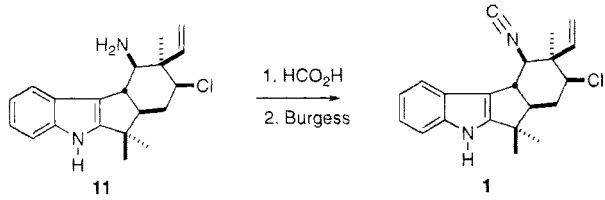


1 **2** **3**

The starting point for the preparation of **1** and **2** was the epoxide **4** of *R*-carvone. Enolization followed by opening with vinyl magnesium bromide **5** delivered the alcohol **6**. The yield of this reaction was modest, but it directly provided **6**, with all of the non-indole carbon skeleton of **1**, suitably oxidized, in enantiomerically-pure form.



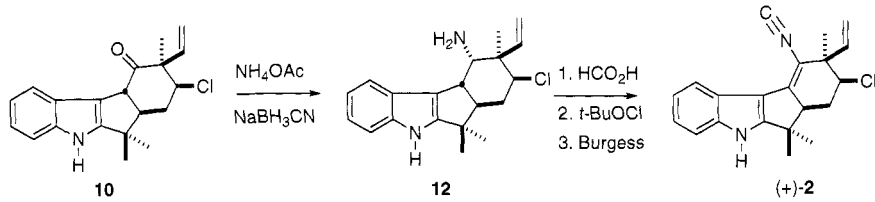
4 **5** **6** **7** **8** **9** **10**



11 1

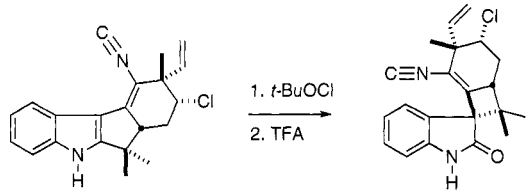
Remarkably, chlorination of the hindered secondary cyclohexyl alcohol proceeded cleanly, to give **7**. Oxidative condensation of the enolate of **7** with indole **8** gave the key intermediate **9**. After some experimentation, it was found that the clay Montmorillonite K-10 would effect the cyclization to **10**. There is not yet a general reductive amination procedure for converting a cyclohexanone to the equatorial amine, so **10** was reduced to the axial alcohol, which was converted to the equatorial azide. Selective reduction then delivered the amine **11**, the formamide of which was dehydrated to give **1**. The alkaloid **1** so prepared was the enantiomer of the natural product.

It was not possible to dehydrogenate **1** or the precursor formamide to **2**. The ketone **10** was therefore reduced selectively to the axial amine **12**. Exposure of the derived formamide to *t*-BuOCl followed by silica gel and Et_3N installed the desired double bond. Dehydration with the Burgess reagent then gave **2**.



10 12 (+)-2

With the absolute configuration of the series established by the preparation of **1**, the enantiomer of the alkaloid **2** was prepared from *S*-carvone. Both *R*-carvone and *S*-carvone are inexpensive and available in bulk. Exposure of the **2** so prepared to *t*-BuOCl followed by trifluoroacetic acid induced oxidative rearrangement to (+)-weltwitindoline A **3**, identical, including sign of rotation, with the natural product.



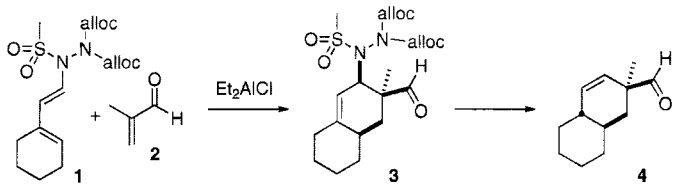
(-)-2 3

These three syntheses, which remarkably proceed without resort to functional group protection, underline the power of the oxidative indole coupling illustrated by the union of **7** and **8** to give **9**. The authors suggest that the facile conversion of **12** to **2**, contrasted to the difficulties encountered in attempting to prepare **2** from **11**, could indicate that it is in fact the axial amine **12** or a derivative that is the biosynthetic precursor to **2**.

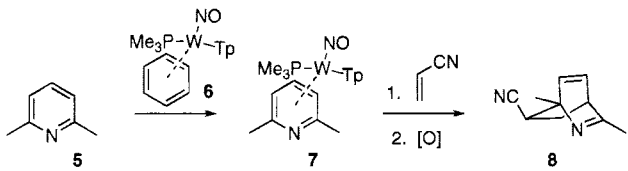
New Dienes and Dienophiles for Intermolecular and Intramolecular Diels-Alder Cycloadditions

August 14, 2006

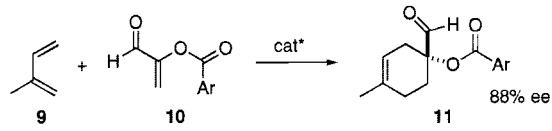
The Diels-Alder reaction is a powerful tool for the construction of substituted cyclohexenes. Erik J. Sorenson of Princeton University has developed (*J. Am. Chem. Soc.* **2005**, *127*, 8612) a class of hydrazinodienes, exemplified by **1**. Lewis acid-mediated cycloaddition to give **3** proceeded smoothly. Protection of the aldehyde followed by sigmatropic loss of N_2 led to the product **4**. This new class of dienes opens access to cyclohexenes having substitution patterns that cannot be prepared by direct Diels-Alder addition.



Aromatics and heteroaromatics are potentially inexpensive dienes, as strategies can be developed for breaking up their aromaticity. Stoichiometric transition metal complexes have been used for this purpose, but this approach is seldom practical, because of the expense of the transition metal used. W.D. Harman of the University of Virginia has now shown (*J. Am. Chem. Soc.* **2005**, *127*, 10568) that the 1:1 complex **7** of 2,6-lutidine **5** and the inexpensive tris(pyrazolo)borate tungsten **6** serves as an effective Diels-Alder diene, adding acrylonitrile to deliver, after oxidative removal of the tungsten, the highly functionalized adduct **8**.



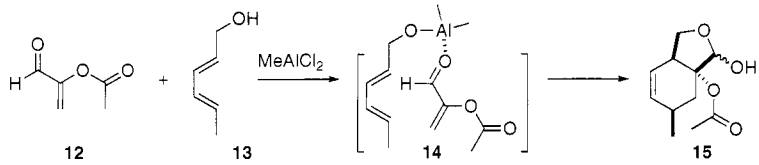
One of the most important advances for the Diels-Alder reaction in recent years has been the development of effective enantioselective organocatalysts. To date, this work had focused on α-unsubstituted or α-haloacroleins. Kazuaki Ishihara of Nagoya University has now prepared (*J. Am. Chem. Soc.* **2005**, *127*, 10504) a family of triamine catalysts that are effective with α-acyloxy acroleins.



New Dienes and Dienophiles for Intermolecular and Intramolecular Diels-Alder Cycloadditions

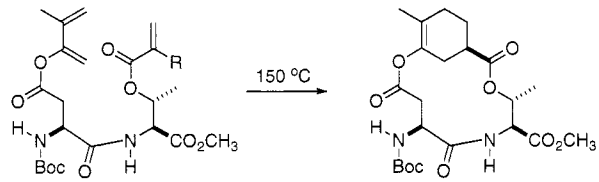
August 14, 2006

In a parallel development (*Organic Lett.* **2005**, *7*, 4515), Dimitris Georgiadis of the University of Athens has found that a Lewis acid effectively promotes the Diels-Alder cycloaddition of α-acetoxy acrolein **12** to sorbyl alcohol **13**. This reaction is apparently intramolecular, with the Lewis acid linking the diene and the dienophile.



12 **13** **14** **15**

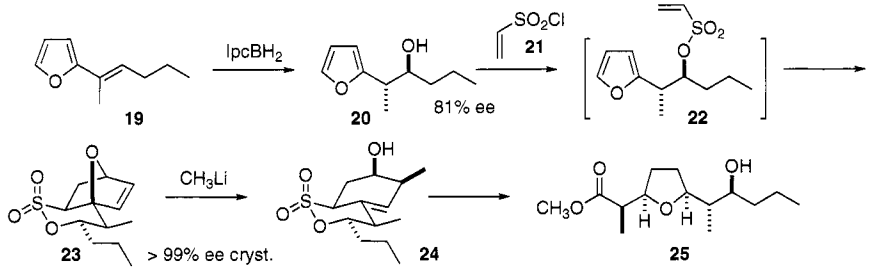
Enantiomerically-pure linkers can also be used to direct Diels-Alder cycloaddition. Takayuki Doi and Takashi Takahashi of the Tokyo Institute of Technology designed (*Chem. Commun.* **2005**, 4908) the dipeptide linker of **16** and **17**. They observed that **16** cyclized with high diastereocontrol to **18**, while **17** gave a ~ 1:1 mixture. These results were predicted qualitatively by computational analysis of the competing transition states.



16, R = H
17, R = CH_3

18

The intramolecular Diels-Alder cycloaddition is a powerful tool for polycarbocyclic construction. The continuing work of Peter Metz of the Technische Universität Dresden (*Angew. Chem. Int. Ed.* **2005**, *44*, 6231) demonstrates that the IDA is also an effective tool for the enantioselective construction of heterocycles. Alcohol **20** was prepared by enantioselective hydroboration. Formation of the sulfonate ester **22** led directly to the Diels-Alder adduct **23**, which was brought to enantiomeric purity by recrystallization. Methyl lithium opening followed by oxidative cleavage and reductive cyclization delivered the hydroxy ester **25**, a key intermediate in the total synthesis of pamamycin-621A.



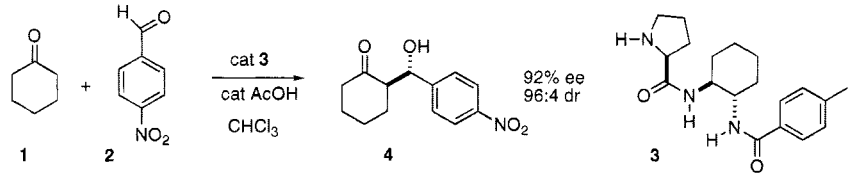
19 **20** 81% ee **22**

23 > 99% ee cryst. **24** **25**

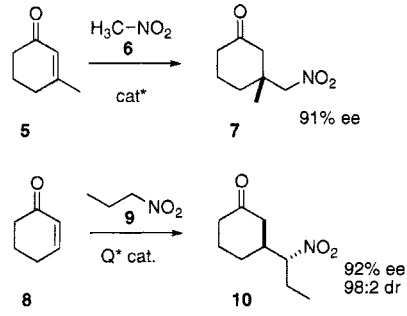
Organocatalytic Preparation of Enantiomerically-Pure Carbocycles

August 21, 2006

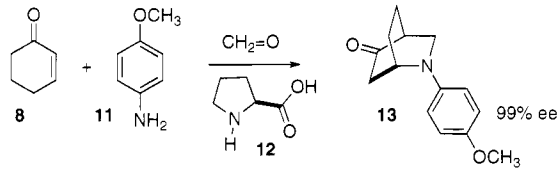
Enantiomerically-pure carbocycles can be prepared either *de novo*, or by desymmetrization of prochiral rings. A classic illustration of the latter approach is the condensation of cyclohexanone **1** with *p*-nitrobenzaldehyde **2**. Wen-Jing Xiao of Central China Normal University in Wuhan has reported (*Organic Lett.* **2005**, *7*, 4543) that the L-prolinamide **3** is a particularly effective organocatalyst for this transformation.



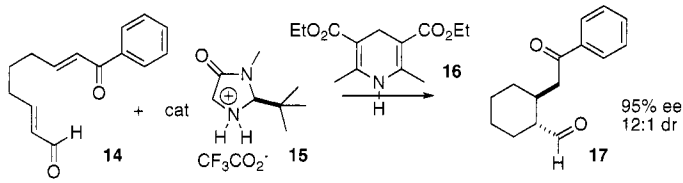
Cyclohexenones such as **5** and **8** are also prochiral. Steven V. Ley of the University of Cambridge (*Chem. Commun.* **2005**, 5346) and Keiji Maruoka of Kyoto University (*Organic Lett.* **2005**, *7*, 5143) independently developed organocatalysts that effect enantioselective conjugate addition of nitroalkanes. Nitromethane and primary and secondary nitroalkanes participated efficiently in the addition. Addition to acyclic enones also proceeded with high ee. Professor Ley has shown that quaternary centers can be formed with high ee, and Professor Maruoka has shown that the sidechain stereocenter is also controlled. Note that the primary nitro group of adducts such as **7** is readily converted into the nitrile or the carboxylic acid.



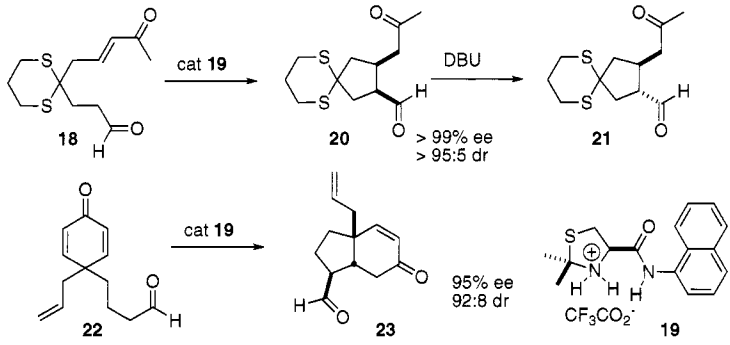
New applications are still being found for proline **12**, one of first substances shown to be an enantioselective organocatalyst. Armando Córdova of Stockholm University has found (*Angew. Chem. Int. Ed.* **2005**, *44*, 4877) that three-component coupling of cyclohexenone **8**, formaldehyde, and an aromatic amine **11** catalyzed by proline delivered the bicyclic amine **13** in high ee.



Enantioselective ring construction can also be effected by organocatalysts. Benjamin List of the Max-Planck-Institut, Mülheim has devised (*J. Am. Chem. Soc.* **2005**, *127*, 15036) a combination of organocatalyst **15** and organic reductant **16**. The transient iminum salt formed with the aldehyde **14** is reduced to a chiral enamine, that adds in an intramolecular fashion to the acceptor enone, to give **17**.



Yujiro Hayashi of the Tokyo University of Science has shown (*J. Am. Chem. Soc.* **2005**, *127*, 16028) that **19** is an excellent catalyst for enantioselective intramolecular Michael addition. The conditions are mild enough that the kinetic cis product **20** is formed exclusively. Exposure to DBU converts **20** to the trans diastereomer **21**, without loss of ee. The enantioselective intramolecular Michael addition can also be used to construct bicyclic systems such as **23**. As expected for intramolecular addition, the reaction proceeds to give exclusively the cis ring fusion.

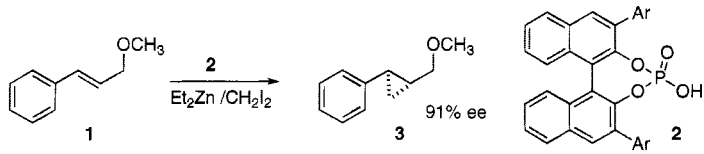


Carbocycle Construction by the Opening of Strained Rings: Synthesis of Tremulenolide A

August 28, 2006

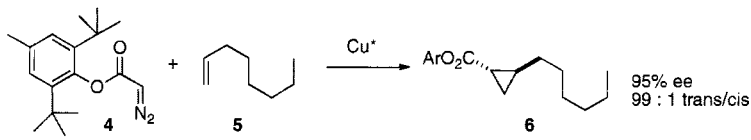
Strained three- and four-membered rings can be used to construct larger rings. The release of the strain energy facilitates bond formation, and the stereochemistry of the small ring can be transmitted to the larger ring.

The first step in this approach is the stereocontrolled construction of the smaller ring. Significant progress in asymmetric cyclopropanation has been reported this year. André B. Charette of the Université de Montreal has found (*J. Am. Chem. Soc.* **2005**, *127*, 12440) that Binol-derived phosphoric acids directed the Simmons-Smith cyclopropanation of allylic ethers such as **1** with high ee. Allylic ethers react more rapidly than do isolated alkenes. Other alkyl and silyl ethers work well also. Patrick J. Walsh of the University of Pennsylvania has reported (*J. Am. Chem. Soc.* **2005**, *127*, 13138) a complementary approach that is equally effective for the high ee construction of cyclopropanes derived from allylic alcohols.



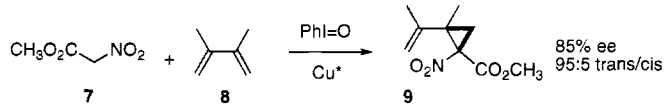
1 3 2

Preformed diazo carbonyl compounds such as **4** are common precursors to cyclopropanes. Andreas Pfaltz of the University of Basel has described (*Angew. Chem. Int. Ed.* **2005**, *44*, 4888) a family of enantiomerically-pure Cu catalysts that effect alkene insertion. It is particularly noteworthy that these catalysts are effective even with simple alkyl-substituted alkenes such as **5**.



4 5 6

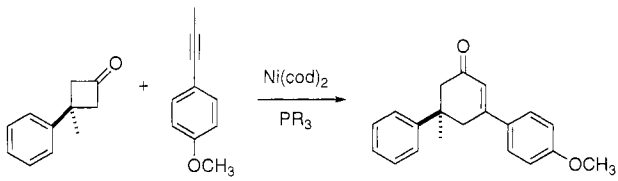
Carbenes can also be generated directly from activated methylene compounds such as **7**. Professor Charette (*J. Am. Chem. Soc.* **2005**, *127*, 18014) has been able to combine this approach with chiral Cu catalysis, leading to the cyclopropane amino acid precursor **9** in high de and ee.



7 8 9

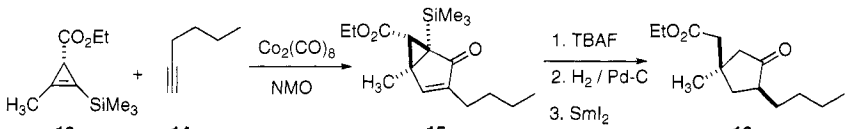
Release of ring strain from small rings can drive the formation of larger rings. Masahiro Murakami of Kyoto University has shown (*J. Am. Chem. Soc.* **2005**, *127*, 6932) that inexpensive Ni catalysts mediate the addition of an alkyne such as **10** to a cyclobutanone such as **11** to give, with substantial

regiocontrol, the cyclohexenone **12**. Michael E. Jung of UCLA has described (*J. Am. Chem. Soc.* **2005**, *127*, 11206) an alternative strategy for expanding readily-prepared cyclobutanols to cyclohexenones.



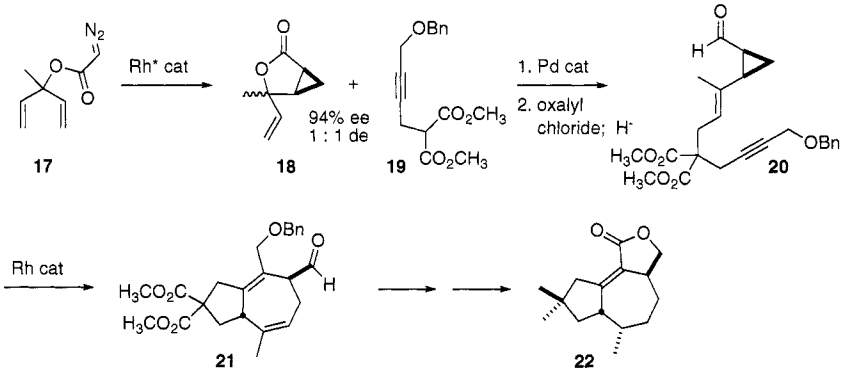
10 **11** **12**

Cyclopropenes such as **13** are readily available in enantiomerically-pure form. Joseph M. Fox of the University of Delaware has shown (*Organic Lett.* **2005**, *7*, 3593) that unlike ordinary alkenes, these strained alkenes participate smoothly in Pauson-Khand cycloaddition, and that the additions proceed with very high regio- and diastereocontrol. The resulting cyclopropanes are readily carried on to substituted cyclopentanones such as **16**.



13 **14** **15** **16**

The utility of strained rings in target-directed synthesis is illustrated by the construction of tremulenolide A **22** recently reported (*Organic Lett.* **2005**, *7*, 4535) by Stephen F. Martin of the University of Texas. Cyclization of the prochiral diazo ester **17** with the Doyle MEPY catalyst delivered the cyclopropane **18** in high ee, as an inconsequential mixture of diastereomers. Pd-mediated coupling to **19** gave **20** with high geometric control. Rh-catalyzed opening, following the Wender precedent, gave **21**, with the relative and absolute configuration derived from the cyclopropane of **20**. The diester **21** was then carried on to **22**.

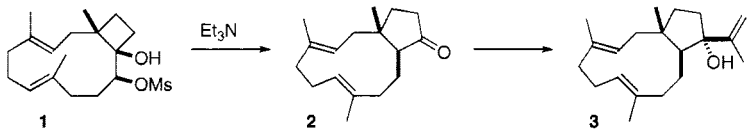


17 **18** **19** **20** **21** **22**

The Corey Route to the Dolabellanes: Isoedunol and β-Araneosene

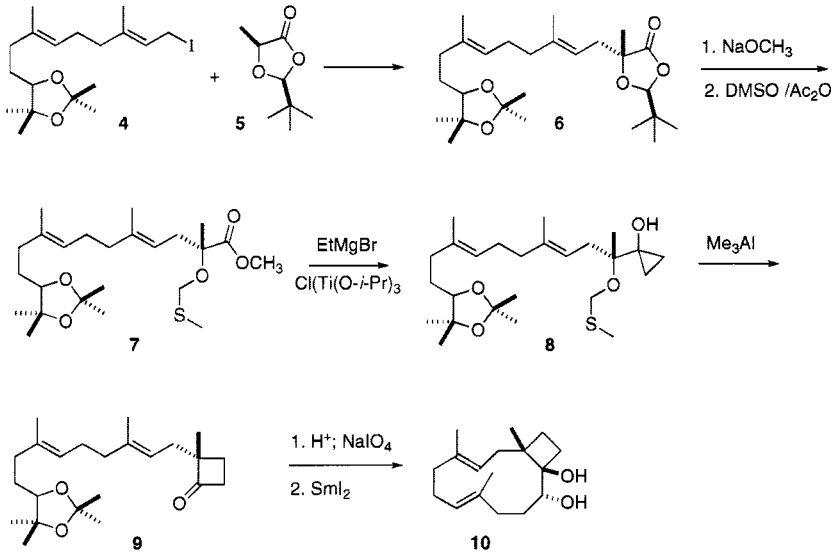
September 4, 2006

A variety of dolabellanes, some of which show substantial physiological activity, have been isolated from natural sources. E. J. Corey of Harvard University has introduced (*J. Am. Chem. Soc.* **2005**, *127*, 13813) a unified approach to the dolabellanes, represented by isoedunol **3**, based on the designed rearrangement of the mesylate **1** to **2**.



1 **2** **3**

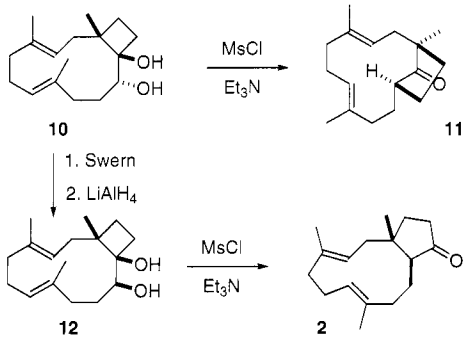
The key to this approach was the stereocontrolled construction of the cyclobutane **1**. The starting material was the racemic iodo acetonide **4** derived from farnesol. Alkylation of **5** using the Seebach protocol followed by hydrolysis led the methylthiomethyl ether **7**. The ester was converted to the hydroxy cyclopropane **8** by the Kulinkovic procedure. On activation with Me_3Al, **8** was smoothly carried on to the enantiomerically-pure cyclobutanone **9**. The ring expansion must not be proceeding by



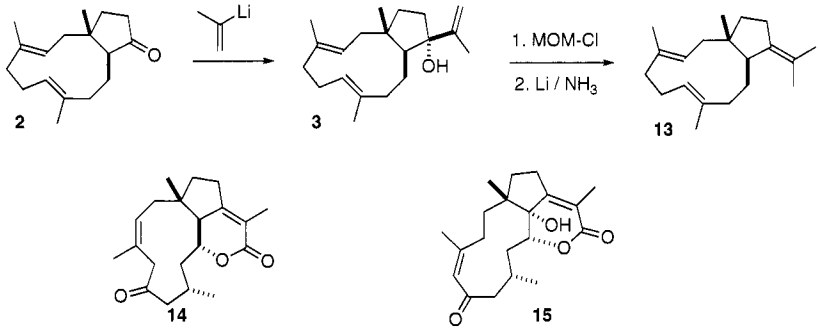
4 **5** **6** **7** **8** **9** **10**

full ionization, as carbocation formation would have led to the racemic product. The aldehyde derived from **9** was cyclized with SmI_2 to the trans diol **10**.

In medium ring derivatives such as **10**, one substituent on a ring carbon will be inside, and the other will be outside. The conformation of **10** is such that formation of the mesylate from the secondary alcohol led to migration of the more substituted cyclobutane bond, delivering **11**. It follows that the conformation of the diol **12** will be flipped, to keep the OH outside the ring. Formation of the mesylate from the secondary alcohol of **12** led cleanly to migration of the *less* substituted cyclobutane bond, to give the desired cyclopentanone **2**.



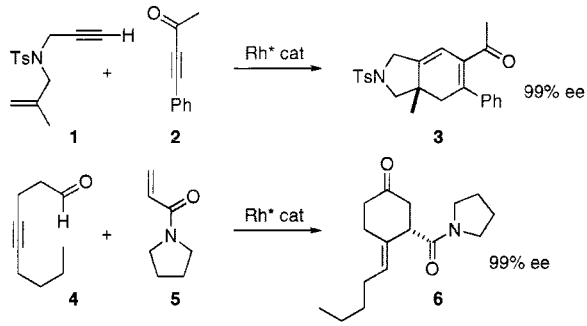
Addition of 2-propenyl lithium to the cyclopentanone **2** gave the dolebellane isoedunol **3**. Deoxygenation converted **3** to the dolabellane β-araneosene **13**. This strategy for the construction of the dolabellanes may open a route for the preparation of the cytotoxic dolabellanes clavulactone **14** and clavirolide **15**.



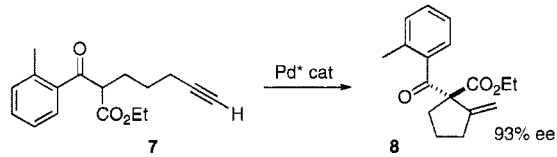
Transition-Metal Catalyzed Enantioselective Ring Construction

September 11, 2006

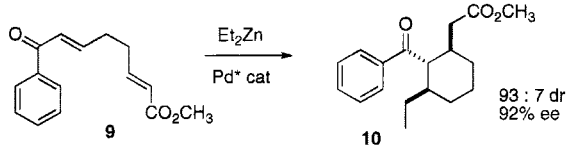
Powerful transition metal-catalyzed methods for the conversion of prochiral alkenes and alkynes to carbocyclic rings have been developed over the past several years. Three recent reports are representative. P. Andrew Evans, now at the University of Liverpool, has shown (*J. Am. Chem. Soc.* **2005**, *127*, 12466) that on exposure to an enantiomerically-pure Rh catalyst, the sulfonamide **1** added to the alkyne **2** to give **3** in high ee. Ken Tanaka of the Tokyo University of Agriculture and Technology has found (*Angew. Chem. Int. Ed.* **2005**, *44*, 7260) that **4**, again with an enantiomerically-pure Rh catalyst, added to **5** to give **6** in high ee.



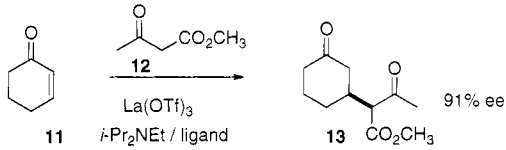
F. Dean Toste of the University of California at Berkeley has developed (*J. Am. Chem. Soc.* **2005**, *127*, 17168) an enantioselective Pd-catalyzed Conia ene reaction. The β-ketoester **7** is cyclized to **8** in high ee.



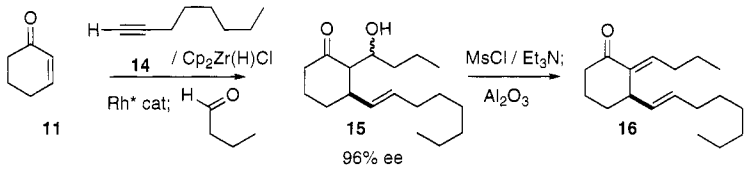
Alexandre Alexakis of the University of Geneva has devised powerful methods for enantioselective conjugate addition. He has now (*Tetrahedron Lett.* **2005**, *46*, 8019) applied those methods to dienes such as **9**. The intermediate enolate from the initial conjugate addition effects Michael addition to the α,β-unsaturated ester, leading to the product **10** in high ee.



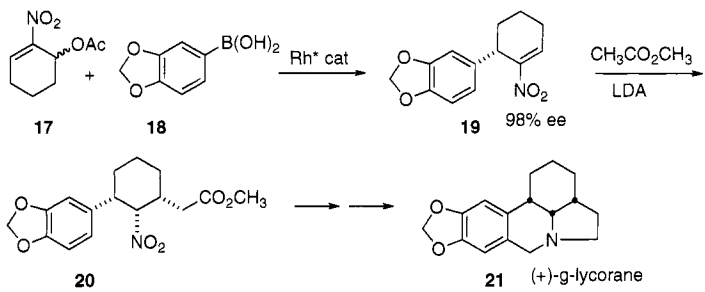
Enantiomerically-pure ring systems can also be prepared by the asymmetric transformation of performed prochiral rings. Masakatsu Shibasaki of the University of Tokyo had developed La catalysts for the enantioselective addition of acetoacetate **11** to cyclohexenone **12**. He has now shown (*Tetrahedron Lett.* **2005**, *46*, 5377) that commercial, easily-handled La(OTf)$_3$ in conjunction with an amine base and the same Binol-derived ligand gives equally good results.



Three-component conjuate addition-enolate trapping, pioneered by Gilbert Stork, is a powerful strategy for the rapid assembly of complex structures. K. C. Nicolaou of Scripps-La Jolla has developed (*Angew. Chem. Int. Ed.* **2005**, *44*, 3874) a chiral catalytic version of this approach. The enolate from Rh-mediated conjugate addition of the alkyne **14** to cyclohexenone **11** was trapped with *n*-butanal, leading to the aldol product **15** in high ee.



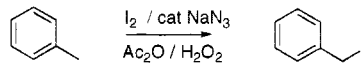
In a variant on this approach, Liu-Zhu Gong of the Chengdu Institute of Organic Chemistry has described (*Organic Lett.* **2005**, *7*, 4285) enantioselective conjugate addition of the boronic acid **18** to the racemic acetate **17**. Spontaneous elimination of acetic acid led to the nitroalkene **19** in high ee. Conjugate addition of acetate delivered the all-cis product **20**, the relative and absolute configuration of which were confirmed by conversion to (+)-γ-lycorane **21**.



Best Synthetic Methods: Functional Group Transformation

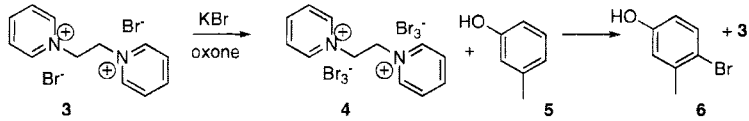
September 18, 2006

Selective halogenation can be a direct route to high value added materials from inexpensive hydrocarbons. José Barluenga of the Universidad de Oviedo has developed (*Angew. Chem. Int. Ed.* **2005**, *44*, 5841) a procedure for iodination that allows the incorporation of *both* iodines of I_2 into the product. Saturated hydrocarbons can also be iodinated.



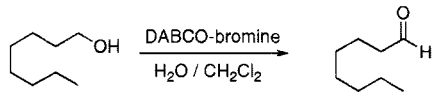
1 **2**

Both ketones and active aromatics are easily brominated by a reagent devised (*J. Org. Chem.* **2005**, *70*, 4267) by Bhisma K. Patel of the Indian Institute of Technology Guwahati. On oxidation with oxone and KBr, the bis pyridinium salt **3** is converted to the bis tribromide **4**. Bromination was effected by grinding the solid starting material and **4** together, without added solvent. The spent reagent **3** was easily removed from the brominated product by a simple water wash. It could be recovered and recycled.



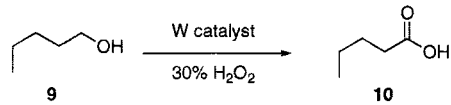
3 **4** **5** **6**

Majid M. Heravi of Azzahra University, Tehran has described (*Tetrahedron Lett.* **2005**, *46*, 6243) the preparation of a DABCO-bromine complex. An alcohol on being stirred at room temperature with the complex is converted to the corresponding aldehyde or ketone. Notably, the easily brominated aldehyde does not react further.



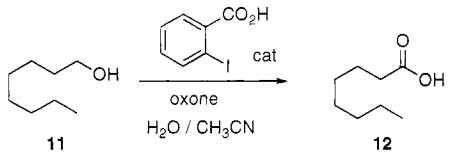
7 **8**

Xiaolai Wang of the Lanzhou Institute of Chemical Physics has devised (*Tetrahedron Lett.* **2005**, *46*, 7023) a more vigorous oxidizing system, a tungsten catalyst coupled with 30% aqueous hydrogen peroxide. Secondary alcohols are oxidized to ketones, and primary alcohols go on to acids. The latter transformation is currently most commonly carried out in two steps.



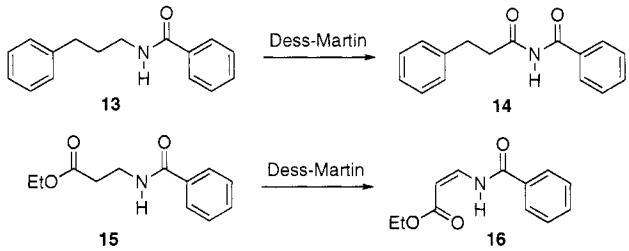
9 **10**

Thottumkara K. Vinod of Western Illinois University has found (*Organic Lett.* **2005**, *7*, 2933) that the commonly-available *o*-iodobenzoic acid can also serve as a catalyst for the oxidation of primary alcohols to acids and of secondary alcohols to ketones. In this case, oxone is the bulk oxidant.



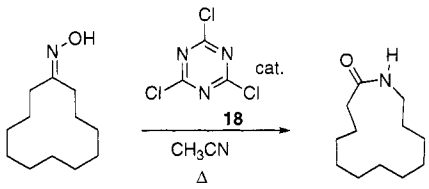
11 **12**

K. C. Nicolaou of Scripps La Jolla has been exploring organic synthesis applications of the *o*-iodobenzoic acid-derived Dess-Martin periodinane. He has found (*Angew. Chem. Int. Ed.* **2005**, *44*, 5992) that amides such as **13** are oxidized to the corresponding imide **14**, the net transformation being the oxidation of a primary amine to the acid. A β-alanine derivative such as **15** is oxidized to the *(Z)*-vinylogous carbamate **16**.



13 **14** **15** **16**

Another route to amides is the Beckmann rearrangement of ketoximes such as **17**. Hisashi Yamamoto of the University of Chicago and Kazuaki Ishihara of Nagoya University have shown (*J. Am. Chem. Soc.* **2005**, *127*, 11240) that 5 mol % of the inexpensive cyanuric chloride **18** is sufficient to catalyze this reaction. The reaction is even faster with 2 mol % of **18** and 2 mol % of $ZnCl_2$.

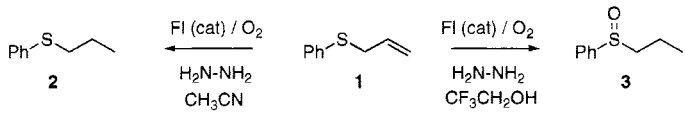


17 **19**

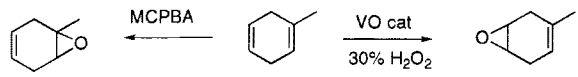
Selective Reactions of Alkenes

September 25, 2006

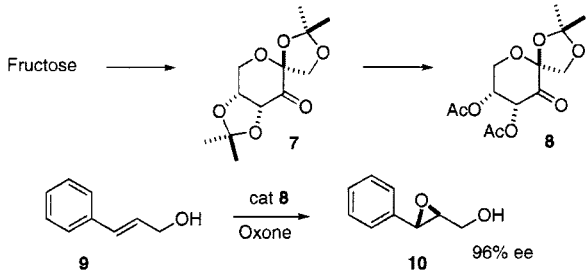
Diimide (H-N=N-H) is an effective reagent for reducing alkenes. Yasushi Imada and Takeshi Naota of Osaka University have devised (*J. Am. Chem. Soc.* **2005**, *127*, 14544) a flavin-catalyzed protocol for diimide generation by O_2 oxidation of hydrazine. The selectivity of diimide as a reductant is illustrated by the smooth conversion of **1** to **2**. Because these are oxidizing conditions, **1** can alternatively be converted directly to **3**, by running the reaction in trifluoroethanol.



Many polyoxometalates have been developed that catalyze the hydrogen peroxide epoxidation of alkenes. Usually, these are simple electrophilic processes. Noritaka Mizuno of the University of Tokyo has now reported (*Angew. Chem. Int. Ed.* **2005**, *44*, 5136) a vanadium catalyst that gives preferential epoxidation of the *less*-substituted alkene.



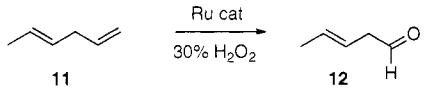
The most general procedure for catalytic *enantioselective* epoxidation is that developed by Yian Shi of Colorado State University, using the Oxone-generated dioxiranes from **7** and **8**. Ketone **7** usually is



used at 30% catalyst loading, while the more robust ketone **8** serves effectively at 8-10% loading. A. Vidal-Ferran of the Institute of Chemical Research of Catalonia has developed (*J. Org. Chem.* **2005**, *70*, 10143) an efficient and scalable procedure for the preparation of **7** and of **8** from fructose.

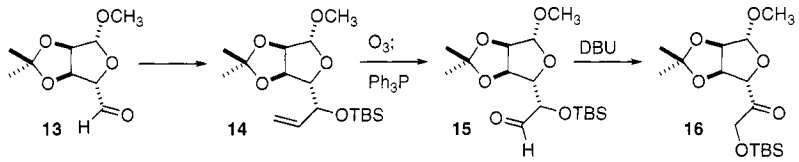
Terminal vinyl groups are particularly good ligands for transition metals, and so can often react selectively even in the presence of more electron rich alkenes. Ronny Neumann of the Weizmann

Institute has found (*Organic Lett.* **2005**, *7*, 5039) a Ru catalyst/H_2O_2 combination that selective cleaves terminal vinyl groups to the corresponding aldehydes. Note that the conditions are mild enough that the other alkene is not brought into conjugation.



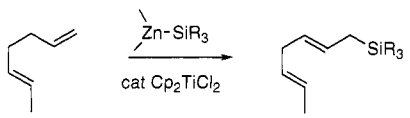
11 **12**

Yung-Son Hon of National Chung Cheng University, Taiwan, who more than ten years ago introduced the reduction of ozonides with Et_3N, has now (*Tetrahedron Lett.* **2005**, *46*, 1365) described the facile conversion of α-silyloxy aldehydes to the corresponding α-silyloxy ketones. The rearrangement works equally well with α-acyloxy aldehydes. The net transformation is the one-carbon homologation of the starting aldehyde.



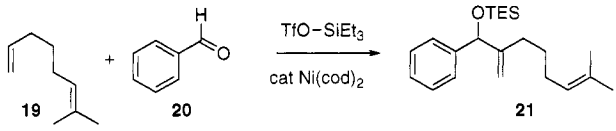
13 **14** **15** **16**

In another illustration of the selective reactivity of terminal vinyl groups, Masanobu Uchiyama, also of the University of Tokyo, has found (*J. Am. Chem. Soc.* **2005**, *127*, 13116) that with the silyl zincate, Ti-catalyzed Heck type addition proceeds smoothly. Allyl silanes are useful nucleophiles for organic synthesis.



17 **18**

Terminal vinyl groups can also be converted into alkenyl nucleophiles. Timothy F. Jamison of MIT has shown (*J. Am. Chem. Soc.* **2005**, *127*, 14194) that in the presence of silyl triflates, $Ni(cod)_2$ catalyzes the addition of a terminal vinyl group to an alkene. Again, an internal alkene does not interfere.

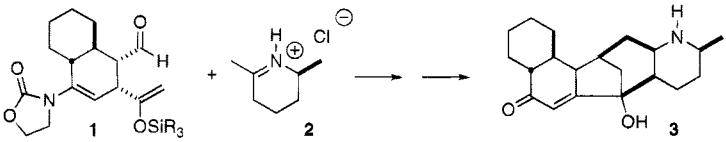


19 **20** **21**

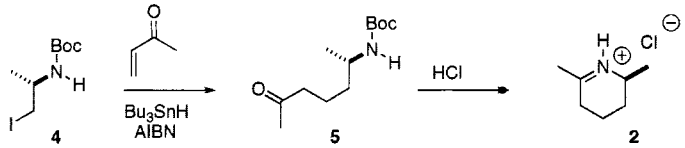
Synthesis and Absolute Stereochemical Assignment of (-)-Galbulimima Alkaloid 13

October 2, 2006

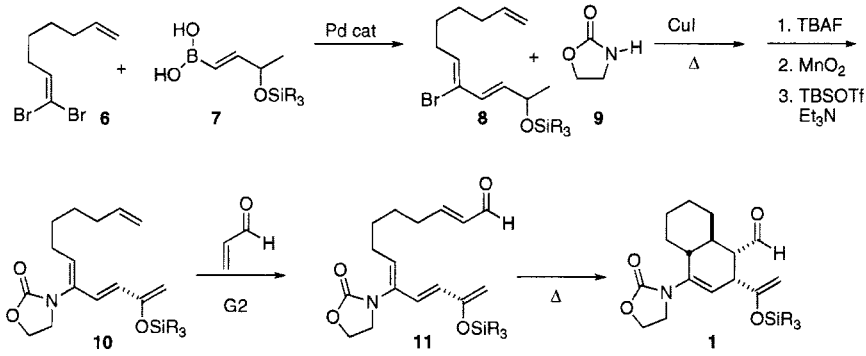
The galbulimima alkaloids have intriguing physiological activity, but the absolute configuration of glabulimima alkaloid 13 **3** had not been assigned. Mohammad Movassaghi of the Massachusetts Institute of Technology has developed (*J. Am. Chem. Soc.* **2006**, *128*, 8126) an elegant route to **3**, based on the convergent coupling of racemic **1** with the enantiomerically-pure **2** (for a racemic synthesis of **3**, see OHL Feb 23 2004).



The enantiomerically-pure iodide **4** was prepared from L-alaninol. Conjugate addition of the derived radical to methyl vinyl ketone gave **5**, which was hydrolyzed to **2**.

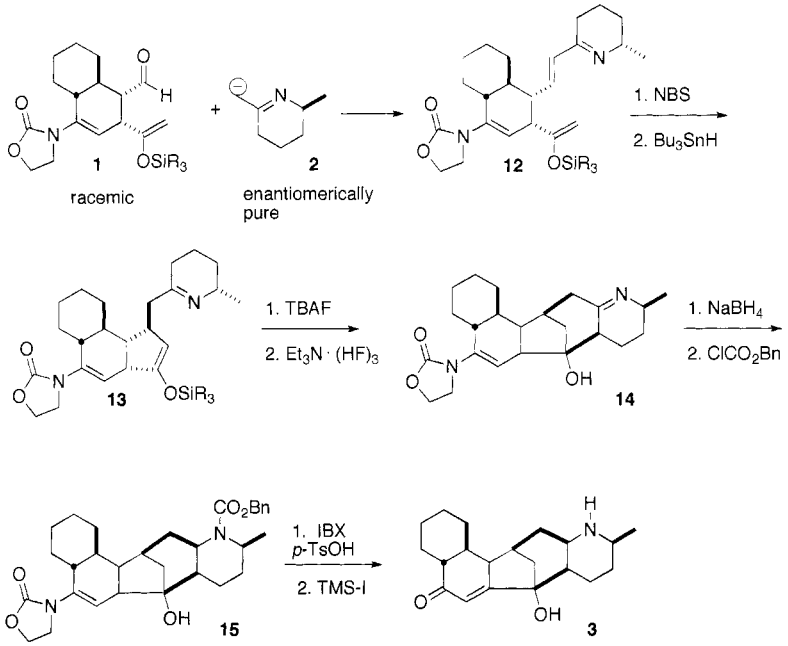


The Diels-Alder substrate **11** was prepared from the 1,1-dibromo alkene **6**. Pd-mediated coupling of **6** with **7** gave **8**. Further coupling with **9** followed by oxidation and enol ether formation gave **10**, which underwent smooth cross-coupling with acrolein, yielding **11**. The anticipated intramolecular Diels-Alder cycloaddition led to (racemic) **1** with the expected high diastereocontrol.



Synthesis and Absolute Stereochemical Assignment of (-)-Galbulimima Alkaloid 13
October 2, 2006

The enantiomerically-pure imine **2** was readily deprotonated, and the resulting anion was condensed with the aldehyde **1** to give, after dehydration, the imine **12**. The enol ether was selectively brominated. Free radical reduction led to smooth cyclization, to give **13**. On unmasking of the ketone, spontaneous enamine addition ensued, to give the imine **14**. Stereocontrolled reduction with $NaBH_4$ and protection then gave the pentacylic **15**, accompanied by the diastereomer resulting from condensation of **2** with the other enantiomer of **1**. These two diastereomers were readily separable by flash chromatography.



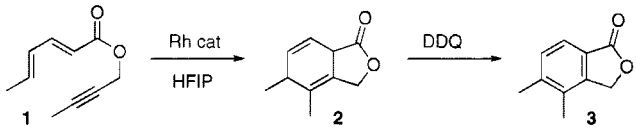
To complete the synthesis, the enamide **15** was hydrolyzed by aqueous acid. In situ reduction carried the liberated ketone on to the enone, which was deprotected to give glabulimima alkaloid 13 **3**. Both enantiomers of **3** were prepared this way, beginning with each of the enantiomers of **4**. The enantiomer derived from L-alaninol gave the same rotation as the natural product, allowing the assignment of the absolute configuration.

The convergent coupling employed here allowed the ready preparation of each of the four enantiomerically-pure diastereomers of the natural product. There are real advantages to such an approach, because it provides not just one substance, the natural product, but each of the four, for further evaluation of physiological activity.

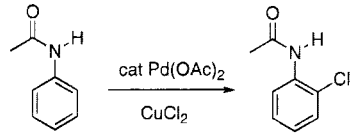
Preparation of Benzene Derivatives

October 9, 2006

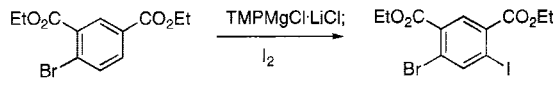
Benzene derivatives lie at the heart of pharmaceutical chemistry. While most are prepared from pre-existing benzene rings, direct assembly of the benzene ring can allow access to substitution patterns that are not otherwise easily prepared. Akio Saito and Yuji Hanzawa of the Showa Pharmaceutical University in Tokyo recently described (*Tetrahedron Lett.* **2006**, *47*, 891) the Diels-Alder cyclization of esters such as **1**. The reaction proceeded at room temperature using a cationic Rh catalyst, in hexafluoroisopropanol (HFIP) solvent. The adduct **2** tended to aromatize, so the cyclization was most conveniently worked up with DDQ, to give **3**.



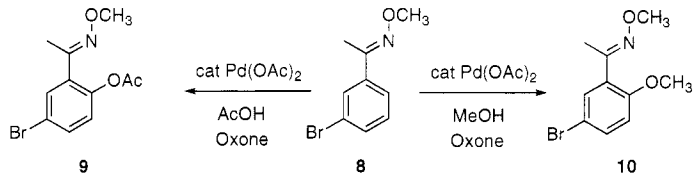
Simple aromatic halogenation could be considered to be "C-H activation". What sets apart recent developments in the field of aromatic C-H activation is the ability to direct reactivity to particular sites on the benzene ring. This selectivity is illustrated by the recent work (*J. Am. Chem. Soc.* **2006**, *128*, 7416) of Zhangjie Shi of Peking University (known in China as Beida). Pd-catalyzed oxidation converts acetanilide **4** specifically into the ortho chlorinated **5**. The para product is not observed. Bromides can be prepared this way also.



Benzene derivatives can also be halogenated by stoichiometric metalation. Paul Knochel of the Universität München has found (*Angew. Chem. Int. Ed.* **2006**, *45*, 2958) that a 1:1 mixture of *i*Pr$_2$NMgCl·LiCl and 2,2,6,6,-tetramethylpiperidine worked particularly well. Exposure of the ester **6** to these conditions followed by the addition of I$_2$ gave the iodide **7**. Note that the aromatic bromide is not eliminated, even though these are strongly basic conditions.

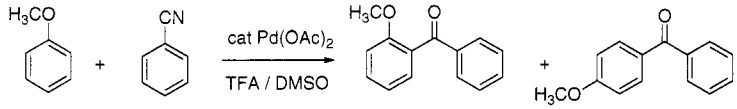


C-H activation can also be used to oxygenate benzene rings. Melanie S. Sanford of the University of Michigan has developed (*Organic Lett.* **2006**, *8*, 1141) a Pd-mediated protocol to incorporate an acetoxy group or a methoxy group adjacent to an aryl ketone, protected as the methoxime. The bulk oxidant is the inexpensive Oxone®.



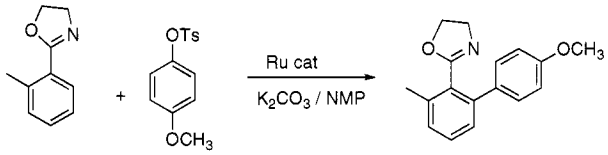
9 **8** **10**

Friedel-Crafts acylation could also be classified as "C-H activation". Again, the difference comes in the observed regioselectivity. Thus, the observation by Richard C. Larock of Iowa State (*J. Org. Chem.* **2006**, *71*, 3551) that the Pd-mediated condensation of **11** with **12** leads to a 52 : 48 ratio of **13** and **14** suggests that this reaction is probably proceeding by electrophilic addition to the benzene ring.



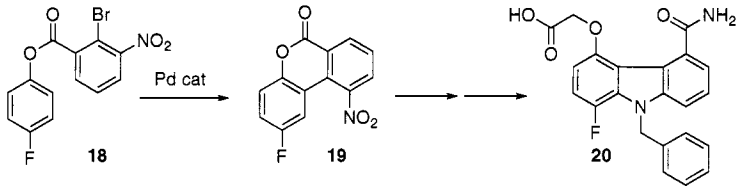
11 **12** **13** **14**

In contrast, the Ru-catalyzed condensation of the aryl oxazoline **15** with aryl tosylates such as **16**, developed by Lutz Ackermann of the Universität München (*Angew. Chem. Int. Ed.* **2006**, *45*, 2619), does proceed with high regiocontrol. Other heterocycles, including 2-pyridyls, also direct well.



15 **16** **17**

Pd-mediated activation can be effective even on scale. The cyclization of **18** to **19** was the key step in the preparation of the phospholipase $sPLA_2$ inhibitor LSN426891 **20** recently described (*Tetrahedron Lett.* **2006**, *47*, 1351) by Scott A. May of Lilly Process.

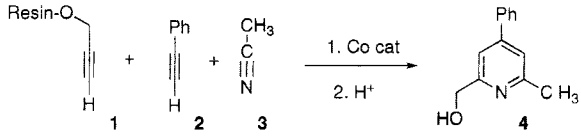


18 **19** **20**

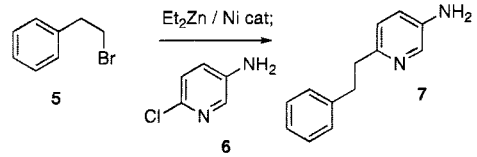
Preparation of Heteroaromatic Derivatives

October 16, 2006

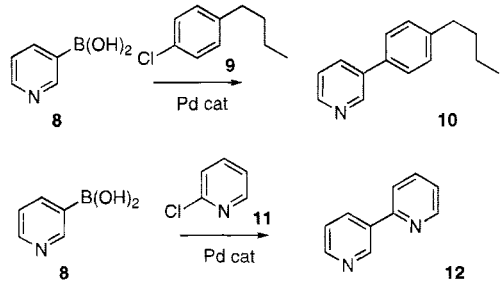
Heteroaromatics, including pyridines and indoles, play a prominent role in pharmaceutical chemistry. A new method for pyridine construction has recently been developed (*Chem. Commun.* **2006**, 1313) by Alexander Deiters of North Carolina State University. Propargyl alcohol was immobilized on a polystrene resin using a trityl linker. Exposure to an alkyne **2** and a ten-fold excess of a nitrile **3** in the presence of a Co catalyst led to the pyridine **4**. The steric bulk of the trityl contributed to the observed regiocontrol. This resin-based approach allowed the ready assembly of a family of substituted pyridines.



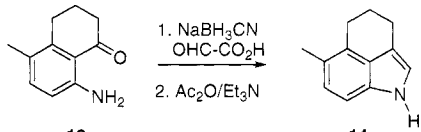
Several methods for the specific functionalization of pyridines have also been introduced. Iain A.S. Walters of AstraZeneca R&D in Loughborough has found (*Tetrahedron Lett.* **2006**, *47*, 341) that (dppp)$NiCl_2$ catalyzes the exchange of an alkyl halide **5** with Et_2Zn and also effects the subsequent coupling of the derived organozinc with a halopyridine such as **6**. The result is a simple one-pot procedure that gives **7**.



Gregory C. Fu of MIT has shown (*Angew. Chem. Int. Ed.* **2006**, *45*, 1282) that pyridine boronic acids also participate efficiently in couplings. Several other heteroaromatic boronic acids also work well. The procedure is even effective when the halide to be coupled is also part of a heteroaromatic.

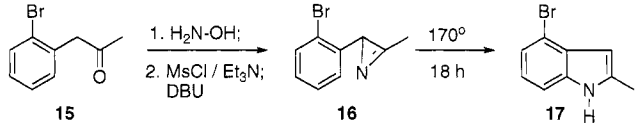


There has also been a great deal of interest in indoles over the past six months. Several new methods for indole construction have been developed. Raymond L. Funk of Pennsylvania State University has demonstrated (*J. Am. Chem. Soc.* **2006**, *128*, 4946) that cyclic *o*-acyl anilines such as **13** can be cyclized to the corresponding amides.



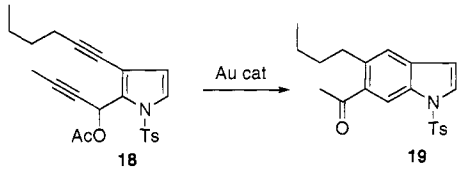
13 **14**

Most routes to indoles, including the classic Fischer synthesis, start with aminated aromatics such as **13**. We have uncovered (*J. Am. Chem. Soc.* **2006**, *128*, 1058) a complementary approach, starting with an alkylated aromatic such as **15**. The oxime of the ketone **15** could be converted to the (remarkably stable!) azirine **16**, which on heating rearranged to the indole **17**.



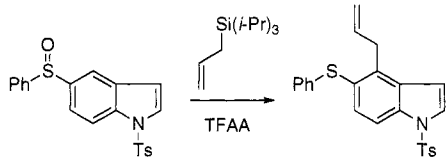
15 **16** **17**

F. Dean Toste of the University of California at Berkeley has described (*J. Am. Chem. Soc.* **2006**, *128*, 7436) an Au catalyzed aromatization of bis alkynes. This protocol smoothly converted the pyrrole derivative **18** to the indole **19**.



18 **19**

Procedures for the specific functionalization of preformed indoles are also of interest. Yasayuki Kita of Osaka University had reported a general preparation for the preparation of 5-phenylsulfinyl indoles such as **20** from the corresponding anilines. He has now found (*Tetrahedron Lett.* **2006**, *47*, 1881) that under Pummerer conditions, these undergo smooth 4-alkylation. For leading references to other procedures for functionalizing indoles, see *Tetrahedron Lett.* **2006**, *47*, 2517; *J. Am. Chem. Soc.* **2006**, *128*, 1060; and *J. Am. Chem. Soc.* **2006**, *128*, 581.

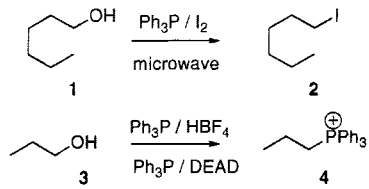


20 **21**

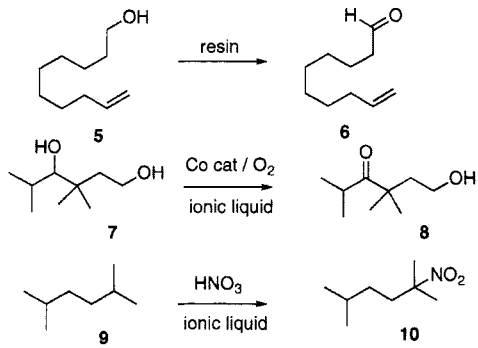
Functional Group Transformation

October 23, 2006

Two particularly useful conversions of alcohols were recently reported. Abdol Reza Hajipour of the University of Wisconsin has found (*Tetrahedron Lett.* **2006**, *47*, 4191) that grinding an alcohol such **1** with triphenylphosphine and I_2, then microwaving the resulting solid mixture for a minute or less gives the corresponding iodide **2**. The work up is particularly convenient. Phosphonium salts such as **4** have usually been prepared from the corresponding alkyl halides. Roman Mazurkiewicz of the Silesian University of Technology has now shown (*Tetrahedron Lett.* **2006**, *47*, 4219) that Mitsunobu coupling of the alcohol **3** with Ph_3PHBF_4 gives the phosphonium salt **4** directly.

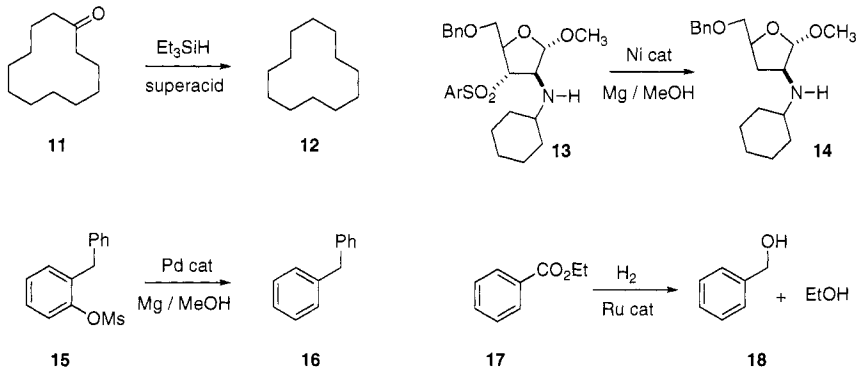


For small-scale oxidation of alcohols to aldehydes and ketones, it is often desirable to be able to simply filter away the spent (and any excess) reagent. Viktor Z. Zhdankin of the University of



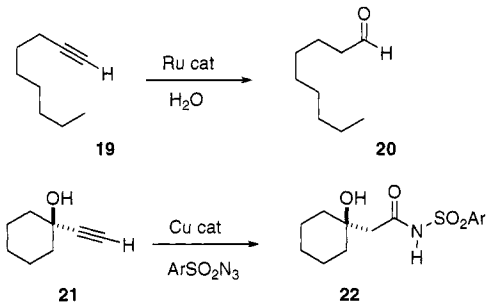
Minnesota, Duluth has developed (*Organic Lett.* **2006**, *8*, 167) a hypervalent iodine-based oxidizing resin (0.7 – 0.8 mmol/gram) that looks attractive for this application. For larger scale work, Tomoya Kitazume of the Tokyo Institute of Technology has reported (*Tetrahedron Lett.* **2006**, *47*, 2797) an ionic liquid based oxidation using catalytic N-hydroxyphthalimide, catalytic Co complex and O_2. Remarkably, replacement of the Co and O_2 with HNO_3 gives a mixture that efficiently converted **9** to the nitroalkane **10**.

Several useful methods for reduction have also been introduced. G. K. Surya Prakash and George A. Olah of the University of Southern California have found (*J. Org. Chem.* **2006**, *71*, 3952) that in the presence of the superacid formed from trifluoroethanol and BF_3, triethylsilane will reduce a ketone such as **11** to the corresponding hydrocarbon **12**. Tanmaya Pathak of the Indian Institute of Technology, Kharagpur has developed (*Organic* Lett. **2006**, *8*, 1303) a protocol for reductive desulfurization, e.g. of **13**, using catalytic $NiBr_2$ and stoichiometric Mg in methanol. Benzyl ethers are stable to the conditions. Although tosylates are unreactive, Hironao Sajiki of Gifu Pharmaceutical University has found (*Organic Lett.* **2006**, *8*, 987) that mesylates such as **15** are inexpensive replacements for triflates for reductive deoxygenation of phenols. And, David Milstein of the Weizmann Institute, revisiting a traditional transformation, has designed (*Angew. Chem. Int. Ed.* **2006**, *45*, 1113) a Ru catalyst that effects hydrogenation of esters under Parr shaker conditions at 115 °C.



11 **12** **13** **14** **15** **16** **17** **18**

Two important new transformations of terminal alkynes have recently been reported. Bernhard Breit of the Universität Freiburg has prepared (*Angew. Chem. Int. Ed.* **2006**, *45*, 1599) a Ru catalyst that converts terminal alkynes such as **19** into the corresponding aldehydes. Valery P. Fokin of Scripps La Jolla has found (*Angew. Chem. Int. Ed.* **2006**, *45*, 3154) that under Cu catalysis, a terminal alkyne such as **21** reacts with an arenesulfonyl azide to deliver the corresponding amide **22**.

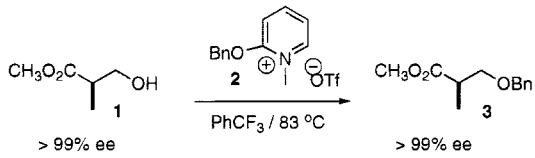


19 **20** **21** **22**

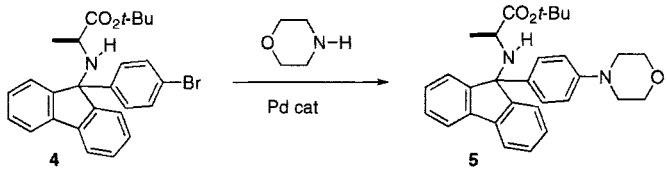
Functional Group Protection

October 30, 2006

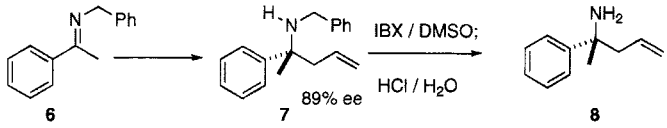
Alcohols are the most common functional group protected, and benzyl is the most commonly used alcohol protecting group. Gregory B. Dudley of Florida State University has developed (*J. Org. Chem.* **2006**, *71*, 3923) the reagent **2** for benzylation of alcohols under strictly neutral conditions. The environmentally-friendly benzotrifluoride is the solvent of choice for the reaction.



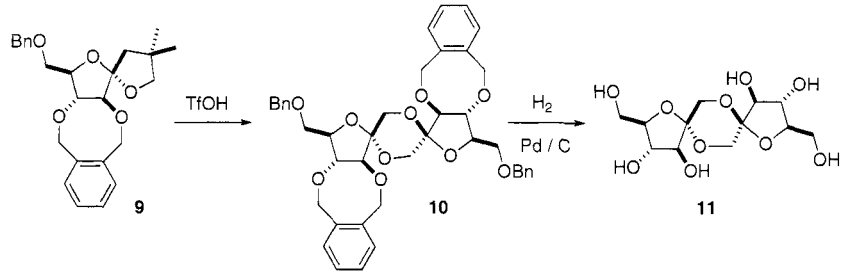
The 9-phenyl-9-fluorenyl group offers many advantages for amine protection. It is stable to mild acid conditions, and removable either with strong acid, hydrogenolysis or reduction. William D. Lubell of the Université de Montréal has reported (*J. Org. Chem.* **2006**, *71*, 848) that the 9-(4-bromophenyl)-9-fluorenyl group, illustrated by **4**, offers complementary advantages. Stable to acid, it remains in place while Boc groups and *t*-butyl esters are removed. Pd-mediated coupling with morpholine converts it into **5**, which is selectively removed with mild acid in the presence of the Boc, *t*-butyl ester and 9-phenyl-9-fluorenyl groups.



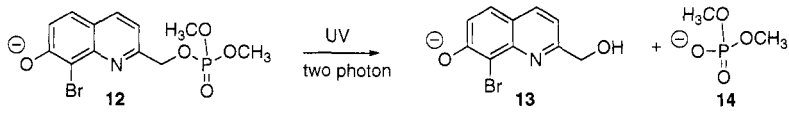
Many procedures have been developed for enantioselective transformations of aryl and benzyl imines. The problem, then, is removal of the N protecting group. Motomu Kanai and Masakatsu Shibasaki of the University of Tokyo have found (*J. Am. Chem. Soc.* **2006**, *128*, 7687) that the IBX oxidation reported by K. C. Nicolaou is particulary efficient for removing benzyl protecting groups from amines.



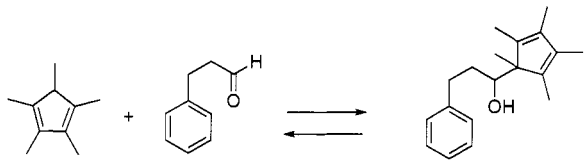
Protecting groups can be used to direct the shape and reactivity of the protected molecule(s). Dimerization of fructose leads to a mixture of the 13 diastereomers of difructose dianhydride, of which **11** is representative. Carmen Ortiz Mellet of the Universidad de Sevilla and José M. García Fernández of CSIC, Sevilla have now shown (*Chem. Commun.* **2006**, 2610) that dimerization of the *o*-xylylene-protected fructose **9** leads *exclusively* to **10**. Catalytic hydrogenation then delivers **11**.



Current advances in biology require that particular areas of a cell be specifically addressed. Two-photon excitation, with the intersecting laser beams coming from different directions, can effect the required three-dimensional control. The challenge has been to develop protecting groups that will release functionality under two-photon excitation. Timothy M. Dore of the University of Georgia has established (*J. Am. Chem. Soc.* **2006**, *128*, 4267) that BHQ **12** can be used to release phosphate (illustrated), carboxylates and alcohols under such two-photon excitation.



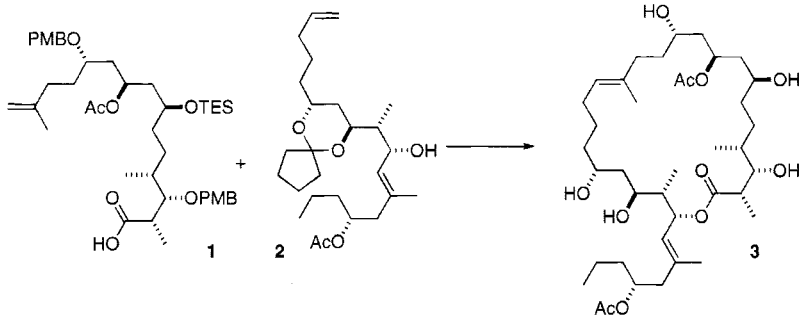
Pentamethylcyclopentadiene **15** was developed as a ligand for transition metals. Now, Hideki Yorimitsu and Koichiro Oshima of Kyoto University have shown (*Tetrahedron Lett.* **2006**, *47*, 163) that **15** can be used as a *protecting* group for aldehydes and ketones. The anion of **15** adds smoothly, to give **17**. The addition is reversed by warming with a trace of DDQ.



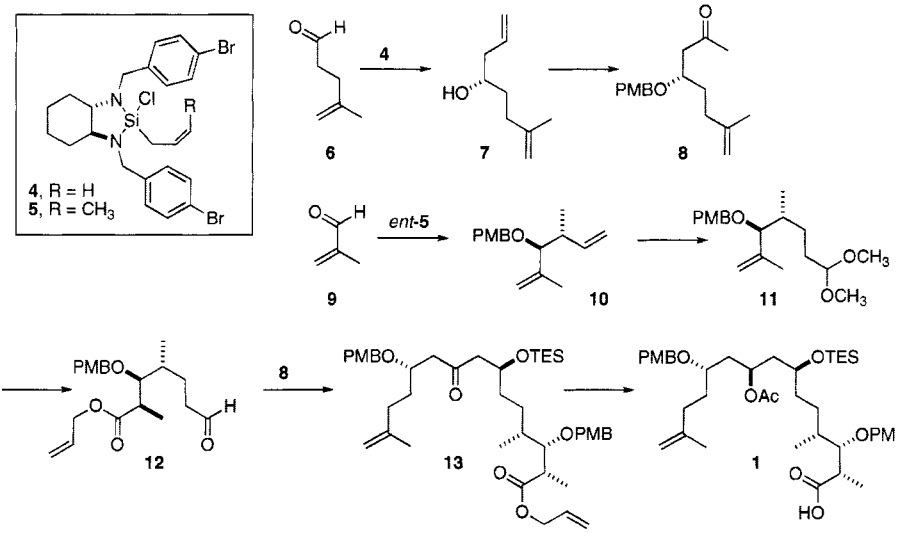
The Leighton Synthesis of Dolabelide D

November 6, 2006

The macrolides dolabelides A-D, isolated from the sea hare *Dolabella*, are cytotoxic against HeLa-S3 cells at concentrations of 1.3 – 6.3 μg/mL. The recent (*J. Am. Chem. Soc.* **2006**, *128*, 2796) synthesis of dolabelide D **3** by James L. Leighton of Columbia University nicely highlights the powerful reagent-based methods for acyclic stereoselection that they have recently developed.

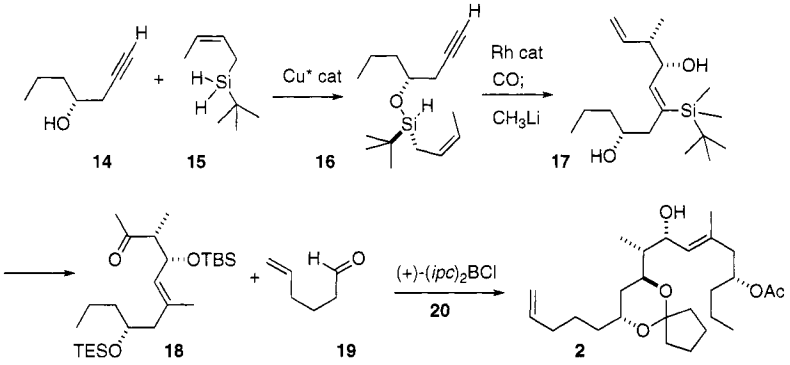


Two such reagents, easily prepared on a large scale, are the amino silanes **4** and **5**. These were used to prepare **8** and **12**, which were combined to prepare **1**. Homologation of the aldehyde **6** with **4** gave **7**.

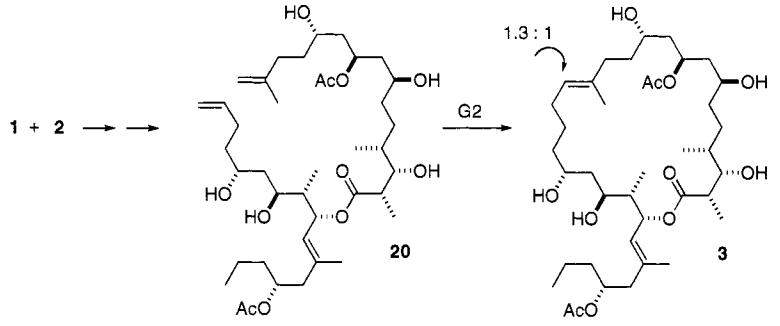


Protection followed by Wacker oxidation then delivered **8**. To prepare **12**, methacrolein **9** was homologated with *ent*-**5**. Hydroformylation followed by in situ acetal formation gave **11**. Diastereroselective hydroboration followed by oxidation and esterification then led to **12**. Aldol condensation of **12** with **8**, taking advantage of the inherent chirality of the alkoxy enolate, proceeded to give, after protection, a 10:1 ratio of **13** and its diastereomer.

The preparation of alkene **2** depended on a third reagent the Leighton group has developed, the silane **15**. Enantioselective condensation of **14** with **15** set the absolute configuration around Si. In the next step, intramolecular carbonylative silylation followed by intramolecular crotylation of the transient aldeyde, the absolute configuration at the Si in **16** directed the new stereogenic centers of **17**. To achieve the requisite diastereoselectivity in the aldol condensation of the derived ketone **18** with the aldehyde **19**, the enolate of **18** was prepared using the chiral director **20**.



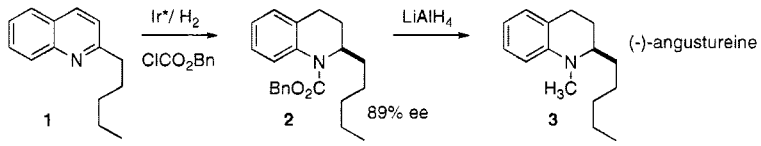
To complete the synthesis, it was necessary to form the lactone between **1** and **2**, and also to effect alkene metathesis. The esterification proceeded smoothly, to give, after functional group deprotection, the linear precursor **20**. Alkene metathesis was efficient, but proceeded with little geometric control. It would have been interesting to know what influence the several protecting groups might have had on the geometry of the metathesis step.



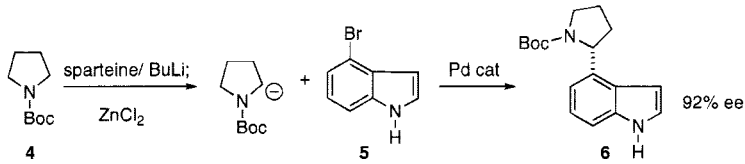
Stereocontrolled Construction of N-Heterocycles

November 13, 2006

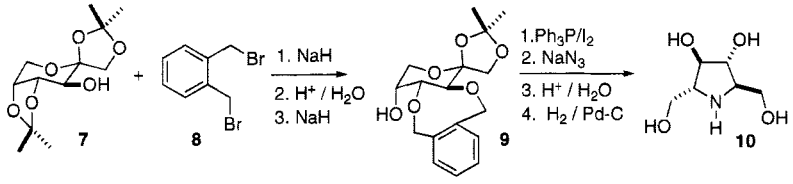
Yong-Gui Zhou of the Dalian Institute of Chemical Physics (*Angew. Chem. Int. Ed.* **2006**, *45*, 2260) and Manfred T. Reetz of the Max-Planck-Institut, Mülheim (*Chem. Commun.* **2006**, 2159) have individually reported enantioselective Ir-catalyzed hydrogenation of quinolines and, in the Zhou paper, isoquinolines. The Zhou group used this approach to prepare several enantiomerically-enriched alkaloids, including (-)-angustureine **3**.



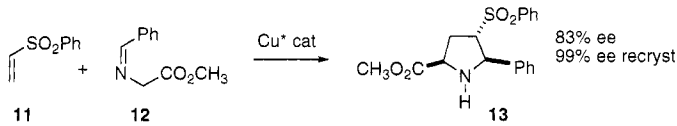
Kevin R. Campos of Merck Rahway (*J. Am. Chem. Soc.***2006**, *128*, 3538), building on the work of Peter Beak of the University of Illinois, has shown that it is possible to enantioselectively arylate N-Boc pyrrolidine **4**. Metalation in the presence of the enantiomerically-pure alkaloid sparteine gave the anion, which underwent Pd-mediated coupling with aryl halides, including **5**. The enantiomeric excess of the product was independent of the aryl halide used.



Carmen Ortiz Mellet of the Universidad de Sevilla and José M. Garcia Fernández of CSIC Sevilla have been investigating the use of ortho xylylene protecting groups for carbohydrates. They have found (*Organic Lett.* **2006**, *8*, 297) that monoprotection of the fructose acetonide **7** followed by hydrolysis and cyclization gave **8**. Conversion to the azide followed by hydrogenation delivered the highly-substituted pyrrolidine **10**.

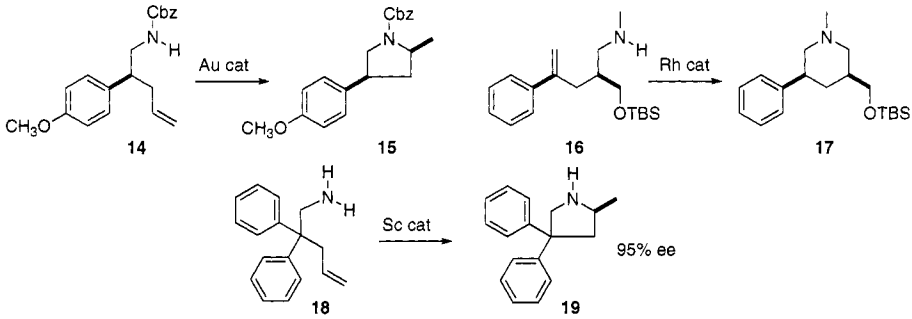


Ultimately, the most powerful methods for ring constuction willl be those that use chiral catalysts. Juan C. Carretero of the Universidad Autónoma de Madrid has devised (*Organic Lett.* **2006**, *8*, 1795) a Cu catalyst that effects the condensation of phenyl vinyl sulfone **11** with the dipole precursor **12**. The product pyrrolidine **13** is readily recrystallized to high ee.



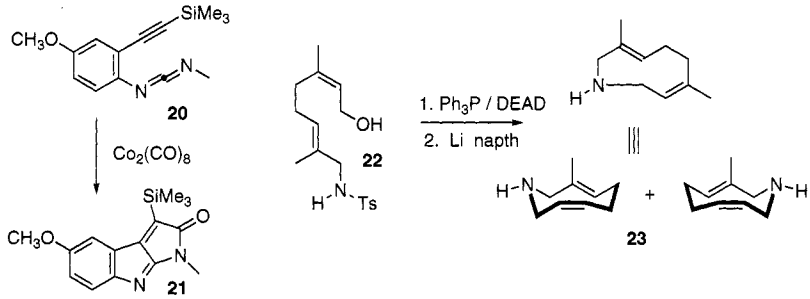
11 **12** **13**

C-N ring construction by intramolecular alkene hydroamination is now well developed as a synthetic method. Recent developments include the observation (*Angew. Chem. Int. Ed.* **2006**, *45*, 1747) by Ross A. Widenhoefer of Duke University that N-Boc amines such as **14** can cyclize efficiently, using a cationic Au catalyst. Using a Rh catalyst (*J. Am. Chem. Soc.* **2006**, *128*, 6042), John F. Hartwig of Yale University was able to effect *anti*-Markovnikov intramolecular hydroamination, converting **16** to **17**. And, using a Sc catalyst(*J. Am. Chem. Soc.* **2006**, *128*, 3748), Kai C. Hultzsch of the Universität Erlangen-Nürnberg was able to effect the cyclization of **18** with high ee.



14 **15** **16** **17** **18** **19**

Two other developments are particularly noteworthy. Chisato Mukai of Kanazawa University has shown (*Organic Lett.* **2006**, *8*, 83) that Co-mediated cyclization of the carbodiimide **20** delivers **21**, having *two* new rings. The enone **21** is prochiral, so there is the real possibility that chiral conjugate addition could set the absolute configuration of the ring system. Katsuhiko Tomooka of the Tokyo Institute of Technology has been studying (*Organic Lett.* **2006**, *8*, 963) the medium-ring amine **23**. The sulfonylamine **22** cyclizes under Mitsunobu conditions. The amine **23** is readily resolved, and is configurationally stable – it has a half-life of optical activity in hexane at room temperature of 203 days.

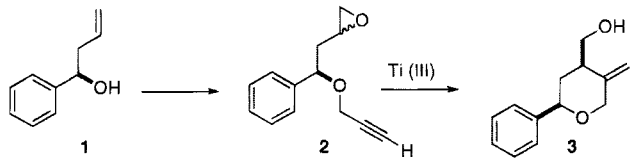


20 **21** **22** **23**

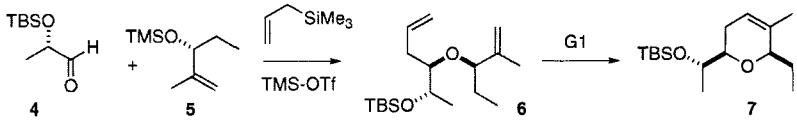
Stereocontrolled Construction of O-Heterocycles

November 20, 2006

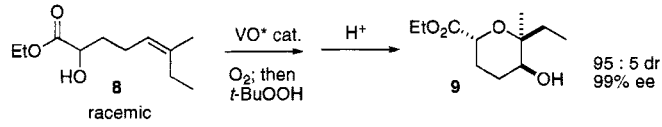
Homoallylic secondary alcohols such as **1** are readily prepared in enantiomerically-pure form by enantioselective addition of allyl anions to the aldehyde. Subhas Chandra Roy of the Indian Association for the Cultivation of Science, Jadavpur, has found (*Eur. J. Org. Chem.* **2006**, 489) that the epoxides of the derived propargylic ethers can be cyclized with Ti(III) to the corresponding cyclic ethers. The reaction proceeds with high diastereoselectivity, even though the epoxide **2** is a 1:1 mixture of diastereomers.



István Markó of the Université Catholique de Louvain has uncovered (*Angew. Chem. Int. Ed.* **2006**, *45*, 3357) conditions for the highly diastereoselective Sakurai condensation of an aldehyde such as **4**, readily derived in enantiomerically-pure form from ethyl lactate, an enantiomerically-pure secondary silyl ether such as **5**, and allyltrimethyl silane. The product ethers **7** are readily cyclized by the first-generation Grubbs catalyst.

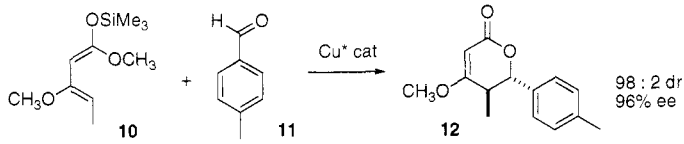


5-Exo addition of an alcohol to an epoxide is easy to achieve. 6-Endo addition is much less common. F. Dean Toste of the University of California, Berkeley has reported (*Angew. Chem. Int. Ed.* **2006**, *45*, 2096) a cascade of enantioselective alcohol oxidation, hydroxy-directed epoxidation by the residual, enantiomerically-enriched alcohol, and finally acid-mediated cyclization, to convert **8** into **9**. Yoshiki Morimoto of Osaka City University has described (*Angew. Chem. Int. Ed.* **2006**, *45*, 810) a complementary approach to 6-endo epoxy alcohol cyclization.

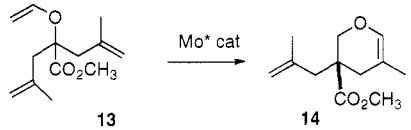


The catalytic establishment of contiguous stereogenic centers with control of both relative and absolute configuration is one of the most sought-after of organic transformations. Xiaoming Feng of

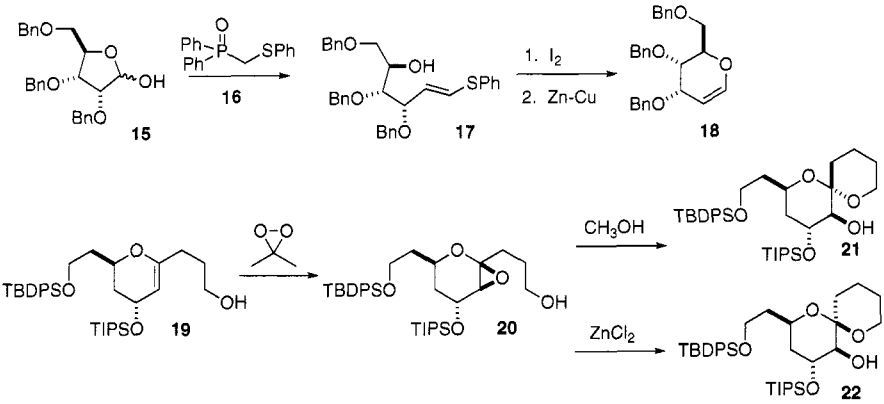
Sichuan University in Chengdu has found (*J. Org. Chem.* **2006**, *71*, 4141) that the diene **10** participates efficiently in hetero Diels-Alder cycloaddition with aromatic aldehydes, delivering the adducts **12** in high diastereomeric and enantiomeric excess.



Amir H. Hoveyda of Boston College continues to develop outstanding catalysts for alkene metathesis. Most recently, he has shown (*J. Am. Chem. Soc.* **2006**, *128*, 5153) that an enantiomerically-pure Mo complex will convert prochiral trienes such as **13** to the cyclic ether **14**, establishing in the process an otherwise difficult to prepare cyclic quaternary stererogenic center.



Pyranoid glycals such as **17** are important intermediates for carbohydrate synthesis. Yolanda Díaz and Sergio Castillón of the Universitat Rovira I Virgili, Tarragona, have developed (*Organic Lett.* **2006**, *8*, 673) a general strategy for homologating any pentose, including **15**, to the corresponding glycal.

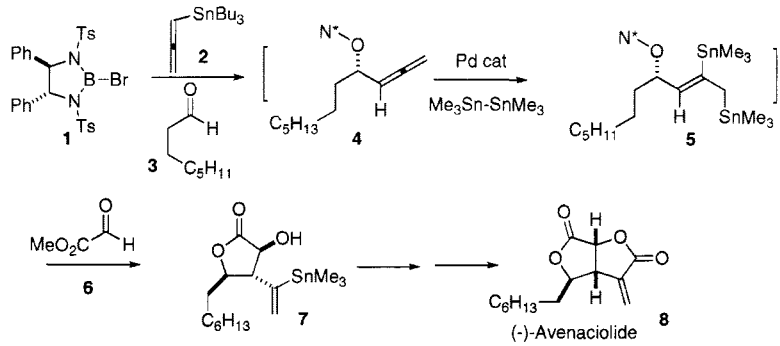


Derek S. Tan of the Memorial Sloan-Kettering Cancer Center, New York, has been extensively investigating (*J. Am. Chem. Soc.* **2006**, *128*, 1792) the stereocontrolled construction of spiro ethers such as **20** and **21**. From the same glycal epoxide **19**, either **20** or **21** can be formed, depending on the acid used. An obvious question is whether an alkylated version of **16** could be used to prepare 1-alkyl glycals such as **19**.

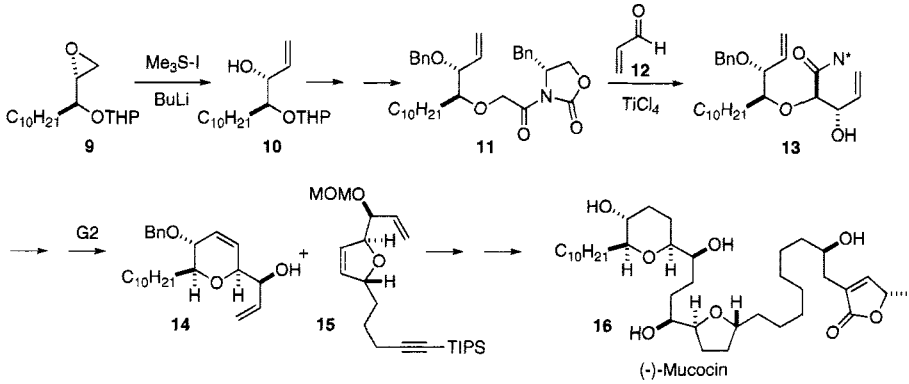
Stereocontrolled Synthesis of O-Heterocyclic Natural Products

November 27, 2006

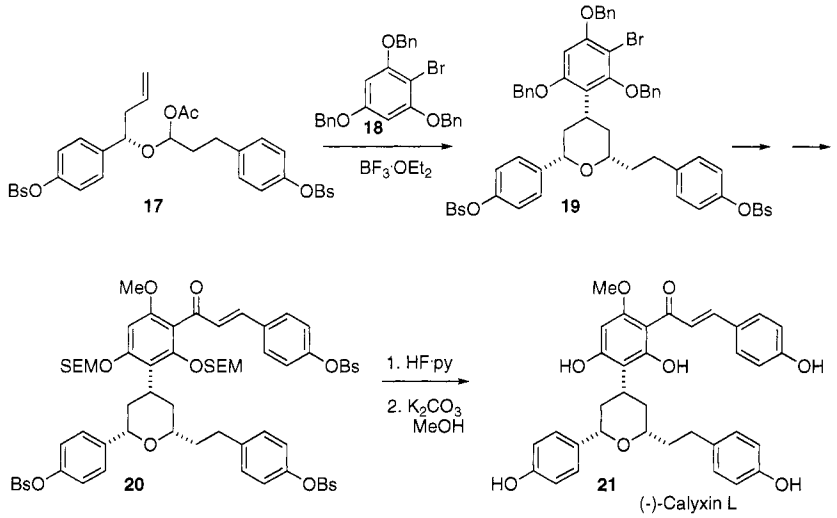
Chan-Mo Yu of Sungkyunkwan University, Suwon, has developed (*Angew. Chem. Int. Ed.* **2006**, *45*, 1553) a powerful strategy for assembling arrays of stereogenic centers, using the chiral controller **1**. The absolute configuration of the final product is set by the chiral controller, and the relative configuration is set by the order of addition of the two aldehydes **3** and **6**. This approach allowed the efficient assembly of the antifungal lactone (-)-avenaciolide **8**.



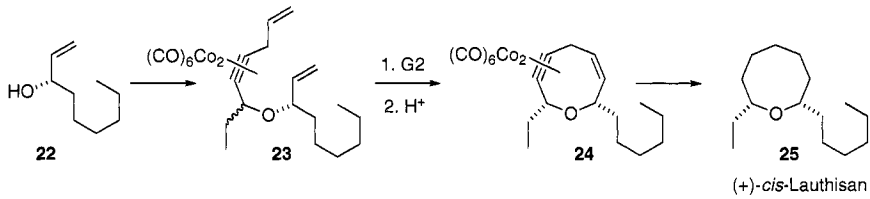
Michael T. Crimmins of the University of North Carolina has reported (*Organic Lett.* **2006**, *8*, 2369) the application of his glycolate anion approach to the synthesis of the selective anticancer polyether natural product (-)mucocin **16**. Condensation of **11** with acrolein **12** gave **13** with high diastereocontrol. The second-generation Grubbs catalyst worked well to close the six-membered ring of **14** and the five-membered ring of **15**, while a Hoveyda Ru catalyst worked better for the cross-coupling that combined **14** and **15**, leading to **16**.



A family of tetrahydropyran natural products, some of which are active against human fibrosarcoma and murine carcinoma, has recently been isolated. Scott D. Rychnovsky of the University of California, Irvine has described (*J. Org. Chem.* **2006**, *71*, 3176) the preparation of several members of this family, including (-)-calyxin L **21**, and also a correction of several of the stereochemical assignments in this series. The absolute configuration of **17** was set by enantioselective allylation. The tandem Prins cyclization / Friedel-Crafts alkylation then proceeded with high diastereocontrol. Note that the benzenesulfonyl protecting group for the phenols could be carried all through the synthesis. Teck-Peng Loh of Nanyang Technological University, Singapore has reported (*Tetrahedron Lett.* **2006**, *47*, 1641) modifications that suppress stereochemical leakage in related Prins cyclizations.



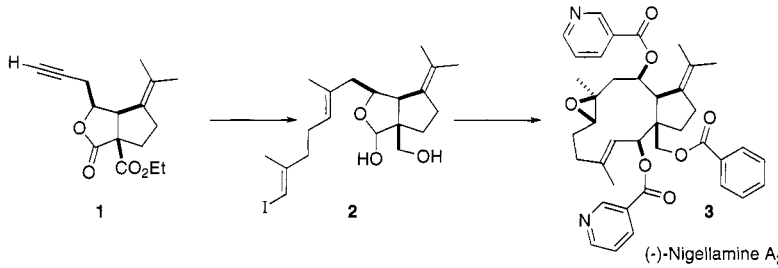
There are entropic and enthalpic barriers to the formation of medium rings, including medium ring ethers. Victor S. Martín of the Universidad de La Laguna, Tenerife has shown (*Organic Lett.* **2006**, *8*, 871) that the "bent" alkyne complex, as in **23**, can be used to direct ring formation. The Co complex also promotes the acid-catalyzed equilibration to the more stable *cis* diastereomer of **24**. The result is a facile synthesis of (+)-*cis*-lauthisan **25**.



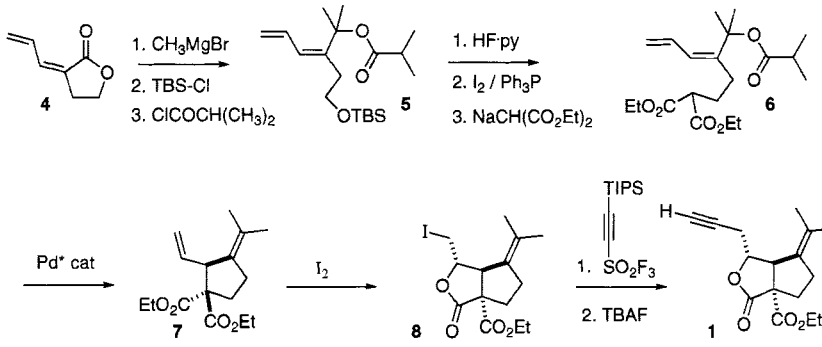
The Ready Synthesis of (-)-Nigellamine A_2

December 4, 2006

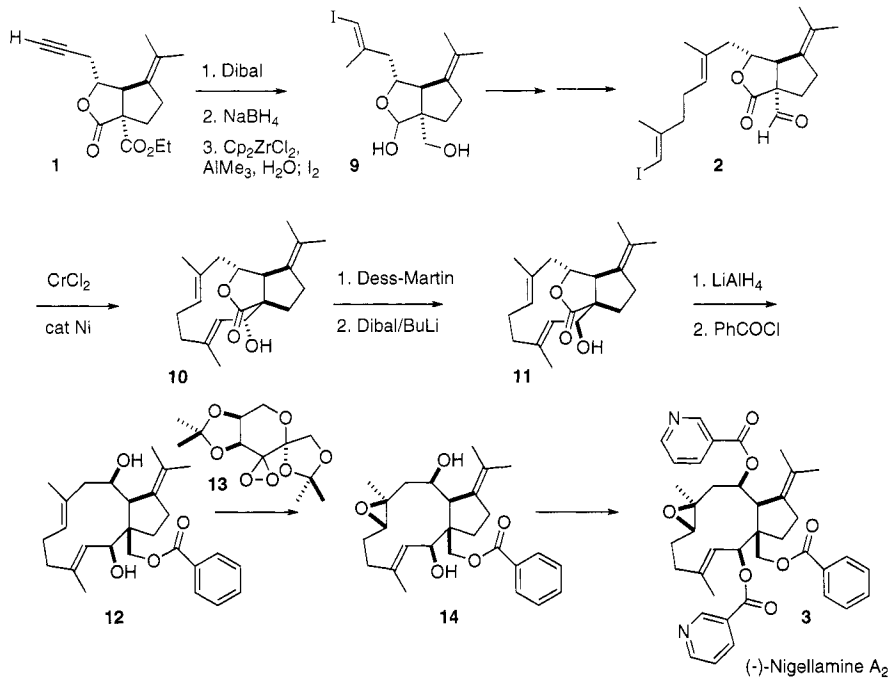
The nigellamine alkaloids, represented by (-)-nigellamine **3**, dolabellane diterpenes isolated from black cumin, apparently have lipid metabolism promoting activity. Joseph M. Ready of UT Southwestern Medical Center has described (*J. Am. Chem. Soc.* **2006**, *128*, 7428) the first synthesis of a nigellamine, (-)-nigellamine A_2 **3**. Key steps in the synthesis include an enantioselective cyclization to prepare **1**, and the Cr-mediated cyclization of the aldehyde **2**.



(-)-Nigellamine A_2 **3** has an angularly substituted *trans* ring fusion. The key to the synthesis was the preparation of the angularly-substituted *cis*-fused lactone **1**. The absolute configuration of **1** was set by the Pd-mediated S_N2' cyclization of the malonate **6**, which proceeded in 95% ee. Equally important was the seemingly mundane iodine-mediated cyclization of **7** to **8**. This one transformation differentiated the two esters of **6**, secured the relative configuration of one of the two secondary alcohols of **3**, and established the requisite *cis* ring fusion of the lactone **1**. Nucleophilic displacement of the iodide **8** failed, but two-carbon homologation to the alkyne could be accomplished by the free radical Fuchs procedure.



There were intial difficulties with the Negishi methylation/iodination of the terminal alkyne, as the Cp_2ZrCl_2 reacted preferentially with the lactol. Remarkably, repeating the reaction in the presence of water led to clean addition to the alkyne. Homologation followed by, again, wet Negishi methylation/iodination set the stage for oxidation to the lactone aldehyde **2**.



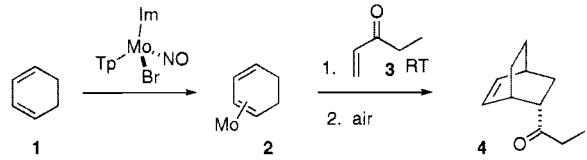
Both the bicyclic skeleton of **2** and the geometry of the two alkenes direct the pendant chain toward the aldehyde. In fact, Ni-catalyzed cyclization proceeded smoothly. The product alcohol emerged as a single diastereomer, but unfortunately the wrong one, so an oxidation/reduction cycle was required to correct the secondary alcohol center.

The final challenge was the selective epoxidation of the triene **12**. There are two concerns: facial selectivity, and chemoselectivity. The facial selectivity is inherent, as the geometry of the medium ring is such that only the desired face is exposed. Chemoselectivity was more challenging. MCPBA reacted indiscriminantly with each of the three alkenes. Reasoning that a bulkier epoxidizing agent might be more selective, they found that the Shi dioxirane **13** delivered a 7:1 ratio of the two trisubstituted epoxides. It is interesting that the enantiomer of **13** gave only a 2:1 ratio.

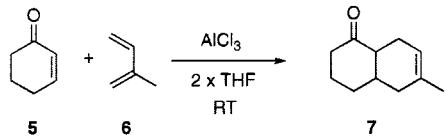
Advances in the Diels-Alder Reaction: Synthesis of (±)-Lycoridine and of Dolabellatrienone

December 11, 2006

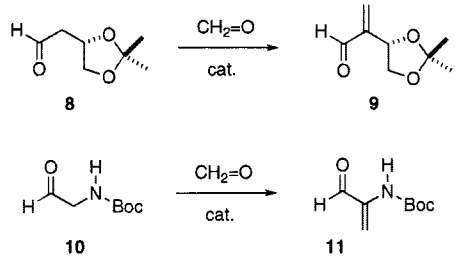
Cyclic dienes such as **1** are reluctant participants in Diels-Alder cycloaddition. W. Dean Harman of the University of Virginia has shown (*J. Am. Chem. Soc.* **2006**, *128*, 1426) that such dienes are activated by complexation to Mo. After cycloaddition, exposure of the product to air liberates the product **4**.



Cyclohexenone **5** is a sluggish dienophile, requiring activation by $AlCl_3$. Francesco Fringuelli and Ferdinando Pizzo of the Università di Perugia have developed (*Organic Lett.* **2006**, *8*, 2487) a somewhat milder alternative, $AlCl_3$ complexed to THF. Operationally, a catalytic amount (5 mol %) of $AlCl_3$ and exactly twice that much THF were combined. The diene **6** and the dienophile **5** were then added, in this case in a 2:1 ratio, without additional solvent. After 12 hours at 30 °C, the cycloadduct **7** was isolated in 80% yield. Increasing or decreasing the amount of THF dropped the efficiency of the reaction.



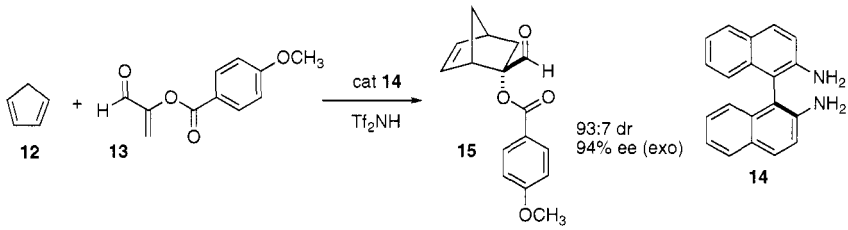
Effective procedures for the α-methylenation of aldehydes go back at least sixty years (*J. Am. Chem.Soc.* **1948**, *70*, 1694). Nevertheless, the results reported (*J. Org. Chem.* **2006**, *71*, 2538) by Petri M. Pihko of Helsinki University of Technology are compelling. Using 37% aqueous formaldehdye and 10 mol % of the dimeric peptide L-Pro-β-Ala, they were able to effect α-methylenation of sensitive aldehydes such as **8** and **10**.



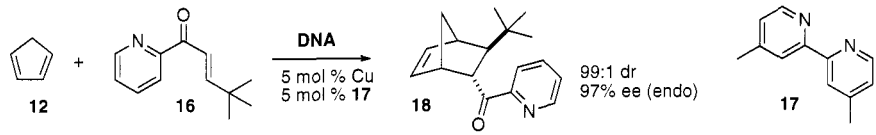
Advances in the Diels-Alder Reaction: Synthesis of (±)-Lycoridine and of Dolabellatrienone

December 11, 2006

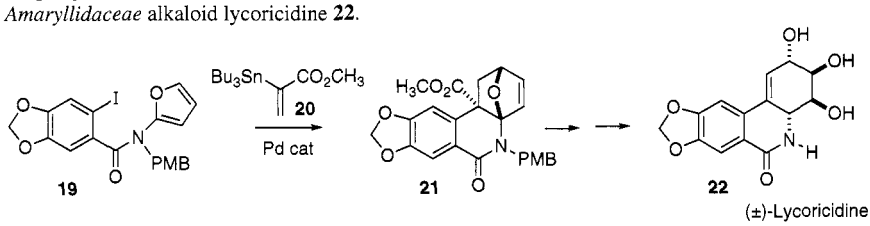
α-Substituted acroleins are difficult substrates for enantioselective catalysis. Kazuaki Ishihara of Nagoya University has developed polyamine catalysts that direct cycloaddition of α-substituted acroleins with high enantioselectivity. For cyclopentadiene **12** and the dienophile **13** (*Organic Lett.* **2006**, *8*, 2229), the polyamine of choice is **14**, 5 mol %, activated with an equimolar amount of Tf_2NH.



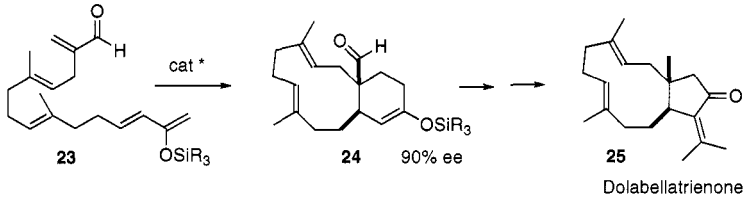
Ben L. Feringa and Gerard Roelfes of the University of Groningen have taken advantage (*Chem. Comm.* **2006**, 635) of the inherently chiral environment of DNA to direct the absolute sense of Diels-Alder cycloaddition.



Two particularly elegant applications of the *intramolecular* Diels-Alder reaction have recently been reported. Albert Padwa of Emory University has shown (*Organic Lett.* **2006**, *8*, 247) that Pd-mediated coupling of **19** and **20** directly delivers the cycloadduct **21**. This was carried on over several steps to the *Amaryllidaceae* alkaloid lycoricidine **22**.



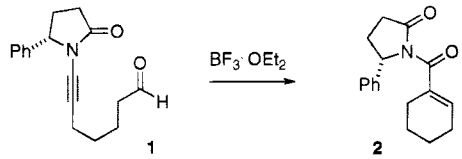
E.J. Corey of Harvard University has applied (*J. Am. Chem. Soc.* **2006**, *128*, 740) the chiral Diels-Alder catalysts he has developed to the cyclization of the triene **23**. The adduct **24** was carried on to the dolabellane marine natural product dolabellatrienone **25**.



Enantioselective Carbocyclic Construction

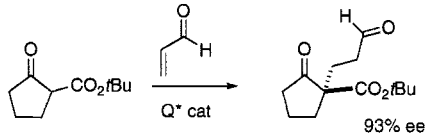
December 18, 2006

Richard P. Hsung, now of the University of Wisconsin, has reported (*Organic Lett.* **2006**, *8*, 231) the intramolecular addition of ynamides to aldehydes. One might classify this as an intramolecular aldol condensation. It is known that the conjugate addition of organometallics to chiral imides such as **2** proceeds with high facial control.



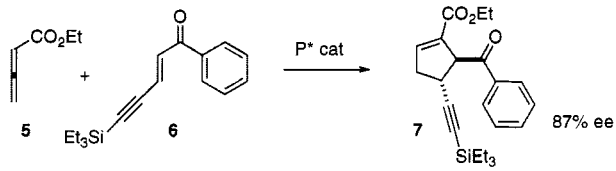
1 2

Many methods have been developed for the enantioselective transformation of preexisting prochiral rings. The work (*Angew. Chem. Int. Ed.* **2006**, *45*, 947; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301) of Li Deng of Brandeis University is particularly noteworthy. He has shown that in the presence of a catalytic amount of enantiomerically-pure base, Michael donors such as **3** add to Michael acceptors with high facial selectivity.



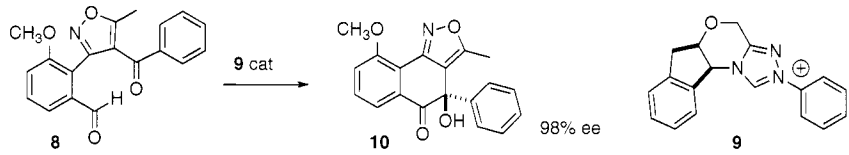
3 4

The "cycloaddition" of **5** to **6** developed by Gregory C. Fu of MIT (*Angew. Chem. Int. Ed.* **2006**, *45*, 1426) is in fact a stepwise ionic process. An enantiomerically-pure phosphine catalyst directs the absolute sense of the reaction. The cycloaddition works equally well if the alkyne of **6** is replaced by another aromatic ring.

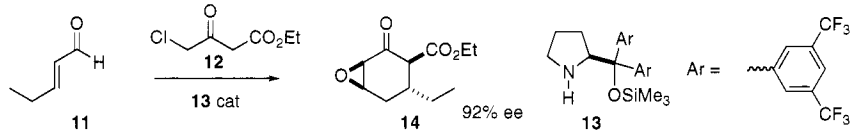


5 6 7

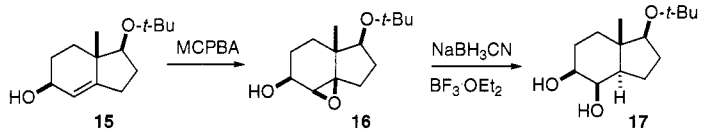
Keisuke Suzuki of the Tokyo Institute of Technology has found (*Angew. Chem. Int. Ed.* **2006**, *45*, 3492) that the Rovis triazolium salt **9** nicely catalyzes the intramolecular benzoin condensation of keto aldehydes such as **8**, with high ee.



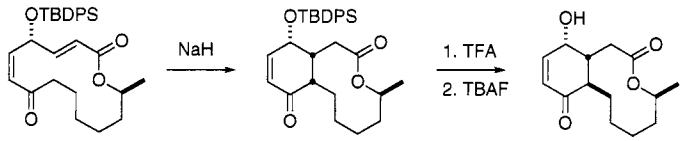
A truly spectacular approach to catalytic carbocyclic construction has been reported (*J. Am. Chem. Soc.* **2006**, *128*, 5475) by Karl Anker Jorgensen of Aarhus University. Condensation of the commercially-available chloroester **12** with an α,β-unsaturated aldehyde such as **11** proceeds, via a series of three bond-forming steps, to give the epoxy ketone **14** in high ee.



A long-standing problem in the synthesis of Vitamin D and its metabolites has been the establishment of the requisite angularly-substituted trans 6/5 C-D ring fusion. Jerzy Wicha of the Polish Academy of Sciences in Warsaw has now put forward (*Organic Lett.* **2006**, *8*, 2551) an elegant solution to this problem. Peracid oxidation of **15** gave the epoxide **16**. Reduction of **16** by the Hutchins protocol proceeded with inversion, as expected, to give **17**.



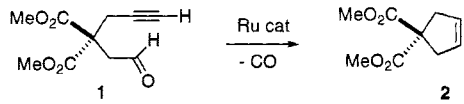
Schering-Plough isolated the macrolactone (+)-Sch 642305 **20** from a soil sample collected near Tucson, AZ. Barry B. Snider of Brandeis University (*Organic Lett.* **2006**, *8*, 1283) reasoned that the substituents on **18** would set the conformation of the medium ring, so that intramolecular Michael addition would proceed selectively across one face of the acceptor. Indeed, on exposure to NaH **18** cyclized to **19** as a single diastereomer. Acid-catalysed epimerization followed by desilylation then delivered **20**.



Transition Metal Mediated Carbocyclic Construction

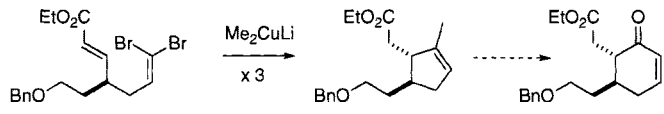
December 25, 2006

Alkene and alkyne metathesis have, in a relatively short time, become important tools for organic synthesis. Carlos Saá of the Universidad de Santiago de Compostela has developed (*J. Am. Chem. Soc.* **2006**, *128*, 9576) a complementary tool for ring construction, the metathetical coupling of an aldehyde or ketone with a terminal alkyne to give the cyclic alkene, illustrated by the conversion of **1** to **2**. It seems likely that the oxygen of the CO being expelled comes from the aldehyde, and the carbon comes from the terminal carbon of the alkyne.



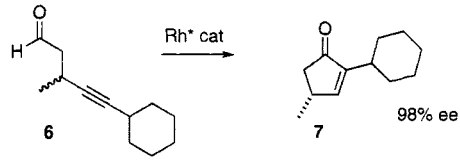
1 **2**

1,1-Dibromoalkenes such as **3** are easily prepared from the corresponding aldehyde. Keiji Tanino and Masaaki Miyashita of Hokkaido University have shown (*Tetrahedron Lett.* **2006**, *47*, 861) that on exposure of **3** to three equivalents of Me_2CuLi, methylation, reduction and intramolecular conjugate addition take place, to give the ester **4** as a 10:1 ratio of diastereomers. Note that ozonolysis of **4** followed by aldol condensation would give the cyclohexenone **5**.



3 **4** **5**

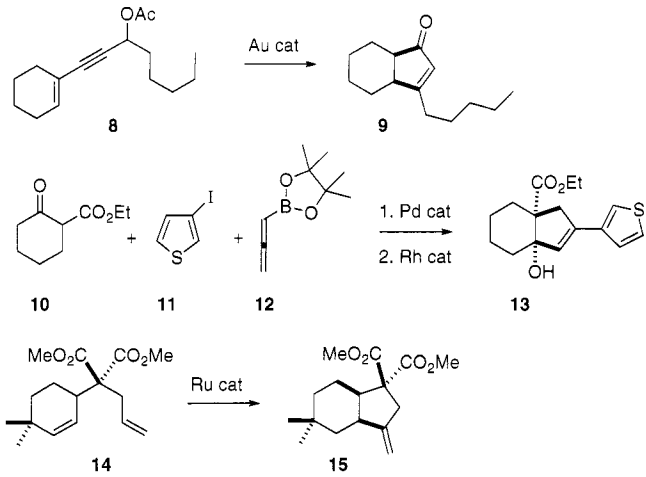
Many methods have been developed for the enantioselective construction of carbocyclic rings, either by cyclization of an enantiomerically-pure precursor, or by asymmetric catalysis. Ken Tanaka of the Tokyo University of Agriculture and Technology has devised (*Angew. Chem. Int. Ed.* **2006**, *45*, 2734) a third approach. On exposure of the inexpensive *racemic* **6** to an enantiomerically-pure Rh catalyst, only one enantiomer of **6** reacts, so the product cyclopentenone **7** is delivered in high ee.



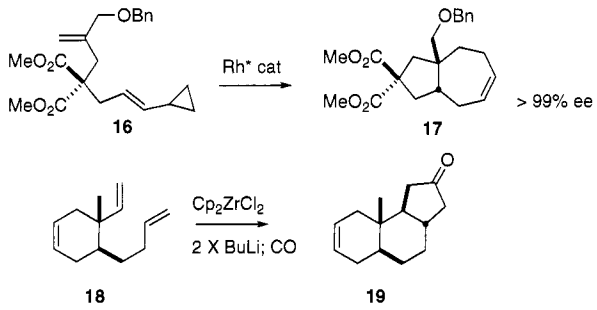
6 **7**

The construction of efficient routes to polycarbocyclic scaffolds for medicinal chemistry exploration is an important objective for organic synthesis. Three useful methods for stitching ("annealing") a new ring onto a pre-existing ring have recently appeared. Liming Zhang of the University of Nevada, Reno, has found (*J. Am. Chem. Soc.* **2006**, *128*, 1442) an Au catalyst that converts **8**, by rearrangement and subsequent Nazarov cyclization, to the enone **9**. Kenichiro Itami of Nagoya University and Jun-ichi

Yoshida of Kyoto University have developed (*Organic Lett.* **2006**, *8*, 1419) a Pd-catalyzed three-component coupling of a β-keto ester **10**, an aryl iodide **11**, and the allenylboronate **12**. Exposure of the resulting condensation product to Rh catalysis converts it into the cyclized alcohol **13**. Ian J.S. Fairlamb of the University of York has extended (*Chem. Commun.* **2006**, 988) Ru-catalyzed cycloisomerization, showing that **14** is converted cleanly to **15**. In each of these examples, the cyclization precursors are easily prepared.



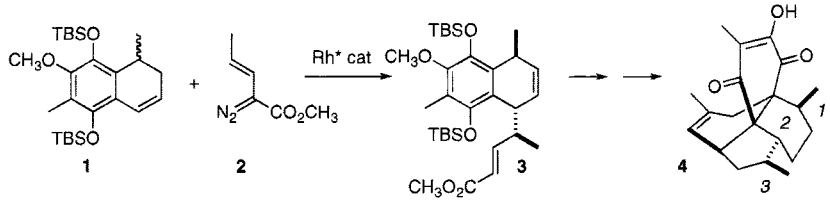
Transition-metal mediated cyclizations that directly produce two or more rings offer a powerful entry to polycyclic systems, dramatically reducing the number of steps required for a target-directed synthesis. As exemplified by the recent work (*J. Am. Chem. Soc.* **2006**, *128*, 6302) of Paul A. Wender of Stanford University (**16** → **17**), a chiral catalyst can effect cyclization and also direct the absolute configuration of the product. In a complementary approach that we have reported (*J. Org. Chem.* **2006**, *71*, 2797), the transition metal, in this case the inexpensive Zr, is used stoichiometrically as a scaffold. Carrying out the cyclization of **18** under equilibrating conditions followed by carbonylation gives the tricyclic ketone **19**.



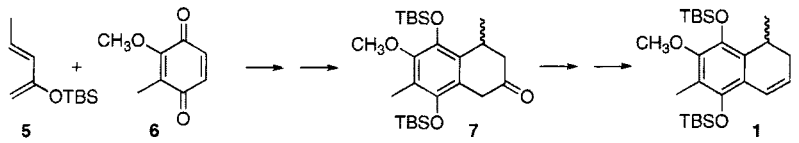
Synthesis of (-)-Colombiasin A and (-)-Elisapterosin B

January 1, 2007

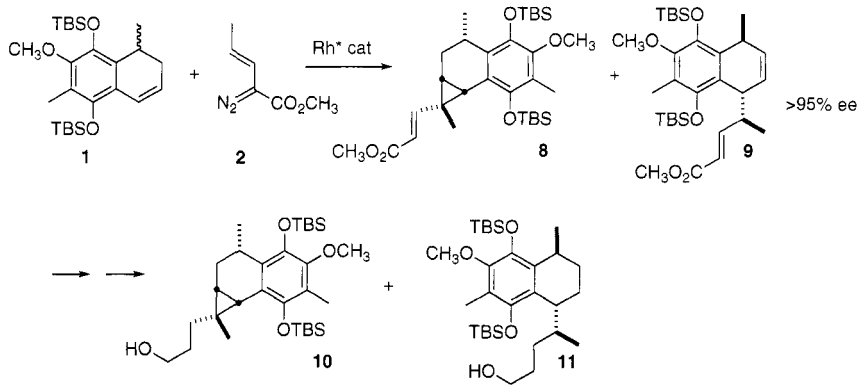
Historically, there have been three methods for assembling enantiomerically-pure carbocycles: cyclization of an enantiomerically-pure starting material, enantioselective cyclization of a prochiral substrate, and enantioselective transformation of a prochiral cyclic starting material. Recently, a fourth strategy has been developed, enantioselective transformation of a *racemic* starting material, with only *one* enantiomer of the starting material going on to the desired product. This approach is illustrated by the transformation of racemic **1** to enantiomerically (and diastereomerically) pure **3**. The conversion of **1** to **3** is the key step in a general route established (*J. Am. Chem. Soc.* **2008**, *128*, 2485) by Huw M. L. Davies of the University at Buffalo to the diterpenes isolated from the gorgonian coral *Pseudoterogoria elisabethae*, exemplified by (-)-colombiasin A **4**.



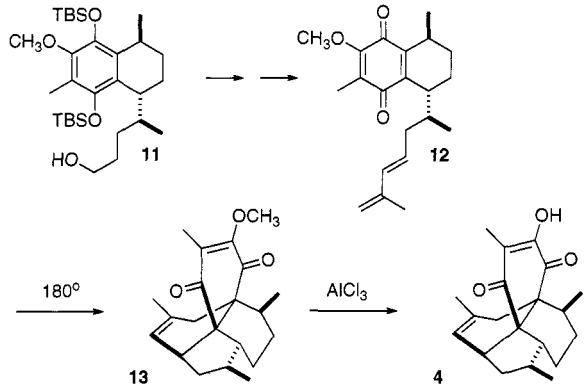
The dihydronaphthalene **1** was prepared by Diels-Alder cycloaddition of the diene **5** to the benzoquinone **6**, the preparation of which had been reported by Nicolaou in the course of a previous synthesis of (-)-colombiasin A **4**. Silylation of the cycloadduct followed by selective hydrolysis gave the ketone **7**. The ketone was converted to the enol triflate **8**, which was reduced with triethylsilane to give racemic **1**.



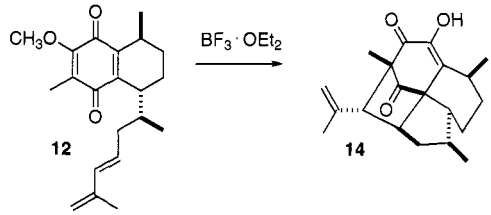
Exposure of **1** to **2** in the presence of the DOSP Rh catalyst, designed by Davies, delivered the two adducts **8** and **9**. These were carried together to the alcohols **10** and **11**, which were separated. The overall yield of diasteromerically- and enantiomerically-pure **11** from racemic **1** was 34%. This was 68% of theoretical, since was derived from only one of the two enantiomers of **1**.



Homologation of **11** to the diene followed by desilylation under oxidative conditions led to the quinone **12**. Followed the precedent of Rychnovsky, on heating **12** was converted to the Diels-Alder adduct **13**. Demethylation then gave (-)-colombiasin A **4**.



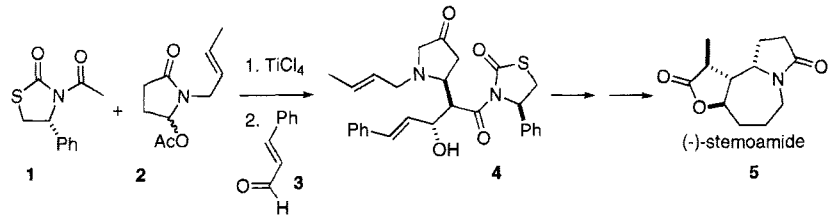
The tetracyclic triketone (-)-elisapterosin B **14**, also a *Pseudoterogoria elisabethae* diterpene, is the intramolecular [5 + 2] cycloaddition product from **12**. Again following a Rychnovsky procedure, exposure of the diene **12** to BF_3 etherate led directly to **14**, accompanied by minor amounts of the methyl ether **13**.



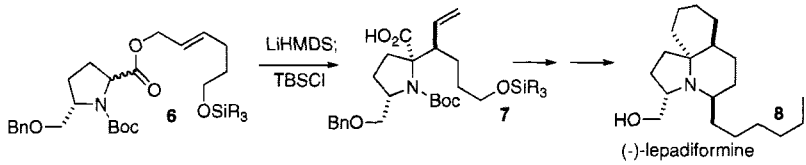
Enantioselective Synthesis of C-N Ring Containing Natural Products

January 8, 2007

Enantioselective addition to a prochiral ring is a powerful approach for the preparation of C-N rings in high ee. This is elegantly illustrated by the report (*J. Org. Chem.* **2006**, *71*, 3287) by Horacio F. Olivo of the University of Iowa of the condensation of **1** with **2**, followed by the addition of the product to cinnamaldehyde **3**. This net three-component coupling delivered **4**, having one of the rings and three of the four contiguous stereogenic centers of (-)-stemoamide **5**.

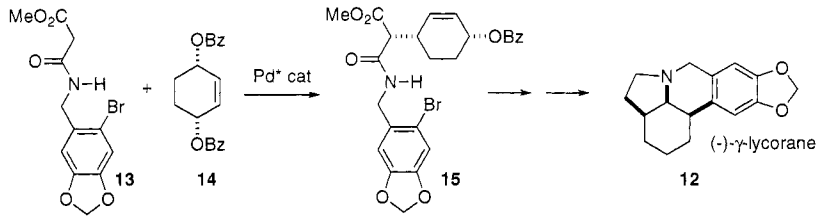


A complementary strategy for the simultaneous control of both ring and sidechain configuration was described (*Organic Lett.* **2006**, *8*, 745) by Sanghee Kim of Seoul National University. The ester **6**, as a diastereomeric mixture, was readily prepared from pyroglutamic acid. On deprotonation followed by silylation, Ireland-Claisen rearrangement proceeded with high diastereocontrol. The product **7** was carried on to (-)-lepadiformine **8**.

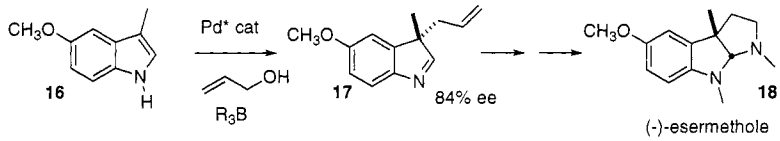


Two recent syntheses of (-)-γ-lycorane **12** started with prochiral *carbocyclic* rings. Hiromichi Fujioka and Yasuyuki Kita of Osaka University began (*Chem. Commun.* **2006**, 832) with the dihydrobenzene derivative **9**. Condensation with the diaryl diamine **10** followed by N-bromosuccinimide gave the tricyclic amine **11**, the stereogenic centers of which were preserved in its conversion to (-)-γ-lycorane **12**.

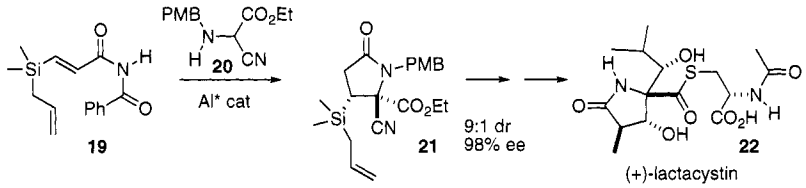
Iwao Ojima of SUNY Stony Brook focused (*Organic Lett.* **2006**, *8*, 1395) on the enantioselective coupling of the β-keto ester **13** with the diastereomerically-pure bis-benzoate **14**. Judicious ligand choice improved this coupling from the previously reported 54% to 99% ee. The product **15** was carried on to (-)-γ-lycorane **12** following a modification of the procedure of Mori.



The key to the synthesis of the physostigmine alkaloids, exemplified by (-)-esermethole **18**, is the establishment of the alkylated quaternary center. The Pd-catalyzed allylation of 3-methyl indoles had been described. Barry M. Trost of Stanford University found (*J. Am. Chem. Soc.* **2006**, *128*, 6314) that using the ligands they had developed, the allylation could be carried out with high ee. The optimization of the trialkylborane was the key to the success of this transformation. The product **17** was carried on to (-)-esermethole **18**.



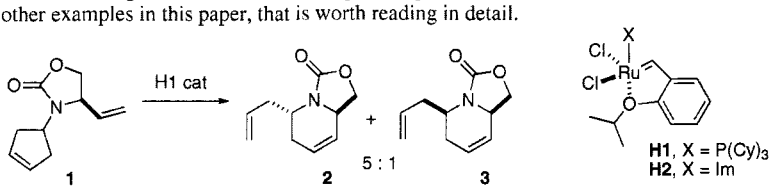
(+)-Lactacystin **22** is a potent and selective inhibitor of the 26S proteasome. In the synthesis of **22** recently reported (*J. Am. Chem. Soc.* **2006**, *128*, 6810) by Eric N. Jacobsen of Harvard University, the chirality was set by the Al-salen catalyzed conjugate addition of the cyano ester **20** to the silyl amide **19**. The silyl group in the adduct **21** served as a surrogate for one the ring alcohol of **22**.



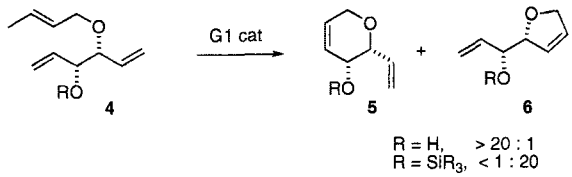
New Catalysts and Strategies for Alkene and Alkyne Metathesis

January 15, 2007

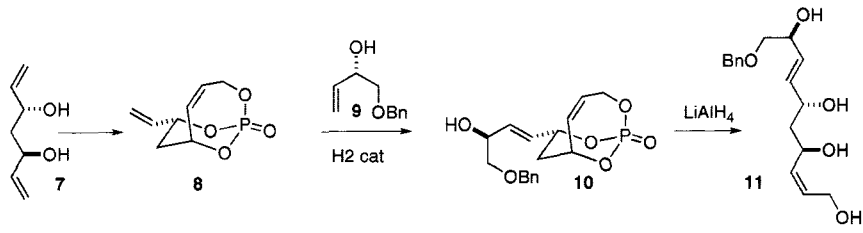
Diastereoselectivity in ring-closing metathesis can be achieved under either kinetic or thermodynamic control. Siegfried Blechert of the Technische Universität Berlin has found (*Angew. Chem. Int. Ed.* **2006**, *45*, 1302) that using the first-generation Hoveyda catalyst, **1** cyclizes to **2** and **3** with useful diastereocontrol. Product **2** was recovered unchanged on resubmission to the reaction conditions, indicating that in this case, the ring-closing metathesis is under kinetic control. There are many other examples in this paper, that is worth reading in detail.



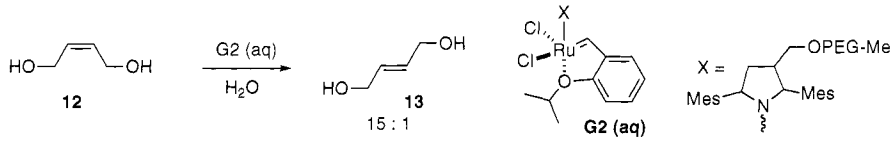
Bernd Schmidt of the Universität Potsdam has observed (*Chem. Commun.* **2006**, 2489) high chemoselectivity in the ring-closing metathesis of **4**. For protected **4**, the reaction proceeded to give the expected cyclopentene **6**. The free alcohol, however, cyclized to **5**, suggesting a directing or activating influence of the free OH. Cyclic ethers such as **5** and **6** can easily be oxidized to the corresponding lactones.



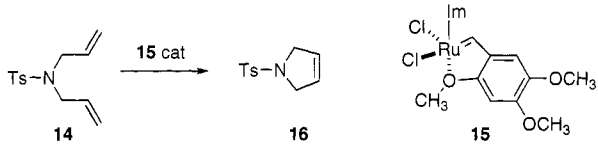
Paul R. Hanson of the University of Kansas has developed (*Organic Lett.* **2006**, *8*, 1673) a creative program around phosphates such as **8** derived from the diol **7**. Cross metathesis with the allylic alcohol **8**, for instance, proceeds without interference from the cyclic alkene. Reductive removal of the protecting phosphate then delivered the triol **11**. The cyclic phosphates are also substrates for diastereoselective cuprate coupling.



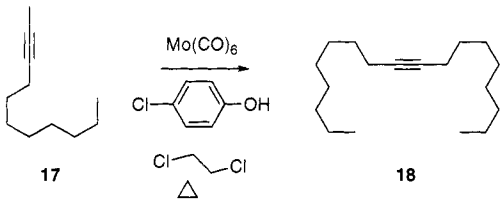
Although the first and second generation Grubbs and Hoveyda catalysts are very good, there is still room for the development of new catalytic complexes. Ricardo Castarlenas and Pierre H. Dixneuf of the Université de Rennes have described (*J. Am. Chem. Soc.* **2006**, *128*, 4079) indylidene Ru complexes that are very active catalysts for alkene metathesis. Robert H. Grubbs of Caltech has devised (*J. Am. Chem. Soc.* **2006**, *128*, 3508) a Ru complex G2 (aq) that is stable and active in water. *Inter alia*, this allows the ready equilibration, in water, of the inexpensive cis diol **12** to the trans diol **13**, a valuable starting material for target-directed synthesis.



Karol Grela of the Polish Academy of Sciences in Warsaw has prepared (*Chem. Commun.* **2006**, 841) the dimethoxy Hoveyda Ru complex **15**. In what promises to be a very useful protocol, after the cyclization of **14** to **16** in CH_2Cl_2 is complete, the reaction mixture is simply filtered through a pad of silica gel with additional CH_2Cl_2. This delivers the pure product **16**, containing only 110 ppm Ru. Elution of the silica pad with EtOAc then brings the recovered catalyst **15**, that can be re-used.



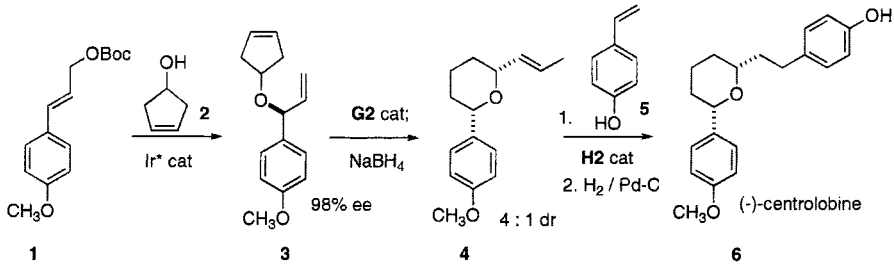
Alkyne metathesis is usually carried out with W and Mo carbyne complexes. Jeffrey S. Moore of the University of Illinois has developed (*Angew. Chem. Int. Ed.* **2006**, *45*, 585) a protocol for depositing a Mo carbyne catalyst on silica gel. The resulting supported catalyst is very active at room temperature in toluene. Remi Chauvin of the Laboratoire de Chimie de Coordination in Toulouse has prepared (*Tetrahedron Lett.* **2006**, *47*, 2155) a less active but even more convenient catalyst by combining $Mo(CO)_6$, *p*-chlorophenol, and the alkyne, then heating at 85° in 1,2-dichloroethane. Both aromatic and aliphatic alkynes are smoothly dimerized.



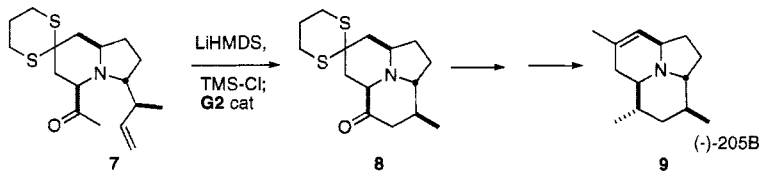
Heterocyclic Natural Products by Alkene Metathesis

January 22, 2007

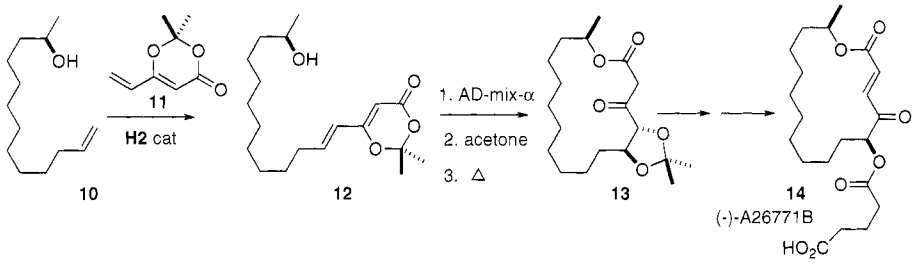
The recent (*Chem. Commun.* **2006**, 1968) synthesis of (-)-centrolobine **6** by Siegfried Blechert of the Technische Universität Berlin is a tour de force of organometallic catalysis. The absolute configuration of the natural product was set by the Ir*-mediated S_N2' coupling of **1** and **2**. Diastereoselective ring closure with the second-generation Grubbs catalyst was terminated by the addition of $NaBH_4$, to reduce the Ru catalyst to a Ru-H species, which mediated the migration of the terminal alkene that was the initial metathesis product. Cross metathesis with **5** using the second-generation Hoveyda catalyst followed by catalytic hydrogenation then delivered **6**. The second-generation Hoveyda catalyst is sometimes termed the "Hoveyda-Grubbs" catalyst.



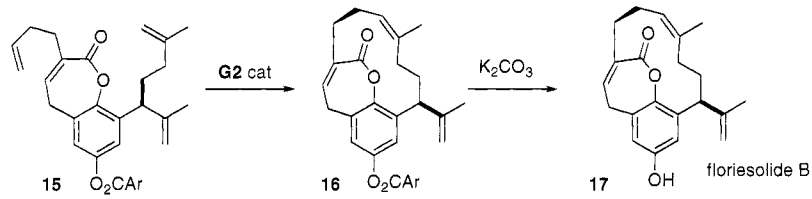
The cyclization of **7** to **8** was a key step in the synthesis (*J. Org. Chem.* **2006**, *71*, 2547) of the Dendrobatid alkaloid (-)-205B **9** by Amos B. Smith III of the University of Pennsylvania. In this reaction, which was based on the precedent of Masakatsu Shibasaki of the University of Tokyo (*Tetrahedron Lett.* **2001**, *42*, 8023) the silyl enol ether derived from **7** underwent ring-closing metathesis, followed by hydrolysis of the product enol ether.



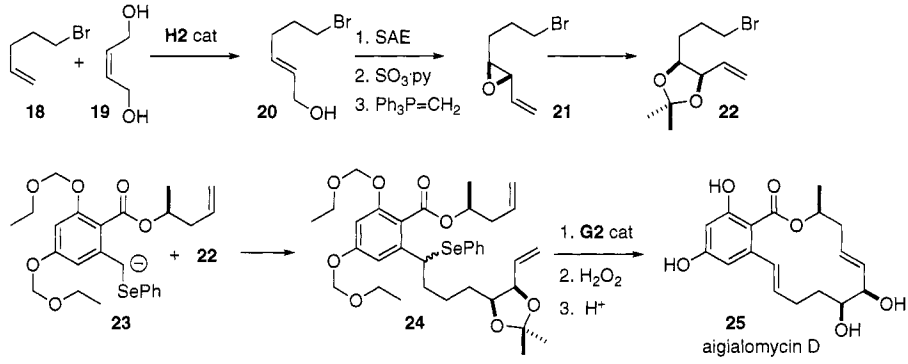
In what promises to be a general approach to macrolactones, Professor Blechert has prepared (*J. Org. Chem.* **2006**, *71*, 2021) the diene lactone **11**. Cross metathesis with the unsaturated alcohol **10** led to **12**, which after dihydroxylation and protection was heated to generate the macrolactone **13**, by way of the intermediate ketene. The acetonide **13** was carried on the macrolide antibiotic (-)-A26771B.



The macrolide floreside **17** is in fact a [10]metacyclophane, further bridged by the lactone ring. This led to the question of which ring to form first. K. C. Nicolaou of Scripps, La Jolla found (*Chem. Commun.* **2006**, 600) that cyclophane formation was reluctant under metathesis conditions, but that if the lactone was formed first, the second-generation Grubbs catalyst smoothly closed the carbocyclic ring. The product **16** was formed as a single atropisomer, corresponding to the natural product **17**.



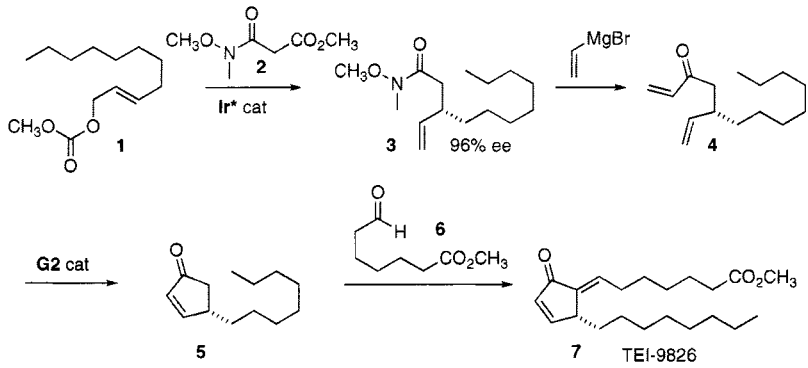
In a modular synthesis of the macrolide aigialomycin D **25** (*Angew. Chem. Int. Ed.* **2006**, *45*, 3951), Nicolas Winssinger of the Université Louis Pasteur in Strasbourg prepared the substrate **20** for Sharpless asymmetric epoxidation using the method that we introduced (*J. Org. Chem.* **2003**, *68*, 6047), equilibrating homologation with the inexpensive 2-butene-1,4-diol **19**. Acetonide formation from **21**, with single inversion, then delivered the alkylating agent **22**. The selenide of **23** enabled anion formation, and also served as a masked alkene. The authors observed that it was important to effect ring-closing metathesis *before* the oxidative elimination.



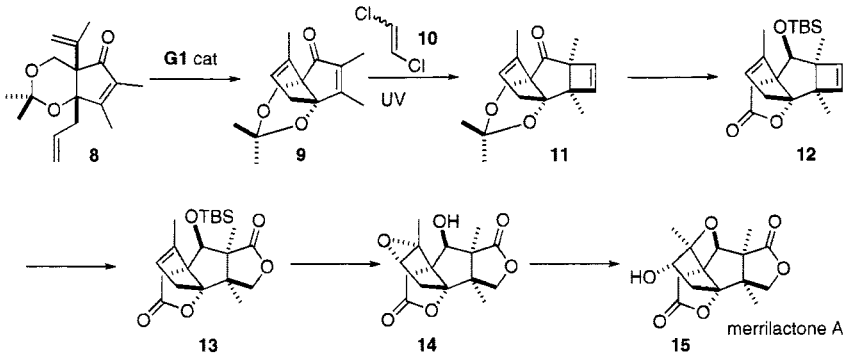
Carbocyclic Natural Products by Alkene Metathesis

January 29, 2007

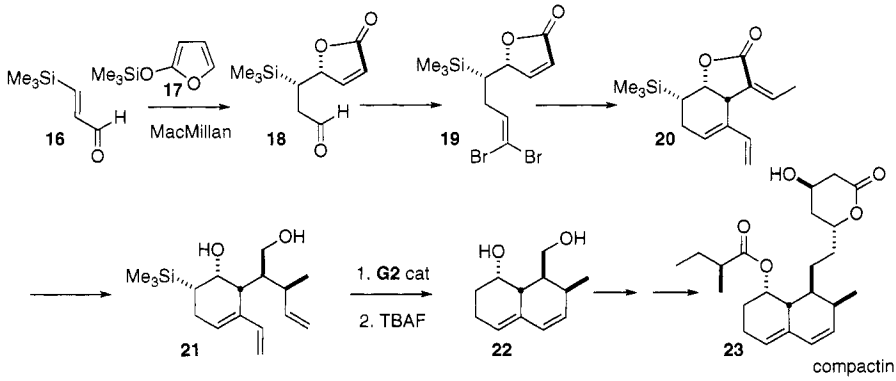
TEI-9826 **7** is a prostaglandin analogue that shows high activity against cisplatin-resistant tumors. Günter Helmchen of the Universität Heidelberg has devised (*Angew. Chem. Int. Ed.* **2006**, *45*, 2466) a simple but elegant route to **7**, based on the Ir*-catalyzed condensation of **2** with the allylic carbonate **1**. Remarkably, the easily-epimerized stereogenic center of **5** survives not just metathesis, but also the alkaline conditions of the aldol reaction used to attach the upper sidechain.



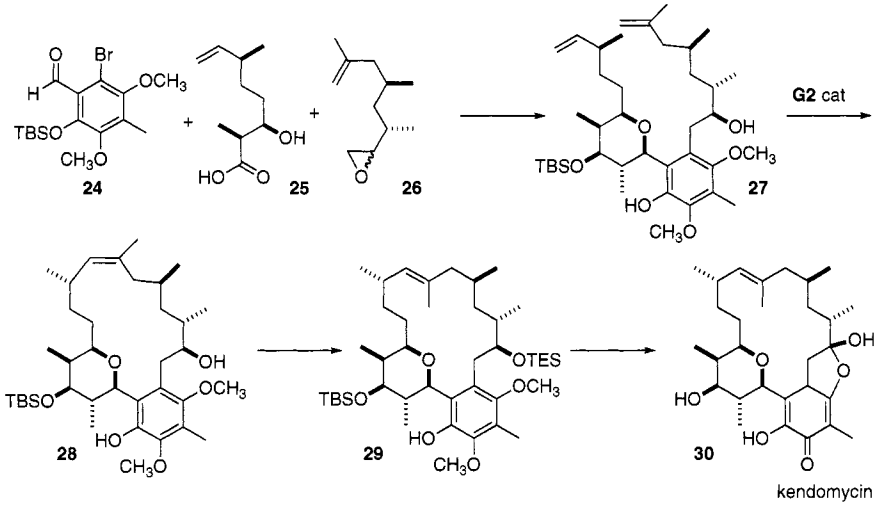
The pentacyclic merrilactone A **15** is a potent neurotropic agent, promoting neurite outgrowth in cortical neuron cell culture. In the synthesis of **15** by Goverdhan Mehta of the Indian Institute of Science, Bangalore (*Angew. Chem. Int. Ed.* **2006**, *45*, 953) alkene metathesis is deployed early, in the transformation of **8** to **9** that establishes the second of the two carbocyclic rings.



The aptly-named compactin **23**, the parent of the clinically-important statin cholesterol-lowering agents, indeed has a compact carbocyclic core. The formal synthesis (*Organic Lett.* **2006**, *8*, 597) of **23** by Joël Robichaud of Merck Frosst Canada, delivered, with control of relative and absolute configuration, the diol **22**. Initial stereocontrol was achieved by the addition of **17** to **16**, using the MacMillan protocol. Free radical cyclization of the dibromide **19** led to the cyclic bromoalkene, which was homologated with vinyl tributyl tin to give the diene. Conjugate addition to the exocyclic alkene of **20** again proceeded with high diasterocontrol, to deliver **21**, the substrate for alkene metathesis.



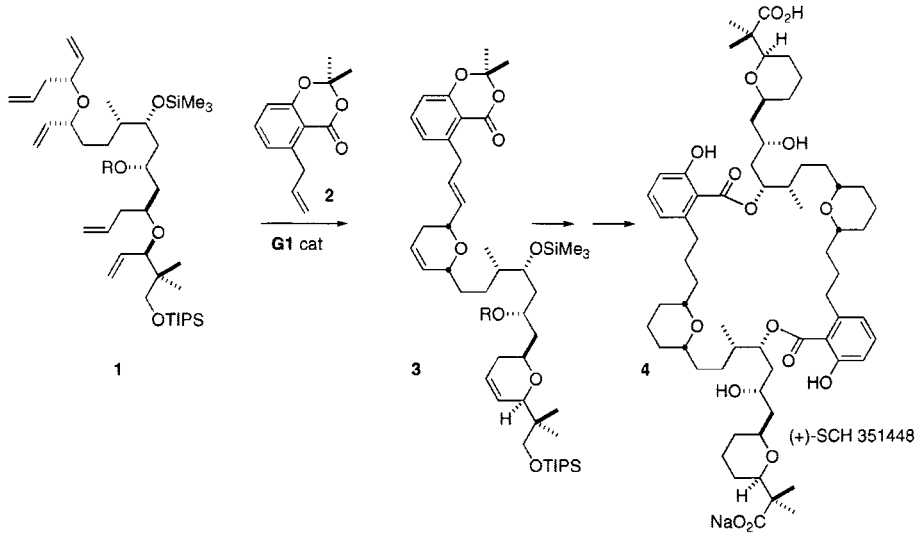
In the preparation of the antibiotic kendomycin **30** by Amos B. Smith III of the University of Pennsylvania (*J. Am. Chem. Soc.* **2006**, *128*, 5292), the metathesis substrate **27** was assembled using a triply convergent strategy, combining **24**, **25**, and **26**. The influence of the substituents on the conformation of the incipient medium ring were such that only one of the two diastereomers of the alcohol **27** would cyclize. The product **28** was the undesired *Z* alkene, fortunately exclusively, so it could be inverted by cis dihydroxylation followed by stereocontrolled epoxide deoxygenation.



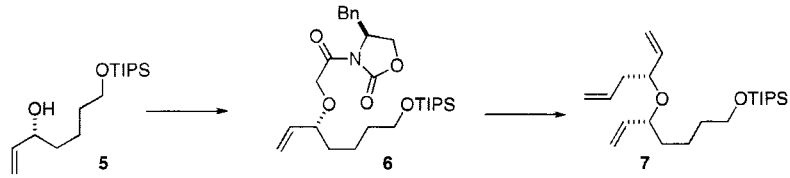
The Crimmins Synthesis of (+)-SCH 351448

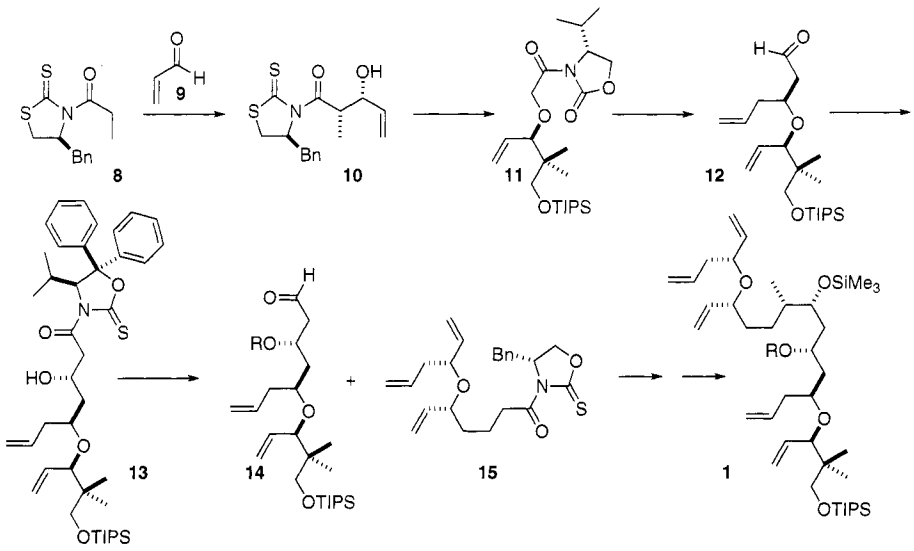
February 5, 2007

The symmetrical macrodiolide (+)-SCH 351448 **4** is the only known selective activator of transcription from the low density lipoprotein receptor. The highly convergent synthesis of **4** from **1** and **2** reported (*Organic Lett.* **2006**, *8*, 2887) by Michael T. Crimmins of the University of North Carolina illustrates the power of the chiral glycidyl anion approach for the preparation of α,α'-bis chiral ethers.

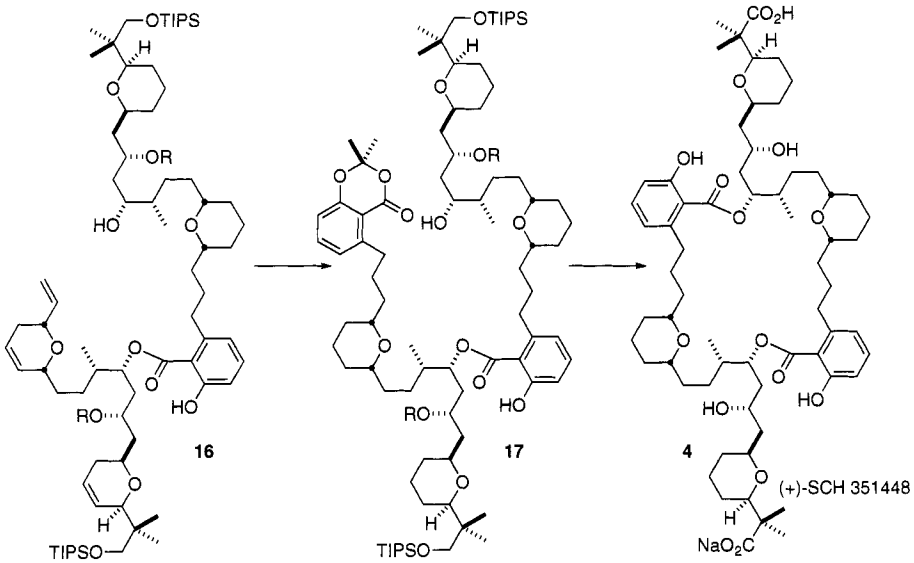


The upper half of **1** was assembled by Sharpless resolution of the alcohol **5**. Allylation of the enolate derived from **6** then delivered, after reduction and methylenation, the triene **7**. The lower half of **1** was prepared by condensation of the anion derived from **8** with acrolein **9**. Methylation of product **10** led to **11**, which was again allylated, to give, after homologation, the aldehyde **12**. Condensation with a chiral acetate equivalent gave **13**. The corresponding aldehyde **14** was then added to the enolate of **15**, derived from **7**, to arrive at **1**.





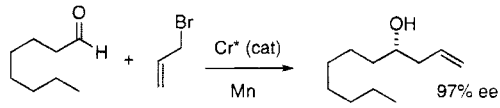
Although the tandem ring closing metathesis – homologation of **1** with **2** proceeded spectacularly well, to give **3** in 88% yield, simple dimerization of **3** did not deliver the desired **4**. As an alternative, **15** was cyclized with **G1**, then acylated with reduced **3** to give **16**. Intramolecular acylation of **17** then worked well, leading to **4**.



Enantioselective Construction of Alcohols and Amines

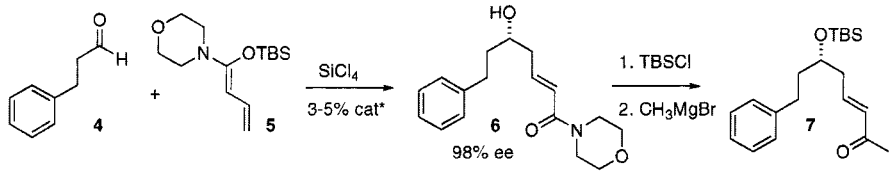
February 12, 2007

Enantioselective allylation is one of the most commonly used methods for constructing secondary alcohols with high enantiocontrol. Hisashi Yamamoto of the University of Chicago has introduced (*J. Am. Chem. Soc.* **2006**, *128*, 2554) an improved protocol, a Nozaki-Hiyama coupling with allyl bromide using a chiral Cr catalyst. Mn is the bulk reductant.



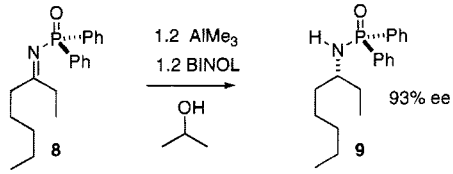
1 **2** **3**

To add a longer chain, Scott E. Denmark of the University of Illinois has developed (*J. Am. Chem. Soc.* **2006**, *128*, 1038) a strategy based on $SiCl_4$ activation of ketene silyl hemiaminals such as **5**, using 2-5% of a commercially-available organocatalyst. The product **6** condenses with CH_3MgBr to give the enone **7**. More highly substituted ketene silyl hemiaminals also add to aldehydes with high ee.



4 **5** **6** **7**

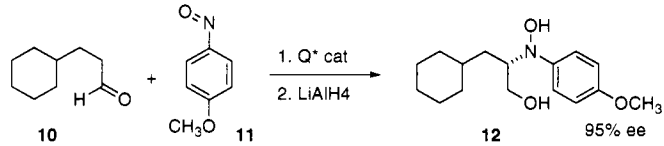
Enantiomerically-pure secondary amines have often been prepared from the corresponding alcohols. Karl A. Scheidt and SonBinh T. Nguyen of Northwestern have devised (*Organic* Lett. **2006**, *8*, 1229) an alternative, a BINOL-mediated imine reduction that proceeds with high ee. Remarkably, the reagent even differentiates between ethyl and pentyl.



8 **9**

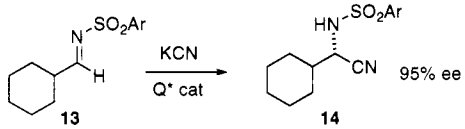
Keiji Maruoka of Kyoto University has found (*J. Am. Chem. Soc.* **2006**, *128*, 6046) that chiral quaternary ammonium salts effectively catalyze the enantioselective α-amination of an aldehyde.

$LiAlH_4$ reduction delivers the amino alcohol **12** in high ee. The advantage of the *p*-methoxyphenyl protected amine is that the protecting aryl group can be oxidatively removed.



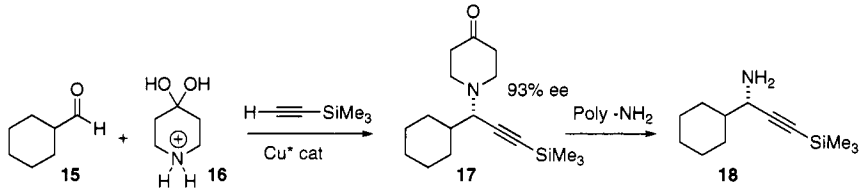
10 **11** **12**

Working in conjunction with Takashi Ooi, also of Kytoto University, Keiji Maruoka had earlier (*J. Am. Chem. Soc.* **2006**, *128*, 2548) shown that the same family of chiral quaternary ammonium catalysts can also be used to form primary amines by enantioselective cyanation of imines such as **13**.



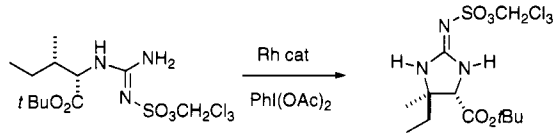
13 **14**

Most methods for the enantioselective construction of primary amines deliver the protected amine. Erick M. Carreira of ETH Zurich has devised (*Organic Lett.* **2006**, *8*, 2437) an approach to propargylic amines that leads to the *unprotected* primary amine **18**. The key to this approach is the use of a polymer-bound primary amine to efficiently transfer divinyl ketone from the initial adduct **17**.



15 **16** **17** **18**

The examples above are of amines substituted with secondary centers. The enantioselective construction of amines substituted with quaternary centers is even more challenging. Justin Du Bois of Stanford University has developed (*Organic Lett.* **2006**, *8*, 1073) a general solution to this problem, Rh-mediated insertion into a defined ternary center by an *in situ* generated Rh nitrene. This paper focuses on guanidines such as **19** and ureas. The Du Bois group had earlier reported Rh-mediated intramolecular C-H amination by carbamates and by sulfamates.

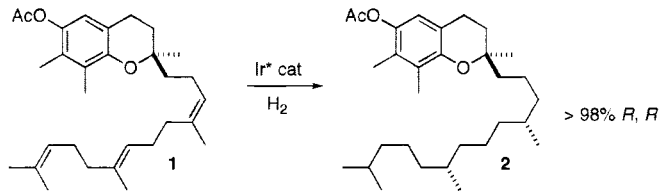


19 **20**

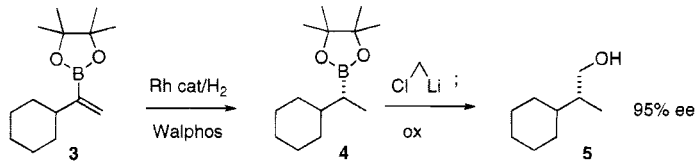
Enantioselective Construction of Alkylated Stereogenic Centers

February 19, 2007

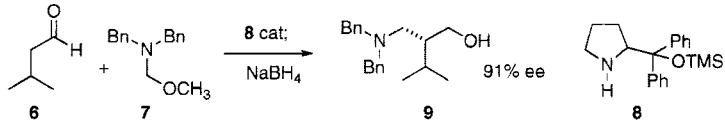
One of the simplest ways to establish an enantiomerically-pure ternary center is to selectively hydrogenate a trisubstituted alkene. While there are many examples of the enantioselective reduction of more highly substituted alkenes, Andreas Pfaltz of the University of Basel is the first to report (*Science* **2006**, *311*, 642) a family of catalysts that reduce simple alkyl-substituted alkenes with high ee. The efficacy of this approach was illustrated in spectacular fashion by the reduction of **1** to γ-tocopheryl acetate **2**. The authors demonstrated that the ring stereogenic center did not direct the hydrogenation.



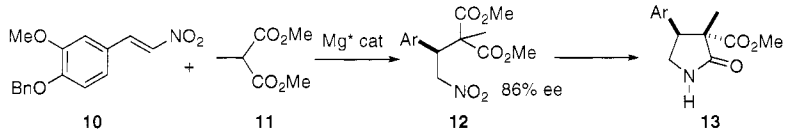
In a conceptually related approach, James P. Morken, now of Boston College, has found (*Organic Lett.* **2006**, *8*, 2413) that Rh/Walphos catalyses the reduction of vinyl boronates such as **3** to the saturated boronate **4** with high ee. The product **4** was homologated and oxidized to give **5** without loss of enantiomeric excess. Academic investigators should note that the Walphos ligands used in this study were donated by Solvias under the University Ligand Kit Program.



Samuel H. Gellman of the University of Wisconsin has shown (*J. Am. Chem. Soc.* **2006**, *128*, 6804) that the organocatalyst **8** mediates the Mannich condensation of **6** with **7** to give, after reduction, the amino alcohol **9** in high ee. The inclusion of LiCl is required to achieve the ee's reported. The homologation works well for a range of aliphatic aldehydes.

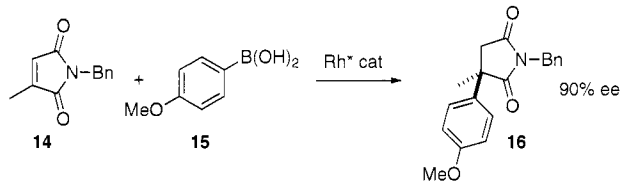


Enantioselective addition of malonate to nitro alkenes such as **10** has been extensively developed. Masahiro Terada of Tohuko University recently described (*J. Am. Chem. Soc.* **2006**, *128*, 1454) a new guanidine catalyst for this transformation. This article includes a thorough overview of the transition metal catalysts and of the organocatalysts that have been used for this transformation. Paul J. Nichols of Array BioPharma Process in Boulder, CO has found (*Organic Lett.* **2006**, *8*, 1495) that ee's are maintained with *alkyl* malonates such as **11**. The crystalline **12** was isolated in 87% yield in 87% ee on a 4 kg scale. Reduction and cyclization led to the lactam **13** in 4:1 dr, establishing a chiral quaternary center.



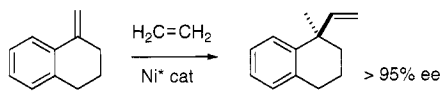
10 **11** **12** **13**

Tamio Hayashi of Kyoto University has developed (*J. Am. Chem. Soc.* **2006**, *128*, 5628) a general route to chiral quaternary centers, based on the Rh-catalyzed chiral conjugate of aryl boronic acids to imides such as **14**. Remarkably, bond formation occurs selectively at the *more* substituted position of **14**.



14 **15** **16**

Organometallic catalysis allows the development of reactions that are beyond the range of conventional C-C bond formation. One such is illustrated by the hydrovinylation of styrene derivatives, including **17**, with ethylene, developed (*J. Am. Chem. Soc.* **2006**, *128*, 5620) by T. V. RajanBabu of Ohio State University. This appears to be a general route to cyclic and acyclic chiral quaternary centers. An alternative protocol for the hydrovinylation of substituted styrenes was published earlier in the year (*J. Am. Chem. Soc.* **2006**, *128*, 2780) by Qi-Lin Zhou of Nankai University. The RajanBabu procedure appears to have advantages in efficacy and practicality, including both the commercial availability of the chiral ligand employed, and the ee's achieved.

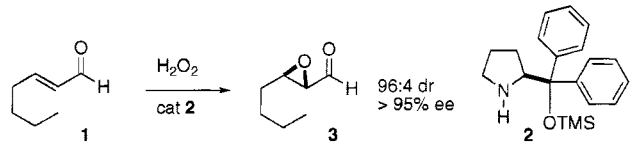


17 **18**

Enantioselective Construction of Arrays of Stereogenic Centers

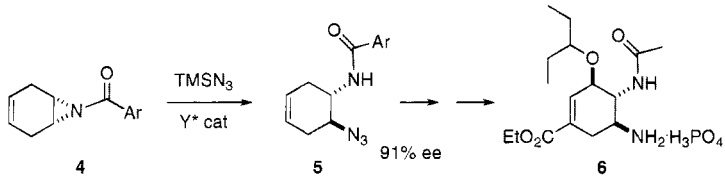
February 26, 2007

The controlled construction of extended arrays of stereogenic centers is one of the central challenges of organic synthesis. One of the earliest methods to become available, and still one of the most valuable, is Sharpless asymmetric epoxidation. Karl Anker Jørgensen of Aarhus University, Denmark, devised (*J. Am. Chem. Soc.* **2005**, *127*, 6964) (OHL 13 Feb 2006) an elegant alternative, the direct epoxidation of α,β-unsaturated aldehydes such as **1**. Armando Córdova of Stockholm University has now shown (*Tetrahedron Lett.* **2006**, *47*, 99) that the simple catalyst **2** works at least as well in this application as does the more expensive Jørgensen catalyst.



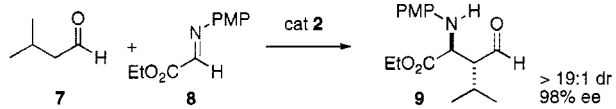
1 **3** **2**

Motomu Kanai and Masakatsu Shibasaki of the University of Tokyo have developed (*J. Am. Chem. Soc.* **2006**, *128*, 6312) an enantioselective lanthanide-catalyzed opening of prochiral aziridines such as **4** to the amido azide **5**. Acyclic aziridines work equally well. They carried the inexpensive **5** on the important antiviral agent Tamiflu **6**.



4 **5** **6**

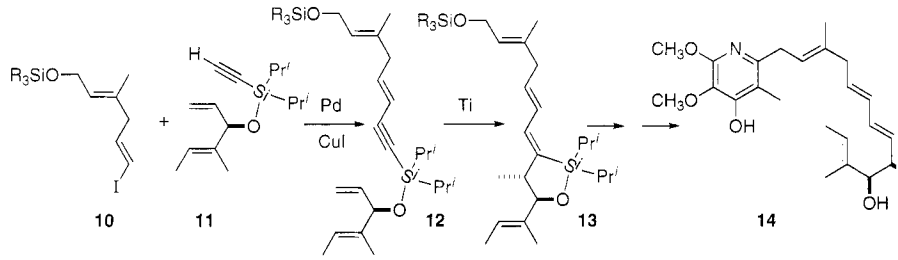
Construction of alkylated centers is also important. Both Professor Córdova (*Chem. Commun.* **2006**, 1760) and Carlos F. Barbas, III of Scripps / La Jolla (*J. Am. Chem. Soc.* **2006**, *128*, 1040) have found that organocatalysts can effect smooth anti-selective Mannich condensation of imines such as **8** with aldehydes such as **7**. Professor Córdova found that the simple catalyst **2** also worked well in this application.



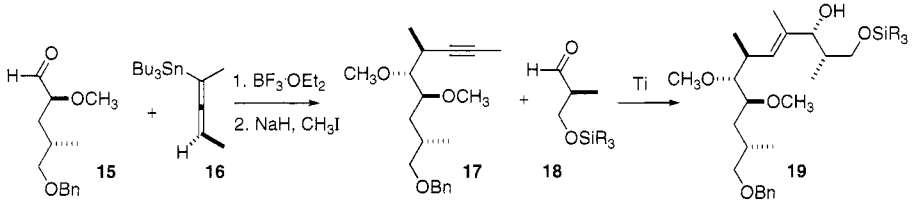
7 **8** **9**

Convergent synthesis strategies are inherently the most efficient. The key to a convergent approach is a protocol for coupling the two highly-functionalized intermediates so as to control relative and absolute configuration. Andrew J. Phillips of the University of Colorado has illustrated the coupling protocol they developed by a synthesis (*J. Am. Chem. Soc.* **2006**, *128*, 408) of the pyridine antibiotic 7-

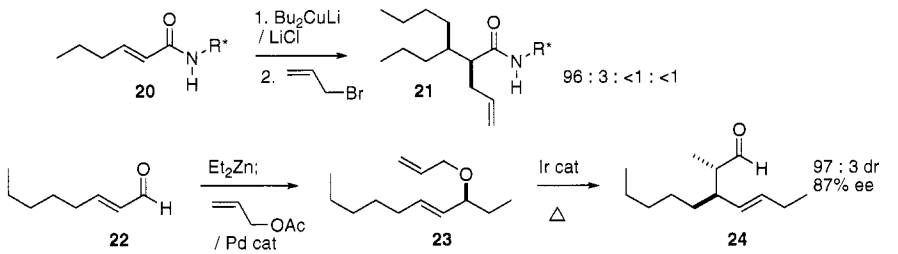
demethylpiericidin A, **14**. Sonagashira coupling of **10** and **11** gave **12**. Ti-mediated reductive coupling then proceeded with high regio- and diastereocontrol, to give **13**, which was carried on to **14**.



Another approach for the convergent coupling of two fragments is to use a third fragment as a linchpin. In particular, there is a need for chiral linchpins, that can set absolute configuration as bonds are formed. Glenn A. Micalizio of Yale University has reported (*Organic Lett.* **2006**, *8*, 2409) work in this direction, using the chiral linchpin **16**, based on the work of James A. Marshall. Condensation of enantiomerically-pure **16** with the aldehyde **15** gave, after protection, the alkyne **17**. Ti-mediated reductive coupling of **17** with **18** to give **19** proceeded with 5:1 regiocontrol and 3:1 diastereocontrol.



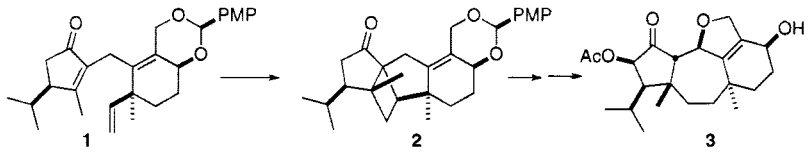
The establishment of arrays of alkylated stereogenic centers is particularly challenging. Dolores Badía of the Universidad del País Vasco in Bilbao has found (*Organic Lett.* **2006**, *8*, 2535) that the pseudoephedrine chiral auxiliary of Andrew G. Meyers works particularly well for conjugate addition followed by enolate trapping, delivering the product **21** in high de and ee. In a complementary approach, Scott G. Nelson of the University of Pittsburgh has shown (*J. Am. Chem. Soc.* **2006**, *128*, 4232) that the ether **23** is readily prepared in high ee by the addition, using the amino alcohol developed by William A. Nugent, of diethylzinc to the aldehyde **22**, followed by Pd-mediated coupling of the Zn alkoxide with allyl acetate. Ir-catalyzed bond shift then proceeded selectively on the terminal alkene to give, after Claisen rearrangement, the aldehyde **24**.



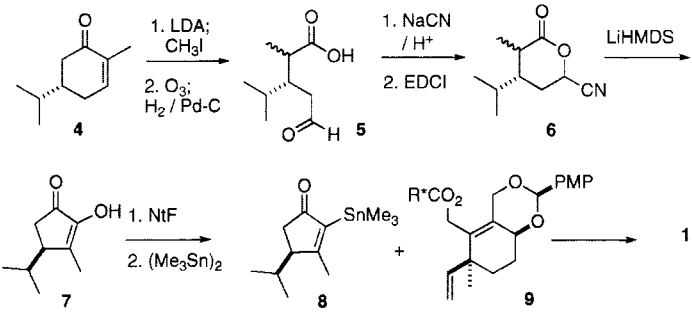
The Sorensen Synthesis of (-)-Guanacastepene E

March 5, 2007

The guanacastepenes, of which guanacastepene E **3** is representative, initially elicited excitement because of their activity against drug resistant bacterial strains. Although the systemic toxicity of the guanacastepenes has cooled that enthusiasm, the guanacastepenes remain as architectural challenges. In particular, a convergent synthesis plan requires the development of a strategy for constructing the central 7-membered ring with control of relative and absolute configuration, particularly of the two angularly methylated quaternary centers. Erik J. Sorensen of Princeton University (*J. Am. Chem. Soc.* **2006**, *128*, 7025) solved this problem by the intramolecular photochemical dimerization of **1**, which delivered **2** with high diastereocontrol. Directed ring fragmentation then led to **3**.

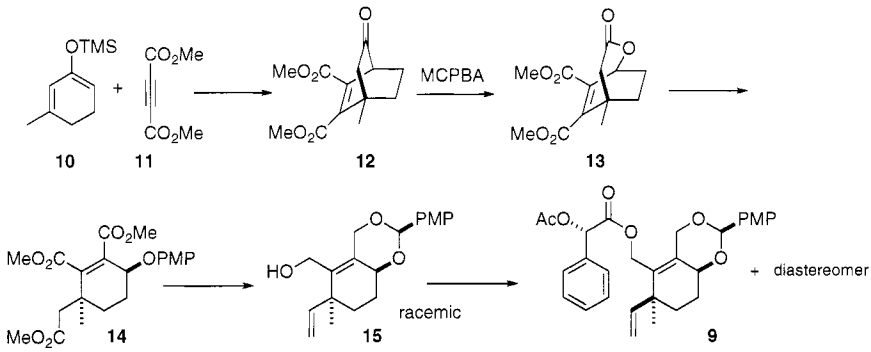


The enantiomercially-pure cyclopentenone of **1** was prepared from the chiral pool starting material dihydrocarvone **4**. Methylation followed by ozonolytic cleavage gave the aldehyde acid **5**, which was converted into the cyanohydrin lactone **6**. Intramolecular acylation of the derived nitrile anion proceeded smoothly, to give, after fragmentation, the 1,2-diketone **7**. Stannylation of the nonaflate led to **8**, which was coupled with enantiomerically-pure **9** to give **1**.

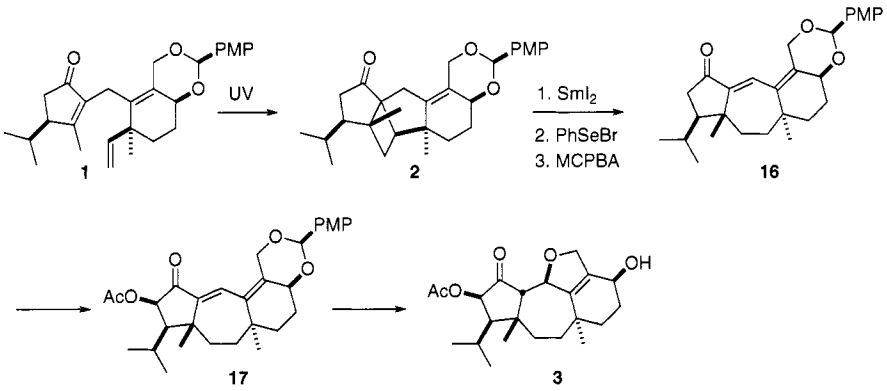


Construction of the cyclohexene **9** began with the Diels-Alder cycloaddition of the alkyne **11** to the diene **10**, followed by Baeyer-Villiger cleavage to give **13**. This established the quaternary center, and at the same time set the relative configuration of the secondary alcohol of **9**, and thus of **3**. The alcohol

15 so prepared was racemic. Screening of esters led to the mandelate acetate **9**, the diastereomers of which could be separated by open column chromatography. The mandelate ester also proved to be an effective leaving group for the Pd-mediated coupling of **8** and **9** to give **1**.



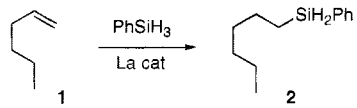
As anticipated, the intramolecular 2+2 photocyclization was directed by the adjacent isopropyl group, to give **2** with high diastereocontrol. While opening of carbonyl-activated fused cyclopropanes is amply precedented, far less was known about the opening of carbonyl-activated fused cyclobutanes. Happily, double one-electron reduction with excess SmI_2 opened the desired bond, to give, after selenation and oxidation, the dienenone **16**. The acetoxy group adjacent to the ketone was introduced by Rubottom oxidation. On deprotection of **17**, the released primary alcohol spontaneously added to the enone, to give (-)-guanacastepene E **3**.



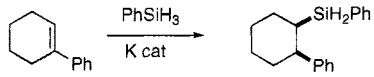
Selective Reactions of Alkenes

March 12, 2007

Peter W. Roesky of the Freie Universität Berlin has devised (*Chem. Commun.* **2006**, 874) a La catalyst that effects hydrosilylation of a terminal alkene **1** to **2**. Sjoerd Harder of the Universität Duisberg-Essen has developed (*Angew. Chem. Int. Ed.* **2006**, *45*, 2741) alternative Ca and K catalysts for hydrosilylation. He notes that **3** is converted cleanly into **4**, an outcome that is complementary to hydroboration. The product silanes are easily oxidized to the corresponding alcohols.

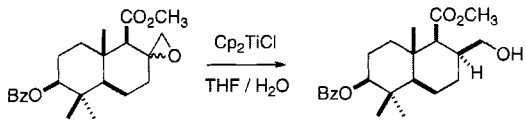


1 **2**



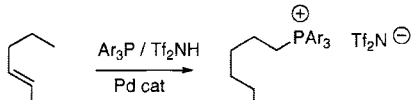
3 **4**

Another alternative to hydroboration is epoxidation followed by selective reduction of the more substituted end of the epoxide. Juan M. Cuerva and J. Enrique Oltra of Universidad de Granada and Diego J. Cárdenas of the Universidad Autónoma de Madrid have found (*Angew. Chem. Int. Ed.* **2006**, *45*, 5522) that the Cp_2Ti reagent prepared by stirring Cp_2TiCl_2 with Mn dust in THF works well, and that water is a particularly effective additive. Note that both diastereomers of the epoxide **5** are converted to the same axial (equatorial H delivery) product **6**.



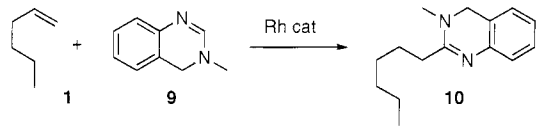
5 **6**

Phosphonium salts, used to prepare alkenes, are commonly prepared by displacement of the corresponding halide. Masahiko Yamaguchi of Tohoku University has shown (*J. Am. Chem. Soc.* **2006**, *128*, 50) that phosphonium salts can also be prepared from alkenes (**7** → **8**). Both internal alkenes and terminal alkenes are converted into the terminal phosphonium salt.

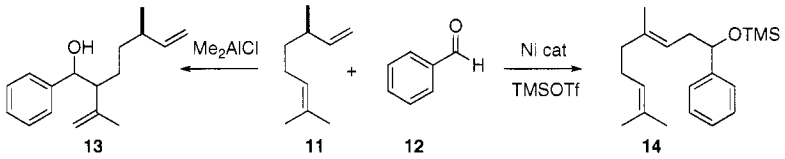


7 **8**

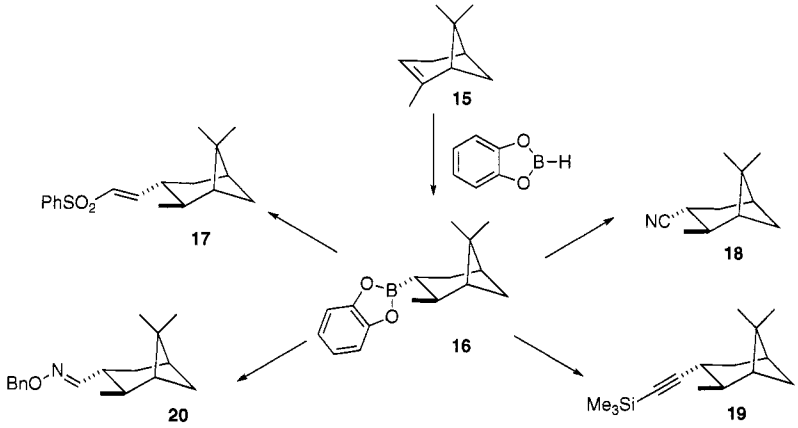
Alkenes can also be *homologated* catalytically. Jonathan A. Ellman and Robert G. Bergman of the University of California at Berkeley have found (*J. Org. Chem.* **2006**, *71*, 1969) that Rh catalyzes the addition of *NH*-3,4-dihydroquinazoline **9** to terminal alkenes such as **1**. The product **10** is valuable in itself, and it can also be hydrolyzed to the carboxylic acid, for a net one-carbon homologation.



Timothy F. Jamison of MIT has developed (*J. Am. Chem. Soc.* **2006**, *128*, 5362) Ni catalysts for the specific ene reaction of monosubstituted alkenes. Thus, with the Ni catalyst, the diene **11** reacts with benzaldehyde **12** to give **14**. With a conventional Lewis acid catalyst, **11** is converted to **13**. Both aromatic and *t*-alkyl aldehydes work well in the Ni reaction.



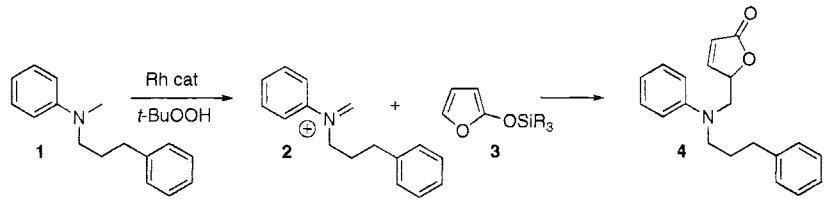
It has been known for some time that alkenes can be homologated via the corresponding organoboranes, but such procedures are in fact little used. Philippe Renaud of the Universität Bern has put forward (*Angew. Chem. Int. Ed.* **2006**, *45*, 5847) a simple protocol that makes it easier to carry out such alkene homologations. Dimethylacetamide-catalyzed hydroboration of **15** with catecholborane gave the initial borane **16**, which was not isolated, but was carried on directly to **17** – **20**.



Best Synthetic Methods: C-C Bond Formation

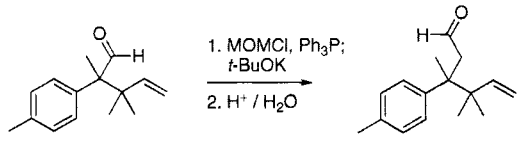
March 19, 2007

Most methods for C-C bond formation involve the coupling of two already-functionalized carbons. Michael P. Doyle of the University of Maryland has developed (*J. Am. Chem. Soc.* **2006**, *128*, 5648) an elegant method for directly homologating C-H bonds adjacent to amines. In the presence of aqueous *t*-butylhydroperoxide, amines such as **1** were oxidized to the corresponding iminium ions (e.g. **2**), which coupled with the siloxy furan **3** to give **4**.



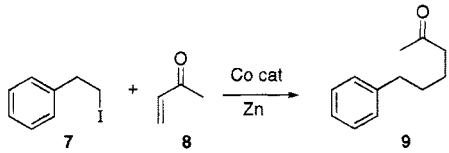
1 2 3 4

The one-carbon homologation of an aldehyde to the extended aldehyde has usually been carried out with $Ph_3P{=}CH{-}OCH_3$. Mukund G. Kulkarni of the University of Pune has described (*Tetrahedron Lett.* **2006**, *47*, 3027) an inexpensive alternative. Combination of commercial MOM-Cl with Ph_3P in THF followed by the addition of *t*-BuOK gave a reagent that converted **5** to the homologated enol ether, hydrolysis of which gave **6**.



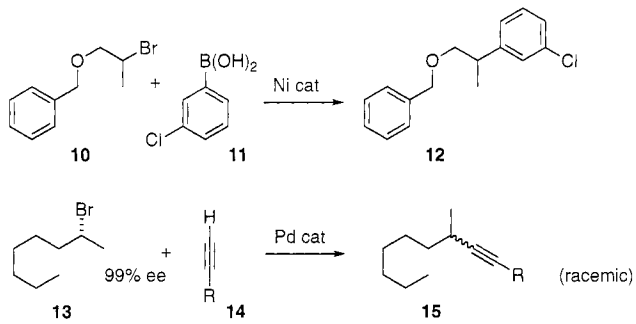
5 6

Conjugate addition of an alkyl halide to an enone usually entails initial formation of the Grignard reagent. Paul Knochel has championed the Cu-mediated conjugate addition of alkyl zinc halides. Chien-Hong Cheng of the National Tsing Hua University, Hsinchu, has found (*J. Org. Chem.* **2006**, *71*, 655) that the reagent prepared by in situ reduction of an alkyl halide with Zn powder in the presence of a Co catalyst adds in a conjugate fashion to unsaturated ketones, esters, nitriles and sulfones. Like the Knochel protocol, this procedure is compatible with an ester on the alkyl halide.

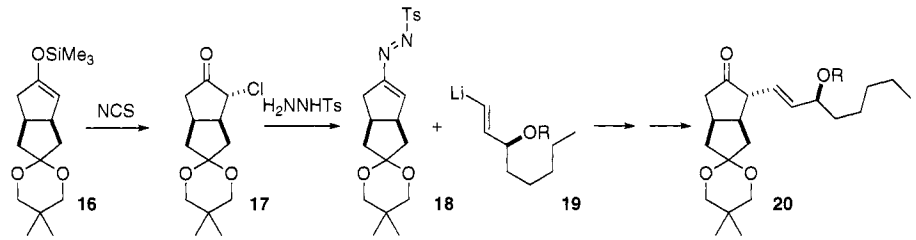


7 8 9

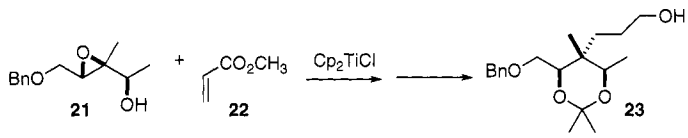
Coupling reactions that have long been known to work well for halides attached to sp^2-hybridized carbons are now being extended to halides attached to sp^3-hybridized carbons. Gregory C. Fu of MIT has worked out (*J. Am. Chem. Soc.* **2006**, *128*, 5360) conditions for Ni-catalyzed Suzuki coupling to secondary halides (**10** +**11** → **12**), and Frank Glorius of the Philipps-Universität, Marburg has extended (*Tetrahedron Lett.* **2006**, *47*, 2925) Sonogashira coupling to primary and secondary halides (**13** +**14** → **15**). This latter method is compatible with esters, epoxides and alkenes. Although bond formation is efficient, the enantiomeric excess of the leaving group is not maintained.



The α-alkenylation of a ketone is a delicate process, as the products (e.g. **20**) easily go on to (undesired) conjugation. In the course of a synthesis of carbacyclin (*J. Org. Chem.* **2006**, *71*, 4642), Hans-Joachim Gais of RWTH Aachen optimized a protocol based on halogenation of a defined silyl enol ether **16**.



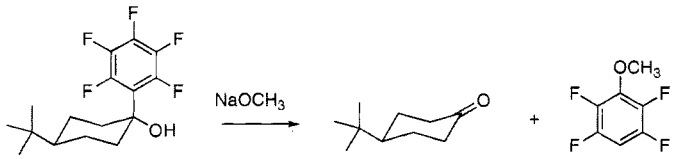
The enantioselective construction of quaternary alkylated centers is a continuing challenge. Tushar Kanti Chakraborty of the Indian Institute of Chemical Technology, Hyderabad has shown (*J. Org. Chem.* **2006**, *71*, 3321) that addition to methyl acrylate **22** of the radical from Ti(III) reduction of the Sharpless-derived epoxy alcohol **21** proceeds with high facial selectivity, leading to the acetonide **23**.



Functional Group Protection and Deprotection

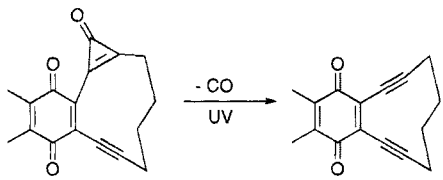
March 26, 2007

Charles M. Garner of Baylor University has described (*Tetrahedron Lett.* **2006**, *47*, 7405) the fragmentation of alcohols such as **1** to give the ketone **2**. The alcohols are prepared by the addition of pentafluorophenyl magnesium bromide to the ketone, so this is a method for ketone protection and deprotection.



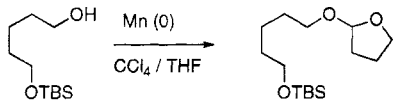
1 **2** **3**

Vladimir V. Popik, now at the University of Georgia, has observed (*J. Org. Chem.* **2006**, *71*, 7417) that UV light effficiently converts the cyclopropenone **3** into the diyne **4**. The cyclopropenone is prepared by the addition of dichlorocarbene to the alkyne, followed by hydrolysis. This approach allows the alkyne to be released under mild, controlled conditions.



4 **5**

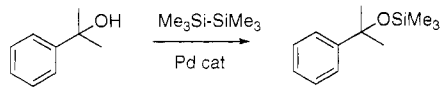
Tetrahydrofuranyl is a good protecting group for alcohols, but it has been little used. J. R. Falck of UT Southwestern Medical Center and Charles Mioskowski of the Université Louis Pasteur, Illkirch have devised (*Tetrahedron Lett.* **2006**, *47*, 5111) a convenient procedure for attaching this protecting group, using Mn powder. Primary, secondary, and tertiary alcohols are easily protected using this procedure.



6 **7**

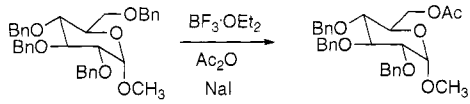
TMS ethers of hindered alcohols such as **8** are usually prepared using the unstable and corrosive TMS triflate. Eiji Shirakawa and Tamio Hayashi of Kyoto University have now found (*Chem. Commun.*

2006, 3927) that Pd catalyzes the transfer of *both* silyl groups from the easily handled $Me_3Si\text{-}SiMe_3$. Again, primary, secondary and tertiary alcohols work well.



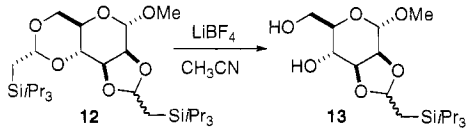
8 **9**

Benzyl ethers are usually removed by hydrogenation or by dissolving metal reduction. Yashwant D. Vankar of the Indian Institute of Technology, Kanpur has developed (*Tetrahedron Lett.* **2006**, *47*, 5207) an alternative, BF_3 ethereate in the presence of acetic anhydride and NaI. Silyl ethers are also converted to the corresponding acetates under the reaction conditions.



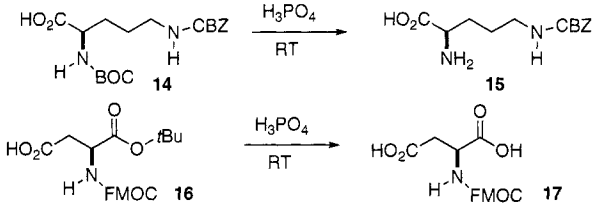
10 **11**

The selective protection of 1,2- and 1,3-diols is also important. To this end, Jun'ichi Uenishi of Kyoto Pharmaceutical University has prepared (*Tetrahedron Lett.* **2006**, *47*, 5553) the dimethyl acetal of triisopropylsilyl acetaldehyde. The derived cyclic acetals, such as **12**, are orthogonal to acetonides – each can be selectively removed in the presence of the other.



12 **13**

There have been several important developments in N protection. BOC groups are usually removed with trifluoroacetic acid. Bryan Li of Pfizer in Groton, CT has now shown (*J. Org. Chem.* **2006**, *71*, 9045) that commercial, environmentally benign 85% phosphoric acid at room temperature works equally well. *t*-Butyl esters are also cleaved. Mona Hosseini-Sarvari and Hashem Sharghi of Shiraz University, Iran have found (*J. Org. Chem.* **2006**, *71*, 6652) that ZnO with formic acid serves to formylate amines. Toshio Nishikawa and Minoru Isobe of Nagoya University have developed a mild protocol (*Organic Lett.* **2006**, *8*, 3263) for converting trichloroamides (from trichloroacetimidate rearrangement) into readily deprotectable carbamates. Floris P. J. T. Rutjes of Radboud University, Nijmegen has found (*Tetrahedron Lett.* **2006**, *47*, 8109) that the inexpensive trichloroisocyanuric acid serves to efficiently dearylate *p*-methoxyphenyl amines.

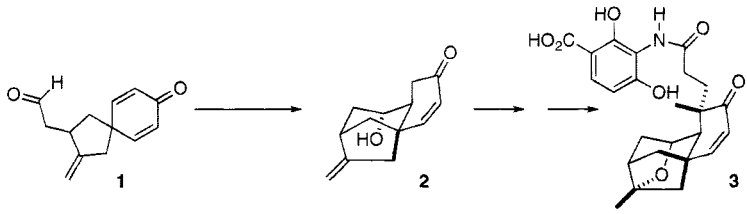


14 **15** **16** **17**

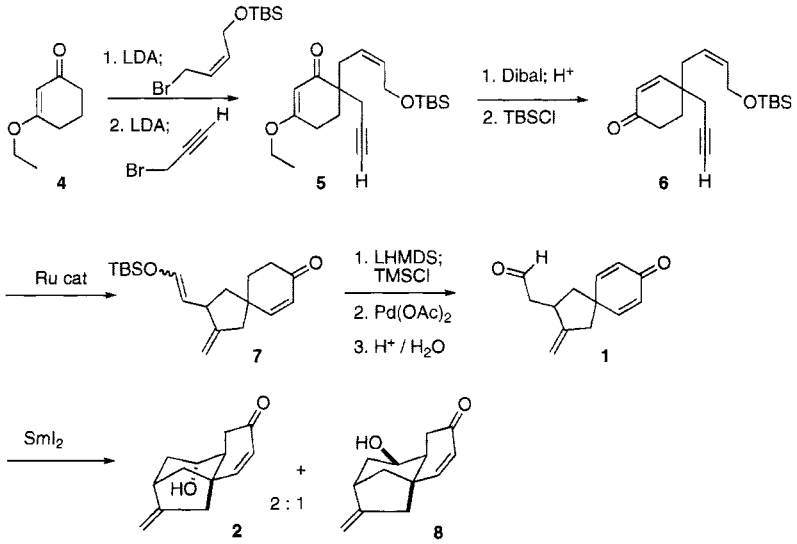
The Nicolaou Synthesis of Platensimycin

April 2, 2007

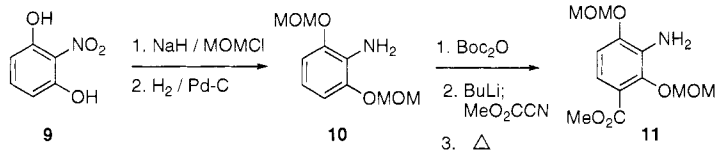
The report last year by scientists at Merck of an antibiotic, platensimycin **3**, with a novel mechanism of action has led to much effort toward the total synthesis of this degraded diterpene. K. C. Nicolaou of Scripps, La Jolla has now (*Angew. Chem. Int. Ed.* **2006**, *45*, 7086) reported the first preparation of **3**. The key step in the synthesis is the elegantly concise cyclization of **1** to **2**.



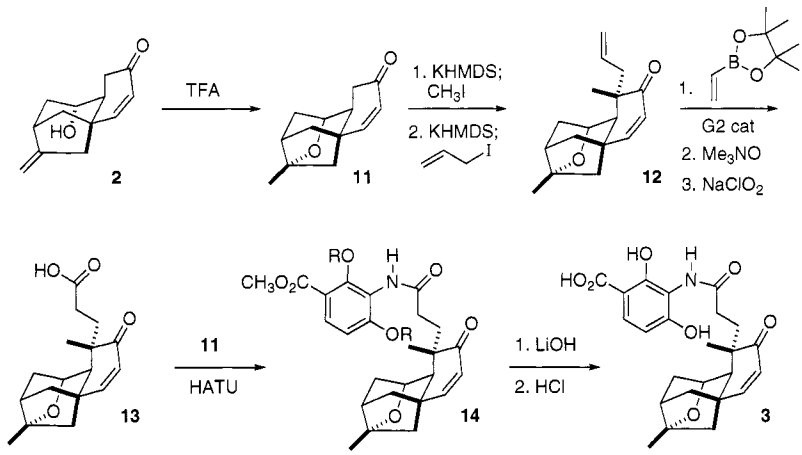
The preparation of **1** started with iterative Stork-Danheiser alkylation of **4** to give **5**. Reduction followed by hydrolysis unraveled the enol ether to give the enone, which was re-silylated to give **6**. Ru-catalyzed intramolecular ene cyclization of **6** gave the enol ether **7**, which was selectively oxidized to **1**. Reductive cyclization of **1** gave **2** as a 2:1 mixture with its diastereomer **8**.



The aniline of platensimycin was prepared from 2-nitroresorcinol **9**. MOM ether formation followed by reduction gave **10**. Metalation of the protected amine followed by acylation with Mander's reagent and thermolysis gave **11**.



The cyclization of **2** to **11** proceeded smoothly, as did the alkylation of **11** to **12**. The diastereoselectivity of the alkylation followed from the conformational bias of the ring system. The conversion of the terminal alkene to the acid **13** initially was troublesome, but a solution was found in metathesis with vinyl boronate followed by oxidation. Coupling with **11** followed by deprotection then gave **3**.



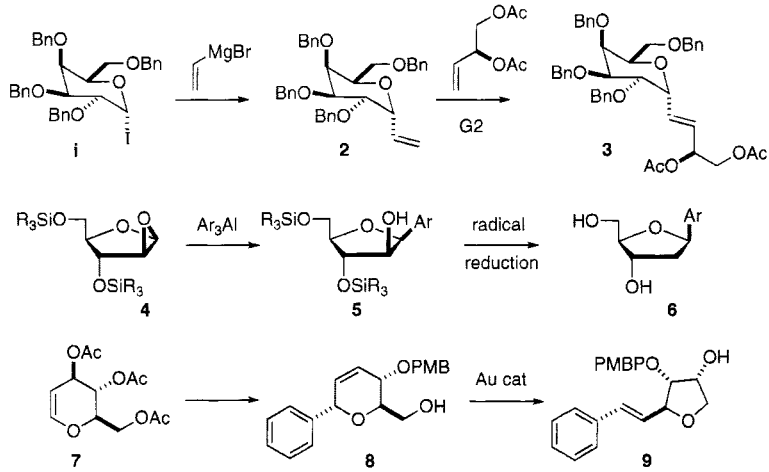
The absolute configuration of the tricyclic core of **3** was set in the intramolecular ene cyclization of **6** to **7**. There is the possibility that with an enantiomerically-pure catalyst, the product **7** and so **3** could be prepared in high enantiomeric excess.

Total syntheses of platensimycin **3** are underway in several other research groups. The diversity of the approaches being explored will enrich organic synthesis.

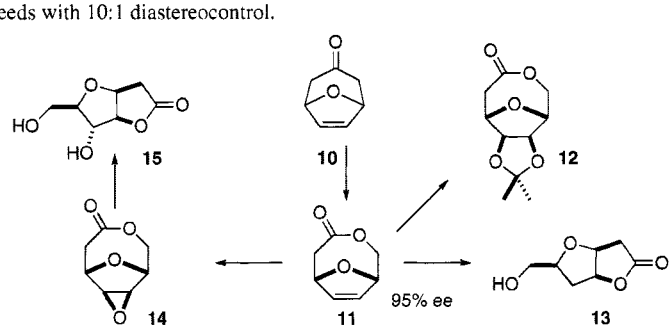
Stereocontrolled C-O Ring Construction

April 9, 2007

Sugars are still useful chiral pool starting materials for the preparation of cyclic ethers. Jacquelyn Gervay-Hague of the University of California, Davis, has extended (*Organic Lett.* **2006**, *8*, 5765) her β-galactosyl iodide work, showing that **1** couples with vinyl magnesium bromide to give **2** with high diastereocontrol. The alkene **2** is easily homologated to the C-glycoside **3**. Oliver Seitz of the Humboldt-Universität, Berlin, has developed (*Organic Lett.* **2006**, *8*, 4319) a simple three-step

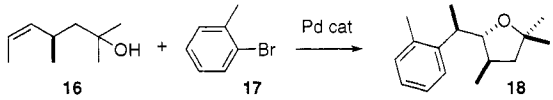


preparation of the epoxide **4** from thymidine. Opening of **4** with Ar_3Al delivered the β-aryl-C-nucleoside **5** with high diastereocontrol. Free radical deoxygenation then gave **6**. John A. Porco, Jr. and Scott E. Schaus of Boston University have found (*Organic Lett.* **2006**, *8*, 5065) a route from the inexpensive glucal **7** to the enantiomerically-pure tetrahydrofuran **9**. The Au-catalyzed rearrangement of **8** to **9** proceeds with 10:1 diastereocontrol.



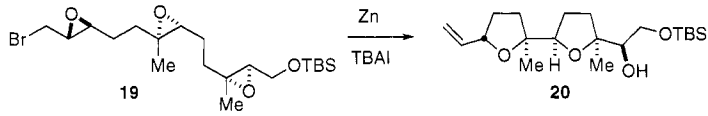
It is also possible to expand the chiral pool with enantioselective catalysis. Marko D. Mihovilovic of the Vienna University of Technology has been working (*Chem. Comm.* **2006**, 3214) toward making biocatalysis more practical by employing enzymes, in this case cyclopentanone monooxygenase, over-expressed in whole cell systems. Using this approach, it is not necessary to add expensive co-factors. In a bioreactor, he was able to carry out the enantioselective Baeyer-Villiger oxidation of **10** on a multi-gram scale. The lactone **11** was readily carried on to **12** – **15**.

John P. Wolfe of the University of Michigan has been exploring (*J. Am. Chem. Soc.* **2006**, *128*, 2893; *Tetrahedron Lett.* **2006**, *47*, 2793) Pd-catalyzed diastereoselective tetrahydrofuran formation. Remarkably, the single stereogenic center of **16** directed the cyclization, leading to predominant (86:9:5) formation of **18**.



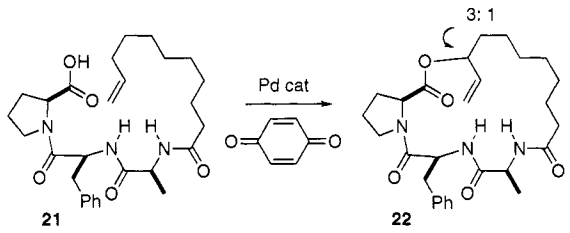
16 **17** **18**

The bis-tetrahydrofuran **20** is the core of the antibiotic ionomycin. James A. Marshall of the University of Virginia has shown (*Organic Lett.* **2006**, *8*, 4375) that the enantiomerically-pure tris epoxide **19**, readily prepared from farnesol, underwent smoooth reductive cyclization to **20**.



19 **20**

Macrolactone ("macrolide") natural products are widely distributed. Both C-O and C-C bond forming strategies have been used for the preparation of macrolides. In either case, two functionalized carbon atoms were being connected. M. Christina White of the University of Illinois has now reported (*J. Am. Chem. Soc.* **2006**, *128*, 9032) what appears to be a general route to macrolides using C-H activation, as represented by the conversion of **21** to **22**. It is impressive that a particular C-H bond can be specifically replaced with a C-O bond. It is even more impressive that the reaction proceeded with substantial diastereocontrol.

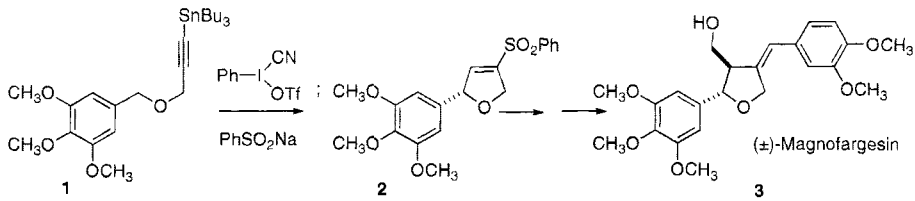


21 **22**

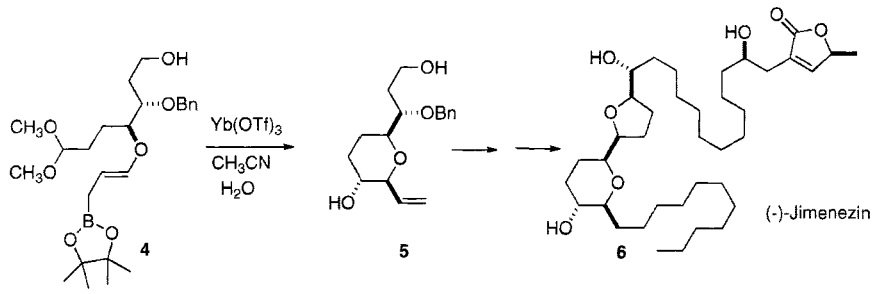
Stereocontrolled Natural Product Synthesis: Cyclic Ethers and Macrolides

April 16, 2007

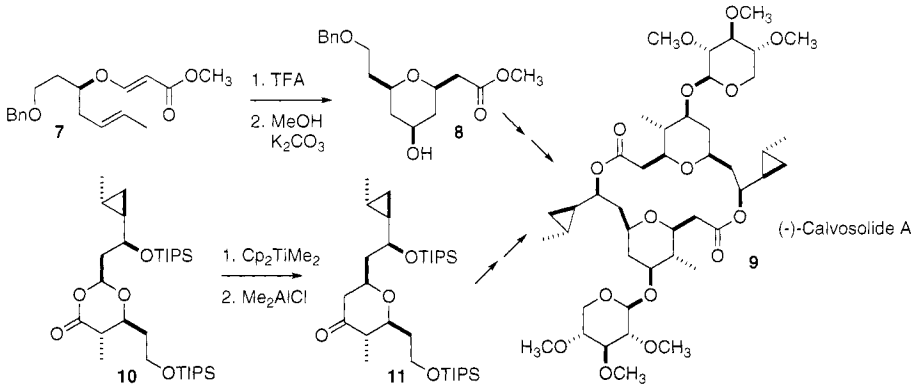
Duncan J. Wardrop of the University of Illinois, Chicago, established (*Organic Lett.* **2006**, *8*, 3659) the five-membered ether ring of (±)-magnofargesin **3** by the addition of benzenesulfinate to the activated alkyne derived from **1**. The alkylidene carbene so generated then inserted into the C-H bond adjacent to the ether oxygen, to give **2**.



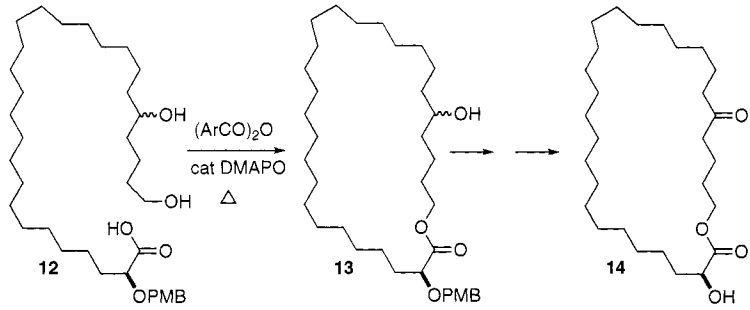
Six-membered ring cyclic ethers, in particular 2,6-dialkyl tetrahydropyrans, are ubiquitous in natural products. Several of the Annonacae acetogenins show remarkable antitumor activity. (-)-Jimenezin **6** is unusual in that it contains a six-membered ring. In the course of a synthesis of **6**, Reinhard W. Hoffmann and Ulrich Koert of the Philipps-Universität Marburg (*Organic Lett.* **2006**, *8*, 3829) assembled that ring by cyclization of the allyl borinate **4** to **5** with high diastereocontrol.



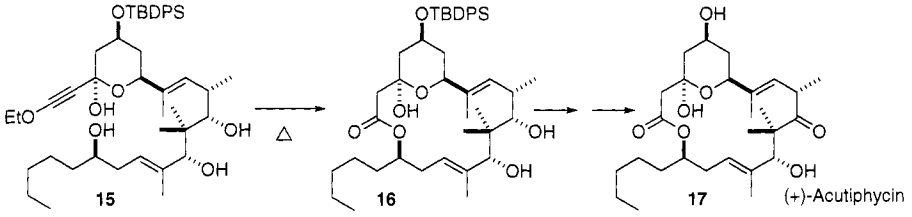
Both Christine Willis of the University of Bristol (*Organic Lett.* **2006**, *8*, 3319) and Amos B. Smith III of the University of Pennsylvania (*Organic Lett.* **2006**, *8*, 3315) have reported syntheses of the dimeric (-)-calvosolide A **9**. In the Willis synthesis, the 2,6-dialkyl tetrahydropyran was prepared by the acid-catalyzed ("Prins") cyclization of **7** to **8**. In the Smith synthesis, the 2,6-dialkyl tetrahydropyran was prepared by the Petasis-Ferrier rearrangement of **10** to **11**.



In each case, completion of the synthesis of (-)-calvosolide A **9** involved macrolide construction by the Yamaguchi method, formation of the mixed anhydride with 2.4.6-trichlorobenzoyl chloride. Extending macrolactonization to larger rings, to prepare **14**, a component of the defensive secretion of a soldier termite, Isamu Shiina of the Tokyo University of Science found (*Organic Lett.* **2006**, *8*, 4955) that a modified protocol using the anhydride of 2-methyl-6-nitrobenzoic acid was more effective.



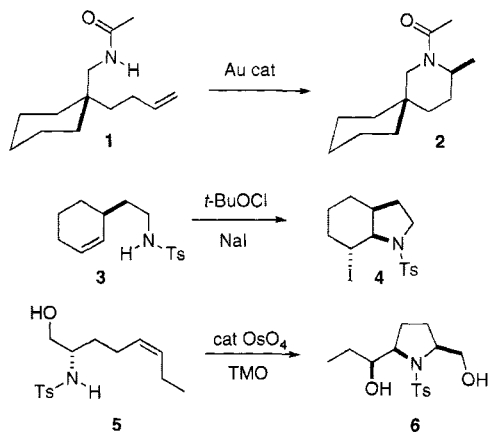
Timothy F. Jamison of MIT has put forward (*J. Am. Chem. Soc.* **2006**, *128*, 15106) a complementary method for macrolide formation, pyrolysis of the ethoxy acetylene **15**, to prepare (+)-acutiphycin **17**. This method for ketene generation was originally developed by Raymond L. Funk.



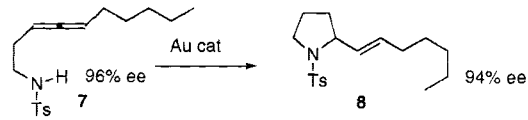
Stereocontrolled C-N Ring Construction

April 23, 2007

There have been significant advances in the intramolecular addition of amines to alkenes. Ross A. Widenhoefer of Duke University has found (*Chem. Commun.* **2006**, 4143) conditions for the long-sought intramolecular hydroamination of a carboxamide **1** to the cyclic amine **2**. Satoshi Minakata and Mitsuo Komatsu of Osaka University have shown (*Organic Lett.* **2006**, *8*, 3335) that cyclization of alkenyl sulfonamides with *in situ* generated *t*-butylhypoiodite proceeds with high diastereocontrol. Timothy J. Donohoe of the University of Oxford has coupled (*Angew. Chem. Int. Ed.* **2006**, *45*, 8025) osmylation with intramolecular amination, allowing the cyclization of **5** to **6** with total diasterocontrol.

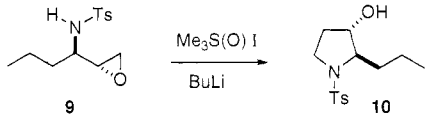


Allenes such as **7** are readily prepared in high enantiomeric excess. Yoshinori Yamamoto of Tohoku University has established (*Tetrahedron Lett.* **2006**, *47*, 4749) that the Au-catalyzed cyclization of **7** leads to **8** with nearly perfect enantiocontrol.



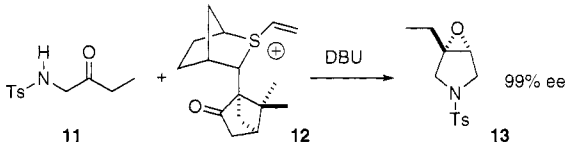
Sharpless aziridination followed by aza-Payne rearrangement allows easy access to epoxy sulfonamides such as **9**. David Hodgson of the University of Oxford has found (*Chem. Commun.* **2006**, 3226) that on exposure to dimethylsulfoxonium methylide, **9** is converted to the hydroxy pyrrolidine **10**.

The reaction is presumably proceeding by epoxide opening followed by displacement of the sulfoxonium leaving group by the sulfonamide anion.



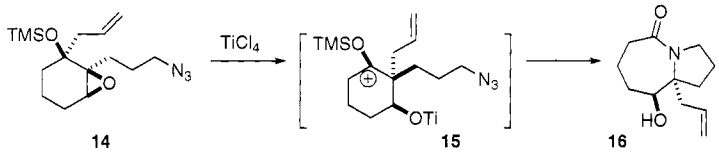
9 10

In a conceptually related development, Varinder K. Aggarwal of the University of Bristol has designed (*Angew. Chem. Int. Ed.* **2006**, *45*, 7066) the vinyl sulfonium salt **12**, condensation of which with an amino ketone **11** proceeded to give the epoxy pyrollidine **13** in high enantiomeric excess.



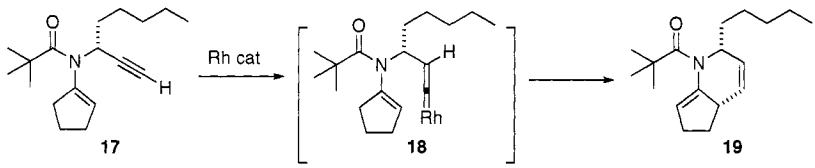
11 12 13

Azides can be seen as chemical chameleons, serving sequentially both as nucleophilic and then as electrophilic centers. This is nicely illustrated by the observation (*Organic Lett.* **2006**, *8*, 5271) by Yong Qiang Tu of Lanzhou University that the cation **15** from pinacol rearrangement of **14** is trapped by the pendant azide to give, after loss of N_2, the lactam **16**.



14 15 16

Chulbom Lee of Princeton University has applied (*J. Am.Chem. Soc.* **2006**, *128*, 6336) modern understanding of mechanistic organometallic chemisty to the preparation of cyclic amines. Terminal alkynes such as **17** are rearranged by Ru catalysts to the corresponding vinylidene complex **18**. This is electophilic enough to react with the tethered enamine, leading with high diasterecontrol to the amine **19**.

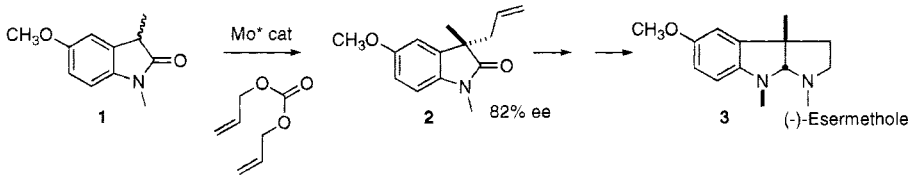


17 18 19

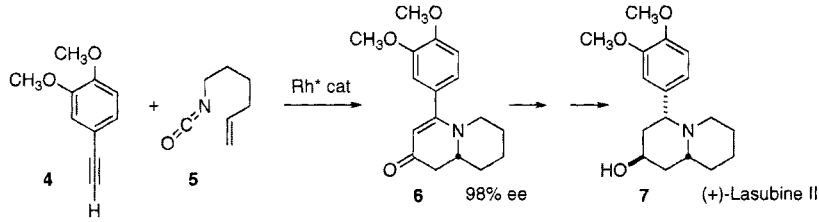
Stereocontrolled Alkaloid Total Synthesis

April 30, 2007

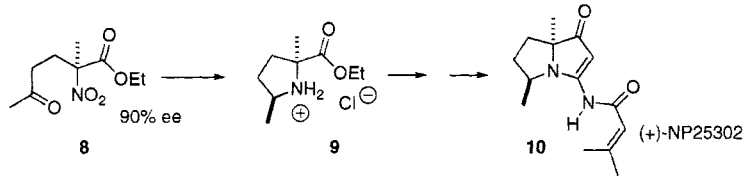
Barry M. Trost of Stanford University has developed powerful methods for catalytic enantioselective allylation. In a recent application (*J. Am. Chem. Soc.* **2006**, *128*, 4590) he has applied this approach toward the preparation of the physostigmine alkaloids. Allylation of **1** proceeded in high ee to give **2**, which was carried on to (-)-esermethole **3**. Other oxindoles were allylated in up to 95% ee.



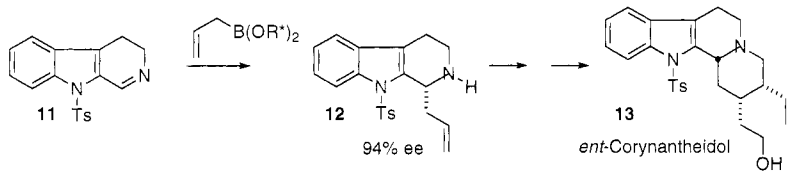
Tomislav Rovis of Colorado State University has reported (*J. Am. Chem. Soc.* **2006**, *128*, 12370) a particularly powerful method for the construction of fused amines such as **6**, by the enantioselective condensation of alkynes with unsaturated isocyanates such as **5**. The vinylogous amide **6** was readily carried on to (+)-lasubine II **7**.



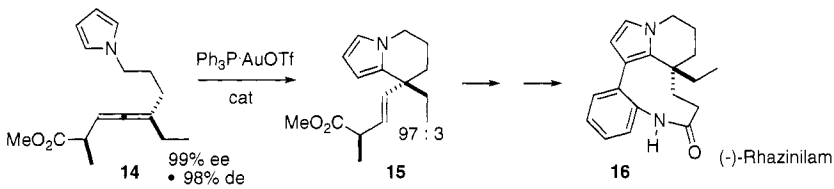
Using (*J. Org. Chem.* **2006**, *71*, 8579) a protocol developed by Li Deng of Brandeis University, Barry B. Snider, also of Brandeis, added ethyl 2-nitropropionate to methyl vinyl ketone to give **8** with high ee. Reductive cyclization proceeded with 95:5 diastereocontrol, leading to **9** and thus to natural (+)-NP25302 **10**. This study established the absolute configuration of **10**.



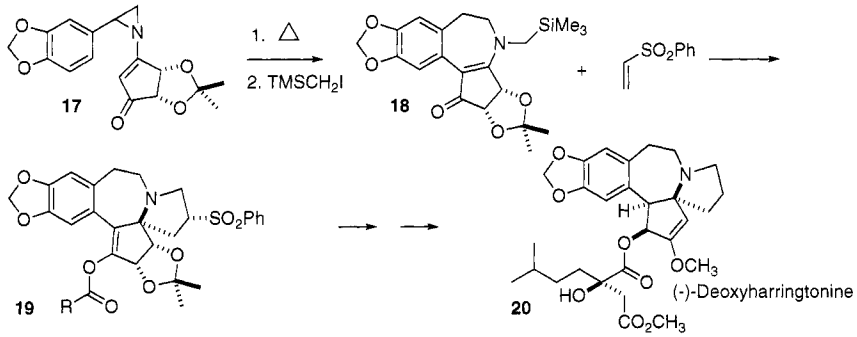
Cyclic imines such as **11** are easily prepared. J. Michael Chong of the University of Waterloo has now found (*J. Am. Chem. Soc.* **2006**, *128*, 9646) that BINOL-derived allylboronates add to such imines to give the cyclic amines such as **12** in high ee. The conversion of **12** to *ent*-corynantheidol **13** involved a very interesting diastereoselective Michael addition.



Starting with the enantiomerically-pure allene **14**, prepared by the methods he had previously developed, Scott G. Nelson of the University of Pittsburgh established (*J. Am. Chem. Soc.* **2006**, *128*, 10352) that an Au catalyst effected cyclization onto the electron-rich pyrrole with high diastereoselectivity. This set the stage for the enantioselective synthesis of (-)-rhazinilam **16**. The pendant methyl of **15** served as an internal reporter, making it easy to follow the stereochemical course of the cyclization.



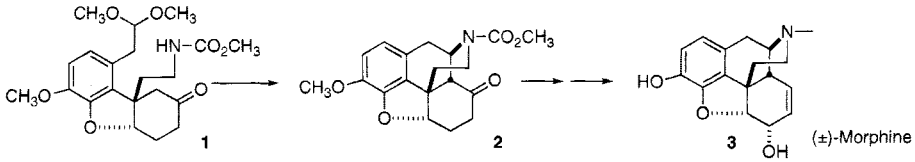
David Y. Gin, now at the Memorial Sloan-Kettering Cancer Center in New York, has been exploring (*J. Am. Chem. Soc.* **2006**, *128*, 10370) ring-strain releasing rearrangment of N-vinyl 2-aryl aziridines such as **17**. Thermal rearrangment followed by alkylation with Me_3SiCH_2I gave **18**. Sequential O-acylation and exposure to fluoride ion gave a 1,3-dipole, that added to phenyl vinyl sulfone with high diastereocontrol to give **19**. This was carrried on to the potent anti-leukemia alkaloid (-)-deoxyharringtonine **20**.



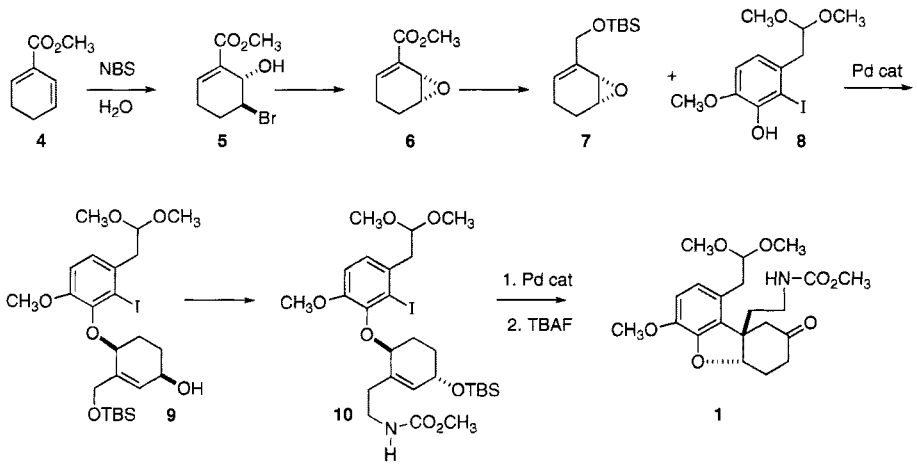
The Fukuyama Synthesis of Morphine

May 7, 2007

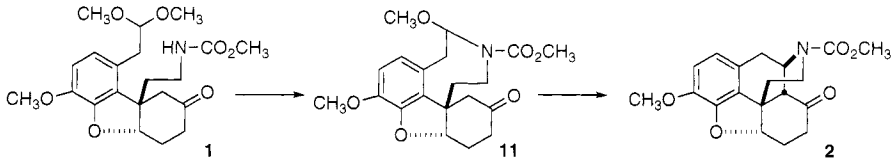
Tohru Fukuyama of the University of Tokyo has recently reported (*Organic Lett.* **2006**, *8*, 5311) an elegantly conceived total synthesis of (±)-morphine **3**, based on the recognition and reduction to practice of the highly diastereoselective intramolecular Mannich cyclization of **1** to **2**.



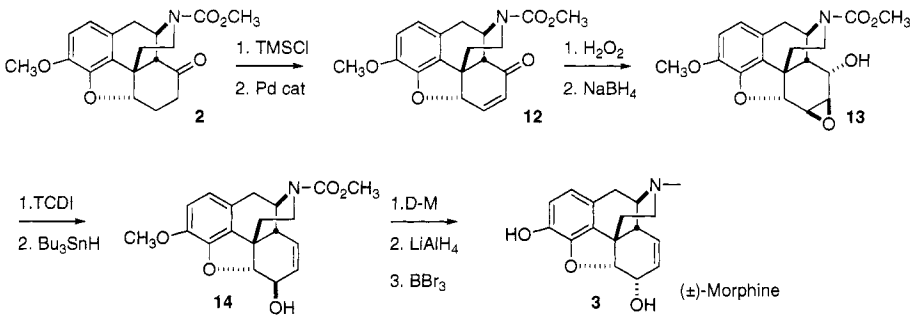
The stereocontrolled preparation of **1**, a considerable challenge, started with the epoxidation of the diene **4** to give **6**. Although racemic **6** was used for this synthesis of morphine, Professor Fukuyama had previously demonstrated that high ee **6** could be prepared by lipase resolution of the intermediate bromohydrin **5**. Coupling of **6** with **7** led to **8**, by net syn S_N2' displacement. The secondary alcohol was then inverted, to put the α-H syn to what would be the adjacent C-Pd bond, to undergo β-hydride elimination in the course of the intramolecular Heck cyclization of **10** to **2**.



The intramolecular Mannich cyclization of **1** to **2** takes advantage of the native functionality of morphine **3**. The intermediate in the cyclization is apparently the expected **11**, which could be isolated. Note that under the equilibrating conditions of the cyclization, the desired cis ring fused **2** was the only diastereomer observed.



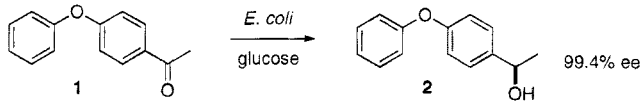
The Ito-Saegusa procedure was used to oxidize the ketone **2** to the enone **12**. It was then necessary to convert the enone into the allylically-inverted alcohol **14**. With the morphine skeleton assembled, the aromatic ring blocks the bottom face of the enone, so both hydrogen peroxide and hydride attacked from the top face, to give **13**. Conversion of the derived thiocarbamate to the free radical then led to epoxide cleavage, delivering the desired **14**. The last three steps to complete the total synthesis of (±)-morphine **3**, oxidation, addition of hydride to the open top face of the ketone with concomitant reduction of the urethane protecting group to the N-methyl, and O-demethylation, then followed literature procedures.



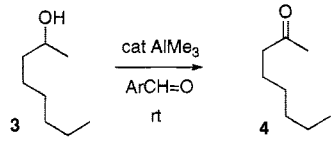
Oxidation and Reduction in Organic Synthesis

May 14, 2007

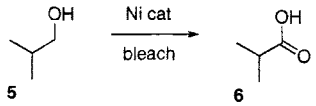
The enantioselective reduction of ketones by alcohol dehydrogenases is a valuable synthetic procedure, but the required co-factors are expensive. If the reduction can be carried out with intact cells, the expense of added co-factors can be avoided. Harald Gröger and Oliver May of Degussa AG, Hanau, Germany have demonstrated (*Angew. Chem. Int. Ed.* **2006**, *45*, 5677) reductions on a substantial scale, using an *E. coli* strain into which both an alcohol dehydrogenase and a glucose dehydrogenase had been incorporated. The reduction of ketone **1**, for instance, used 40 mmol of the ketone in a total buffer plus glucose (1.5 eq) volume of 40 mL. This delivered **2** in 88% yield and 99.4% ee. This procedure should be easily scaled, particularly if the investigators are willing to share their engineered microorganisms.



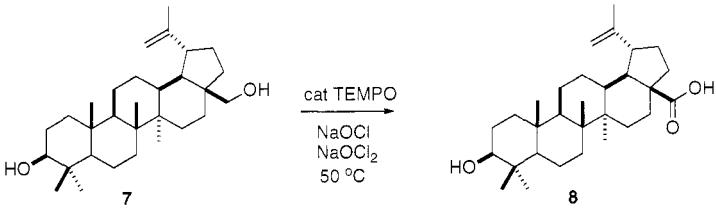
The Openauer oxidation has the advantage of using the inexpensive and environmentally-innocuous aluminum. The disadvantage, until recently, has been that the Al was used in stoichiometric quantities. SonBinh T. Nguyen of Northwestern University has now found (*J. Am. Chem. Soc.* **2006**, *128*, 12596) that 10 mol% of $AlMe_3$ in toluene serves well to catalyze this reduction. They found it convenient to use *m*-nitrobenzaldehyde as the hydride acceptor. Primary alcohols were oxidized to the corresponding aldehdyes, and secondary alcohols such as **3** to the ketones.



Commercial bleach (5% aqueous NaOCl) is an inexpensive oxidant. Stephen A. Miller of Texas A&M University has shown (*J. Org. Chem.* **2006**, *71*, 9291) that 2.5 mol % of $NiCl_2$ or $Ni(OAc)_2$ in the presence of bleach oxidizes primary alcohols such as **5** efficiently to the corresponding carboxylic acid. Secondary alcohols are oxidized to ketones, and 1,2-diols are cleaved to the bis carboxylic acid. The Ni can presumably be recovered and recycled.

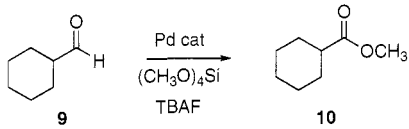


Selective oxidation is not limited to simple systems. René Csuk of Martin-Luther-Universität Halle-Wittenberg has developed (*Tetrahedron Lett.* **2006**, *47*, 8769) conditions for the selective oxidation of betulin **7** to betulinic acid **8**. If the oxidation is carried out at 35 °C, the aldehyde corresponding to **8** can be isolated in good yield.



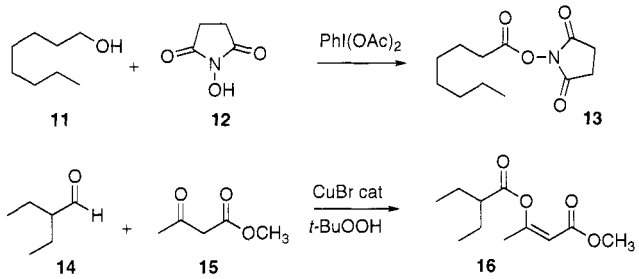
7 **8**

The direct oxidative esterification of aldehdes is also a useful synthetic conversion. This has usually been effected with stoichiometric Cr reagents. Christian Wolf of Georgetown University has now shown (*J. Am. Chem. Soc.* **2006**, *128*, 13052) that a Pd catalyst in the presence of $(CH_3O)_4Si$ effects this transformation. Other tetra-alkyl orthosilicates work as well.



9 **10**

For exacting coupling of the acid with an expensive partner, it would be desirable to be able to isolate an activated ester intermediate. Two research groups have introducted strategies for doing this. Xinmiao Liang of the Dalian Institute of Chemical Physics has found (*Chemistry Lett.* **2006**, *35*, 566) that N-hydroxysuccinimide **12** activates $PhI(OAc)_2$, and that the combination converts a primary alcohol **11** or the intermediate aldehyde into the activated O-Su ester **13**. In a complementary approach, Chao-Jun Li of McGill University, Montreal, has demonstrated (*J. Org. Chem.* **2006**, *71*, 6266) that an aldehyde **14** will undergo oxidative coupling with a β-dicarbonyl compound **15**, to give the activated ester **16**. Both **13** and **16** are stable enough to purify, and are expected to efficiently acylate alcohols and amines.



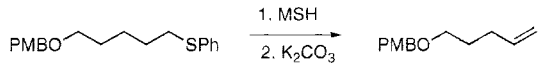
11 **12** **13**

14 **15** **16**

Interconversion of Organic Functional Groups

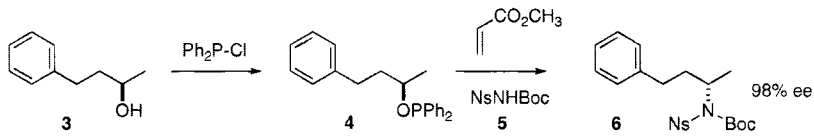
May 21, 2007

The thermal elimination of aryl sulfoxides is widely used, but requires elevated temperatures. Junichi Matsuo and Hiroyuki Ishibashi of Kanazawa University have now shown (*Organic Lett.* **2006**, *8*, 6095) that exposure of a sulfide **1** to *O*-mesitylenesulfonylhydroxylamine (MSH) at room temperature followed by K_2CO_3 led to smoooth elimination to the alkene **2**.



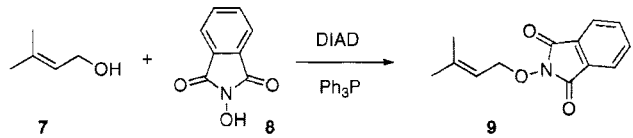
1 **2**

Teruaki Mukaiyama of Kitasato Institute in Tokyo recently reported (*Chemistry Lett.* **2006**, *35*, 456) a convenient protocol for Mitsunobu coupling. The alcohol to be displaced is first converted into the diphenylphospinite **4**. Exposure to methyl acrylate and the nucleophile **5** then leads to the coupled product **6** with near-perfect inversion of absolute configuration.



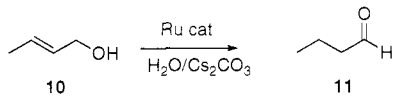
3 **4** **5** **6**

Another improvement in Mitsunobu coupling comes (*Tetrahedron Lett.* **2006**, *47*, 5151) from David W. Knight at Cardiff University. He has found that after carrying out a Mitsunobu reaction in the usual way, with Ph_3P and diethylazodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD), filtration through a plug of silica gel with CH_2Cl_2, exposure to 15% aqueous H_2O_2, and again filtration through a plug of silica gel with CH_2Cl_2 led to pure product **9** as a powdery solid. This protocol is easily scaled up.

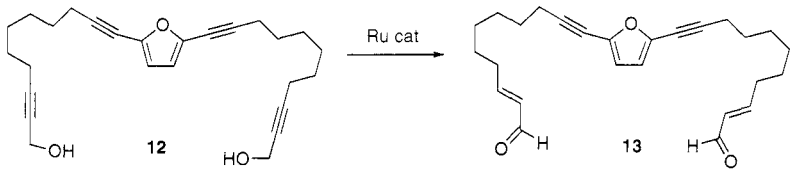


7 **8** **9**

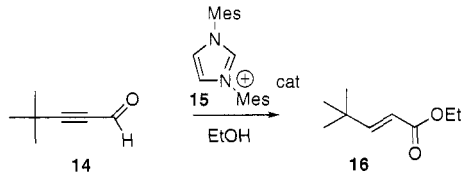
The Ru-catalyzed "redox" isomerization of an allylic alcohol **10** to the corresponding aldehyde **11** is a useful synthetic transformation. Victorio Cadierno, José Gimeno and José A. Sordo of the Universidad de Oviedo have described (*J. Am. Chem. Soc.* **2006**, *128*, 1360) a detailed study of this reaction. Secondary alcohols also participate efficiently, leading to ketones.



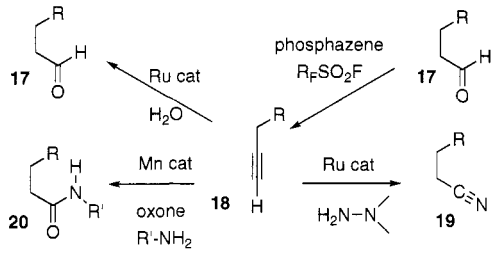
Barry M. Trost of Stanford University has shown (*Organic Lett.* **2006**, *8*, 4461) that propargyl alcohols such as **12** can also be isomerized. The product is the α,β-unsaturated aldehyde **13**.



Kirsten Zeitler of the Universität Regensburg has found (*Organic Lett.* **2006**, *8*, 637) that acetylenic aldehydes such as **14** can also be isomerized, in this case with the organocatalyst **15**. The product is the ester **16**.



A remarkable series of transformations around terminal alkynes have recently been reported. Ilya M. Lyapkalo of the Institute of Chemical & Engineering Sciences, Singapore, has shown (*Angew. Chem. Int. Ed.* **2006**, *45*, 4019) that aldehydes **17** react with the inexpensive nonafluorobutanesulfonyl fluoride in the presence of a phosphazene base to give first the enol sulfonate, and then the terminal alkyne **18**. Lukas Hintermann of RWTH Aachen University has developed (*Organic Lett.* **2006**, *8*, 5853) a Ru catalyst for the inverse transformation, the hydration of the terminal alkyne **18** to the aldehyde **17**. Several years ago, Yoshiya Fukumoto of Osaka University reported (*Organomet.* **2002**, *21*, 3845) the Ru-catalyzed conversion of terminal alkynes to the corresponding nitriles **19**. This has been little used, but we have found that it works well. The oxidation of alkynes **18** to the amide **20** described (*J. Am. Chem. Soc.* **2006**, *128*, 14796) by Man-Kin Wong and Chi-Meng Che of the University of Hong Kong also works well with internal alkynes.

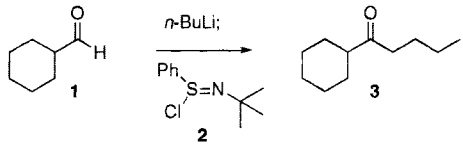


Best Synthetic Methods: Carbon-Carbon Bond Formation

May 28, 2007

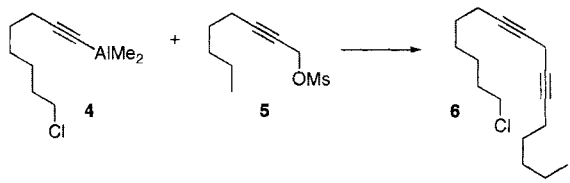
Carbon-carbon bond construction is the basis for all of organic chemistry. Important methods for the construction of single, double, and triple bonds have been described.

While ketones can be prepared by the addition of organometallic reagents to amides or to nitriles, they are often prepared by the addition of the organometallic reagent to an aldehyde such as **1**. In a subsequent step, the product secondary alcohol is oxidized to the ketone. William J. Kerr of the University of Strathclyde has now found (*Organic Lett.* **2006**, *8*, 5073) that if the intermediate alkoxide is worked up with the Mukaiyama reagent **2**, the ketone **3** is formed directly. The alkoxides derived from the addition of Grignard reagents can be converted to the ketones, but yields are better with the alkoxides derived from organolithium reagents.



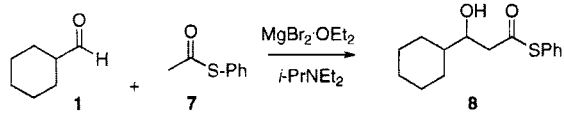
1 **2** **3**

Skipped diynes such as **6** are often prepared as precursors to the skipped *Z*-dienes that are ubiquitous in fatty acids. Sebastian Wendeborn of Syngenta Crop Protection in Basel has developed (*Organic Lett.* **2006**, *8*, 5629) a new route to such skipped diynes, based on the coupling of an alkynylalane **4** with a propargylic methanesulfonate. The regioisomeric allenic products are apparently not formed.



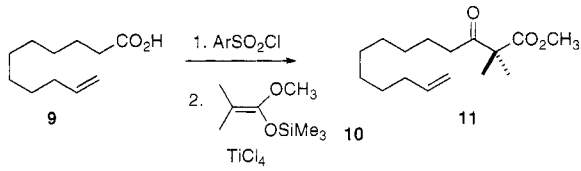
4 **5** **6**

The aldol condensation of esters with aldehydes has required the formation of the stoichiometric ester enolate. Don M. Coltart of Duke University has now shown (*Organic Lett.* **2006**, *8*, 1503) that Hunig's base in the presence of $MgBr_2$ etherate is sufficient to induce the condensation of a thioester such as **7** with the aldehyde **1**. Note that the product thioester **8** could easily be reduced to the aldehyde or homologated to the ketone.

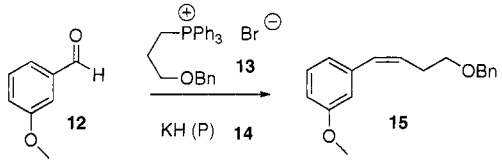


1 **7** **8**

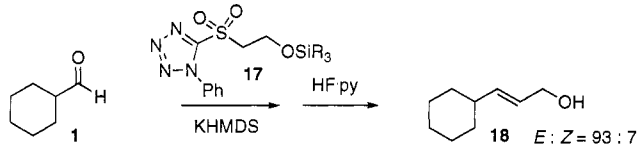
In a continuation of his work on innovative and practical procedures for acylation, Yoo Tanabe of Kwansei Gakuin University, Hyogo, has described (*Organic Lett.* **2006**, *8*, 5215) the activation of a carboxylic acid such as **9** by formation of the mixed anhydride, followed by condensation with a ketene silyl acetal **10**, to give the β-keto ester **11**.



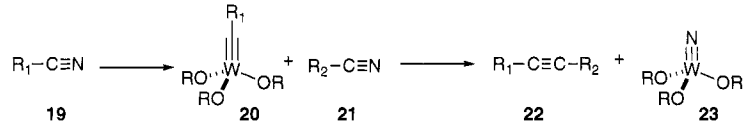
KH is a fast and efficient base, but it has been used far less in organic synthesis than it might have been, because it comes as a slurry in mineral oil, and so is difficult both to handle and to dispense precisely in small quantities. We have found (*J. Org. Chem.* **2006**, *71*, 8973) that KH can be washed clean, then suspended in melted paraffin wax. The cooled wax, KH(P), 50% by weight KH, is easy to dispense, and is stable in air for months at least.



Allylic alcohols are ubiquitous intermediates in organic synthesis. Often, these are prepared by Horner-Emmons homologation of an aldehyde such as **1**, followed by reduction. István E. Markó of the Université catholique de Louvain has now developed (*Organic Lett.* **2006**, *8*, 5983) a practical alternative, Kocienski-Julia homologation using **17**. If the silyl-protected allylic alcohol is desired, the HF·pyridine step can be omitted.



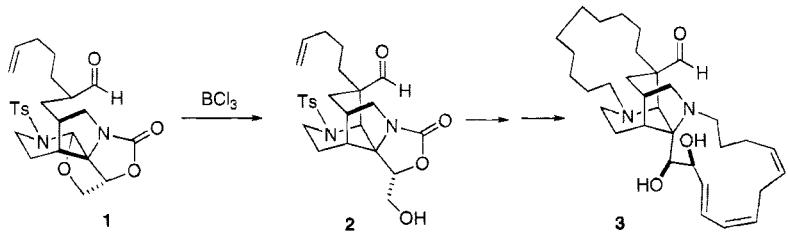
Methods for the direct preparation of C-C triple bonds are limited. Marc J. A. Johnson of the University of Michigan, in the course of work directed toward catalytic C-C triple bond formation (*J. Am. Chem. Soc.* **2006**, *128*, 9614), reminds us that the sequential tungsten-mediated stoichiometric coupling of two nitriles works well. This could be a practical route to high value-added alkynes **22**.



The Overman Synthesis of (-)-Sarain A

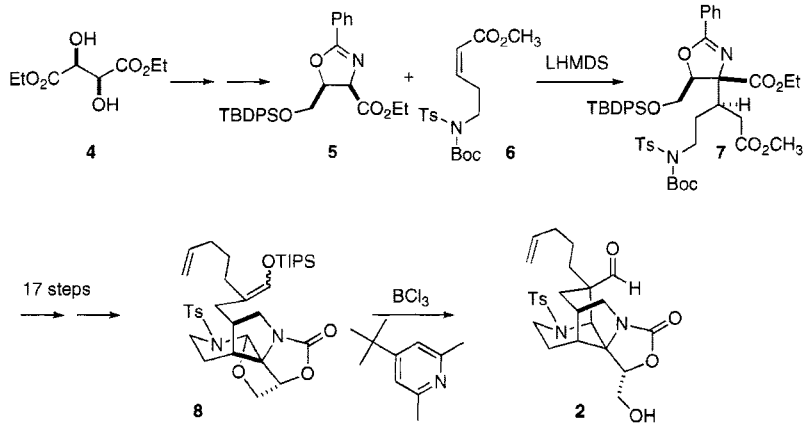
June 4, 2007

Larry E. Overman of the University of California. Irvine has recently (*Angew. Chem. Int. Ed.* **2006**, *45*, 2912) described the first total synthesis of the antibiotic and antitumor alkaloid (-)-sarain A **3**. The structure of **3** is particularly challenging, with two tertiary amines, one of them attached to a quaternary center. Note that although sarain A is drawn as the amino aldehyde, in fact the aldehyde and the proximal amine interact to form zwitterionic species that are difficult to purify.



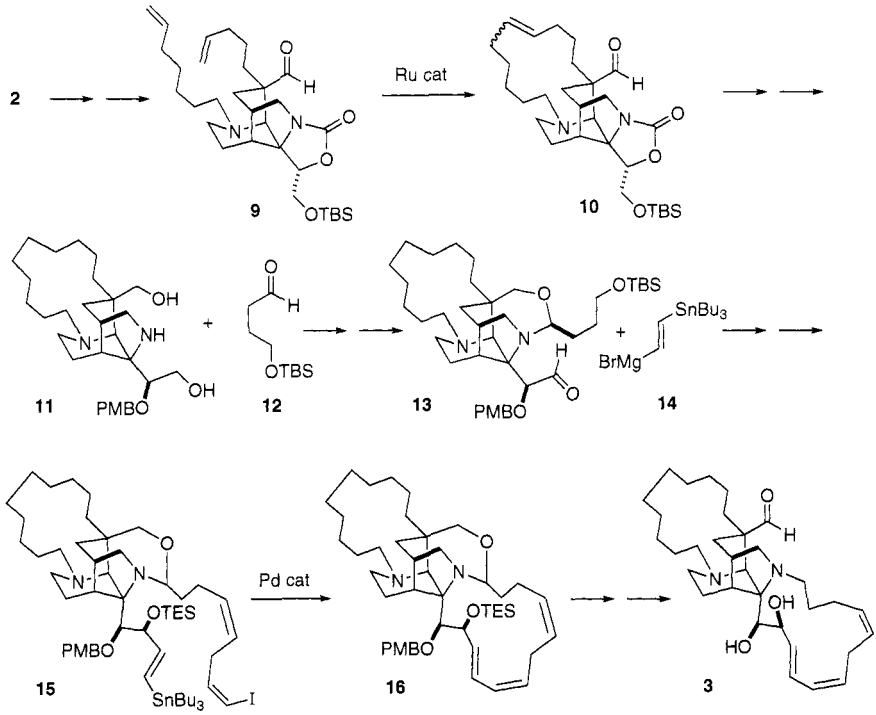
A key transformation in the assembly of **3** was the intramolecular Mannich cyclization of **1** to **2**. This C-C bond forming reaction established the single carbocyclic ring of **3**, while at the same time constructing with high diastereocontrol the tetraalkylated quaternary center.

The enantiospecific preparation of **1** began with diethyl tartrate **4**. The enolate of the derived oxazoline **5** added with high diastereocontrol to the *Z*-α,β-unsaturated ester **6** to give **7**. The diester **7** included the three continguous stereogenic centers of **8**. The details of the conversion of **7** to the hemiaminal **8** had previously been reported by Professor Overman (*J. Org. Chem.* **1998**, *63*, 8096; *Tetrahedron Lett.* **1999**, *40*, 1273; *Organic Lett.* **2005**, *7*, 933).



The aldehyde **1** was in fact not isolated. Rather, the intramolecular Mannich condensation was developed using the silyl enol ether **8** as the starting material. It is not clear whether the striking diastereocontrol observed is steric in origin, with the small aldehyde tucked into the more incumbered space, or if there is an attractive interaction between the aldehyde carbonyl and the polar carbamate. In principle, the Mannich condensation is reversible, so the reaction may be under thermodynamic, not kinetic, control.

Desulfonylation of **2** followed by reductive alkylation delivered **9**, setting the stage for Ru-mediated (G1) closure of the first macrocyclic ring. Note that from **9** on, a basic tertiary amine was carried through the remainder of the synthesis, and from **11** on, each intermediate had *two* basic amines.

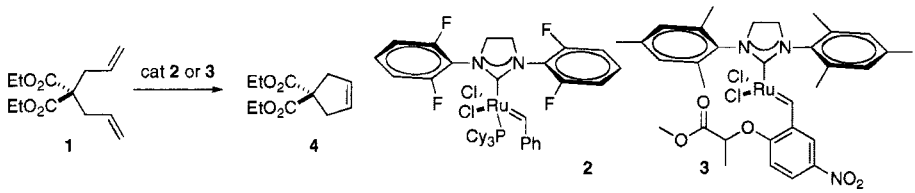


To close the final ring, the amino diol **11** was protected as the hemiaminal, then oxidized to **13**. Diastereoselective (~3-4 : 1) Grignard addition followed by homologation then gave the precursor **15** for Stille coupling to close the last ring. Reduction of the hemiaminal, oxidation with bicarbonate-buffered Dess-Martin reagent to the aldehyde (zwitterionic!) and a delicate deprotection then completed the synthesis of (-)-sarain A **3**.

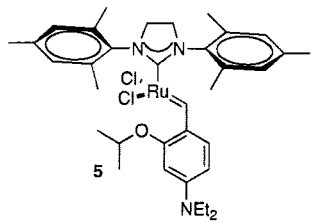
Recent Developments in Alkene Metathesis

June 11, 2007

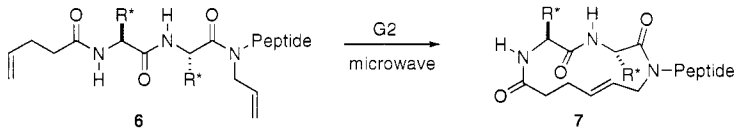
Alkene metathesis has become part of the toolkit of organic synthesis. Nevertheless, there is room for improvement in catalyst efficiency. Robert H. Grubbs of the California Institute of Technology found (*J. Am. Chem. Soc.* **2006**, *128*, 11768) that the fluorinated complex **1** is several times faster than the widely used G2 ruthenium catalyst. Guy Lavigne of the Laboratoire de Chimie de Coordination, Toulouse, Dieter Arlt of of Ligand Chemie GmbH, Lemgo, Germany and Karol Grela of the Polish Academy of Sciences, Warsaw found (*J. Am. Chem. Soc.* **2006**, *128*, 13652) that **3** is similarly fast, and durable, yielding a TON of 3200 in a ring-closing metathesis.



Another approach to high turnover is to immobilize the catalyst. Ned B. Bowden of the University of Iowa has reported (*J. Am. Chem. Soc.* **2006**, *128*, 14434) the inclusion of G2 in polydimethylsiloxane (PDMS). The polymer excludes water, but organic substrates freely diffuse in and out. With MeOH/water as the reaction medium, the cyclization of **1** proceeded readily, with the catalyst visibly remaining in the solid polymer. Professor Grela and Andreas Kirschning of Leibniz Universität Hannover have described (*J. Am. Chem. Soc.* **2006**, *128*, 13261) a complementary approach, binding **5** and an activating sulfonic acid to glass-polymer Raschig rings.

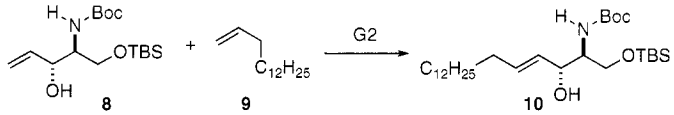


The special activating effects of microwave irradiation are still actively debated. Paramjit S. Arora of New York University has observed (*Organic Lett.* **2006**, *8*, 5825) that the cyclization of **6** with G2 is sluggish (hours) with oil bath heating, but proceeds rapidly (2 – 5 min) with microwave heating.



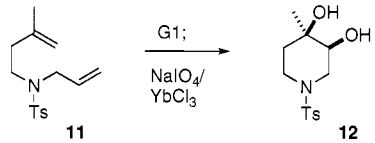
6 7

Allylic alcohols are particularly useful substrates for cross metathesis. Shigeo Katsumura of Kwansei Kakuin University, Hyogo took advantage of this in developing (*Organic Lett.* **2006**, *8*, 5569) a general route to the sphingolipids and substituted sphingosines. The allylic alcohol **8**, readily prepared from L-serine, undergoes smooth cross metathesis with alpha olefins such as **9**.



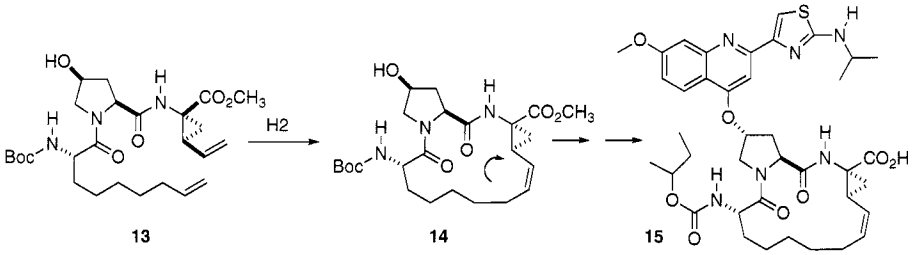
8 9 10

Tandem metathesis-hydrogenation reactions have been described, as have tandem metathesis-alkene migrations, with the Ru species catalyzing both steps. Siegfried Blechert of the Technisches Universität, Berlin (*Angew. Chem. Int. Ed.* **2006**, *45*, 1900) and Marc L. Snapper of Boston University (*Organic Lett.* **2006**, *8*, 4759) have now reported tandem metathesis-alkene dihydroxylation. For example, cyclization of **11** with catalytic G1 followed by the addition of oxidant delivered the cis diol **12**.



11 12

Nathan K. Lee, Vittorio Farina and Kai Donsbach of Boehringer Ingelheim (*J. Org. Chem.* **2006**, *71*, 7133; further studies by Vittorio Farina and Xudong Wei in *J. Org. Chem.* **2006**, *71*, 8864), in the scale-up of the previously-described (OHL July 25, 2005) metathesis-based synthesis of the hepatitis C protease inhibitor BILN 2061 **15**, observed epimerization at the indicated center in the product **14**. They eventually found that this could be minimized by using the Hoveyda catalyst in the cyclization. A crucial quenching of the catalyst at the end of the metathesis was accomplished by adding mercaptonicotinic acid. With these modifications, this approach has been used to produce > 400 kg of cyclized product.

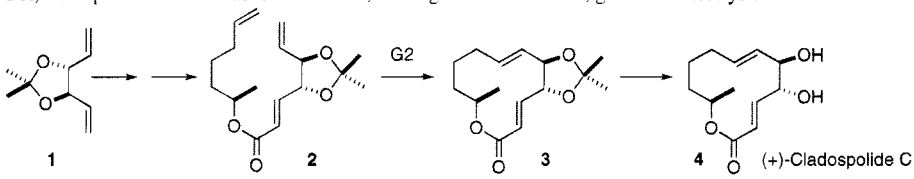


13 14 15

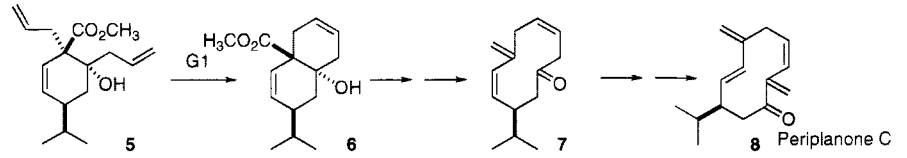
Pushing the Limits of Alkene Metathesis in Natural Product Synthesis

June 18, 2007

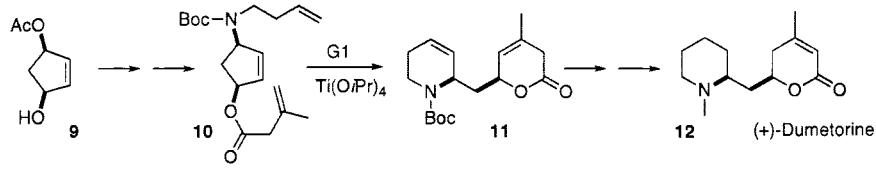
While alkene metathesis has become part of the toolkit of organic synthesis, investigators around the world are pushing the limits of the method as they employ the reaction in total synthesis. Duen-Ren Hou of National Central University, Taiwan prepared (*J. Org. Chem.* **2006**, *71*, 9887) the triene **2** from **1**, itself easily prepared from D-mannitol. Metathesis proceeded cleanly, leading to (+)-cladospolide C. Yet, attempts at the alternative metathesis, closing the other alkene, gave no useful yield.



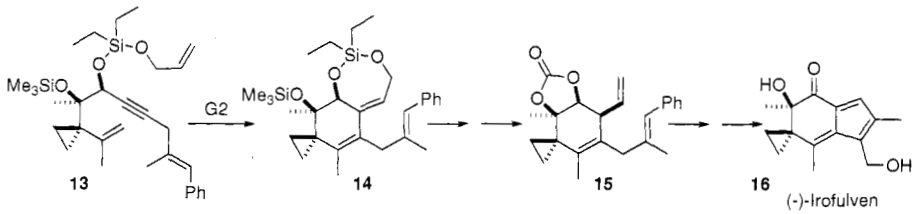
Ring-closing metathesis to form medium rings often leads to mixtures of *Z* and *E* alkenes. If the *Z* is desired, alkyne metathesis followed by selective hydrogenation can be employed. Radomir N. Saicic of the University of Belgrade has put forward (*J. Org. Chem.* **2006**, *71*, 9411) an alternative. RCM of **5** of course gave the *Z* alkene. Reduction followed by selective mesylation of the primary alcohol and Grob fragmentation then delivered the *Z*, *Z*-triene **7**, which was readily carried on to the cockroach pheromone periplanone C **8**.



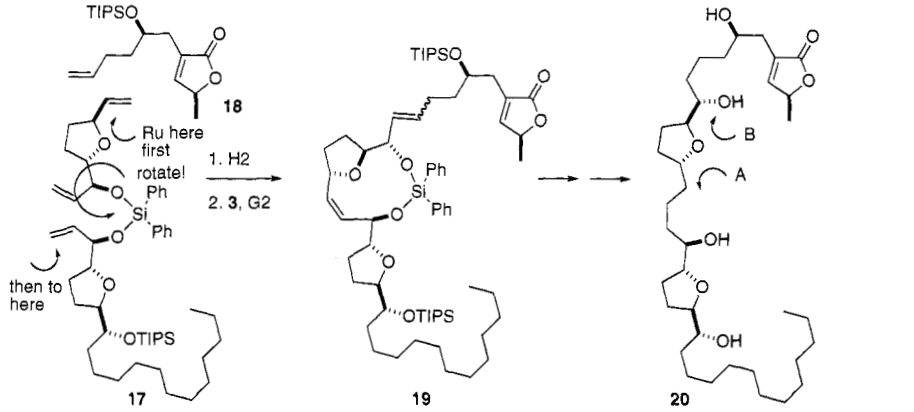
Ring-rearrangement metathesis is a powerful strategy for polycyclic construction. This is nicely illustrated by the synthesis of (+)-dumetorine recently reported (*Tetrahedron Lett.* **2006**, *47*, 7977) by Siegfried Blechert of the Technisches Universität, Berlin. There are at least three other precursors one can draw that could be precursors to **11**. The cyclopentene **10** was chosen partly because it was readily available in enantiomerically-pure form, and also because the modest ring strain of the cyclopentene might drive the conversion of **10** to **11**.



The semsynthetic illudin (-)-irofulven **16** is in clinical trials as an anti-cancer agent. Mohammad Movassaghi of MIT has described (*Angew. Chem. Int. Ed.* **2006**, *45*, 5859) a concise route to the illudins. The key step was a boldly-conceived enyne ring-closing metathesis (EYCRM) that converted **13** to **14**. An additional ring-closing metathesis on **15** followed by oxidation then delivered **16**.



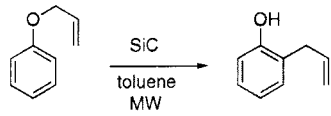
Although the usual relative rates of ring formation often guide metathesis, such is not always the case. In a recent synthesis of (+)-gigantecin **21** (*Organic Lett.* **2006**, *8*, 3383), Thomas R. Hoye of the University of Minnesota anticipated that **17** should first close the seven-membered ring, and then that product would participate in cross-metathesis with **18**, leading to **21**. The reaction, followed by mass spectrometry, seemed initially to be going well. In fact, however, **17** could freely rotate. The Ru catalyst engaged first with the most accessible alkene, then closed the eleven-membered ring, to give, after subsequent cross metathesis, the undesired **19**, and so **20**. The problem was solved, and the synthesis of the desired **21** accomplished, by first carrying out cross metathesis of **17** with an excess of **18**, then effecting ring-closing metathesis to form the seven-membered ring.



Preparation of Benzene Derivatives

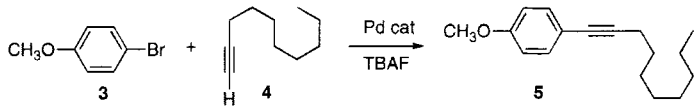
June 25, 2007

There have been much discussion of the benefits of microwave irradiation. C. Oliver Kappe of the University of Graz, among others, has undertaken detailed studies directed toward rationalizing the many reports. In a recent contribution (*J. Org. Chem.* **2006**, *71*, 4651), he has shown that by including sintered silicon carbide (SiC) cylinders as passive heating elements, one can use microwave irradiation to heat solvents such as toluene that do not directly absorb the radiation.



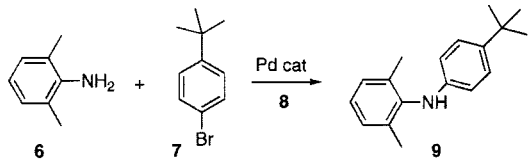
1 **2**

Sonogashira coupling is one of the most reliable of C-C bond forming reactions. Jin-Heng Li of Hunan Normal University, Changsha, has found (*J. Org. Chem.* **2006**, *71*, 379) that a Pd catalyst is effective for the coupling even in the absence of Cu or amines. Note that Pd-only coupling of an alkyne with an aryl halide was initially developed by Heck. The contribution of Sonogashira was to add Cu.



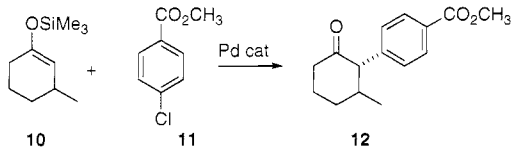
3 **4** **5**

Although effective ligands for the Pd-catalyzed coupling of amines with aryl halides have been designed, many of these are patent protected. Robert A. Singer of Pfizer Global Research, Groton, CT has developed (*Tetrahedron Lett.* **2006**, *47*, 3727) a ligand **8** that is as effective as those previously reported, but that is not proprietary.



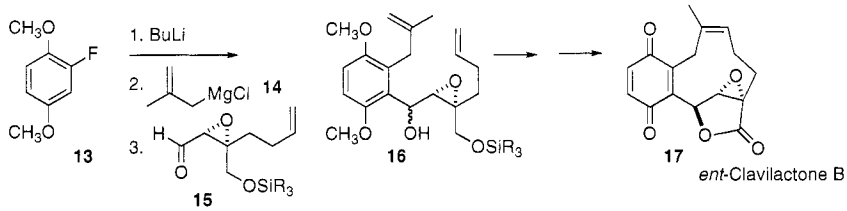
6 **7** **9**

John K. Verkade of Iowa State University and John F. Hartwig, now at the University of Illinois, have reported (*Angew. Chem. Int. Ed.* **2006**, *45*, 5852) what appears to be a robust protocol for the Pd-catalyzed α-arylation of silyl enol ethers. If this procedure is as general as it appears to be, this will be a significant addition to the standard tools of organic synthesis. Professor Hartwig has also reported (*J. Am. Chem. Soc.* **2006**, *128*, 14800) conditions for coupling the Baldwin acyl anion equivalent to an aryl halide.



10 11 12

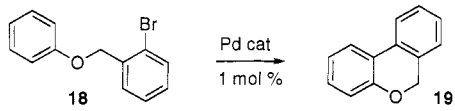
In the course of a synthesis of *ent*-clavilactone B **17**, Anthony G. M. Barrett of Imperial College has described (*J. Am. Chem. Soc.* **2006**, *128*, 14042) an elegant three-component coupling. Addition of methallyl Grignard **14** to the benzyne derived from **13** delivered an intermediate aryl Grignard, that added to **15** to give **16**.



13 15 16 17

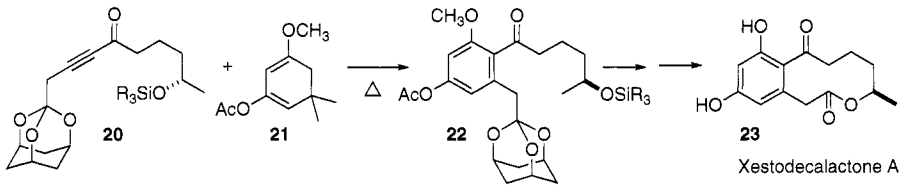
ent-Clavilactone B

In a feature article (*Chem. Commun.* **2006**, *1253*) Keith Fagnou of the University of Ottawa has provided an overview of his elegant preparative and mechanistic work using intramolecular and intermolecular carbopalladation to arylate C-H positions on aromatic rings. The intramolecular reaction, which originally required 10 mol % of the Pd catalyst, can now be run with 1 mol % or less.



18 19

Rather than derivatize an existing benzene ring, it is sometimes more efficient to construct the ring. In the course of a synthesis of xestodecalactone A **23**, Samuel J. Danishefsky of Columbia University showed (*J. Am. Chem. Soc.* **2006**, *128*, 14185) that the Diels-Alder addition of non-symmetrical allenyl and alkynyl dienophiles such as **20** to dienes such as **21** can proceed with high regiocontrol. Gerhard Hilt of the Philipps-Universität Marburg has described (*Angew. Chem. Int. Ed.* **2006**, *45*, 5204) a complementary Diels-Alder approach to benzene construction that delivers *meta* substituted products.



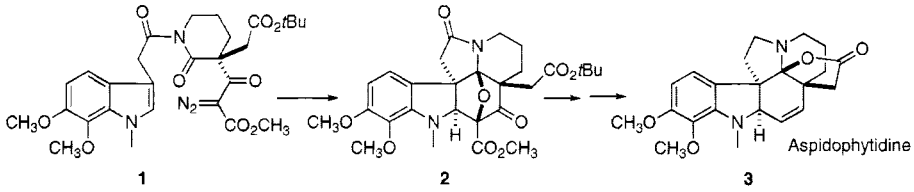
20 21 22 23

Xestodecalactone A

The Padwa Synthesis of Aspidophytidine

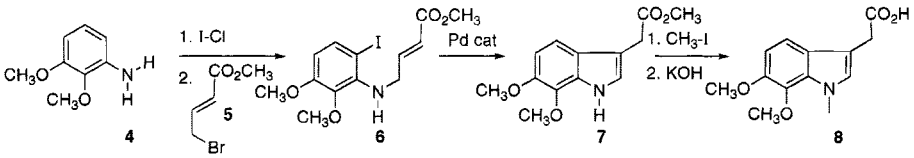
July 2, 2007

Albert Padwa of Emory University has developed (*Organic Lett.* **2006**, *8*, 3275) a productive approach to fused indole alkaloids such as aspidophytidine **3**, based on the dipolar cycloaddition of the ylide derived by exposure of a diazo ketones such as **1** to a Rh(II) carboxylate catalyst.



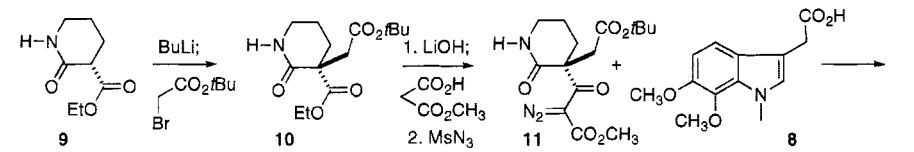
1 **2** **3**

The preparation of **1** started with the aniline **4**. Ortho iodination followed by N-alkylation with **5** delivered the unsaturated ester **6**. Heck cyclization no doubt intially left the alkene still conjugated with the ester, but traces of acid or base would be expected to easily isomerize this to establish the aromaticity of the five-membered indole ring. N-methylation followed by saponification then gave **8**.



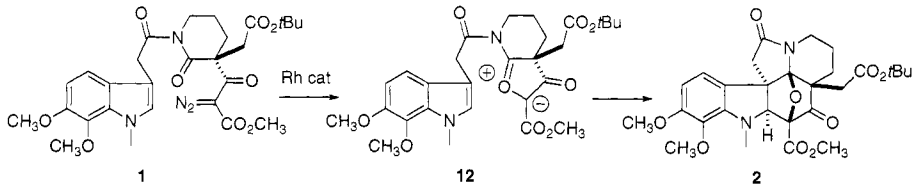
4 **5** **6** **7** **8**

The preparation of **1** continued with the alkylation of **9**. Hydrolysis of **10** followed by homologation and subsequent diazo transfer gave **11**, which was coupled with **8** to give **1**. The quaternary center established in the alkylation of **9** was carried through the synthesis, so if enantiomerically-pure material were desired, an enantioselective route to **10** would have to be devised.

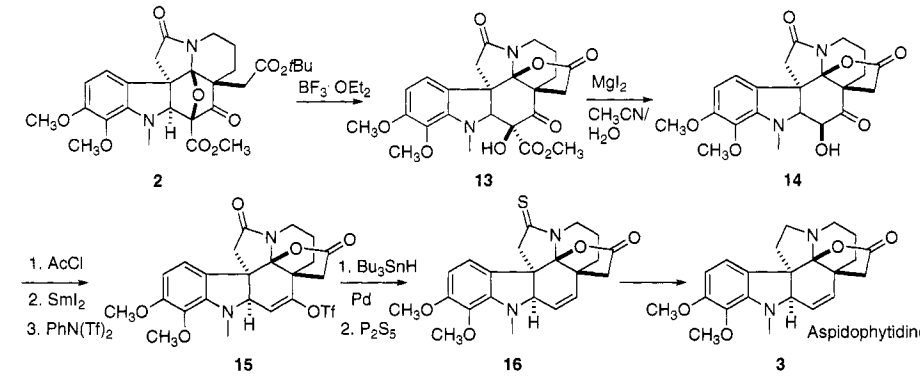


9 **10** **11** **8**

The push-pull dipole **12** was constructed by exposure of **1** to $Rh_2(OAc)_4$. Loss of N_2 gave the Rh carbene, which complexed with the nucleophilic amide carbonyl. The dipole **12** was not isolated, but reacted *in situ* with the tethered indole to give the hexacyclic adduct **2**. Note that two diastereomers of **2** could have been formed, but only **2**, with the bulky *t*-butyl ester exo, was observed.



The dipolar cycloadddition established the requisite stereochemical relationship between the three contiguous quaternary stereogenic centers of **1**. It remained to adjust the functional groups around the newly-formed carbocyclic ring. Exposure to $BF_3 \cdot OEt_2$ led to ring opening, followed by trapping of the intermediate carbocation with the *t*-butyl ester to give the lactone **13**, with concommitant loss of isobutylene. Hydrolysis and decarboxylation gave the alcohol **14**, the acetate of which was removed by reduction with SmI_2. The derived enol triflate **15** was reduced to the alkene, which was deoxygenated by way of the thiolactam **16**.

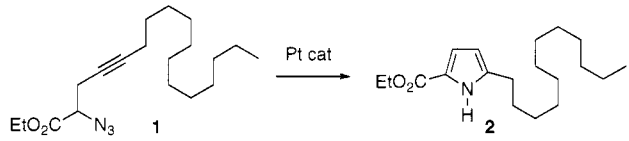


The intramolecular dipolar cycloaddition exemplified by the conversion of **12** to **2** is a specific representative of a general and powerful approach to indole alkaloids, based on cycloaddition of an intermediate indole to a dipole or a diene. For more recent work along these lines by Professor Padwa, see *Org. Lett.* **2007**, *9*, 279 and *Tetrahedron* **2007**, *63*, 5962.

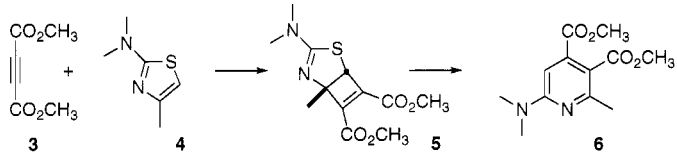
Synthesis of Heteroaromatics

July 9, 2007

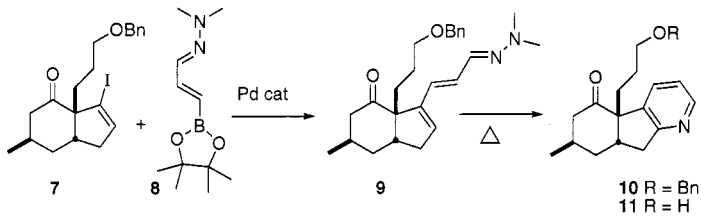
Kou Hiroya of Tohoku University has described (*Org. Lett.* **2006**, *8*, 5349) a versatile new route to pyrroles **2**, based on the Pt-catalyzed rearrangement of azido alkynes such as **1**. A wide range of functional groups appear to be tolerated.



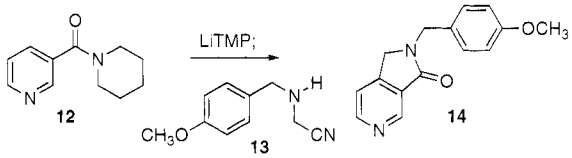
Mateo Alajarín of the Universidad de Murcia has reported (*J. Org. Chem.* **2006**, *71*, 5328) a new route to substituted pyridines **6**, based on the the addition of dimethylacetylene dicarboxylate **3** to 2-aminothiazoles such as **4**. The reaction is apparently proceeding by way of the [2+2] adduct **5**.



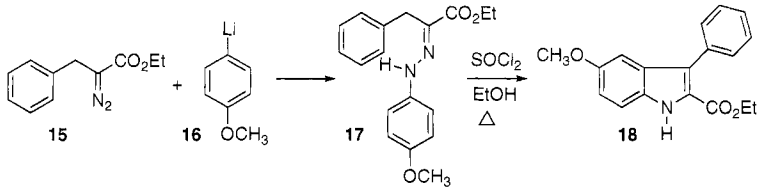
In a synthesis of (+)-lycopladine A **11**, F. Dean Toste of the University of California, Berkeley demonstrated (*Angew. Chem. Int. Ed.* **2006**, *45*, 5991) the power of pyridine construction. Coupling of **7** with the hydrazone **8** gave **9**, which on heating smoothly converted to **10**.



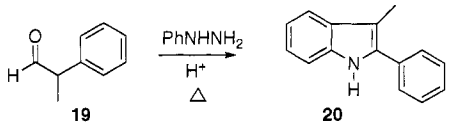
Substituted pyridines can also be prepared from preformed pyridines. Laurent Bischoff of IRCOF-INSA, Rouen, taking advantage (*Organic Lett.* **2006**, *8*, 5889) of the known preference for 4-metalation of nicotinamides such as **12**, condensed the resulting anion with the Mannich equivalent **13** to give, after cyclization, the lactam **14**.



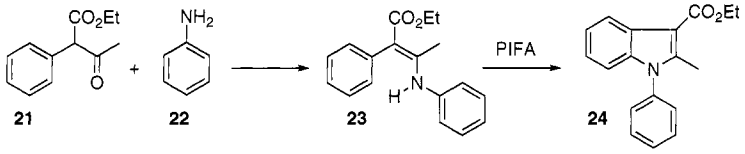
The classic route to indoles is the Fischer synthesis, acid-mediated cyclization of an aryl hydrazone such as **17**. Norio Takamura of Musashino University, Tokyo has reported (*Tetrahedron Lett.* **2006**, *47*, 743) that such hydrazones can be simply prepared by the addition of an aryl lithium to an α-diazo ester.



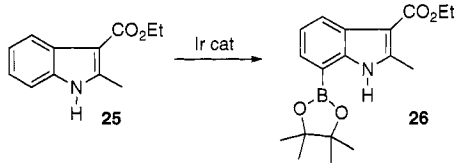
The Fischer synthesis works with aldehydes also. Remarkably, unsymmetrical α-branched aldehydes such as **19** had not been studied in detail. Kevin G. Liu of Wyeth Research in Princeton, N.J. has now found (*Organic Lett.* **2006**, *8*, 5769) that the cyclizations work well, and that the requisite 1,2-shift en route to **20** proceeds with high selectivity.



A complementary approach to indoles begins with an *alkyl* substituent on the benzene ring. Kang Zhao of Tianjin University has devised (*Organic Lett.* **2006**, *8*, 5919) conditions for the oxidative cyclization of an enamine such as **23** to the indole **24**.



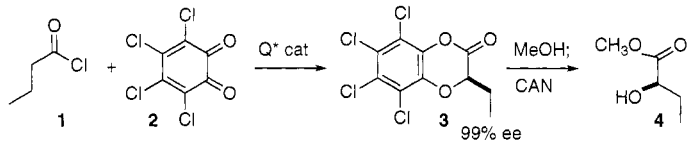
An alternative is to directly functionalize the indole nucleus. Robert E. Malezcka, Jr. and Milton R. Smith III of Michigan State University have shown (*J. Am. Chem. Soc.* **2006**, *128*, 15552) that using an Ir catalyst, it is possible to effectively borylate the 7-position of a wide variety of indoles.



Enantioselective Construction of Alcohols and Amines

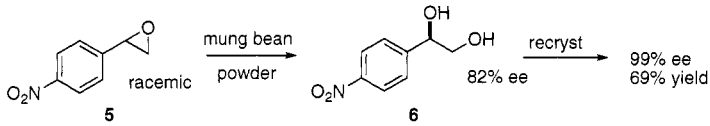
July 16, 2007

Thomas Lectka of Johns Hopkins University has reported (*J. Am. Chem. Soc.* **2006**, *128*, 1810) an elegant method for the enantioselective α-hydroxylation of carboxylic acids. Chiral amine catalyzed condensation of the derived ketene with chloranil **2** proceeded with high enantioselectivity, to give the lactone **3**, which was converted to **4** by transesterification and oxidative deprotection.



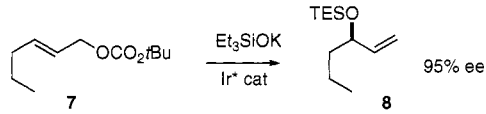
1 2 3 4

The power of enzymatic transformation is illustrated by the work (*Organic Lett.* **2006**, *8*, 1737) of Jian-He Xu of the East China University of Science and Technology in Shanghai. Both enantiomers of styrene oxides such as **5** are converted by mung bean powder largely to the same enantiomer of the product diol **6**. It would be interesting to try the mung bean powder with (meso) cis stilbene oxide.



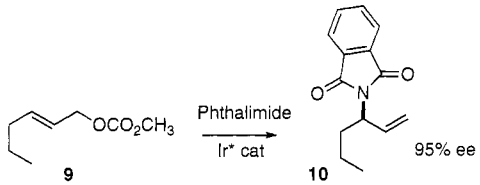
5 6

One of the simplest routes to an enantiomerically-pure secondary alcohol is the enantioselective displacement of a primary allylic leaving group. Erick M. Carreira of the ETH Zurich has extended (*Angew. Chem. Int. Ed.* **2006**, *45*, 6204) this approach, using the potassium salt of triethylsilanol as the nucleophile and a chiral Ir catalyst.



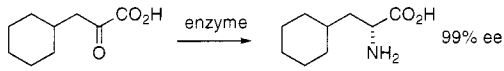
7 8

This same approach has been used to prepare enantiomerically-pure secondary amines, mainly using benzylamines as the nucleophile. Günter Helmchen of the Universität Heidelberg has extended (*Angew. Chem. Int. Ed.* **2006**, *45*, 5546) this approach, using amine nucleophiles bearing more readily removable protecting groups.



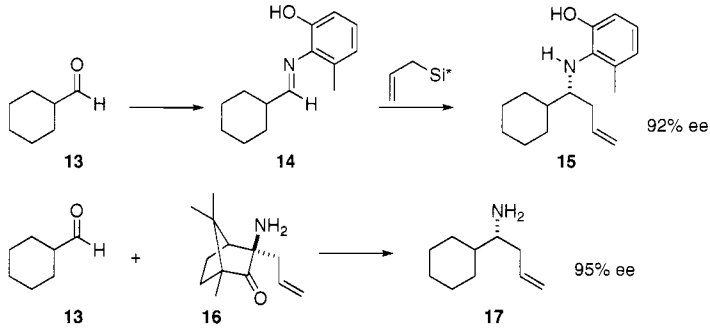
9 10

L-amino acids are available from natural sources. D-amino acids have been much more expensive. Scott J. Novick of BioCatalytics, Inc., Pasadena, CA, through a combination of rational and random mutagenesis, has developed (*J. Am. Chem. Soc.* **2006**, *128*, 10923) a D-amino acid dehydrogenase. This new enzyme converts α-keto acids such as **11** into the corresponding D-amino acids in high ee.



11 **12**

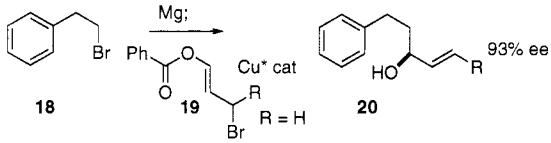
Asymmetric allylation of aldehydes, to prepare enantiomerically pure homoallylic alcohols, has become a reliable tool for organic synthesis. James L. Leighton of Columbia University (*Organic Lett.* **2006**, *8*, 6119) and Shu Kobayashi of the University of Tokyo (*J. Am. Chem. Soc.* **2006**, *128*, 11038) have each developed chiral reagents to add allyl to an imine, to give the enantiomerically pure homoallylic secondary amine.



13 **14** **15**

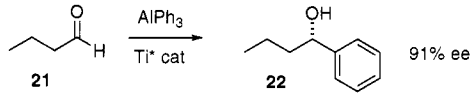
13 **16** **17**

Ben L. Feringa of the University of Groningen has assembled (*J. Am. Chem. Soc.* **2006**, *128*, 15572) a powerful strategy for the three-carbon homologation of an alkyl halide, based on the chiral catalyst mediated coupling of the Grignard reagent derived from the halide with the bromoester **19** (R=H). A key question is whether this coupling works equally well with secondary bromides (R=alkyl).



18 **19** **20**

The enantioselective addition of *alkyl* organometallics to aldehydes has been available for several years. Han-Mou Gau of National Chung-Hsing University in Taichung has now introduced (*J. Am. Chem. Soc.* **2006**, *128*, 14808) a protocol for the chiral catalyst mediated enantioselective addition of *aryl* organometallics to aldehydes.

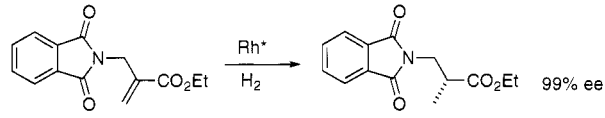


21 **22**

Enantioselective Construction of Alkylated Stereogenic Centers

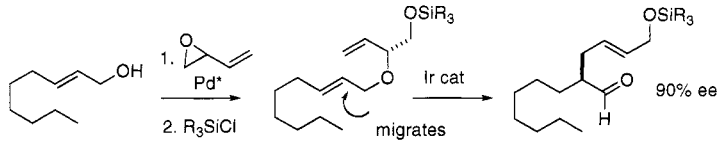
July 23, 2007

A great deal of effort has gone into the enantioselective catalytic preparation of α-amino acids. Zhuo Zheng of the Dalian Institute of Chemical Physics has now (*Organic Lett.* **2006**, *8*, 3359) developed an enantioselective catalytic route to particular class of β-amino acids.



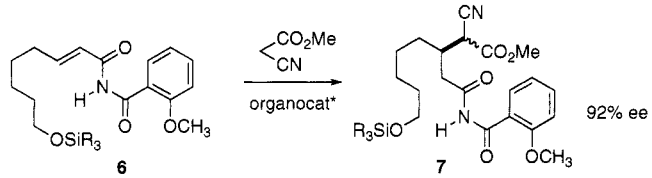
1 2

Barry M. Trost of Stanford University has described (*Organic Lett.* **2006**, *8*, 6007) an elegant Claisen-based approach to alkylated aldehydes. Chiral Pd catalyzed coupling of **3** with racemic butadiene monoepoxide followed by protection gave **4** in 91% ee, as the Trost group had previously reported. Selective migration of the *more* substituted alkene followed by Claisen rearrangement then gave the aldehyde **5**.



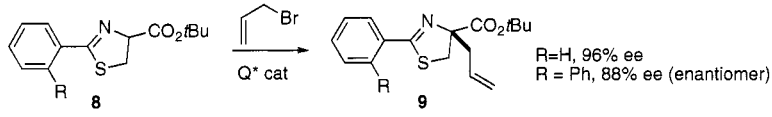
3 4 5

Yoshiji Takemoto of Kyoto University has devised (*J. Am. Chem. Soc.* **2006**, *128*, 9413) a thiourea-based organocatalyst that mediates enantioselective Michael addition, using tuned acceptors such as **6**.



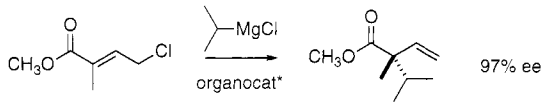
6 7

Hyeung-geun Park and Sang-sup Jew of Seoul National University have found (*J. Org. Chem.* **2006**, *71*, 8276) that chiral phase transfer catalysts can be used to direct alkylation of **8** (R=H) with high ee. Even more remarkably, alkylation of **8** (R=phenyl) proceeds to give the *enantiomer* of **9** in almost as high ee.



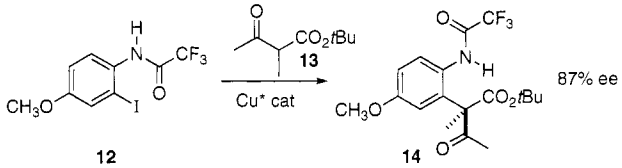
8 9

The direct preparation of tetraalkylated quaternary centers with control of absolute configuration has been a challenge. Several new solutions to this important problem are highlighted here. Amir H. Hoveyda of Boston College has devised (*J. Am. Chem. Soc.* **2006**, *128*, 15604) a chiral organocatalyst that directs the S$_N$2' coupling of Grignard reagents with chlorides such as **10**, to give **11** in high ee.



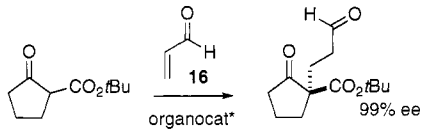
10 **11**

Dawei Ma of the Shanghai Institute of Organic Chemistry has found (*J. Am. Chem. Soc.* **2006**, *128*, 16050) that an aryl iodide such as **12** bearing an *o*-amido group is reactive enough to undergo Ullman coupling with a β-keto ester such as **13**. Using a chiral Cu catalyst, the product **14** was formed in high ee.



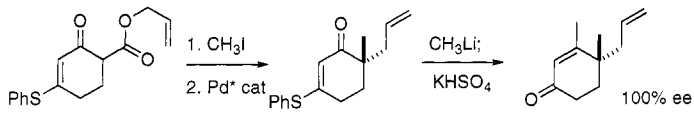
12 **14**

Li Deng of Brandeis University, extending his studies of cinchona-derived catalysts, has found (*Angew. Chem. Int. Ed.* **2006**, *45*, 4301) that they mediate Michael addition of donors such as **15** to unsaturated aldehydes such as acrolein **16**. This appears to be a general method for the construction of cyclic quaternary centers with high ee.



15 **17**

Professor Trost has also reported (*Angew. Chem. Int. Ed.* **2006**, *45*, 3109) what appears to be a general strategy for the assembly of cyclic alkylated quaternary centers with high ee. The easily prepared β-keto ester **18** can be alkylated efficiently. Exposure of the alkylated product to a chiral Pd catalyst established, via loss of CO_2, the cyclic quaternary center in high ee. The ketone **19** so produced is versatile, easily converted into a variety of other cyclohexane derivatives.

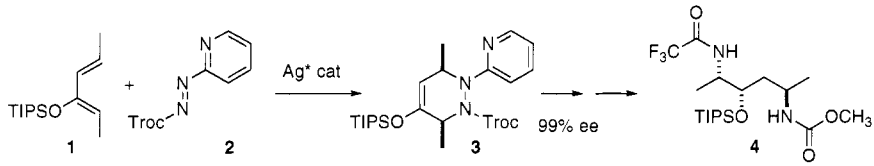


18 **19** **20**

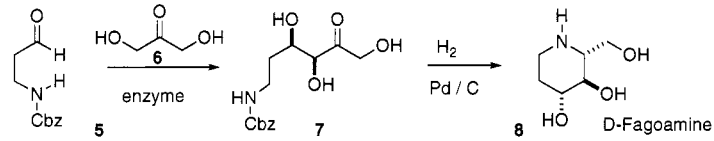
Enantioselective Construction of Arrays of Stereogenic Centers

July 30, 2007

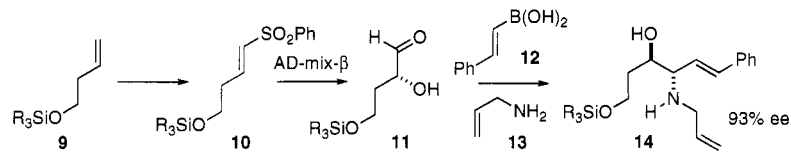
A classic strategy for controlling relative stereocontrol is to imbed the stereogenic centers in a ring. Hisashi Yamamoto of the University of Chicago has developed (*J. Am. Chem. Soc.* **2006**, *128*, 16482) a silver catalyst that directs the absolute sense of the Diels-Alder cyclization of the dienophile **2**. The adduct **3** was easily unraveled to the 1,4-diamine **4**.



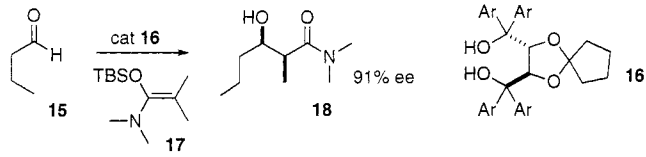
The enzyme-mediated addition of 1,3-dihydroxy acetone **6** to an aldehyde is an attractive strategy for the rapid elaboration of carbohydrates. This approach has been limited, however, by the requirement that **6** first be converted to the phosphate. Jesús Joglar and Pere Clapés of the Institute for Chemical and Environmental Research, Barcelona, have found (*Organic Lett.* **2006**, *8*, 6067) that crude recombidant fructose-6-phospate aldolase works well with **6**, adding it to **5** to give **7** in high ee. The triol **7** was reduced to D-fagomine **8**, N-alkyl derivatives of which are inhibitors of α-D-glucosidase.



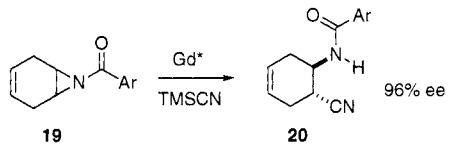
Several years ago (*J. Am. Chem. Soc.* **1998**, *120*, 11798), Nicos A. Petasis of the University of Southern California described a borono-Mannich homologation of chiral α-hydroxy aldehydes such as **11**. The limitation on this was the difficulty of preparing the α-hydroxy aldehydes. Stephen G. Pyne of the University of Wollongong has now devised (*J. Org. Chem.* **2006**, *71*, 7097) a scheme for the enantioselective homologation of a terminal alkene **9** using the Petasis procedure. The alkene was converted into the unsaturated sulfone **10** either by Ru-catalyzed metathesis or, more economically, by iodosulfonylation followed by elimination. Exposure of the unsaturated sulfone to AD-mix-β (or α) gave the crude α-hydroxy aldehyde **11**, which as carried on directly via the Petasis protocol to give **14**.



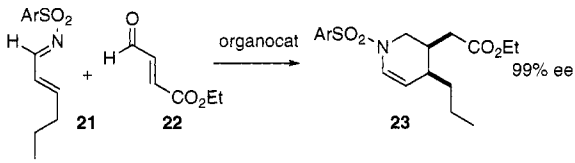
Viresh H. Rawal, also of the University of Chicago, has made (*Angew. Chem. Int. Ed.* **2006**, *45*, 6130) the remarkable observation that the taddol **16**, originally designed as a ligand for early transition metals, is an effective organocatalyst for the Mukaiyama aldol condensation of **17** with aldehydes. Professor Rawal has also found that the product tertiary amides can be reduced with $Cp_2Zr(H)Cl$ to the aldehydes with little or no epimerization.



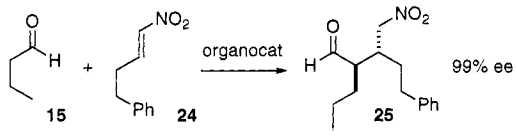
A powerful strategy for the assembly of enantiomerically-pure fragements is the desymmetrization of meso precursors. Masakatsu Shibasaki of the University of Tokyo has designed (*J. Am. Chem. Soc.* **2006**, *128*, 16438) a chiral Gd catalyst for the opening of meso aziridines such as **19** to the amido nitrile **20** in high ee.



Much good work has been reported recently on the enantioselective construction of contiguous alkylated stereogenic centers. One of the most powerful approachs is the organocatalyst-mediated hetero Diels-Alder condensation developed (*J. Am. Chem. Soc.* **2006**, *128*, 8418) by Jeffrey W. Bode of the University of California, Santa Barbara. More recently, Professor Bode reported (*J. Am. Chem. Soc.* **2006**, *128*, 15088)) that the analogous oxa reaction, to make cyclic ethers, also works well.



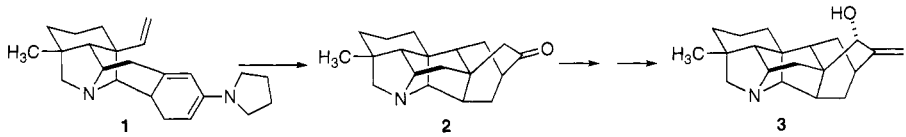
Attention has been focused by several groups on the chiral organocatalyst-mediated conjugate addition of aldehydes to unsaturated nitroalkenes. Claudio Palomo of the Universidad del País Vasco has optimized (*Angew. Chem. Int. Ed.* **2006**, *45*, 5984) additions such as that of **15** to **24**. Eric N. Jacobsen of Harvard University has used (*Angew. Chem. Int. Ed.* **2006**, *45*, 6366) a related approach to prepare *quaternary* alkylated stereogenic centers in high ee.



The Gin Synthesis of Nominine

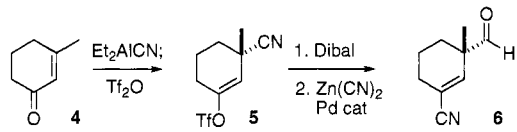
August 6, 2007

Retrosynthetic analysis of the heptacyclic ring structure of nominine **3**, a representative member of the hetisine family of alkaloids, is not for the faint of heart. David Y. Gin, now at the Sloan-Kettering Institute, has presented (*J. Am. Chem. Soc.* **2006**, *128*, 8734) an elegant solution to this problem. One key step in the synthesis was the intramolecular Diels-Alder cyclization of **1** to **2**.

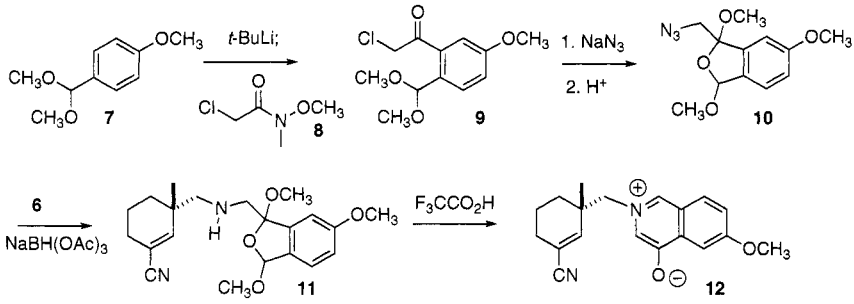


1 **2** **3**

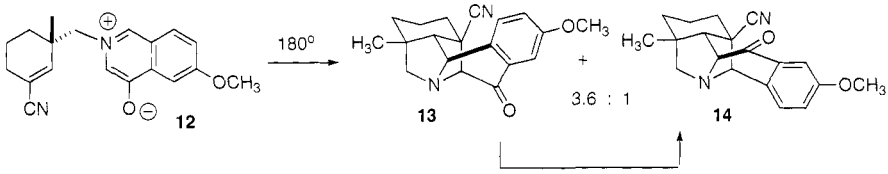
The convergent construction of **1** by dipolar cycloaddition presented some interesting challenges. One half was prepared from 3-methylcyclohexenone **4**. Addition of Et_2AlCN followed by triflation gave **5** in regiocontrolled fashion. Reduction followed by Pd-catalyzed coupling of the enol triflate then led to the aldehyde **6**. An intriguing question is how one would prepare **6** in enantiomerically pure form.



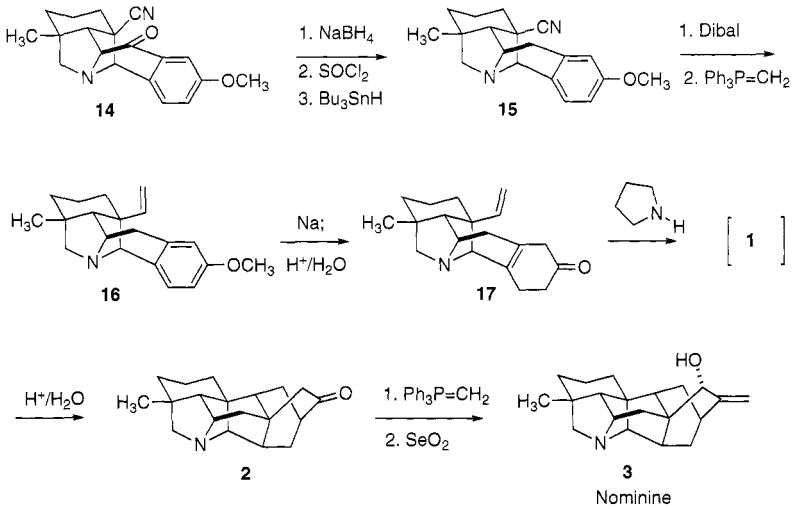
The other half of **1** was prepared from the acetal **7**. Lateral metalation followed by acylation with the Weinreb amide **8** gave the ketone **9**. Displacement with azide followed by exposure to acid gave the bridged acetal **10**, which was condensed reductively with **6** to give the oxidopyridinium betaine **12**.



Two products, **13** and **14**, could arise from the dipolar cycloaddition of **12**. It was not clear at the outset which would be preferred. In the event, it did not matter. Even though the thermal equilbrium favored the undesired **13**, equilibration was efficient, and the two were easily separated.



With **14** in hand, the stage was set for the intramolecular Diels-Alder cyclization. In fact, the diene **1** was not isolated. The evidence for the intermediacy of **1** was the observation that on exposure to pyrollidine in methanol at 60°, the Birch reduction product **17** smoothly cyclized to **2**. Methylenation followed by kinetic, axial-selective SeO_2 oxidation then completed the synthesis of **3**.

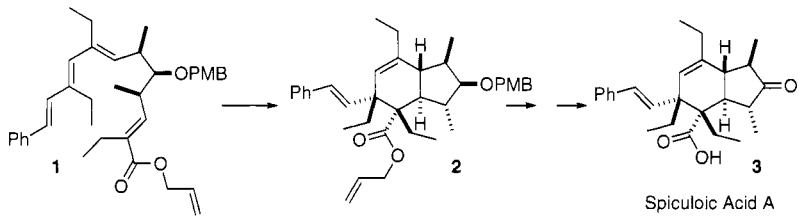


The concise elegance of this 17-step synthesis of the heptacyclic hetesine alkaloid nominine **3** is all the more apparent when it is compared with the only previously-reported synthesis, published just two years earlier, which took 40 steps.

The Intramolecular Diels-Alder Reaction in Natural Product Synthesis

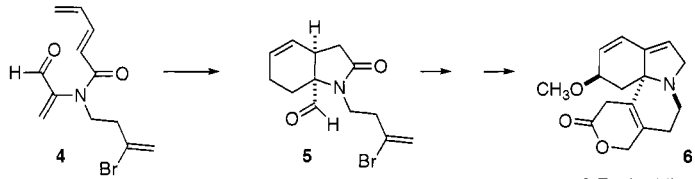
August 13, 2007

A key step in the Gin synthesis of the hetesine alkaloid nominine reviewed last week (OHL August 6, 2007) was an intramolecular Diels-Alder reaction. There have been several other recent applications of intramolecular Diels-Alder cyclizations in natural product synthesis. In the route to spiculoic acid A **3** reported (*Chem. Commun.* **2006**, 2863) by Victor Lee and Jack E. Baldwin of Oxford University, the activating electron-withdrawing ester is located at the end of the nonatriene **1**. Under such circumstances, cyclization is rapid at room temperature, even in this highly substituted example, and it leads to the trans ring fusion, as illustrated.



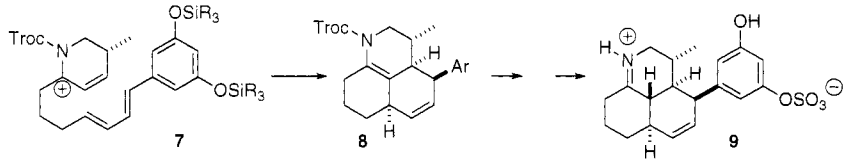
Spiculoic Acid A

Retrosynthetic analysis of β-erythroidine **6** suggested (*Organic Lett.* **2006**, *8*, 3689) to Raymond L. Funk of Pennsylvania State University the intramolecular Diels-Alder cyclization of the triene **4**. Note that in this case, the activating carbonyl is internal on the nonatriene. Under such circumstances, the cyclization requires heating, and leads to the *cis* ring fusion. The contrast between the cyclization of **1** and the cyclization of **4** has been rationalized by charge transfer in this concerted but non-synchronous reaction proceeding to give initially the five-membered ring with nonatrienes such as **1**, but initially the nine-membered ring with nonatrienes such as **4**.



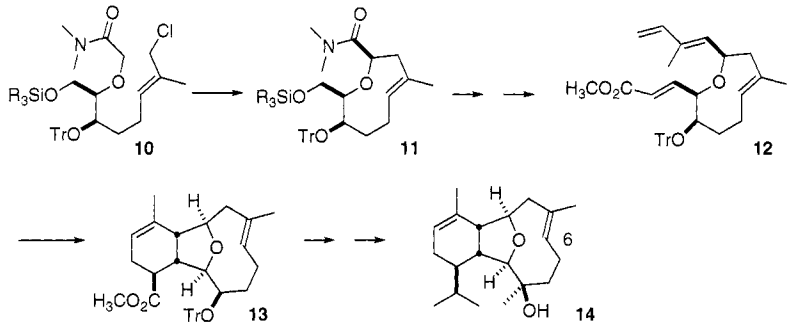
β-Erythroidine

Allylic carbocations can also be effective dienophiles, as illustrated by the cyclization of **7** to **8** in the course of the synthesis of symbioimine **9** developed (*Organic Lett.* **2006**, *8*, 5605) by Barry B. Snider of Brandeis University. A very different route to symbioimine was described (*Angew. Chem. Int. Ed.* **2006**, *45*, 4767) by Martin E. Maier of the Universität Tübingen, based on the intramolecular Diels-Alder cyclization of a decatriene.



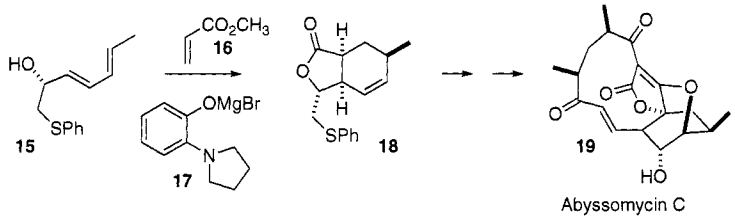
Symbioimine

Syntheses of 6*Z*-cladiellin diterpenes, but not of 6*E*-cladiellins, had been reported. The key to the intramolecular Diels-Alder approach to the *E* cladiellin diterpenes devised (*J. Am. Chem. Soc.* **2006**, *128*, 15851) by Deukjoon Kim of Seoul National University was the intramolecular alkylation that set the relative configuration of **11**.



6*E*-Cladiella-6,11-diene-3-ol

The dienophile and the diene do not have to be covalently attached for a Diels-Alder reaction to be intramolecular. In the course of preparing starting material for the synthesis of abyssomycin C **19**, K. C. Nicolaou of Scripps, La Jolla found (*Angew. Chem. Int. Ed.* **2006**, *45*, 3256) that that addition of methyl acrylate **16** to the sorbic acid-derived alcohol **15** proceeded well only in the presence of the magnesium salt **17**, which is presumably serving to complex the diene and the dienophile prior to cycloaddition.



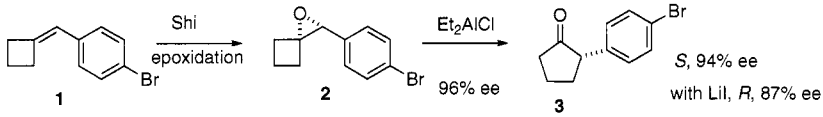
Abyssomycin C

Several other noteworthy advances in intramolecular Diels-Alder cyclization are reported in *Tetrahedron Lett.* **2006**, *47*, 4671, *Chem. Commun.* **2006**, 3646, *J. Org. Chem.* **2006**, *71*, 6701, and *Organic Lett.* **2006**, *8*, 5693. The work described in *Chemistry Lett.* **1989**, 1947 is also worth re-reading.

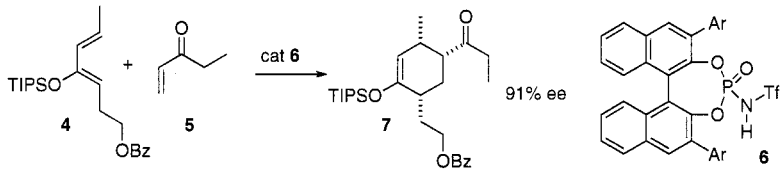
Catalytic Enantioselective Carbon-Carbon Ring Construction

August 20, 2007

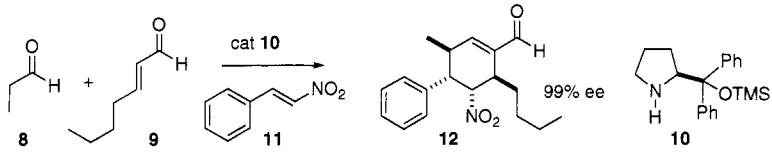
A variety of effective strategies for catalytic enantioselective ring construction have recently been developed. The simplest approach is to start with a prochiral ring. Yian Shi of Colorado State University has applied (*Angew. Chem. Int. Ed.* **2006**, *45*, 1429) his enantioselective epoxidation protocol to arylidene cyclobutanes such as **1**. The epoxide **2**, formed in high ee, on pinacol rearrangement gives the cyclopentanone **3** with retention of the high ee. Alternatively, exposure of **2** to LiI gives the *opposite enantiomer* of **3**, still in high enantiomeric excess. For the same approach with arylidene cyclopropanes to prepare cyclobutanones, see *J. Org. Chem.* **2006**, *71*, 9519.



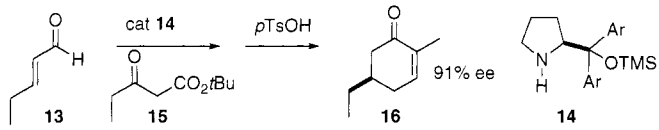
A variety of enantioselective Diels-Alder catalysts work well with highly reactive dienes and dienophiles. Hisashi Yamamoto of the University of Chicago has developed(*J. Am. Chem. Soc.* **2006**, *128*, 9626) a chiral Bronsted acid **6** that promotes the cycloaddition of ethyl vinyl ketone **5** to less reactive dienes such as **4** with high enantioselectivity.



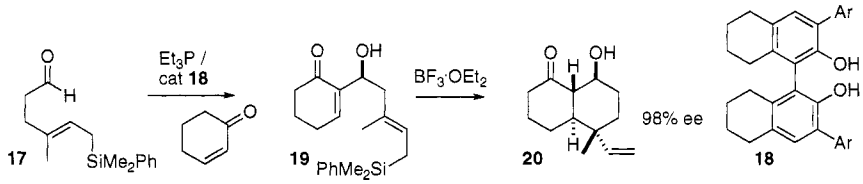
Two elegant methods for enantioselective organic catalyst-mediated Michael addition leading to substituted cyclohexanes in high enantiomeric purity have appeared. The first, reported (*Nature* **2006**, *441*, 861) by Dieter Enders of RWTH Aachen, involves the condensation of an aldehyde, an α,β-unsaturated aldehyde and an aryl nitroalkene, mediated by the now-common proline-derived catalyst **9**. A key question is whether *alkyl* nitroalkenes work as well.



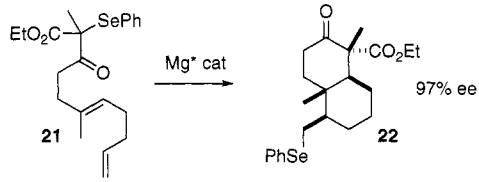
A complementary approach was reported (*Chem. Commun.* **2006**, 4928) by Karl Anker Jørgensen of Aarhus University. Using the proline-derived catalyst **14** that he has championed, Professor Jørgensen condensed α,β-unsaturated aldehydes such as **13** with *t*-butyl acetoacetates such as **15**, to give, after cyclization and hydrolysis with *p*TsOH, the 5-alkyl cyclohexenone **16** in high ee.



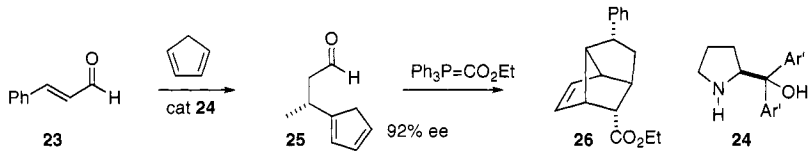
Two elegant strategies for the enantioselective construction of *bicyclic* systems have also appeared. Scott E. Schaus of Boston University, building on his earlier observation that the catalyst **18** directs the aldol condensation (Morita-Baylis-Hillman reaction) of cyclohexenone to aldehydes with high ee, has applied (*Angew. Chem. Int. Ed.* **2006**, *45*, 4929) the reaction to a series of aldehydes such as **17** bearing unsaturated silanes. Exposure of the intial adducts **19** to $BF_3{\cdot}OEt_2$ leads to cyclization to the bicycle **20**, in high ee.



Dan Yang of the University of Hong Kong has been developing the chiral Lewis acid-mediated radical cyclization of selenyl ketones such as **21**. She has now found (*Angew. Chem. Int. Ed.* **2006**, *45*, 255) a Mg catalyst that directs both monocyclic and bicyclic cyclization in high ee.



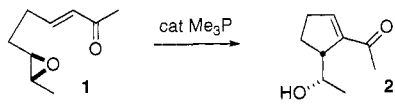
Yujiro Hayashi of the Tokyo University of Science has devised (*Angew. Chem. Int. Ed.* **2006**, *45*, 6853) a very short approach to *tricyclic* products such as **26**. Using yet another proline-derived catalyst, cyclopentadiene added in conjugate fashion to cinnamaldehyde **23** to give **25** as an inconsequential of double bond isomers. Homologation followed by warming then gave the tricyclic adduct **26** in high ee.



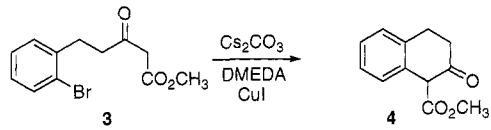
New Directions in C-C Ring Construction: The Overman Synthesis of Guanacastepene N

August 27, 2007

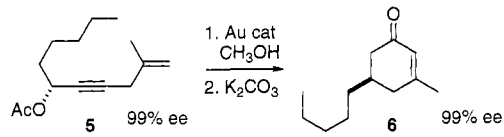
The opening of epoxides by ketone enolates is notoriously difficult. Marie E. Krafft of Florida State University has found (*Chem. Commun.* **2006**, 2977) a simple solution to this problem. On exposure to the simple organocatalyst PMe_3, the epoxy ketone **1**, readily prepared in enantiomerically-pure form, was smoothly converted to the cyclopentane **2**.



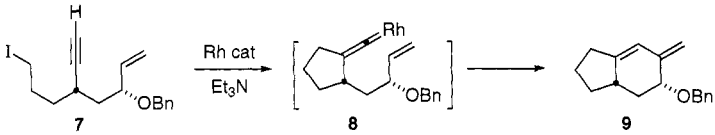
Transition metal catalysis allows many C-C bond-forming reactions that are not otherwise available. Chaozhong Li of the Shanghai Institute of Organic Chemistry has reported (*J. Org. Chem.* **2006**, *71*, 6427) the Cu-mediated cyclization of the *o*-bromophenyl ketone **3** to **4**.



Many examples of Au catalysis for organic synthesis have been reported recently. One of the most elegant is the transformation of **5** to **6** developed (*J. Am. Chem. Soc.* **2006**, *128*, 12614) by Fabien Gagosz of the Ecole Polytechnique. Allylic acetates such as **5** are readily prepared in high ee, by enantioselective reduction of the ketone or by enantioselective addition of an alkynyl anion to the aldehyde. This makes 5-alkyl cyclohexenones such as **6** readily available in high ee.



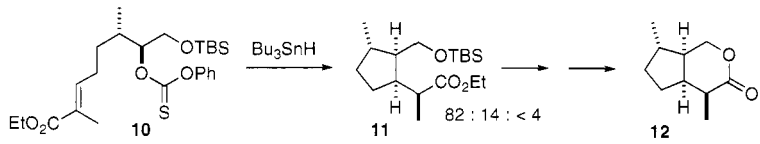
There have also been advances in *polycyclic* ring construction. Chulbom Lee of Princeton University has been exploring (*J. Am. Chem. Soc.* **2006**, *128*, 14818) the reactivity of metal alkynyls and metal vinylidenes derived from terminal alkynes. Deprotonation of the alkynyl Rh-H derived from **7** led to a species that was nucleophilic at the β carbon. Intramolecular alkylation ensued, leading to an intermediate Rh vinylidene **8** that then inserted into the alkene to give **9**. In related work (*J. Am. Chem. Soc.* **2006**, *128*, 15598) the intermediate Rh vinylidene inermediate was used to effect intramolecular conjugate addition.



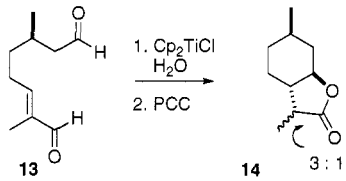
New Directions in C-C Ring Construction: The Overman Synthesis of Guanacastepene N

August 27, 2007

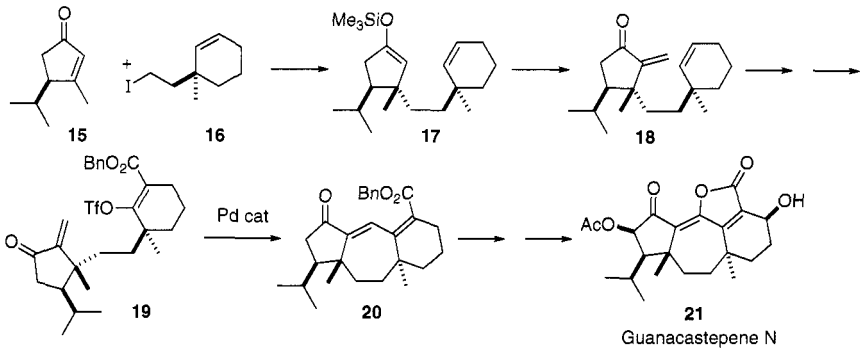
Free radical cyclizations can be surprisingly selective. Johann Mulzer of the Universität Wien has observed (*Eur. J. Org. Chem.* **2006**, 901) that reduction of **10** proceeded to give **11** with high diastereocontrol. The *Z* isomer of **10** worked equally well, but diastereocontrol was much lower with the corresponding methyl ester or with a bulkier silyl ether



The cyclization of **13** reported (*Organic Lett.* **2006**, *8*, 5433) by Juan M. Cuerva and J. Enrique Oltra of the University of Granada, which probably also involves single electron transfer, also proceeded with high diastereocontrol. Note that in this case, the newly-formed bonds are each equatorial on the forming cyclohexane ring.



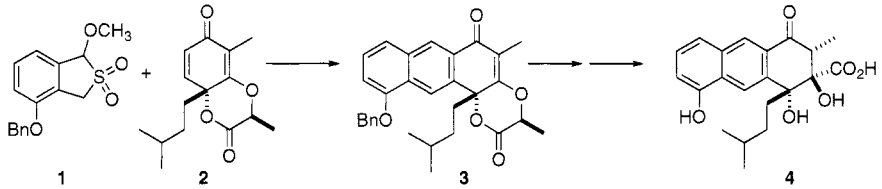
The key feature of the guanacastepenes, represented by guanacastepene N **21**, is the central highly-substituted cycloheptane ring. In his synthesis of **21** (*J. Am. Chem. Soc.* **2006**, *128*, 13095), Larry E. Overman of the University of California, Irvine, prepared this central ring by the intramolecular Heck cyclization of the alkenyl triflate **19**. This 7-endo cyclization, proceeding by initial addition to the distal end of the alkene, is unusual, in that the intramolecular Heck reaction usually proceeds to give the 6-exo product.



The Pettus Synthesis of (+)-Rishirilide B

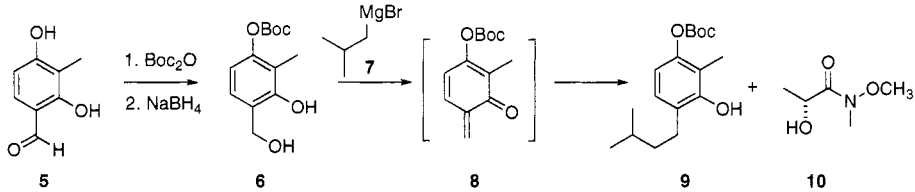
September 3, 2007

(+)-Rishirilide **4**, an inhibitor of α_2-macroglobulin, a tetrameric serum glycoprotein that is an irreversible protease inhibitor, has a deceptively simple structure. Thomas R. R. Pettus of the University of California at Santa Barbara has reported (*J. Am. Chem. Soc.* **2006**, *128*, 15625) a concise route to **4**, based on the highly regioselective Diels-Alder addition of the enantiomerically-pure dienophile **2** to the diene derived from **1**.

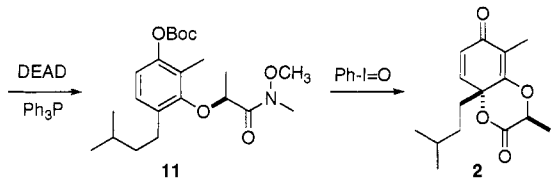


1 **2** **3** **4**

The preparation of **2** was carried out from the aldehyde **5**. Selective protection of the less hindered phenol followed by reduction gave the benzyl alcohol **6**. On exposure to excess Grignard reagent **7**, the primary alcohol of **6** apparently underwent elimination to give the *o*-quinone methide **8**, conjugate addition to which gave **9**. Mitsunobu coupling of **9** with the lactic acid amide **10** proceeded with clean inversion, to give **11**. The methoxy methyl amide of **11** was required for the oxidative dearomatization to **2** to proceed efficiently.

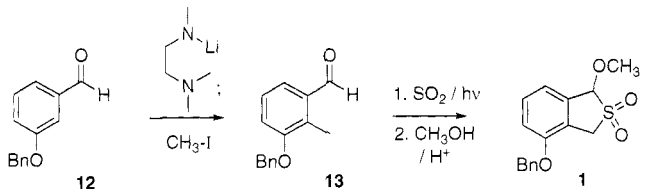


5 **6** **8** **9** **10**

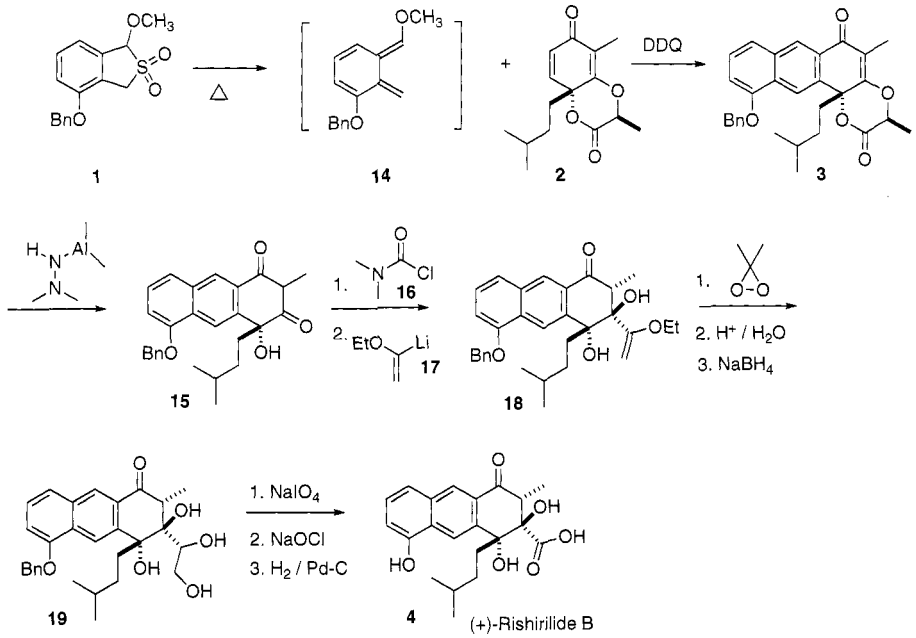


11 **2**

The preparation of the masked diene **1** started with the aldehyde **12**. Following the Comins procedure, metalation of the derived hemiaminal alkoxide and subsequent addition of methyl iodide gave **13**. Addition of SO_2 to the photoenol derived from **13** followed by etherification of the labile secondary alcohol so formed then gave **1**.



The dienophile **2** should undergo cycloaddition with high facial selectivity. That is not relevant in this application, as addition to the intermediate quinone methide **14** was followed by elimination and oxidative aromatization. The regioselectivity of the addition, delivering **3**, was, however, critical for the success of the synthesis.

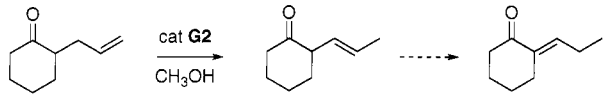


With **3** in hand, what remained was a one-carbon homologation. This was accomplished by selective O-acylation with dimethyl carbamoyl chloride **16**. Subsequent addition of an excess of anion **17** led, via alkoxide-directed addition to the remaining ketone carbonyl followed by deacylation, to the desired adduct **18**. Careful cleavage, to avoid lactone formation, then delivered **4**. Note that this synthesis of (+)-rishirilide B **4** would be classified as enantioselective, since the intial stereogenic center of **2**, that set the absolute configuration of the dearomatized ring of **2**, was not included in the final product.

Selective Reactions of Alkenes

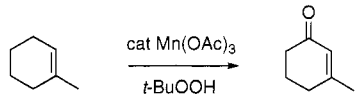
September 10, 2007

Gentle tapping of a terminal alkene specifically to the corresponding methyl-substituted internal alkene is a potentially value-adding transformation, as illustrated by the conversion of the inexpensive allylated ketone **1** to the propenylated ketone **2**, that would be difficult to prepare by other means. The procedure developed (*Organic Lett.* **2006**, *8*, 5481) by Stephen Hanessian of the Université de Montréal is particularly appealing, as many labs already have the second-generation Grubbs catalyst. The mildness of the protocol is underscored by the observation that the isomerization stops at **2**, not going on to the much more stable **3**.



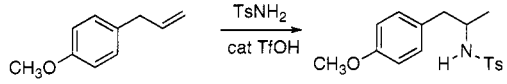
1 **2** **3**

Allylic oxidation, to convert an alkene into the enone, has usually been effected using stoichiometric chromium. Tony K. M. Shing of the Chinese University of Hong Kong has described (*Organic Lett.* **2006**, *8*, 3149) a promising alternative, using catalytic $Mn(OAc)_3$ with *t*-butylhydroperoxide.



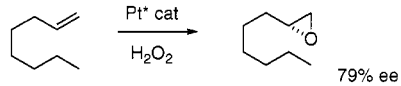
4 **5**

Chuan He of the University of Chicago has shown (*Organic Lett.* **2006**, *8*, 4175) that triflic acid is an effective catalyst for alkene hydroamination and hydroetherification. The reaction works both intermolecularly (illustrated, **6** → **7**) and intramolecularly.



6 **7**

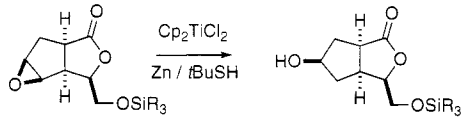
The catalytic epoxidation of a terminal alkene with high ee has been a long-sought goal. Giorgio Strukul of the Università di Venezia recently (*J. Am. Chem. Soc.* **2006**, *128*, 14006) reported a solution to this problem, using a chiral Pt cation catalyst and hydrogen peroxide. If an epoxide of even higher ee were required, it would be possible to polish these products following the Jacobsen procedure,



8 **9**

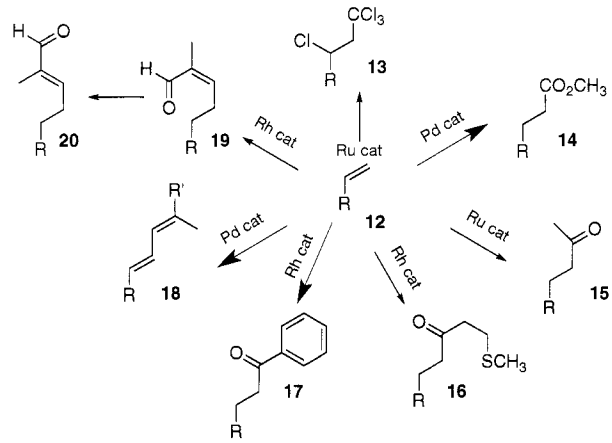
selectively hydrolyzing away the minor enantiomer.

Subrata Ghosh of the Indian Association for the Cultivation of Science, Kolkota has observed (*Organic Lett.* **2006**, *8*, 3781) remarkable regioselectivity in the Ti(III)-mediated reduction of the epoxide **10**. This selectivity may be due to steric interactions between the bulky titanocene and the endo silyloxymethyl group. The overall conversion of the alkene precursor to **11** is stereochemically complementary to the results expected from hydroboration.



10 **11**

Much progress has been reported on the specific homologation of terminal alkenes. Kay Severin of the École Polytechnique Fédéral de Lausanne has developed (*J. Am. Chem. Soc.* **2006**, *128*, 7440) Ru catalysts for the free radical homologation of alkenes, with CCl_4, to give **13**, or with *p*-tosyl chloride. Howard Alper of the University of Ottawa has optimized (*Organic Lett.* **2006**, *8*, 6143) conditions for



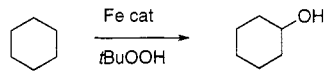
converting alkenes to esters such as **14**. Marc L. Snapper of Boston College has found (*Organic Lett.* **2006**, *8*, 2603) that alkene metathesis to form secondary allylic alcohols can be followed by alkene migration, to give ketones such as **15**. Andrew S. Weller and Michael C. Willis of the University of Bath (*Angew. Chem. Int. Ed.* **2006**, *45*, 7618) and Chul-Ho Jun of Yonsei University, Seoul (*Organic Lett.* **2006**, *8*, 2937) have improved procedures for alkene hydroacylation, giving **16** and **17** respectively. Andreas Kirschning of the Universität Hannover has shown (*Organic Lett.* **2006**, *8*, 135) that Heck conditions work well to couple a simple terminal alkene with an iodoalkene, to give dienes such as **18**. Finally, the C-H activation procedure developed (*J. Am. Chem. Soc.* **2006**, *128*, 5604) by Robert G. Bergman and Jonathan A. Ellman of the University of California, Berkeley leads initially to the *Z* aldehyde **19**. This can be equilibrated under mild conditions to the more stable *E* isomer **20**.

Selective C-H Functionalization

September 17, 2007

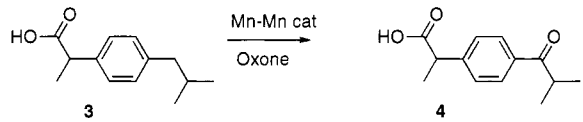
Direct conversion of an unactivated C-H bond to a C-O, C-N or C-C bond is a powerful way to add valuable complexity to a substrate. While this is by no means a new approach (Friedel-Crafts acylation converts a C-H bond to a C-C bond), there have been several useful new developments.

Biosynthetic C-H oxygenation is mediated by the several isozymes of Fe-centered cytochrome P-450. Debkumar Bandyopadhyay of the Indian Institute of Technology, New Delhi has developed (*Chem. Comm.* **2006**, 4823) an Fe complex that catalyzed the oxidation of cyclohexane **1** to cyclohexanol **2**, with about 20 turnovers. Shinobu Itoh of Osaka City University has devised (*Chem. Comm.* **2006**, 4016) a Ni catalyst that effected the same conversion with about 600 turnovers, using MCPBA as the bulk oxidant.



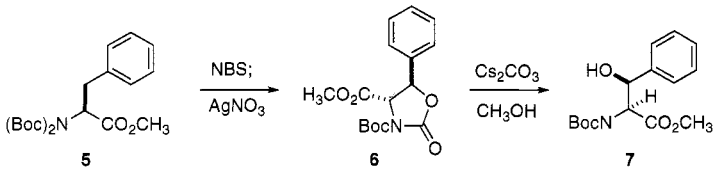
1 **2**

More complex substrates are also interesting. Robert H. Crabtree and Gary W. Brudvig of Yale University have shown (*Science* **2006**, *312*, 1941) that a Mn-Mn complex catalyzed the oxidation of **3** to **4** with high selectivity.



3 **4**

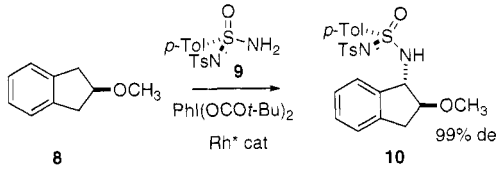
David Crich, now at Wayne State University, has reported (*J. Org. Chem.* **2006**, *71*, 7106) a different approach to C-H functionalization. Exposure of phenylalanine derivatives such as **5** to NBS gave the bromide, presumably as a epimeric mixture. Solvolysis lead to the product **6** and thus to **7** as single diastereomers.



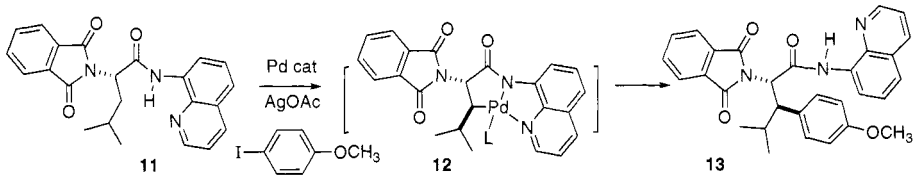
5 **6** **7**

C-H bonds can also be converted to C-N bonds. Paul Müller of the University of Geneva and Robert H. Dodd and Philippe Dauban of Gif-sur-Yvette have reported (*Angew. Chem. Int. Ed.* **2006**, *45*, 4641)

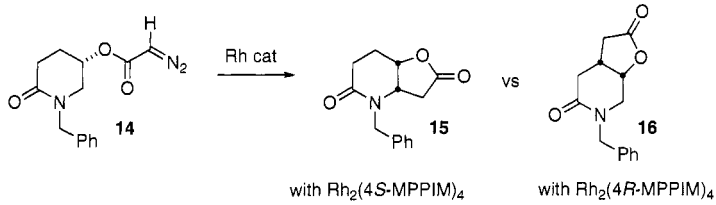
that oxidation of **9** in the presence of the prochiral **8** led to **10** in high de. David A. Powell of Merck Frosst Canada has also described (*Organic Lett.* **2006**, *8*, 6031) a protocol for the direct amidation of allylic and benzylic C-H bonds.



One of the most powerful of C-H functionalizations is the conversion to a C-C bond. E. J. Corey of Harvard University found (*Organic Lett.* **2006**, *8*, 3391) that oxidation of the amino acid derivative **11** with Pd salts led to the C-H activated product **12**. If the palladation was run in the presence of an aryl iodide, intermediate **12** coupled to give **13**, with high diastereocontrol.



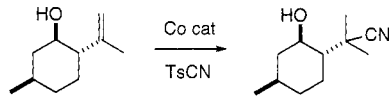
Rh-mediated carbene transfer is also a powerful method for converting a C-H to a C-C bond. Andrew G. H. Wee of the University of Regina has described (*Chem. Commun.* **2006**, 3732) the cyclization of the enantiomerically-pure diazo acetate **14**. The C-H bond adjacent to the N is the more reactive, and is the site of insertion with racemic catalysts, leading to **15**. With the enantiomerically-pure catalyst Rh_2(4*S*-MPPIM)$_4$, **15** was the only product observed. With the enantiomeric catalyst Rh_2(4*R*-MPPIM)$_4$, the chirality of the catalyst dominated, so the major product was **16**. The Rh_2(4*R*-MPPIM)$_4$, and Rh_2(4*S*-MPPIM)$_4$ catalysts were developed by Michael P. Doyle of the University of Maryland.



New Methods for Carbon-Carbon Bond Formation

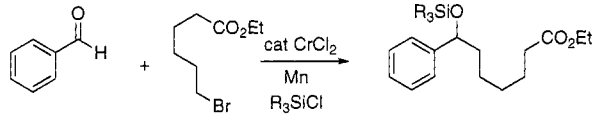
September 24, 2007

Efficient new methods for the construction of C-C single, double and triple bonds have recently been reported. Erick M. Carreira of ETH Zurich has developed (*Angew. Chem. Int. Ed.* **2007**, *46*, 4519) a Co catalyst for the Markovnikov hydrocyanation of alkenes, as illustrated by the conversion of **1** to **2**. This procedure was also found to be compatible with esters, amides, and ethers. A complementary catalyst to deliver the anti-Markovnikov product would certainly be welcome.



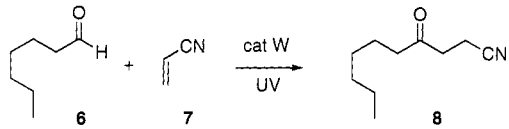
1 **2**

The reductive addition of an organic halide such as **4** to an aldehyde such as **3** is one of the basic transformations of organic synthesis. Ludger A. Wessjohann of the Leibniz Institute of Plant Biochemistry, Halle, Germany, and Henri S. Schrekker of the Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, have described (*Tetrahedron Lett.* **2007**, *48*, 4323) a convenient procedure that is catalytic in Cr, using Mn as the bulk reductant. This approach offers the additional advantage of producing the protected alcohol **5** directly.



3 **4** **5**

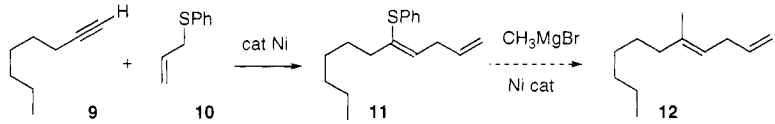
The direct generation of formyl radicals has been a long-sought goal. Maurizio Fagnoni of the Università degli Studi di Pavia has reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 2531) a promising approach, based on the photochemical activation of a tetrabutylammonium tungstate (TBADT) catalyst. Although the intermolecular additions required an activated alkene, intramolecular addition (not reported) to unactivated alkenes may work well.



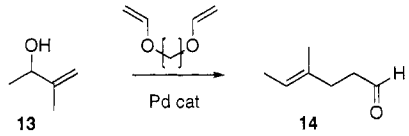
6 **7** **8**

The stereocontrolled construction of alkenes is a continuing problem. Masato Tanaka of the Tokyo Institute of Technology has established (*Organic Lett.* **2007**, *9*, 263) a promising approach, based on the Ni-catalyzed addition of allyl phenyl sulfide **10** to a terminal alkene **9** to give **11** as the dominant

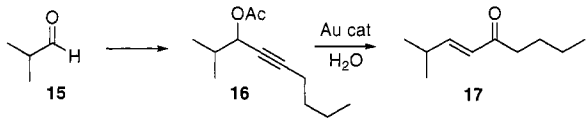
product. The authors do not report further transformations of **11**, but it is likely that Ni-catalyzed coupling with, for instance, CH_3MgBr, would convert **11** into **12**.



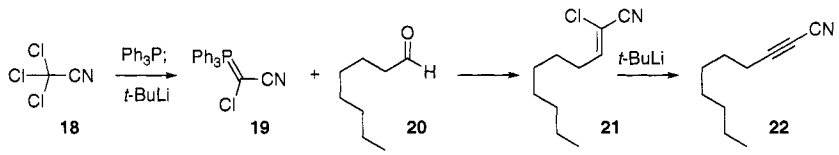
Claisen rearrangement is also a good way to prepare disubstituted and trisubstituted alkenes. The simplest version of this reaction is two-carbon homologation by conversion of an allylic alcohol to the corresponding vinyl ether, followed by heating. Xudong Wei of Boehringer-Ingelheim, Ridgefield, CT has found (*J. Org. Chem.* **2007**, *72*, 4250) that commercial triethylene glycol divinyl ether served well as a high-boiling vinyl donor. Pd was used to catalyze the vinyl ether exchange.



An enone such as **17** would often be prepared by phosphonate homologation of the aldehyde **15**. Liming Zhang of the University of Nevada, Reno has optimized (*Adv. Synth. Cat.* **2007**, *349*, 871) a practical alternative strategy, the key step of which was the Au-catalyzed rearrangement of the easily-prepared propargylic acetate **16**.



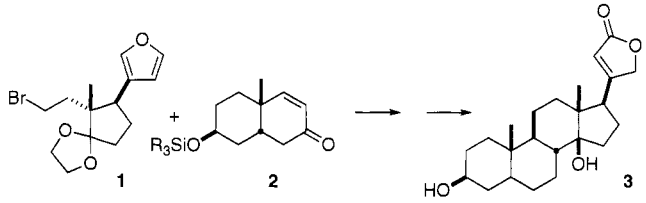
New methods for the construction of C-C triple bonds appear only rarely. Doo Ok Jang of Yonsei University has described (*Tetrahedron Lett.* **2007**, *48*, 2299) such a method. A phosphorane **19** was prepared by combining the nitrile **18** with Ph_3P and *t*-butyl lithium. Condensation of an aldehyde **20** with **19** gave the nitrile **21**, which could be isolated. Alternatively, treatment with an additional equivalent of *t*-butyl lithium in the same pot converted **21** to the alkyne **22**.



The Nakada Synthesis of (+)-Digitoxigenin

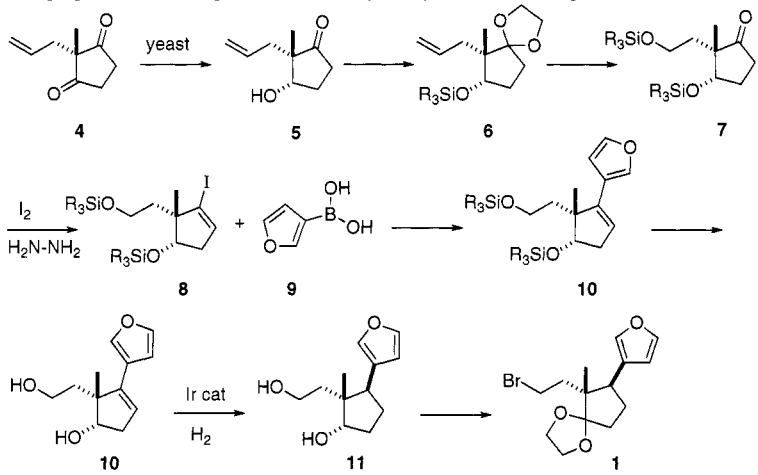
October 1, 2007

The total synthesis of steroids such as (+)-digitoxigenin **3** has been studied for more than sixty years, yet it has never been thought that such studies would lead to a preparative route that would be competitive with partial synthesis from the abundant plant sterols. The enantioselective synthesis of **3** recently (*Tetrahedron Lett.* **2007**, *48*, 1541) described by Masahisa Nakada of Waseda University suggests that the preparative synthesis of even such complex polycarbocycles may in fact be practical. A key step in the synthesis of **3** was the conjugate addition of the cuprate derived from **1** to the enone **2**.

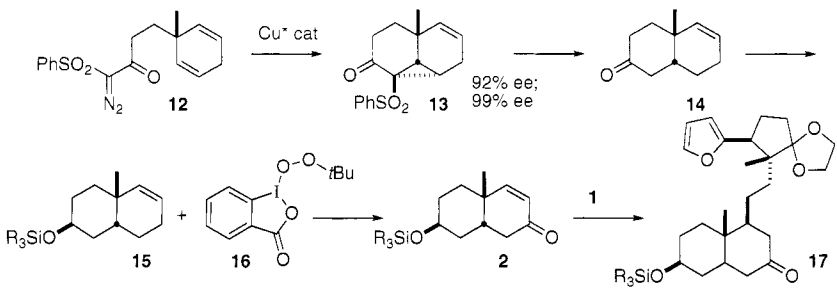


For this convergent approach to be effective, both **1** and **2** had to first be prepared in enantiomerically-pure form. The synthesis of **1** started with the bakers' yeast reduction of the prochiral diketone **4** to give **5** in high ee. The key problem was the establishment of the ternary center of **1**. This was accomplished by coupling the iodide **8** with the boronic acid **9**. Hydroxyl-directed hydrogenation of **10** then led to the desired **1**.

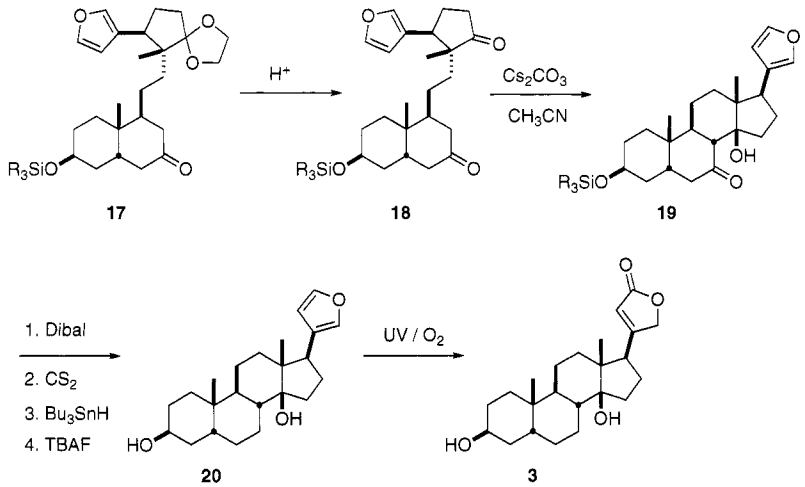
The preparation of **2** began with Cu-catalyzed cyclization of the prochiral diene **12** to give the



crystalline **13**. Recrystallization raised the ee of **13** to >99%. Reductive opening of **13** gave **14**, which was reduced and protected to give **15**. Oxidation of **15** with the Ochiai reagent **16** provided the enone **2**. Conjugate addition of **1** proceeded across the more open face of the enone **2**, to give **17**.



The key step to close the B ring of the steroid was the intramolecular aldol condensation of **18** to give **19**. The β-hydroxy ketone so produced was too sensitive to reduce by direct methods, so the monoxanthate was prepared from the derived diol, and then reduced under free radical conditions, leading to the diol **20**. Singlet oxygenation of **20** then completed the synthesis of **3**.

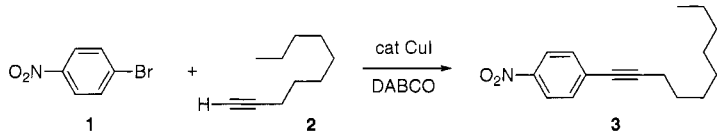


Clearly, the strength of this synthesis is the elegant construction of the AB enone **2**. Even more important is the demonstration of a general convergent route to the steroids, by addition of an enantiomerically-pure D ring moiety to an AB fragment. The power of asymmetric synthesis makes the precursors **1** and **2** readily available in the necessary enantiomerically-pure form.

Preparation of Benzene Derivatives

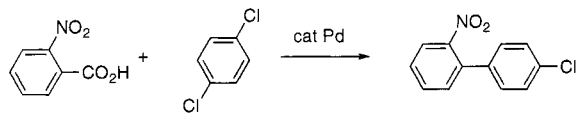
October 8, 2007

There are many ways Pd can be used to catalyze the substitution of an aryl halide. Jin-Heng Li of Hunan Normal University, Changsha, has found (*J. Org. Chem.* **2007**, *72*, 2053) that with the appropriate choice of ligand, Cu can replace Pd in many of these reactions. Sonogashira (**1** +**2** → **3**), Suzuki and Heck couplings have been carried out this way. One limitation is that whereas many of the Pd-catalyzed transformations proceed with > 1000 turnovers, the Cu-mediated reactions require 10 mol % catalyst. In related work, Christopher J. Parkinson of CSIR Biosciences, Modderfontein, South Africa, has shown (*Tetrahedron Lett.* **2007**, *48*, 3289) that the Cu-mediated coupling of acetoacetate with an aryl halide works well.



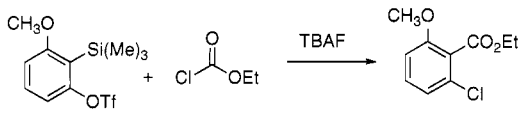
1 **2** **3**

An active Pd intermediate for cross-coupling can also be prepared by decarboxylation. This homologation has been studied independently by Lukas J. Goossen of the TU Kaiserslautern (*J. Am. Chem. Soc.* **2007**, *129*, 4824) and by Jean-Michel Becht of the Université de Haute-Alsace and Alain Wagner of Novalyst Discovery (*Organic Lett.* **2007**, *9*, 1781). In a related development, Marisa C. Kozlowski of the University of Pennsylvania has established (*Organic Lett.* **2007**, *9*, 2441) a protocol for the reduction decarboxylation of aromatic acids.



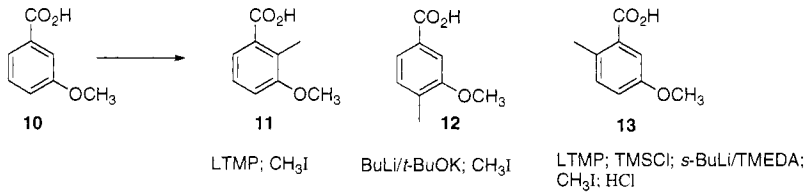
4 **5** **6**

Hiroto Yoshida and Atsutaka Kunai of Hiroshima University have developed (*Chem. Commun.* **2007**, 2405) an elegant procedure for the insertion of arynes into acid chlorides, including ethyl chloroformate **8**. With the unsymmetrical aryne derived from **7**, the addition was directed by the *o*-methoxy group.

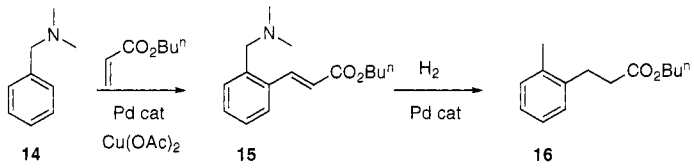


7 **8** **9**

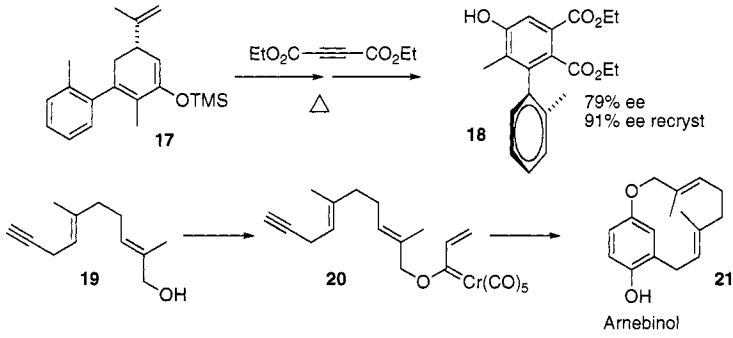
Substitution of a benzene ring can also be effected by directed metalation. Jacques Mortier of the Université du Maine has devised (*J. Org. Chem.* **2007**, *72*, 3419) complementary procedures for the selective metalation and alkylation of *m*-anisic acid **10**. These could be classified as C-H functionalization reactions.



Direct C-H functionalization of benzene derivatives can also be effected using transition metal catalysts. Zhangjie Shi of Peking University has reported (*J. Am. Chem. Soc.* **2007**, *129*, 7666) the Pd-mediated *o*-homologation of benzyl amines such as **14**. Since the benzylic amine is easily hydrogenolyzed, this is also a procedure for selective homologation ortho to the simplest of benzene substituents, a methyl group.



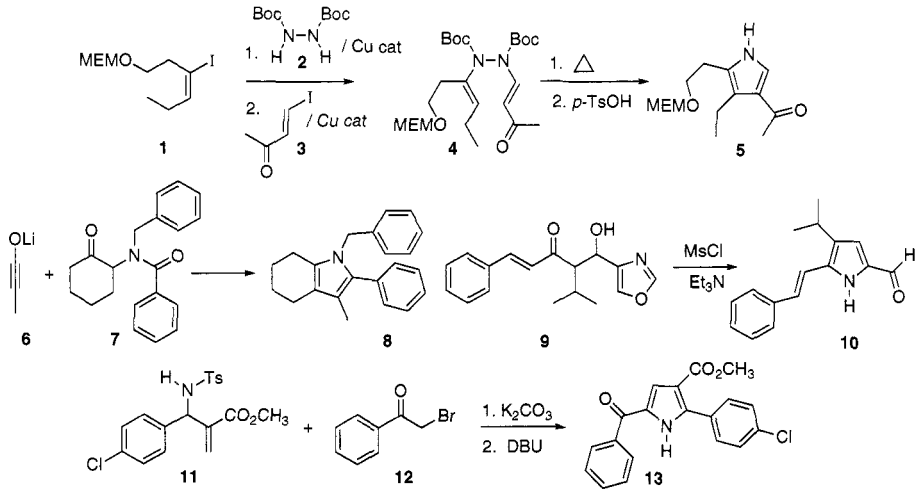
For highly-substituted benzene derivatives, it is sometimes best to build the ring. Two recent contributions are particularly noteworthy. Jiahua Chen, Junmin Quan and Zhen Yang of Peking University found (*Organic Lett.* **2007**, *9*, 805) that dienes such as **17**, readily prepared in enantiomerically-pure form from carvone, underwent cycloaddition and fragmentation to form the atropisomeric biphenyls in high ee. Yoko Saikawa and Masaya Nakata of Keio University have shown (*Tetrahedron Lett.* **2007**, *48*, 203) that the Dötz cyclization is sufficiently powerful to form even the strained metacyclophane natural product arnebinol **21**.



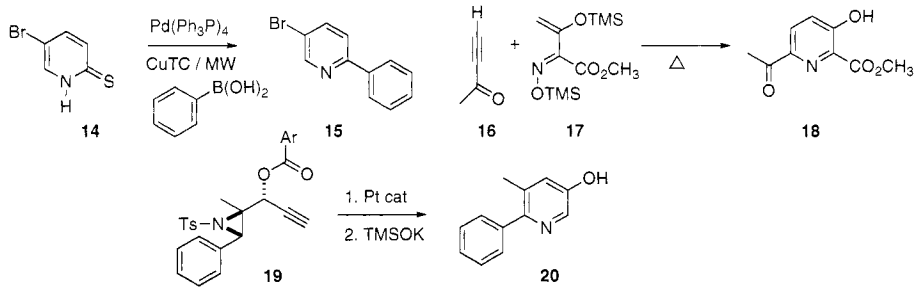
Preparation of Heteroaromatics: The Movassaghi Synthesis of (+)-Chimonanthine

October 15, 2007

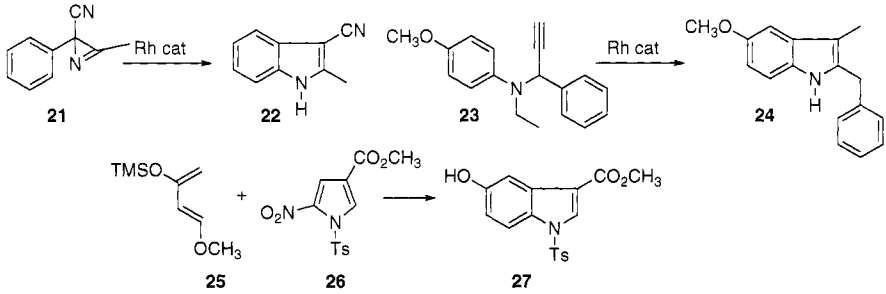
There has been a recent surge of enthusiasm for pyrrole synthesis. Stephen L. Buchwald of MIT has reported (*Organic Lett.* **2007**, *9*, 973) a clever application of his Cu-catalyzed N-vinylation chemistry, leading to hydrazides such as **4**, which on heating rearrange to the pyrroles. Mitsuro Shindo of Kyushu University has expanded (*Organic Lett.* **2007**, *9*, 1963) his studies of ynolate chemistry to include addition to α-amido ketones such as **7**, leading to the pyrrole **8**. Jonathan T. Reeves of Boehringer Ingelheim, Connecticut has found (*Organic Lett.* **2007**, *9*, 1875) that on dehydration, aldol products such as **9** from formyl oxazole rearrange to the pyrrole. And, Jae Nyoung Kim of Chonnam National University, Gwangju has condensed (*Tetrahedron Lett.* **2007**, *48*, 4119) Baylis-Hillman adducts such as **11** with halo ketones to give pyrroles.



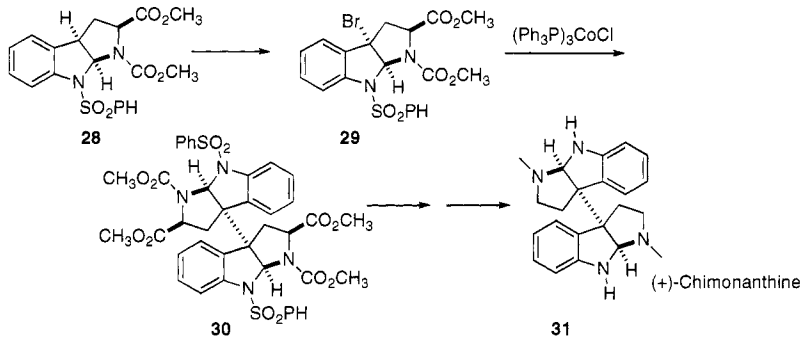
There has also been substantial interest in the synthesis of pyridines. C. Oliver Kappe of the Karl-Franzens-University, Graz has found (*J. Org. Chem.* **2007**, *72*, 4440) that thioamides such as **14** couple smoothly under Pd catalysis with areneboronic acids, even more rapidly than the usually reactive alkenyl bromide. Hans-Dieter Arndt of the Universität Dortmund has developed (*J. Org. Chem.* **2007**, *72*, 4205) a hetero Diels-Alder approach to pyridines, based on the addition of alkynes such as **16** to the diene **17**. Richmond Sarpong of the University of California, Berkeley, has devised (*Organic Lett.* **2007**, *9*, 2167) an elegant Pt-catalyzed rearrangement of alkynyl aziridines such as **19**, giving, after sulfinate elimination, pyridines such as **20**.



A variety of approaches to indoles have been put forward. Koichi Narasaka, now at Nanyang Technical University, Singapore, has extended the utility of the aziridine approach to indoles, finding (*Chemistry Lett.* **2007**, *36*, 52) that the rearrangement is catalyzed by $Rh_2(tfa)_4$. Simple thermolysis of **21** led to a complex mixture that did not include **22**. In a complementary approach, Akio Saito and Yuji Hanazawa of Showa Pharmaceutical University have found (*Angew. Chem. Int. Ed.* **2007**, *46*, 3931) a Rh catalyst that converts propargyl amines such as **23** to indoles such as **24**. In a Diels-Alder route, Pedro Mancini of the Universidad Nacional del Litoral, Santa Fe, Argentina, has shown (*Tetrahedron Lett.* **2007**, *48*, 1435) that dienes add to nitro pyrroles such as **26** to give indoles.



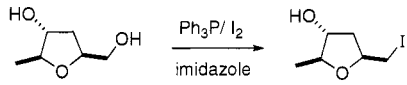
Many indole-derived natural products, exemplified by (+)-chimonanthine **31**, are dimers. Mohammad Movassaghi of MIT has devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 3725) an effective route to such dimers, bromination followed by metal-mediated one-electron reduction.



Organic Functional Group Transformation

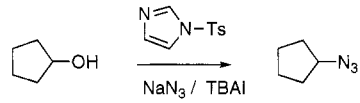
October 22, 2007

Both John Boukouvalas of the Université Laval (*Tetrahedron Lett.* **2007**, *48*, 2971) and Leo A. Paquette of the Ohio State University (*Organic Lett.* **2007**, *9*, 719) have found that the well-established I_2/Ph_3P/imidazole protocol for conversion of alcohols to iodides is primary selective, so **1** was converted smoothly into **2**.



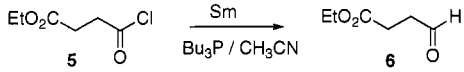
1 **2**

The conversion of alcohols to azides is also well established. Mohammad Navid Soltani Rad of Shiraz University of Technology has developed (*Tetrahedron Lett.* **2007**, *48*, 3445) a mild new reagent combination for effecting this transformation. Iodide is a component of the reaction mixture, so displacement of a secondary benzylic alcohol proceeded with partial racemization. The stereochemical outcome with isolated secondary alcohols was not reported.



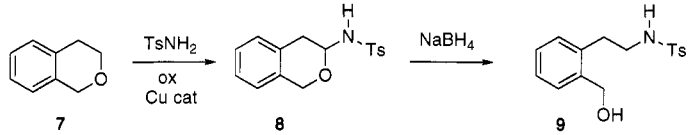
3 **4**

Both hydrogenation (Rosemund) and hydride have been used to reduce acid chlorides to aldehydes. Xueshun Jia of Shanghai University has shown (*Tetrahedron Lett.* **2007**, *48*, 971) that Sm metal also effects this transformation. Nitro groups and alkenes were stable to the conditions.



5 **6**

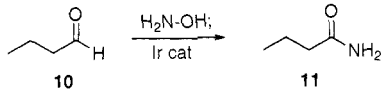
Methods for C-H functionalization are well developed. Xiao-Qi Yu of Sichuan University has taken advantage (*Organic Lett.* **2007**, *9*, 2277) of easy C-H amination to convert the ether **7** to the sulfonamide **8**. Reduction then delivered the hydroxy sulfonamide **9**.



7 **8** **9**

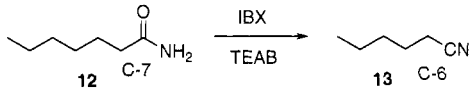
Conversion of an aldehyde to a primary amide would usually take three steps (acid, activation, amide). Jonathan M. J. Williams of the University of Bath has developed (*Organic Lett.* **2007**, *9*, 73) an

Ir catalyst that, in the presence of hydroxylamine, can effect the transformation of **10** to **11** in a single step.



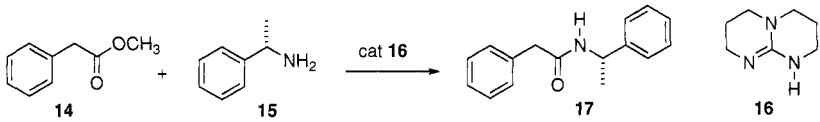
10 **11**

Degradation reactions, reactions that remove carbons, can also be useful. Krishnacharya G. Akamanchi of the University Institute of Chemical Technology, Mumbai has found (*J. Org. Chem.* **2007**, *72*, 662) that IBX converts primary amides such as **12** to the nitrile **13**, with loss of one carbon atom. This reaction is apparently proceeding via N-bromination followed by rearrangement to the isocyanate.



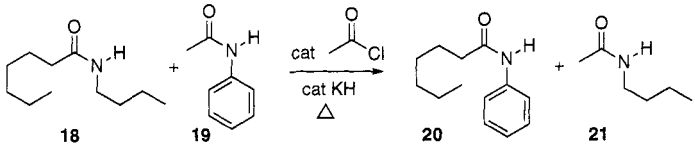
12 C-7 **13** C-6

There have been several other interesting developments in the synthesis of amides. Charles Mioskowski of the Université Louis Pasteur de Strasbourg has uncovered (*Tetrahedron Lett.* **2007**, *48*, 3863) a useful catalyst **16** for the condensation of esters with amines to form amides.



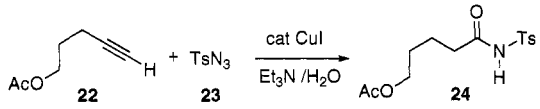
14 **15** **17** **16**

Samuel H. Gellman and Shannon S. Stahl of the University of Wisconsin have devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 761) a simple procedure for amide metathesis. Use of an excess of **19** would be expected to drive the **18** to **20** conversion to completion.



18 **19** **20** **21**

Anti-Markovnikov hydration of a terminal alkyne yields the corresponding carboxylic acid. Sukbok Chang of KAIST, Daejon has reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 1897) that CuI is an effective catalyst for the combination of a terminal alkyne **22** with a sulfonyl azide **23** to give the amide **24**. Internal alkynes are stable to the reaction conditions.



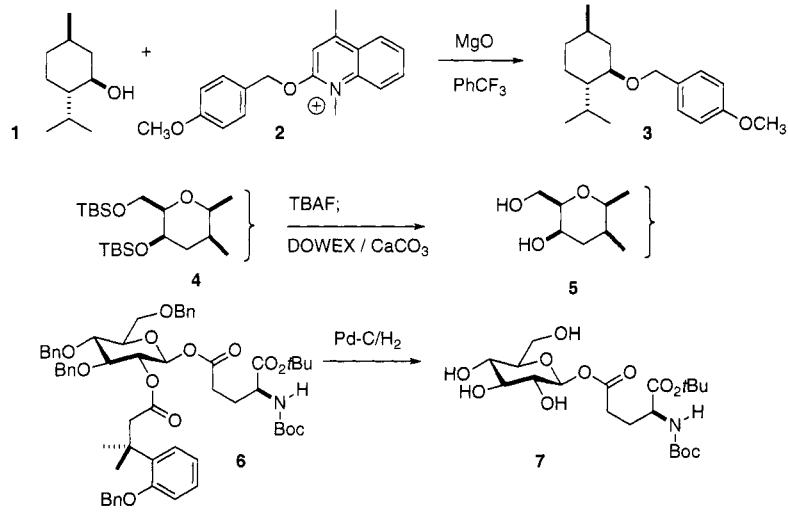
22 **23** **24**

Unfortunately, Professor Charles Mioskowski passed away in June. This column is dedicated to his memory.

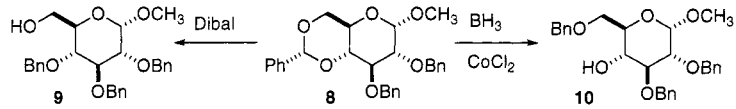
Organic Functional Group Protection

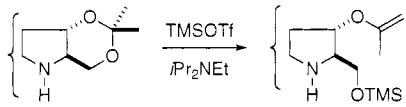
October 29, 2007

There have been several useful developments in alcohol protection. Gregory B. Dudley of Florida State University has devised (*Chem. Commun.* **2007**, 1436) a new reagent **2** for the preparation of *p*-methoxybenzyl (PMB) ethers. Yoshito Kishi of Harvard University, faced with the difficulty of isolating a deprotected natural product via aqueous work-up, found (*Organic Lett.* **2007**, *9*, 723) that the THF/TBAF reaction mixture could be mixed with a sulfonic acid ion exchange resin and $CaCO_3$, then simply filtered and evaporated. Benzyl ethers are commonly removed by hydrogenation at the end of a synthesis. David Crich, now at Wayne State University, desiring (*Organic Lett.* **2007**, *9*, 1613) to simultaneously remove an ester, created the protecting group illustrated in **6**. Hydrogenolysis followed by lactone formation liberated the free OH.



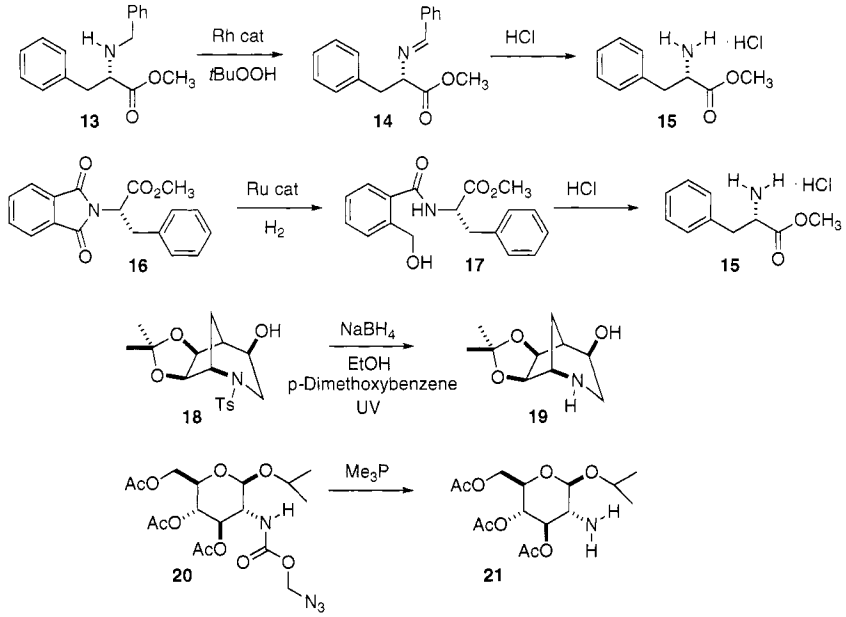
The protection of diols is also important. Usually, reduction of benzylidene protected diols such as **8** would lead to the primary benzyl ether **9**. Ken-ichi Sato of Kanagawa University has developed (*Tetrahedron Lett.* **2007**, *48*, 3103) conditions for the complementary reduction, to give selectively the secondary benzyl ether **10**. Larry E. Overman of the University of California, Irvine, applying a procedure originally developed by Scott D. Rychnovsky, found (*Organic Lett.* **2007**, *9*, 339) that the acetonide **11** could be converted selectively into **12**.





11 12

Nitrogen protecting groups can be removed both oxidatively and reductively. Michael P. Doyle of the University of Maryland has found (*Chem. Commun.* **2007**, 745) that Rh_2(caprolactamate)$_4$ mediates the oxidation of benzylamines such as **13** to the imine **14**. Exposure to HCl then gave the amine salt **15**. Takao Ikariya of Tokyo Institute of Technology has devised (*J. Am. Chem. Soc.* **2007**, *129*, 290) a Ru catalyst that is active for the hydrogenation of imides such as the phthalimide **16**. Exposure to HCl deprotected **17** to give **15**.



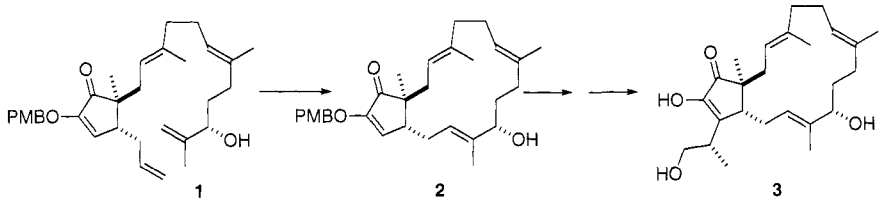
13 14 15 16 17 15 18 19 20 21

Although Ts is a convenient and robust protecting group for amines, it is sometimes difficult to remove. Stephen G. Bergmeier of Ohio University observed (*J. Org. Chem.* **2007**, *72*, 1024) that dissolving metal deprotection of **18** gave a complex mixture, but that the Yonemitsu procedure (*J. Am. Chem. Soc.* **1986**, *108*, 140) worked well. Extending the array of N protecting groups, Nicolas Winssinger of the Université Louis Pasteur has explored (*Organic Lett.* **2007**, *9*, 2223) the azidomethyl (Azoc) carbamate **20**. The Azoc group is compatible with the reagents to remove Fmoc (piperidine) and Mtt (TFA). The conditions for Azoc removal, brief exposure to a phosphine (which can be polymer bound), are compatible with many other protecting groups.

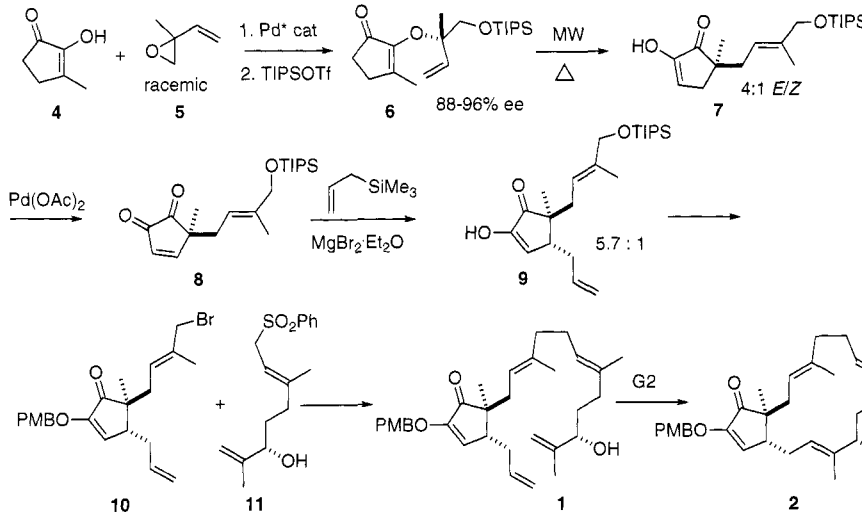
The Trost Synthesis of (-)-Terpestacin

November 5, 2007

(-)-Terpestacin **3**, isolated from *Arthrinium* sp. FA1744, inhibits the formation of syncytia by HIV-infected T cells. A key step in the total synthesis of **3** reported (*J. Am. Chem. Soc.* **2007**, *129*, 4540) by Barry M. Trost of Stanford University was the Ru-catalyzed cyclization of **1** to **2**. This synthesis of (-)-terpestacin **3** elegantly illustrates the power of the Trost enantioselective Pd catalysts.



The preparation of **1** began with the commercially-available diketone **4**. With the enol as the nucleophile, opening of *racemic* isoprene monoepoxide **5** using the Trost chiral Pd catalyst led to the ether **6** in high ee. It is impressive that even though it was directed by a *quaternary* stereogenic center, the subsequent Claisen rearrangement to **7** proceeded with complete facial selectivity. Oxidation to the

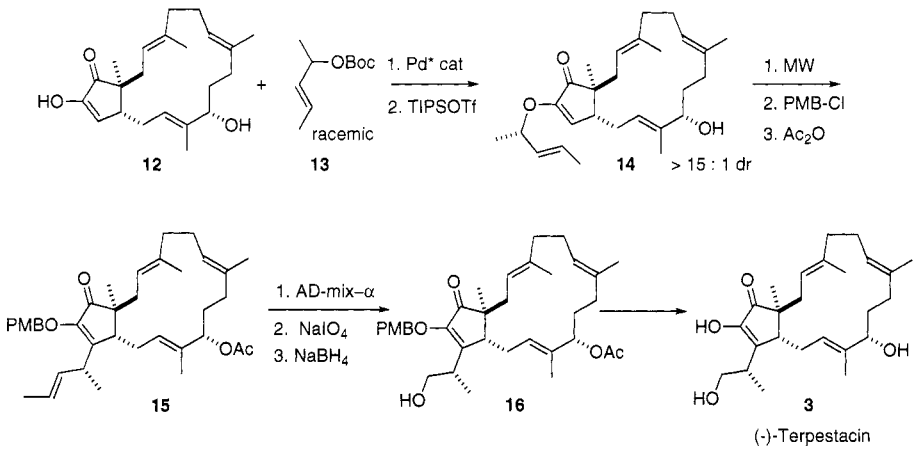


nonenolizable α-diketone **8** then set the stage for the conjugate addition. Again, even though the directing stereogenic center was quaternary, the addition proceeded with substantial diastereocontrol. Further study of the elements that govern the facial selectivity of the Lewis acid-mediated (Sakurai) addition of allyl silanes to enones would certainly be warranted.

The sulfone **11** was prepared in four steps from commericially-available geranyl bromide, with the absolute configuration being set by Sharpless asymmetric epoxidation. Subsequent to the alkylation of **11** with the bromide **10**, the now-surplus sulfone was removed reductively with $Pd(OAc)_2$ and $NaBH_4$. It is noteworthy that the enone of **1** was stable to those conditions.

The cyclization of **1** with the second-generation Grubbs catalyst delivered the desired *E* alkene **2** in 43% yield. As had been observed before by others, the free allylic alcohol was the preferred substrate for the Ru metathesis catalyst. No cyclization was observed with tetraenes that had the alcohol protected.

With **2** in hand, it remained to install the side chain. The relative configuration of the pentenyl side chain of **14** was set by again using chiral Pd catalysis. The Claisen rearrangement proceeded smoothly, to give, after protection, the ether **15**.



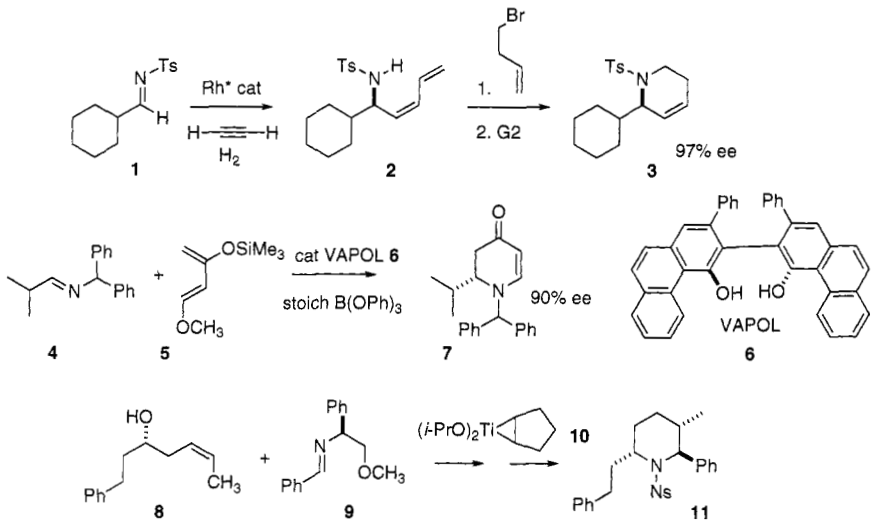
The oxidative cleavage of the side chain of **15** initially presented some difficulties. Eventually, it was found that AD-Mix-α (but not β) could effect selective dihydroxylation. Periodate cleavage followed by reduction then gave **16**, which was deprotected to (-)-terpestacin **3**.

Note that both **5** and **13** were *racemic*. Except for the secondary alcohol on the fifteen-membered ring, the absolute configuration of *every* stereogenic center in the (-)-terpestacin **3** prepared by this synthesis derived from the absolute configuration of the enantiomerically-pure Pd complexes used as first **5** and then **13** were incorporated selectively into the natural product.

Stereoselective C-N Ring Construction

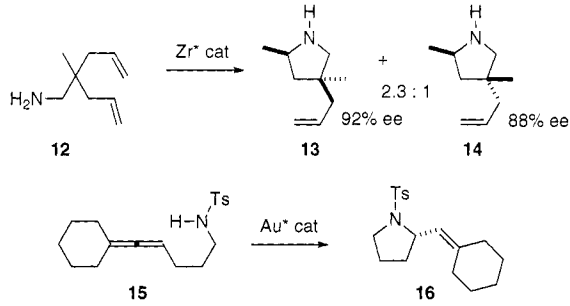
November 12, 2007

Several new methods for C-N ring construction based on enantioselective addition to imines have been reported. Michael J. Krische of the University of Texas has used (*J. Am. Chem. Soc.* **2007**, *129*, 7242) his Rh-mediated reductive dimerization of acetylene to effect enantioselective homologation of N-sulfonyl imines such as **1** to give dienes such as **2**. N-Alkylation followed by alkene metathesis converted **2** into **3**. William D. Wulff of Michigan State University, in another sort of imine addition, has established (*J. Am. Chem. Soc.* **2007**, *129*, 7216) that by using a super stoichiometric amount of Lewis acid to trap the product from the addition of **4** to **5**, a catalytic amount of the VAPOL **6** effectively directed the addition. Ramón Gómez Arrayás and Juan C. Carretero of the Universidad Autónoma de Madrid have described (*J. Am. Chem. Soc.* **2007**, *129*, 1480) a complementary approach. Glenn C. Micalizio of Yale University has shown (*J. Am. Chem. Soc.* **2007**, *129*, 7514) that Ti-mediated coupling of **8** with **9** proceeded with • 50:1 diastereoselectivity, leading to the piperidine **11**. Coupling of **8** with the (mismatched) enantiomer of **9** led to a mixture of three diastereomers in a ratio of 6 : 3 : 1.



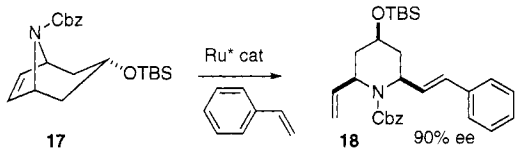
Just three years ago, intramolecular hydroamination, as in the conversion of **12** to **13**, was just being developed as a synthetic method. Now, Laurel L. Schafer has devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 354) a Zr catalyst that directed the cyclization of the prochiral diene **12** not just with high enantioselectivity, but also with substantial diastereocontrol. F. Dean Toste of the University of

California, Berkeley, has created (J. *Am. Chem. Soc.* **2007**, *129*, 2452; *Science* **2007**, *317*, 496) enantioselective Au catalysts for the electronically very different hydroamination of allenes such as **15**.



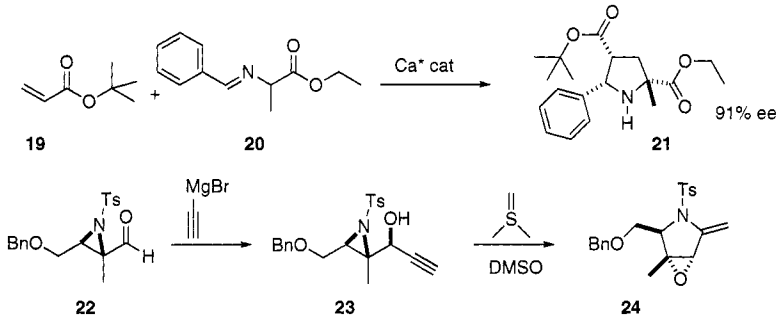
12 **13** **14** **15** **16**

Amir H. Hoveyda of Boston College has created (*Angew. Chem. Int. Ed.* **2007**, *46*, 4534) enantioselective Ru alkene metathesis catalysts. Using such a catalyst, he was able to convert prochiral bicyclic protected amines such as **17** into piperidines such as **18** with high ee.



17 **18**

Other routes to highly-substituted pyrrolidines have been reported. Shu Kobayashi of the University of Tokyo has devised (*J. Am. Chem. Soc.* **2007**, *129*, 5364) a catalyst for the Michael addition of amino ester derivatives such as **20** to acrylates such as **19**. The enolate so generated added to the imine to give **21** with high relative and absolute stereocontrol. Babak Borhan of Michigan State University observed (J. *Am. Chem. Soc.* **2007**, *129*, 3794) that acetylide added to the aziridine aldehyde **22** to give **23** with high diastereoselectivity. Under carefully defined conditions, **23** underwent Payne rearrangement to liberate the sulfonamide anion, which then added to the pendant alkyne, to give **24**. Professor Borhan has also (J. *Am. Chem. Soc.* **2007**, *129*, 1996) reported an alternative approach to highly substituted pyrrolidines.

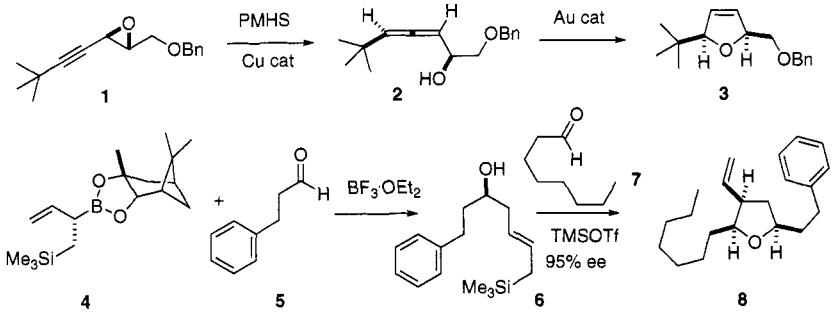


19 **20** **21** **22** **23** **24**

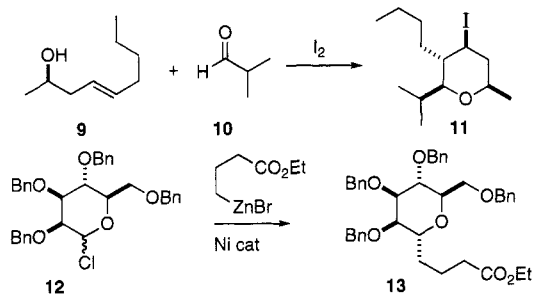
Stereoselective C-O Ring Construction

November 19, 2007

Five-membered cyclic ethers often do not show strong thermodynamic preferences. High diastereocontrol can, however, be achieved. Epoxy alkynes such as **1** can be prepared in high ee by Sharpless asymmetric epoxidation. Norbert Krause of Dortmund University has shown (*Angew. Chem. Int. Ed.* **2007**, *46*, 1650) that Cu hydride reduces epoxides such as **1** to the corresponding allene **2**. The alcohol **2** was then cyclized with an Au catalyst to the dihydrofuran **3**, with high overall diastereocontrol. In a complementary approach, Dennis G. Hall of the University of Alberta has developed (*J. Am. Chem. Soc.* **2007**, *129*, 3070) a simple procedure for the preparation of the enantiomerically-pure allyl borinate **4** and its enantiomer, which can be purified by column chromatography and stored. Addition of **4** to the aldehyde **5** gave the allyl silane **6** in high ee. Addition of **6** to a second aldehyde **7** then gave the all-cis tetrahydrofuran **8**, without loss of ee.

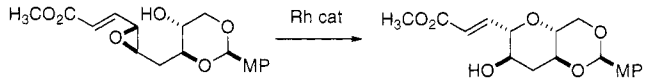


Much energy is going into the development of new methods for the stereocontrolled preparation of 2,6-dialkyl tetrahydropyrans. J. S. Yadav of the Indian Institute of Chemical Technology, Hyderabad, has found (*Tetrahedron Lett.* **2007**, *48*, 2205) that iodine mediated the Prins couplingof **9** and **10**, with



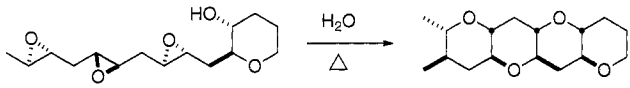
high diastereocontrol. Michel R. Gagné of the University of North Carolina developed (*J. Am. Chem. Soc.* **2007**, *129*, 1908) Negishi conditions for coupling glycosyl chlorides such as **12** with easily-prepared organozinc halides. The coupling tended to give the trans product, and to proceed trans to the adjacent alkoxy substituent.

Intramolecular epoxide opening has also been a reliable method for stereocontrolled cyclic ether construction. Masayuki Inoue and Masahiro Hirama have improved on the usual acid-mediated cyclization of substrates such as **14** by demonstrating (*Tetrahedron Lett.* **2007**, *48*, 2171) that the transformation is even more efficient with a Rh catalyst.



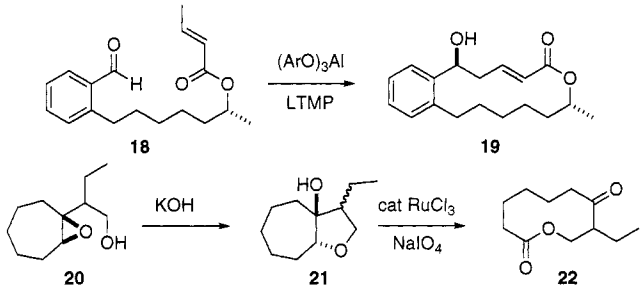
14 **15**

Following the biosynthetic hypothesis of Koji Nakanashi, the cascade cyclization of polyepoxides to ladder polyethers such as **17** has long been a goal of organic chemistry. With the development of methods for the direct enantioselective epoxidation of alkenes, the preparation of the requisite substrates, such as **16**, is now practical. Timothy F. Jamison of MIT found (*Science* **2007**, *317*, 1189) that merely warming **16** in water for three days delivered the cyclized product **17** in 71% yield. K. N. Houk of UCLA and Paul E. Floreancig of the University of Pittsburgh have reported (*J. Am. Chem. Soc.* **2007**, *129*, 7915) an alternative approach to such cyclizations.



16 **17**

There are many macrolactone natural products. Tarek Sammakia of the University of Colorado has shown (*Organic Lett.* **2007**, *9*, 2103) that the conditions developed by Hisashi Yamamoto for intermolecular vinylogous aldol also worked well for the construction of macrolactones, and that the cyclizations proceeded with remarkable diasterocontrol. Helena M. C. Ferraz of the Universidade de São Paulo has reported (*J. Org. Chem.* **2007**, *72*, 2945) a complementary route to macrolactones, from **20** to **22**.



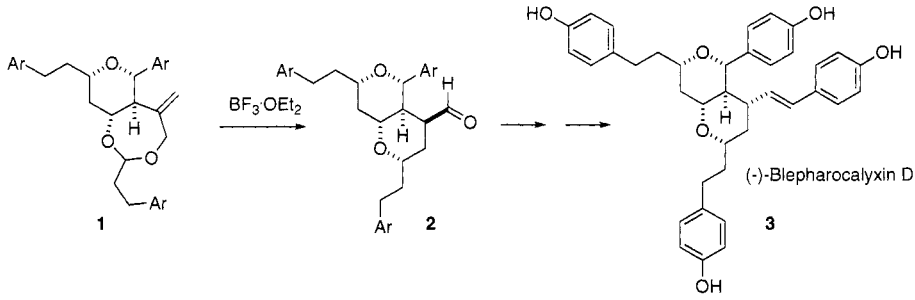
18 **19**

20 **21** **22**

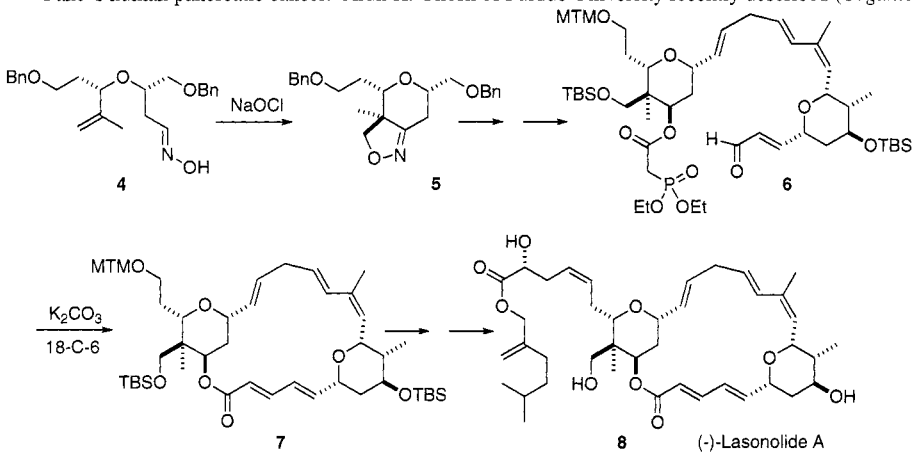
Synthesis of (-)-Blepharocalyxin D, (-)-Lasonolide A, and Attenol A

November 26, 2006

Blepharocalyxin D **3**, isolated from the seeds of *Alpinia blepharocalyx*, shows antiproliferative activity against murine colon 36-L5 carcinoma in cell culture. A key step in the first synthesis of **3**, reported (*Organic Lett.* **2007**, *9*, 141) by Eun Lee of Seoul National University, was the Prins-pinacol rearrangement of **1** to **2**. Remarkably, the *axial* aldehyde was the dominant kinetic product from the cyclization. This could be equilibrated to the equatorial aldehyde, which was then carried on to **3**.

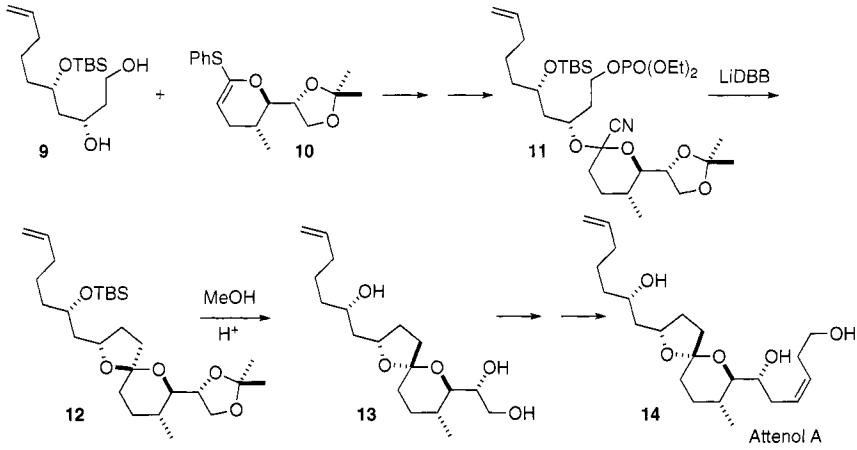


Lasonolide A **8**, isolated from the Caribbean marine sponge *Forceia* sp., showed potent antineoplastic activity, with IC_{50} values of 8.6 nM and 89 nM against A-549 human lung carcinoma and Panc-1 human pancreatic cancer. Arun K. Ghosh of Purdue University recently described (*Organic*



Lett. **2007**, *9*, 1437) a concise synthesis of **8**. The first stage was a clever assembly of the doubly chiral ether of **4**. The key reaction was the selective opening at the distal position of a Sharpless-derived epoxide. The preference for the two anomeric alkyl substituents on the incipient tetrahydropyran ring to be equatorial then set the transition state for the cyclization to **5**. It is particulary impressive that the alkyated quaternary center of **5** was formed with high diastereocontrol. Further elaboration set the stage for the intramolecular Horner-Emmons cyclization that established the macrocyclic ring of **8**.

Attenol A **14**, isolated from the Chinese bivalve *Pinna attenuata*, shows moderate cytotoxic activity against P388 leukemia. Usually, spiro ketals such as **13** are formed under equilibrating conditions. As the anomeric oxygen prefers to be axial on the six-membered ring and the anomeric alkyl group prefers to be equatorial, that diastereomer is usually heavily favored. Scott D. Rychnovsky of the University of California, Irvine has described (*J. Org. Chem.* **2007**, *72*, 2602) a concise convergent synthesis of **14**, combining the protected triol **9** and the vinyl ether **10**.



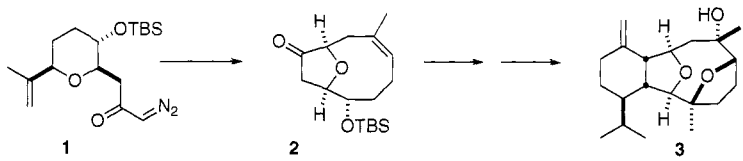
There were two tasks to be acccomplished as **9** and **10** were combined and carried forward, establishment of the carbon connectivity of **14**, and control of the relative configuration of the spiro ether. First, **9** and **10** were coupled to form the crossed cyanohydrin ether **11**. There was no need for stereocontrol at the incipient spiro center, as that center was destroyed in the next transformation. Reductive cyclization then proceeded with selective *axial* bond formation, to give the kinetically-preferred spiroketal **12**. On brief exposure to acid, the spiroketal equilibrated to the more stable **13**, that was carried on to Attenol A **14**.

This reductive cyclization to kinetically form the less stable spiro ketal, first developed in the Rychnovsky group, is a powerful strategy for the construction of spiroketal natural products, as it opens access selectively to *either* diastereomer of the spiroketal.

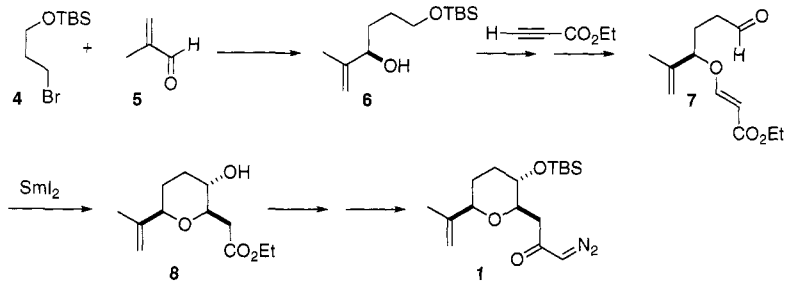
The Clark Synthesis of Vigulariol

December 3, 2007

Vigulariol **3**, isolated from the octocoral *Vigularia juncea* (Pallas), is active against human lung adenocarcinoma cells (IC_{50} = 18 nM). A key step in the synthesis of **3** reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 437) by J. Stephen Clark of the University of Glasgow was the dipolar rearrangement of **1** to **2**.



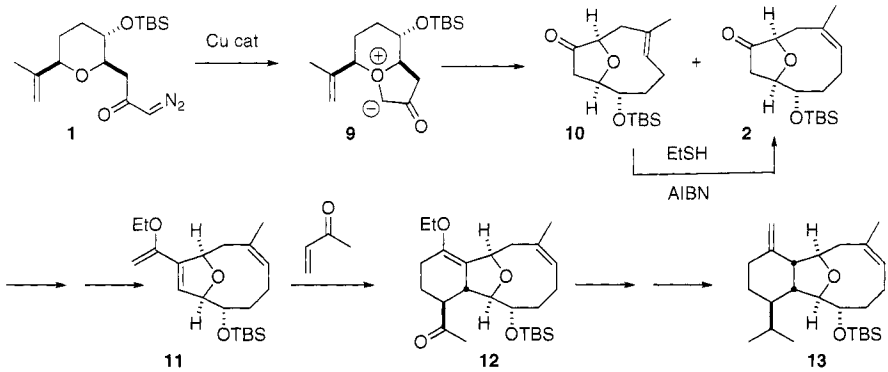
The plan for the diastereoselective construction of **1** was based on the known reductive cyclization of aldehydes such as **7**. To this end, the alcohol **6** was prepared and condensed with ethyl propiolate. As anticipated, the SmI_2-mediated cyclization of **7** proceeded to give **8** with high diasterocontrol. The diazo ketone **1** was prepared by reaction of the mixed anhydride (isobutyl chloroformate) of the acid with diazomethane.



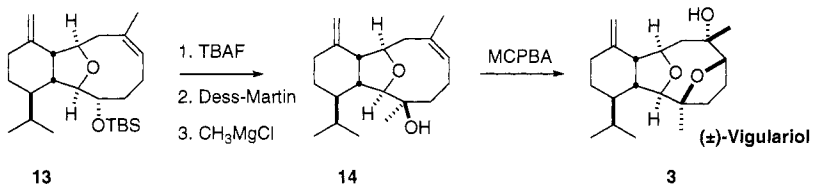
It was anticipated that Cu-catalyzed carbene formation would lead the 1,3-dipole **9**, that would then undergo sigmatropic rearrangement to **2**. In the event, the rearrangement was remarkably efficient, delivering the ten-membered ring carbocycles **10** and the desired **2** in a 1 : 5 ratio. Exposure of the less stable geometric isomer **10** to catalytic thiyl radical effected equilibration to **2**.

Although one might think of medium rings such as that of **2** as being floppy, in fact **2** has a single preferred conformation, and diastereocontrol for the rest of the synthesis took advantage of that preferred conformation. The diene **11** derived from **2** has one open face. Addition of methyl vinyl ketone to that outside face gave a 1 : 2 mixture of the diastereomeric endo and exo cycloadducts. The

mixture was equilibrated to the more stable exo adduct **12**. A four-step sequence then converted **12** into **13**.



The completion of the synthesis again depended on the inside-outside bias of the medium ring. Addition of methyl magnesium chloride to the outside face of the ketone derived from **13** delivered **14** with high diastereocontrol. Epoxidation of **14**, again from the outside face, led directly to vigulariol **3**. The intermediate in the MCPBA reaction is the protonated epoxide, and it may be that the tertiary alcohol poised directly on the opposite face of the alkene opened that activated intermediate directly.

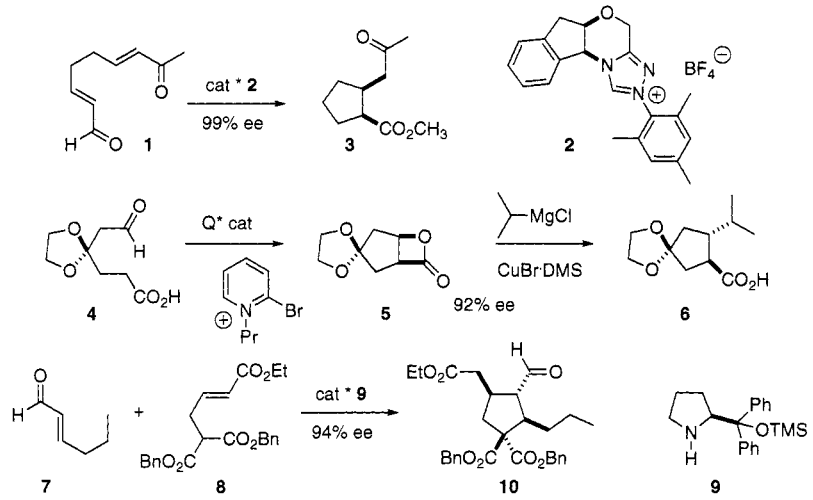


This synthesis of vigulariol **3** is remarkably concise, with four rings and eight stereogenic centers being assembled in just twenty steps. All of the stereogenic centers are derived from the secondary alcohol **6**. Use of the known enantiomerically-pure **6** would have delivered vigulariol **3** in enantiomerically-pure form. This synthesis design once again illustrates the power of conformational analysis of medium rings.

Enantioselective Organocatalytic Synthesis of Carbocycles: The Iwabuchi Synthesis of (+)-Juvabione

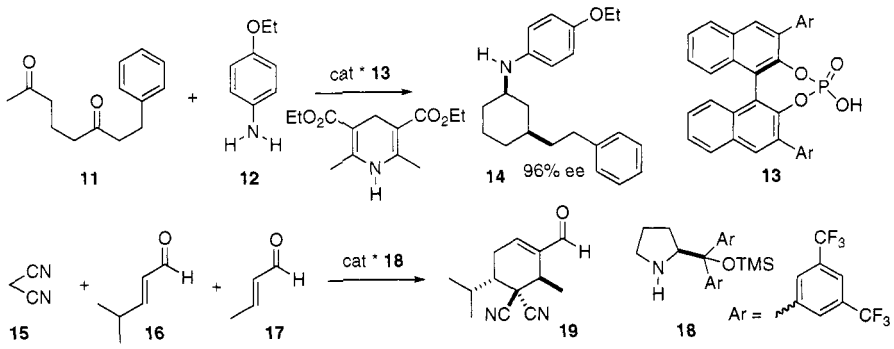
December 10, 2007

With the development of more advanced applications for organocatalysts, several new approaches have been developed for the enantioselective construction of cyclopentanes. Karl A. Scheidt of Northwestern University has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 3107) that the enolates derived from addition of the catalyst **2** to the unsaturated aldehyde **1** show good facial selectivity in the ensuing intramolecular Michael addition, leading to **3** in high ee. Daniel Romo of Texas A&M had already developed the organocatalyst-mediated construction of cyclic β-lactones such as **5**. Now, he has shown (*Organic Lett.* **2007**, *9*, 2111) that under Cu catalysis, **5** will couple with Grignard reagents to give the substituted cyclopentane **6** with clean inversion. Yun Tang of East China University of Science & Technology, Shanghai and Wei Wang of the University of New Mexico, using the simple catalyst **9**, have devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 3732) a cascade process, combining **7** and **8** to give the cyclopentane **10**.



Cyclohexanes have also been prepared using organocatalysts. Benjamin List of the Max-Planck-Institut, Mülheim, has developed (*J. Am. Chem. Soc.* **2007**, *129*, 7498) a tandem aldol condensation – conjugate reduction – reductive amination procedure that converted the diketone **11** into the equatorial amine **14**. Note that in the absence of the organocatalyst, the intramolecular aldol condensation of **11** would be expected to give the alternative regioisomer of the intermediate cyclohexenone. In a related development, Karl Anker Jørgensen of Aarhus University has established (*Angew. Chem. Int. Ed.* **2007**,

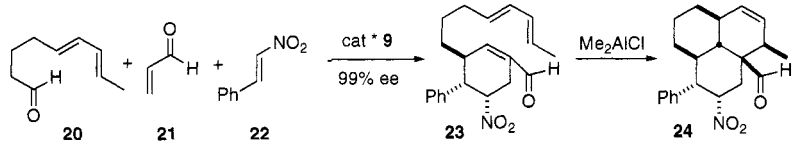
46, 1101) that the **18**-mediated Michael addition of **15** first to **16**, then to **17**, not only proceeded with high ee, but that the subsequent aldol condensation was highly regioselective, leading to **19**.



11 12 14 13

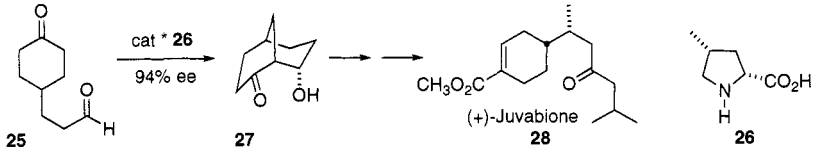
15 16 17 19 18

The cycloalkanes assembled using these strategies can then serve as directing scafffolds for further ring construction. Dieter Enders of RWTH Aachen has established (*Angew. Chem. Int. Ed.* **2007**, *46*, 467) that **23**, prepared by **9**-mediated Michael addition and aldol condensation of **20**, **21**, and **22**, cyclized to **24** with high diastereocontrol.



20 21 22 23 24

Organocatalysis can also be used to establish challenging side chain stereocenters. Yoshiharu Iwabuchi of Tohoku University used (*Chem. Comm.* **2007**, 1175) the bicyclic framework of **27** to guide conjugate addition, leading to the juvenile hormone (+)-juvabione **28** with high enantio- and diastereocontrol.



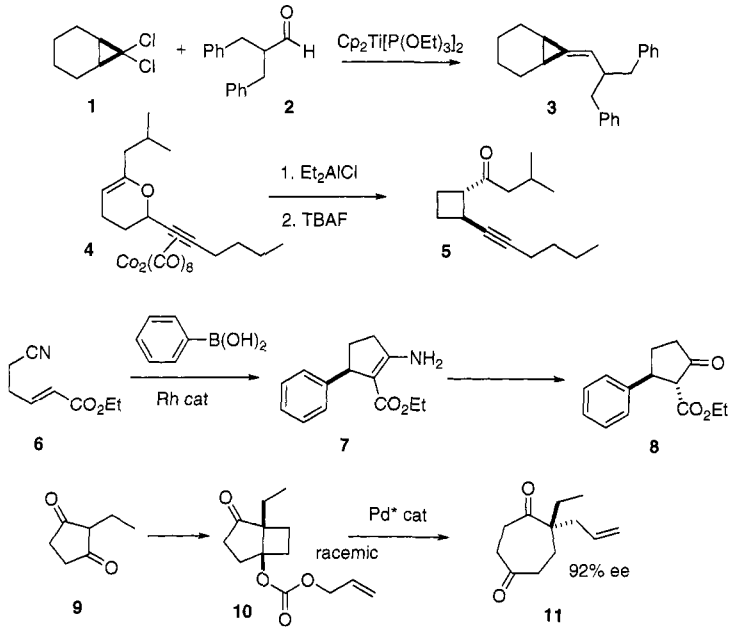
25 27 28 26

Note that most if not all of the catalysts mentioned here are commercially available, making the chemistry described easily accessible.

Transition-metal Mediated Synthesis of Carbocycles: The Snapper Synthesis of Pleocarpenone

December 17, 2007

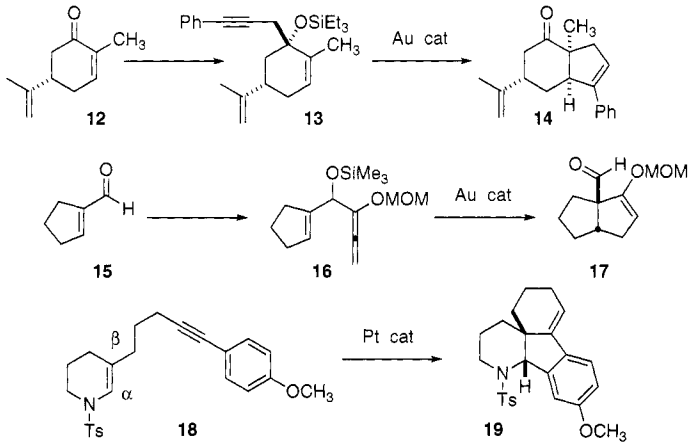
Several creative new approaches to carbocyclic ring construction using transition metals have recently been reported. Dichlorocyclopropanes such as **1** are easily prepared by the addition of dichlorocarbene to the corresponding alkene. Takeshi Takeda of the Tokyo University of Agriculture and Technology has shown (*Tetrahedron Lett.* **2007**, *48*, 3521) that the Ti-mediated coupling of **1** with an aldehyde or ketone proceeded to give the alkylidene cyclopropane **3**. Joseph P. A. Harrity of the University of Sheffield has found (*J. Org. Chem.* **2007**, *72*, 3467) that the Co-supported Ferrier rearrangement he has developed can be extended to dihydropyrans such as **4**, to give the cyclobutane **5** with high diastereocontrol. Rh-catalyzed conjugate addition of boronic acids gives an intermediate enolate that will react with a variety of tethered electrophiles including, as Masahiro Murakami of Kyoto University has demonstrated (*Organic Lett.* **2007**, *9*, 741), a tethered nitrile. This reaction worked well to form 5- and 6-membered rings. 2-Ethyl cyclopentane **9** is prochiral. Siegfried Blechert of the Technische Universität Berlin has devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 3966) an enantiomerically-pure Pd catalyst that converted *racemic* **10**, derived from **9**, into the cycloheptanone **11** with high ee.



TRANSITION-METAL MEDIATED SYNTHESIS OF CARBOCYCLES: THE SNAPPER SYNTHESIS OF PLEOCARPENONE

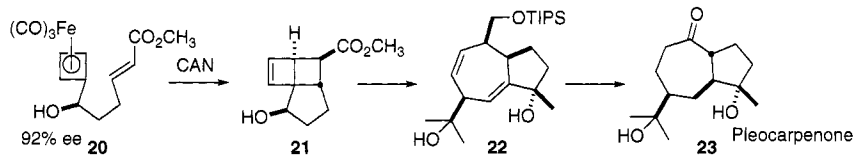
December 17, 2007

Transition metals have also been used to construct multiple ring systems. Stefan F. Kirsch of the Technisches Universität München has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 2310) an Au catalyst that will rearrange an alkoxy enyne such as **13** to the ketone **14**. This is a new method for annealing a new ring onto a cyclic enone. Liming Zhang of the University of Nevada, Reno has described (*J. Am. Chem. Soc.* **2007**, *129*, 6398) a complementary process, the Au-catalyzed conversion of **16** to **17**.



Enamides such as **18** are nucleophilic at the β carbon, leading to an electrophilic center at the α carbon. Gregory R. Dake of the University of British Columbia has used (*Organic Lett.* **2007**, *9*, 367) a Pt catalyst to bring out this inherent reactivity, allowing the conversion of **18** to the tricyclic **19**.

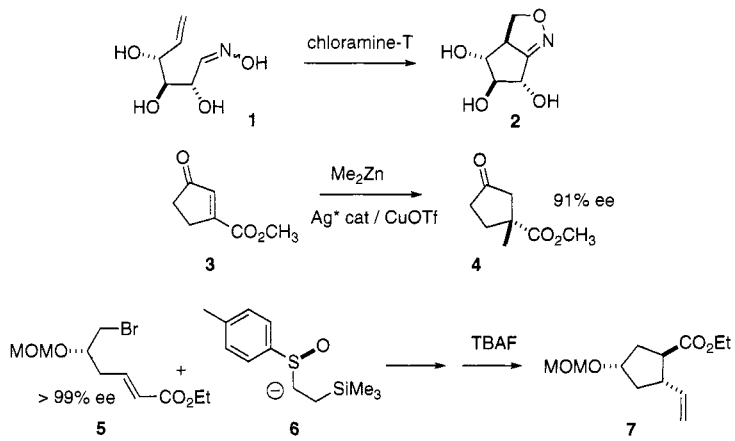
Marc L. Snapper of Boston College has been exploring synthesis applications of Fe-cyclobutadiene complexes. In a recent contribution (*J. Am. Chem. Soc.* **2007**, *129*, 486) he has shown that oxidative decomplexation of the enantiomerically-enriched complex **20** delivered the tricyclic adduct **21** with good diastereocontrol. Cyclopropanation followed by thermal fragmentation led to the 7-5 system **22**, which was carried on to the guaiane sesquiterpene pleocarpenone **23**.



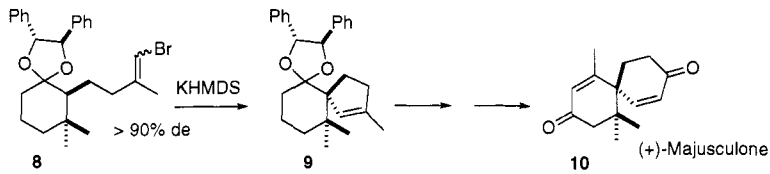
Enantioselective Construction of Carbocycles: The Williams Synthesis of (+)-Fusicoauritone

December 24, 2007

Several creative new approaches to carbocyclic ring construction have recently been reported. Tony K. M. Shing of the Chinese University of Hong Kong has found (*Organic Lett.* **2007**, *9*, 753) that intramolecular nitrile oxide cycloadddition (INOC) is compatible with multiple free OH groups, allowing direct conversion of carbohydrates to carbocycles. Amir H. Hoveyda of Boston College has overcome (*Angew. Chem. Int. Ed.* **2007**, *46*, 1097) the difficulty of enantioselective conjugate addition to substituted cyclic enones by using an activating ester subsituent. These two approaches can be used to prepare both cyclopentanes and cyclohexanes. Charles K. Zercher of the University of New Hampshire, in the course of a synthesis of (+)-brefeldin A, has shown (*J. Org. Chem.* **2007**, *72*, 4390) that highly functionalized cyclopentanes can also be prepared using the chiral sulfoxide conjugate addition developed by Toru.



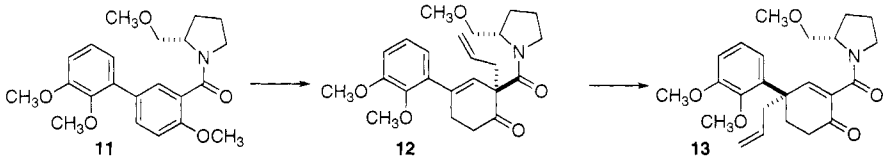
In a synthesis of the chamigrene sesquiterpene (+)-majusculone **10**, we (*J. Org. Chem.* **2007**, *72*, 4098) separated the diastereomers of the ketal **8**. On exposure to KHMDS, **8** cyclized to the enantiomerically-pure spiro alkene **9**. The other diastereomer of **8** could be epimerized and recycled, so all the material could be brought forward to **9**.



Enantioselective Construction of Carbocycles: The Williams Synthesis of (+)-Fusicoauritone

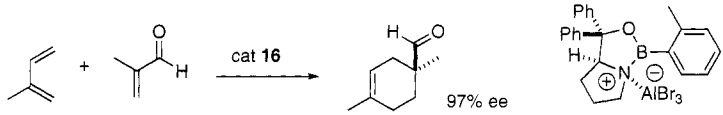
December 24, 2007

In a complementary enantioselective approach to cyclic alkylated quaternary centers, William P. Malachowski of Bryn Mawr College showed (*J. Org. Chem.* **2007**, *72*, 930) that reductive alkylation of the biphenyl amide **11** proceeded with high diastereocontrol, to give **12**. On heating, **12** rearranged to **13**, a key intermediate for the Malachowski synthesis of (-)-lycoramine (*J. Org. Chem.* **2007**, *72*, 6792).



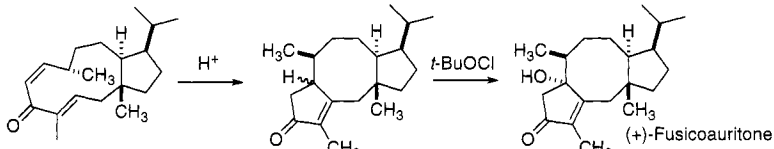
11 **12** **13**

Diels-Alder cyclization is one of the most powerful tools for the construction of carbocyclic rings. It would be even more valuable if there were a general catalyst that worked well with less activated combinations of diene and dienophile. E. J. Corey of Harvard University has designed (*J. Am. Chem. Soc.* **2007**, *129*, 1498) the promising catalyst **16**. Even with a relatively unreactive diene and dienophile combination such as **14** and **15**, the catalyst **16** showed good reactivity and outstanding selectivity.



14 **15** **17** **16**

Enantio- and diastereoselective assembly of medium rings is particularly challenging. The biosynthesis of the tricyclic fusicoccanes, exemplified by (+)-fusicoauritone **20**, was hypothesized to proceed by acid-catalyzed cyclization of the dolabellane skeleton. David R. Williams of Indiana University has now shown (*Angew. Chem. Int. Ed.* **2007**, *46*, 915) that exposure to acid of the diene **18**, which has the dolebellane skeleton, gave clean Nazarov cyclization to the enone **19**, which has the fusicoccane skeleton. Oxidation then completed the synthesis of (+)-fusicoauritone **20**.

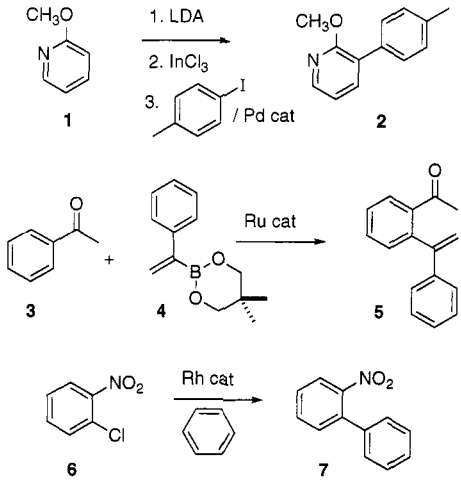


18 **19** **20**

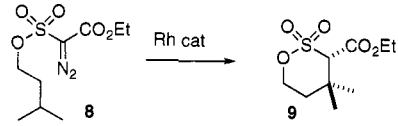
C-H Functionalization: The White Reagent

December 31, 2007

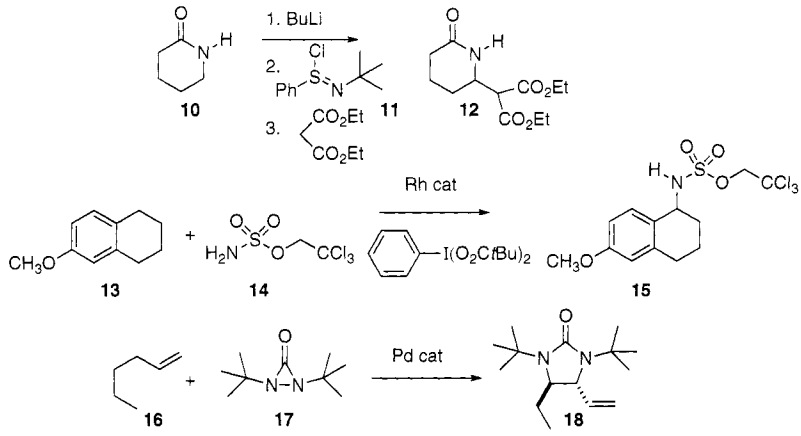
The direct functionalization of a C-H bond is a powerful transformation for organic synthesis, allowing the rapid elaboration of desired complexity from inexpensive starting materials. Even Friedel-Crafts acylation can be seen as a C-H functionalization reaction, from the point of view of the aromatic ring, and aromatic substitution continues to dominate efforts toward C-H functionalization. While the directed metalation of aromatic rings has been known for some time, carbon-carbon bond formation at the metalated site has sometimes been problematic. José Pérez Sestelo and Luis A. Sarandeses of the Universidade da Coruña, Spain, have now shown (*J. Org. Chem.* **2007**, *72*, 1271) that addition of the intermediate metalated aromatic to $InCl_3$ gives an intermediate that couples efficiently to aryl halides under Pd catalysis. Vinyl triflates also work well. In a recent advance in *catalytic* ortho metalation, Fumitoshi Kakiuchi of Keio University has developed (*J. Org. Chem.* **2007**, *72*, 3600) conditions for in situ coupling of the metalated intermediate to an alkenyl boronate. The C-H to be functionalized can be on another ring. Rhett Kempe of the Universität Bayreuth has uncovered (*Angew. Chem. Int. Ed.* **2007**, *46*, 3135) a Rh catalyst that will couple haloaromatics such as **6** directly to solvent benzene.



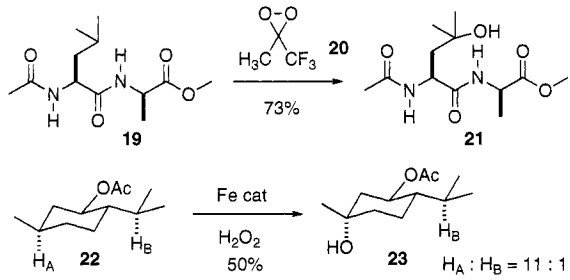
Intramolecular C-C bond formation by C-H functionalization is also a powerful transformation. Alexei V. Novikov of the University of North Dakota has devised (*Organic. Lett.* **2007**, *9*, 61) a new sulfonate tether, exemplified by **8**. As the sulfonate can be removed reductively, the net transformation is the C-2 homologation of a C-H directed by a distal OH.



There have been several recent developments around amine-centered bond formation. Jun-ichi Matsuo and Hiroyuki Ishibashi of Kanazawa University have used (*Tetrahedron Lett.* **2007**, *48*, 3233) the commercial reagent **11** to oxidize the lactam **10** to the intermediate iminium species. Alkyl malonates could then be added directly, to give the C-H alkylated product **12**. Both Justin Du Bois of Stanford University (*J. Am. Chem. Soc.* **2007**, *129*, 562) and Hélène Lebel of the Université de Montréal (*Organic.* Lett. **2007**, *9*, 639) have developed reagent and catalyst combinations for direct C-H amination. In one of the more spectacular recent developments, Yian Shi of Colorado State University has established (*J. Am. Chem. Soc.* **2007**, *129*, 7496) conditions for the diastereoselective activation of *two* C-H bonds, adding **17** to terminal alkenes to give the protected diamine **18**.



The reagent of choice for C-H hydroxylation has been methyl(trifluoromethyl)dioxirane **20**, as illustrated by the recent work of Paul G. Williard of Brown University (*J. Org. Chem.* **2007**, *72*, 525). M. Christina White of the University of Illinois has recently devised (*Science* **2007**, *318*, 718) an Fe complex that *catalytically* effected C-H hydroxylation. This reagent showed substantial (probably steric) selectivity. It will be interesting to learn in what ways this new catalyst and **20** are complementary.



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