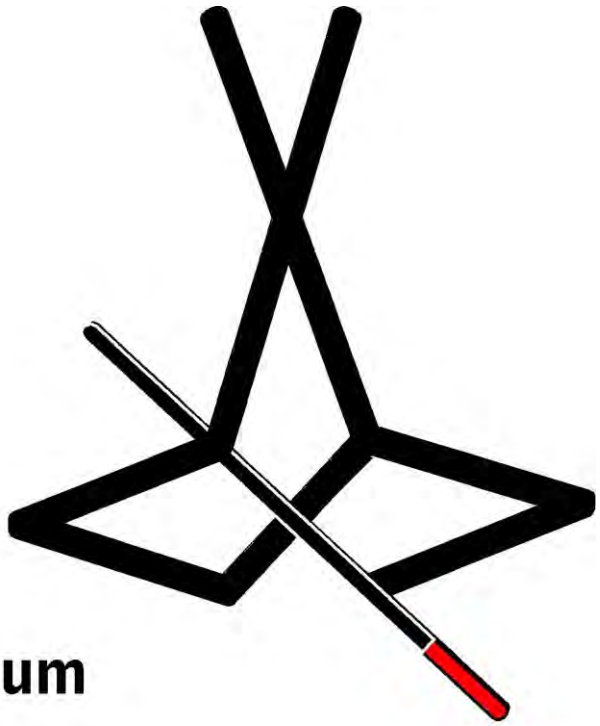
Aalto University
School of Chemical Technology

Department of Chemistry

Laboratory of Organic Chemistry

Espoo 2013

110 Years of Natural Product Synthesis



Komppa Symposium

JUNE 24 - 26, 2013, ESPOO, FINLAND

Abstracts

Welcome!

It is my great pleasure to welcome you all to the 13th Spring Meeting of the Finnish Society for Synthetic Chemistry. Since the embarrassingly late establishment in 1992 as a professional society, initially as a division of the Finnish Chemical Society, our Society of Synthetic Chemistry has become an active forum for meetings and training of graduate students on national level. Soon after the inauguration of the Division, we celebrated the 90th anniversary of the legendary (formal) total synthesis of camphor by Gustaf Komppa in the form of the First Spring Meeting of the Society. This is why we early on chose the structure of camphor as the logo for the meetings. In the first symposium, the logo was a simple line drawing, and over the years it has evolved through molecular modeling structures to the one adopted after the Komppa Centenary Symposium held in 2003 at the Helsinki University of Technology.

The symposium series is aimed at our most valuable asset and resource, the Ph.D. students. This year we celebrate the 110th anniversary of the Komppa synthesis, and we are proud to present a good number of internationally highly recognized speakers. We also allow ample time for the graduate students to present their work both as oral communications and in poster format. We are also particularly happy that the NordForsk Excellent Chemistry Network has sponsored a good number of students from near and far to spend chemistry filled summer days with us.

Originally the symposium was considered to be held every two years, then at some point the pace quickened, which obviously leads to a situation where the potential organizers easily start building up lactic acid. Previous meetings have been held in 1993 in Oulu, followed by 1997 Jyväskylä, 1999 Kuopio, 2000 Espoo, 2001 Turku, 2002 Oulu, 2004 Keuruu, 2005 Åbo Akademi, 2006 Kuopio, 2007 Helsinki, 2009 Espoo, 2011 Jyväskylä.

In 2008, the Division implemented summer schools, to be held every two years in place of the larger symposia. A recent addition has also been the prize for the best publication by Finnish Ph.D. students, which is announced in the Symposia.

Of course, the symposium is possible only because the students and staff of Aalto University deserve our warmest thanks! With these words, I welcome you to enjoy synthetic chemistry with us!

Ari Koskinen

Doctoral Program of

OCCB

Organic Chemistry and Chemical Biology

norden

NordForsk

ORION

Schmp 245° auskrystallisirt. Bei 234° sintert die Substanz; bei 240° tritt Schwarzfärbung ein.

$(C_{17}H_{13}NO_2)HCl$. Ber. C 68.09, H 4.71.
Gef. » 67.74, » 5.19.

Das Platindoppelsalz fällt sofort auf Zusatz von Platinchlorid zur Lösung des salzsauren Salzes als gelber Niederschlag aus. Schmp. 215°; bei 210° Dunkelfärbung.

$(C_{17}H_{13}NO_2.HCl)_2PtCl_4$. Ber. Pt 20.82. Gef. Pt 20.66.

Breslau, Chemisches Universitäts-Laboratorium.

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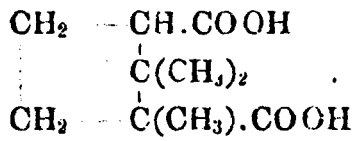
729. Gust. Komppa: Die vollständige Synthese der Campher-säure und Dehydrocamphersäure.

[Vorläufige Mittheilung.]

(Eingeg. am 8. Decbr. 1903; vorgetr. in der Sitzung von Hrn. C. Harries.)

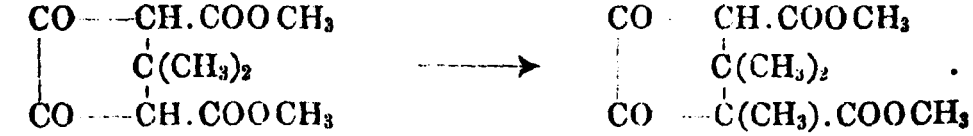
Ich will hier sogleich anführen, dass es mir jetzt gelungen ist, eine Säure synthetisch darzustellen, welche die von Bredt für Campher-säure angegebene Constitution besitzt:



Und diese synthetische Säure war wirklich identisch mit der schon bekannten racemischen Camphersäure. Hierdurch ist also die Bredt'sche Formel für Camphersäure resp. für Campher definitiv als richtig bewiesen. Auch ist hierdurch die vollständige Synthese des Camphers realisirt, da der Campher bekanntlich aus der Camphersäure darstellbar ist[1]).

Der Weg, dessen ich mich hierbei bedient habe, ist der folgende:

Sobald mir die Synthese der Apocamphersäure[2]) gelungen war, versuchte ich den Diketoapocamphersäureester[2]) zu methyliren, um auf diese Weise Diketocamphersäureester zu bekommen:



[1]) Haller, Compt. rend. 122, 446 [1896]; Haller und Blanc, ibid. 130, 376 [1900]; Bredt und Rosenberg, Ann. d. Chem. 289, 1 [1896].

[2]) Gust. Komppa, diese Berichte 34, 2472 [1901].

Bei der Methylirung mit Natrium (1 Atom) und Jodmethyl (1 Mol.) in absolut alkoholischer Lösung entstand aber ein dickes Oel, aus welchem in krystallinischem Zustande nur etwas unverändertes Ausgangsmaterial auszuscheiden war. Es gelang mir jedoch, in diesem Oele durch Behandlung mit Sodalösung die sauer reagirenden (enolisirbaren) Ester der Diketocamphersäure und Diketoapocamphersäure von den neutralen, ätherartigen (nicht enolisirbaren) Methylirungsproducten (siehe weiter unten) zu trennen. Die beiden sodalöslichen Ester konnte ich schliesslich mittels der Kupfersalze voneinander scheiden; das Kupfersalz des erwarteten Diketocamphersäureesters war nämlich in Aether löslich, das andere Kupfersalz war dagegen darin unlöslich.

Das Kupfersalz des Diketocamphersäureesters krystallisirt aus kochendem Alkohol in blaugrünen, kleinen, kurzen, gruppirten Prismen. Es ist löslich in Aceton, Benzol, Alkohol und Aether (schwer löslich), unlöslich in Wasser und Ligroïn.

0.1656 g Subst.: 0.3010 g CO_2, 0.0782 g H_2O. 0.0227 g CuO. — 0.0294 g Subst.: 0.0180 g CuO.

$C_{24}H_{30}O_{12}Cu$. Ber. C 50.21, H 5.23, Cu 11.09.
Gef. » 49.57, » 5.25. » 10.93, 11.13.

Der aus dem Kupfersalz freigemachte Diketocamphersäureester bildet, aus Methylalkohol umkrystallisirt, sehr schöne, dicke, anscheinend monokline Tafeln vom Schmp. 85—88°. Aus Benzol-Ligroïn bekommt man wieder schuppenförmig gruppirte, federförmige Kryställchen. Die wässrig-alkoholische Lösung gab mit Ferrichlorid eine rothbraune Färbung.

0.1230 g Subst.: 0.2530 g CO_2, 0.0702 g H_2O. — 0.1280 g Subst.: 0.2644 g CO_2.

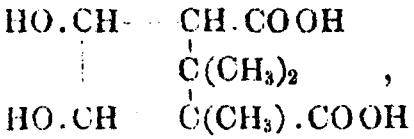
$C_{12}H_{16}O_6$. Ber. C 56.25, H 6.25.
Gef. » 56.23, 56.33, » 6.34.

Später fand ich, dass, wenn man an Stelle von 1 Atom Natrium (entgegen der Theorie) beinahe 2 verwendet, man viel bessere Ausbeute an Ester bekommt; auch bleibt dann kein unveränderter Apoester zurück, sodass die Ueberführung in das Kupfersalz — insbesondere für synthetische Zwecke — ganz unnöthig wird. Dass auch so dargestellter Diketocamphersäureester analysenrein ist, zeigt die folgende Analyse:

0.1251 g Subst.: 0.2580 g CO_2, 0.0716 g H_2O.

$C_{12}H_{16}O_6$. Ber. C 56.25, H 6.25.
Gef. » 56.11, » 6.34.

Diesen Diketocamphersäureester habe ich dann in Sodalösung und im Kohlendioxyd-Strome mit Natriumamalgam in guter Ausbeute zu der entsprechenden Dioxycamphersäure,



reducirt.

reduciren können. Diese Säure war syrupförmig. 0.1239 g derselben verbrauchten bei der Titrirung 9.01 ccm $^1/_{10}$-*n*. Kalilauge, statt 8.86 ccm berechnete.

Das bei 145° getrocknete Baryumsalz enthielt 37.61 Ba; ber. 37.39.

Ein aus dem Letztgenannten dargestelltes Silbersalz enthielt 48.60 Ag; statt 48.43 berechnet.

Kocht man die Dioxysäure mit Jodwasserstoffsäure vom spec. Gewicht 1.7 und wenig amorphem Phosphor längere Zeit im offenen Gefäss, so erhält man eine zähe, nur theilweise krystallinische Masse. Wird aber das Reactionsproduct auf dem Wasserbade zur Trockne verdampft und der Rückstand mit Natronlauge gekocht, so bekommt man aus dem Filtrat beim Zufügen von Salzsäure eine krystallinische Säure. Nach mehrfachem Umkrystallisiren aus heissem, alkoholhaltigem Wasser bildet sie kurze, dicke, sternförmig gruppirte Prismen (unter dem Mikroskope), die bei 221—223° schmelzen. Sie reducirt Kaliumpermanganat in der Kälte und besteht aus einer racemischen Dehydrocamphersäure entweder von der Formel:

oder

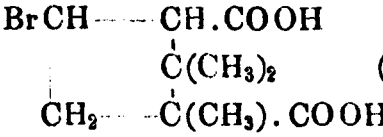
Die Constitution dieser Säure wird später näher bestimmt.

0.1160 g Sbst.: 0.2579 g CO_2, 0.0745 g H_2O. — 0.1208 g Sbst.: 0.2689 g CO_2, 0.0790 g H_2O.

$C_{10}H_{14}O_4$. Ber. C 60.61, H 7.07.
Gef. » 60.63, 60.71, » 7.14, 7.26.

Bei der Titrirung verbrauchten 0.1117 g Säure 11.2 ccm $^1/_{10}$-*n*. Kalilauge. Ber. 11.28 ccm.

Durch längeres Erhitzen mit Bromwasserstoff-Eisessig auf 120—125° gelang es mir, die Dehydrocamphersäure in eine gesättigte β-Bromcamphersäure überzuführen:



(?)

Diese Bromsäure wurde bis jetzt noch nicht genauer untersucht, sondern direct mit Zinkstaub und Eisessig reducirt. Das Reductionsproduct bildete nach der Reinigung mit Kaliumpermanganat — um ungesättigte Verunreinigungen zu zerstören — ein im Exsiccator leicht erstarrendes Oel (wie gewöhnlich die Mesocamphersäuren). Dasselbe wurde mit Acetylchlorid behandelt — zwecks Ueberführung von Camphersäure in ihr Anhydrid — das Product in Aether gelöst und aus der Lösung die nicht anhydrisirbare Säure mit Sodalösung extrahirt. Nach

dem Verdunsten des Aethers blieb eine weisse, krystallinische Masse zurück, die, aus Alkohol umkrystallisirt, schöne Rhomboëder, die Hohlräume enthielten, bildete. Oft zeigen die Krystalle, wie es O. Aschan[1]) nennt, eine briefcouvertähnliche Anordnung. Sie schmolzen bei 217—219°. Das synthetische Anhydrid wurde auch direct mit dem aus Naturproducten dargestellten[2]) verglichen und zeigte sich damit vollkommen identisch. Z. B. wurde der Schmelzpunkt beider Präparate durch Mischung mit einander nicht verändert.

Die aus dem synthetischen Anhydrid regenerirte *r*-Campher-säure bildete, aus alkoholhaltigem Wasser umkrystallisirt, wie auch die schon bekannte, aus Naturproducten erhaltene Säure, platte, keilförmig zugespitzte Prismen. Der Schmelzpunkt lag bei 200—202°. Auch diese Säure zeigte sich nach dem directen Vergleich mit der zuerst von Chautard dargestellten *r*-Camphersäure[2]) vollkommen identisch.

0.1195 g Sbst.: 0.2623 g CO_2, 0.0884 g H_2O.

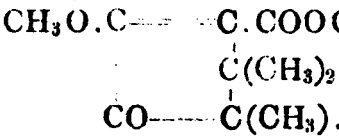
$C_{10}H_{16}O_4$. Ber. C 60.00, H 8.00.

Gef. » 59.86, » 8.22.

Titrirung: 0.0620 g Säure erforderten 6.15 ccm $^1/_{10}$-*n*. Kalilauge. Ber. 6.20 ccm.

Die in die Sodalösung übergegangene, nicht anhydrisirbare Säure (Isocamphersäure?) ist noch nicht näher untersucht worden.

Das bei der Methylirung des Diketoapocamphersäureesters entstandene ätherartige Product hat sich im Verlaufe der Untersuchung als folgende Verbindung erwiesen:



Dieser Ester bildet eine beinahe farblose Flüssigkeit, die unter 12 mm Druck bei 167—168° siedet. Bei der Reduction mit Natriumamalgam liefert sie dieselbe schon weiter oben beschriebene Dioxycamphersäure, welche aus Diketocamphersäureester entsteht. Auf Grund dessen kann man den Diketoapocamphersäureester quantitativ in Dioxycamphersäure überführen.

Die hier vorläufig mitgetheilten Versuche werden weiter geführt und später an anderer Stelle ausführlicher beschrieben.

Meinem Privatassistenten, Hrn. Ingenieur-Chemiker Severi Alanne, sage ich auch an dieser Stelle meinen besten Dank.

Helsingfors (Finland), im Novbr., Laborat. des Polytechnicums.

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[1]) Structur- und stereo-chemische Studien in der Campher-gruppe. Acta Soc. Scient. Fennicae. T. XXI. No. 5.

[2]) Für diese Proben danke ich meinem Collegen Prof. Ossian Aschan.

Aalto University
School of Chemical Technology

XIII Spring Meeting

Monday, 24 June, 2013	
10:00 am to 12:30 pm	Registration
12:30 pm to 1:00 pm	Opening Ceremonies Pekka Joensuu, Chairman of the Finnish Society for Synthetic Chemistry Ari Koskinen, Aalto University
	Chairperson: Pekka Joensuu, Aalto University
1:00 pm to 2:00 pm	Keynote Address 1: **Olivier Riant**, Université catholique de Louvain, Belgium *New Chiral Copper (I)-Bonded Nucleophile Complexes for Enantioselective Catalysis*
2:00 pm to 2:30 pm	Presentation 1: **Nuno Candeias**, Tampere University of Technology *Enantioselective modification of oxindole derivatives: aminooxygenation and syntheses of spirooxindoles*
2:30 pm to 3:00 pm	Coffee break
3:00 pm to 4:00 pm	Keynote Address 2: **Tomas Hudlicky**, Brock University, Canada *Recent progress in the chemoenzymatic synthesis of natural products. Constraints in total synthesis: How to combine the best of academic and industrial principles to achieve efficiency.*
4:00 pm to 5:00 pm	AGM of the FSSC
5:00 pm to 7:00 pm	Get together
Tuesday, 25 June, 2013	
	Chairperson: Reija Jokela, Aalto University
9:00 am to 10:00 am	Keynote Address 3: **Pher Andersson**, Stockholm University, Sweden *Turning Dihydrogen into a Highly Versatile Reagent in Enantioselective Synthesis*
10:00 am to 10:30 am	Presentation 2: **Andrejs Pelss**, Aalto University *Short and modular approach to lepadin alkaloids*
10:30 am to 11:00 am	Coffee Break
11:00 am to 12:00 am	Keynote Address 4: **David MacMillan**, Princeton University, U.S.A. *The use of Photoredox Catalysis in Organic Chemistry*
12:00 am to 1:30 pm	Lunch
	Chairperson: Petri Pihko, University of Jyväskylä
1:30 pm to 2:30 pm	Keynote Address 5: **Varinder Aggarwal**, Bristol University *Assembly line synthesis*

2:30 pm to 3:00 pm	Coffee break
3:00 pm to 4:00 pm	Keynote Address 6: **Victor Snieckus**, Queen's University, Canada *Partnering Aromatic/Heteroaromatic Lithium – Transition Metal Catalyzed Chemistries*
	Chairperson: Pekka Joensuu, Aalto University
4:00 pm to 4:30 pm	Publication prize ceremonies
4:30 pm to 5:00 pm	Presentation 3: **Mikko Leskinen**, University of Jyväskylä *Cross-Dehydrogenative Couplings between Indoles and β-Keto Esters: Mechanistic Evidence from Kinetic Isotope Effects*
5:00 pm to 5:30 pm	Presentation 4: **Oskari Karjalainen**, Aalto University *Allylative 5-endo-trig cyclization: mechanistic insights and applications*
6:00 pm to 8:00 pm	Poster Session and Evening Reception / Speakers' Dinner
Wednesday, 26 June, 2013	
	Chairperson: Ari Koskinen, Aalto University
9:00 am to 10:00 am	Keynote Address 7: **Karl Gademann**, University of Basel, Switzerland *Copy and Paste with Natural Products - from Total Synthesis to Functionalized Surfaces Directing Biological Response*
10:00 am to 10:30 am	Coffee Break
10:30 am to 12:00 am	Keynote Address 8: **Paul Wender**, Stanford University, U.S.A. *The Ideal Synthesis, Step Economy And Function Oriented Synthesis: First-In-Class Strategies For Treating AIDS, Resistant Cancer And Alzheimer's Disease*
12:00 pm to 12:30 pm	**Closing Ceremonies**

Plenary Talks

Assembly line synthesis

Aggarwal, V.K.
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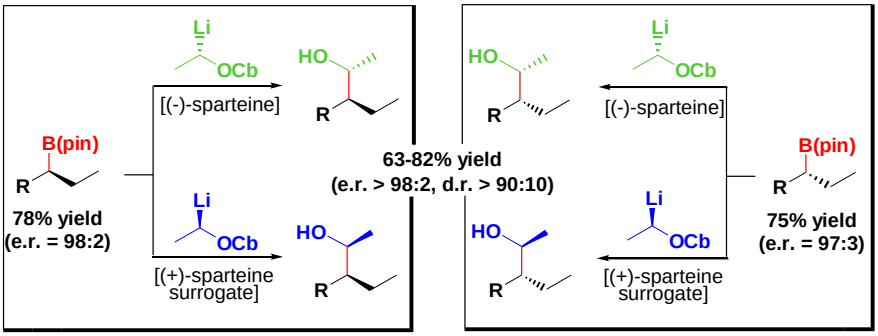
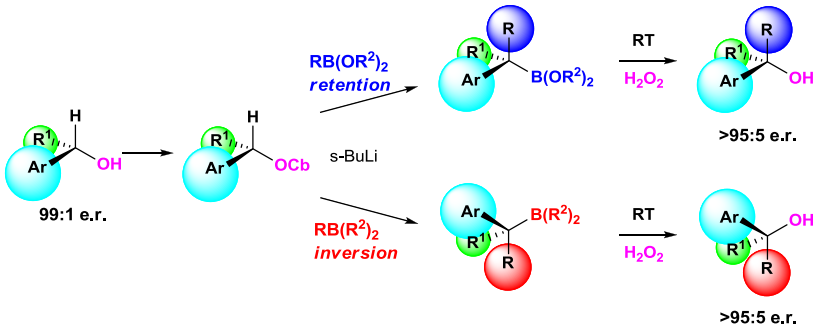
Bristol BS8 1TS
UK
v.aggarwal@bristol.ac.uk

In this lecture I will present our work on the reactions of primary and secondary lithiated carbamates with boranes and boronic esters.[1]



I will also discuss our recent methodology for the synthesis of tertiary boronic esters[2] and how such intermediates can be used in further stereospecific transformations.



I will show how electrophilic boronic esters can be transformed into nucleophiles which then react with a broad range of electrophiles with inversion of stereochemistry.[3] I will also describe a new method for the stereospecific cross-coupling of secondary and tertiary chiral boronic esters with aryl halides. Finally, I will also describe our recent applications of organocatalysis to a short synthesis of the prostaglandin PGF2α.[4]

[1] J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46*, 7491-7494.

[2] J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature*, **2008**, *456*, 778-782.

[3] R. Larouche-Gauthier, T G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.*, **2011**, *133*, 16794-16797.

[4 G. Coulthard, W. Erb, V. K. Aggarwal, *Nature*, **2012**, *489*, 278-281.

Turning Dihydrogen into a Highly Versatile Reagent in Enantioselective Synthesis

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Telephone(+46)-18-4713801, Fax(+46)-18-4713818,
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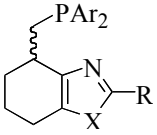
Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis. While ruthenium- and rhodium-catalyzed asymmetric hydrogenations of chelating olefins have a long history, unfunctionalised olefins still represent a challenging class of substrates. The corresponding Iridium-catalysed asymmetric hydrogenation are still highly substrate dependent and the development of new efficient chiral ligands that tolerate a broad range of substrates remains a challenge.

This lecture will deal with the preparation of a new class of chiral heteroaromatic *N,P* ligands along with their applications in catalytic asymmetric synthesis.



Leading references

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J. Am. Chem. Soc. 2012, 134, 13592.

Copy and Paste with Natural Products - from Total Synthesis to Functionalized Surfaces Directing Biological Response

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Switzerland
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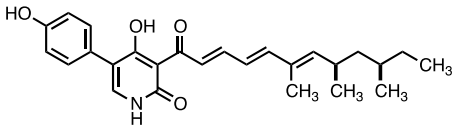
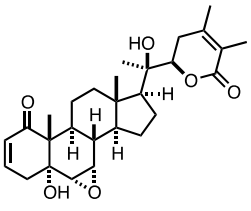
The reconstitution of neuronal networks by neurotrophins has been demonstrated as a viable strategy for addressing neuritic atrophy with regard to neurodegenerative diseases or spinal cord lesions.[1] However, limited efficacy was found for these proteins, due to poor bioavailability and the difficulty of reaching the central nervous system ('the blood/brain barrier'). Small molecule neurotrophins could overcome many of these problems and present thus a promising chemical alternative.[2] In addition, with regard to applications such as autologous nerve grafting for the treatment of spinal cord lesions, immobilized small molecules could offer unique advantages when compared to their protein counterparts.



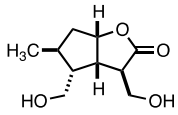
Militarinone D

Angew. Chem. Int. Ed. Engl. **2011,** *50*, 4222



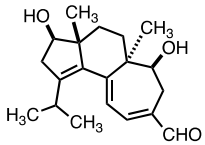
Withanolide A

Angew. Chem. Int. Ed. Engl. **2011**, *50*, 8407



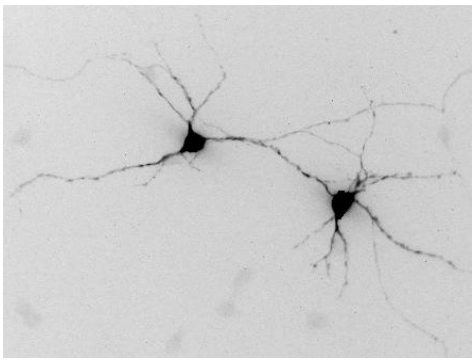
Gelsemiol

Chem. Eur. J **2013,** *19*, 2589



Cyrneine A

Angew. Chem. Int. Ed. Engl. **2012**, *51*, 4071



In this communication, we will report (1) on the development of a versatile molecular platform for the generation of biologically active surfaces[3] and (2) on the total synthesis and biological evaluation of a series of small molecule neurotrophin mimics.[4] Both lines of research have converged,[5] and the design and biological evaluation of natural product functionalized surfaces for nerve regeneration is presented. Potential applications with regard to nerve grafting and guiding or the man/machine interface are discussed.

1. Review. Aebischer, P.; Ridet, J. L. *Trends Neurosci.* **2001,** *24,* 533

2. Review: Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006,** *39,* 539

3. Gomes, J.; Grunau, A.; Lawrence, A. K.; Eberl, L.; Gademann, K. *Chem Commun* **2013**, *49*, 155–157; Malisova, B.; Tosatti, S.; Textor, M.; Gademann, K.; Zuercher, S. *Langmuir* **2010**, *26*, 4018; Saxer, S.; Portmann, C.; Tosatti, S.; Gademann, K.; Zuercher, S.; Textor, M. *Macromolecules* **2010**, *43*, 1050; Wach, J.-Y.; Bonazzi, S.; Gademann, K. *Angew Chem Int Edit* **2008**, *47*, 7123; Zürcher, S.; Wäckerlin, D.; Bethuel, Y.; Malisova, B.; Textor, M.; Tosatti, S.; Gademann, K. *J Am Chem Soc* **2006**, *128*, 1064.

4. Burch, P.; Binaghi, M.; Scherer, M.; Wentzel, C.; Bossert, D.; Eberhardt, L.; Neuburger, M.; Scheiffele, P.; Gademann, K. *Chem. Eur. J.* **2013**, *19*, 2589–2591; Elamparuthi, E.; Fellay, C.; Neuburger, M.; Gademann, K. *Angew Chem Int Edit* **2012**, *51*, 4071; Jessen, H. J.; Schumacher, A.; Shaw, T.; Pfaltz, A.; Gademann, K. *Angew Chem Int Edit* **2011**, *50*, 4222; Jana, C. K.; Hoecker, J.; Woods, T. M.; Jessen, H. J.; Neuburger, M.; Gademann, K. *Angew Chem Int Ed Engl* **2011**, *50*, 8407.

5. Hoecker, J.; Liffert, R.; Burch, P.; Wehlauch, R.; Gademann, K. *Org. Biomol. Chem.* **2013**, *11*, 3314.

Recent progress in the chemoenzymatic synthesis of natural products. Constraints in total synthesis: How to combine the best of academic and industrial principles to achieve efficiency.

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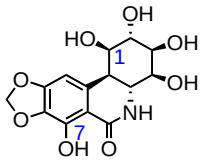
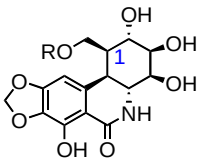
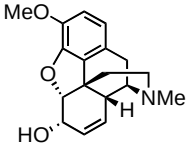
This lecture will focus on the recent progress in chemoenzymatic synthesis of Amaryllidaceae alkaloids such as pancratistatin **1** and its unnatural C-1 homologues **2** that were found highly active against human cancer cell lines. Several new approaches to codeine **3** will also be disclosed. The philosophy of academic versus industrial pursuits in attaining maximum efficiency will be discussed at the beginning of the lecture. The various factors that determine process efficiency will be illustrated in connection with recently attained improvements in the semi-synthesis of various opiate-derived medicinal agents such as buprenorphine **4**, naltrexone **5**, and others.



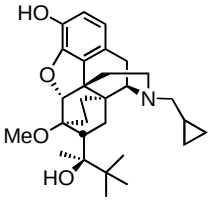
pancratistatin **1**



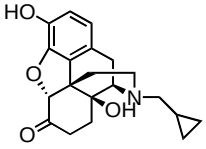
2 R = H, Ac, Bz



codeine **3**



buprenorphine **4**



naltrexone **5**

Komppa Symposium
JUNE 24 - 26, 2013, ESPOO, FINLAND

The use of Photoredox Catalysis in Organic Chemistry

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This lecture will discuss the advent and development of new concepts in chemical synthesis, specifically the combination of photoredox catalysis with organic catalysis. This new approach to "synergistic catalysis" will demonstrate that multiple yet separate catalytic cycles can be aligned to generate activated intermediates that rapidly combine with each other, thereby allowing new approaches to enantioselective C–C and C-heteroatom bond formation.

We will also introduce an approach to the discovery of new chemical reactions that we term accelerated serendipity. Accidental or 'serendipitous' discoveries have led to some of the most important breakthroughs in scientific history, many of which have directly affected human life. Given our overarching goal of developing fundamentally new and useful chemical transformations using catalysis and by acknowledging the tremendous impact of serendipity in scientific discovery, we questioned whether this phenomenon could be forced or simulated and therefore employed as a tool for reaction discovery.

In this presentation, we will describe several new transformations that have been discovered via "accelerated serendipity" that we expect will find widespread adoption throughout the field of chemical synthesis. Moreover, we will further describe how mechanistic understanding of these processes has led to the design of a valuable, new yet fundamental chemical transformation.

Acknowledgements

Financial support was provided by NIHGMS (R01 01 GM093213-01) and kind gifts from Merck, Amgen, and Abbott.

New Chiral Copper (I)-Bonded Nucleophile Complexes for Enantioselective Catalysis

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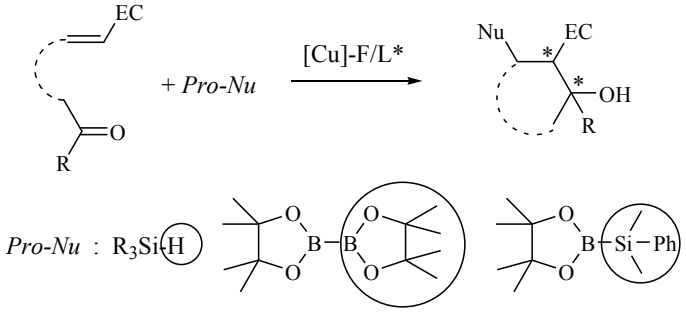
The development of new catalytic systems for the design of domino reactions, which allow to carry out various elementary steps in a single-pot procedure, is especially attractive for the stereoselective construction of C-C bonds. During the past few years, our group has focussed on the reductive aldolisation process which allows the coupling of a Michael acceptor and a carbonyl electrophile in the presence of a stoichiometric reducing agent (silane) to yield various aldol adducts.



We have developed a new family of chiral pre-catalysts by combining various chiral diphosphines with a stable copper (I) fluoride precursor which allows to generate in situ a copper (I) hydride catalysts after proper activation by a silane reagent. This reaction was optimised for both inter and intramolecular processes and the corresponding adducts were obtained with high diastereo and enantioselectivities. We have also shown that the hydride nucleophile could be replaced by a silyl or a boron based nucleophile, yielding thus new functionalised adducts through a three component catalytic reaction.

Partnering Aromatic/Heteroaromatic Lithium – Transition Metal Catalyzed Chemistries

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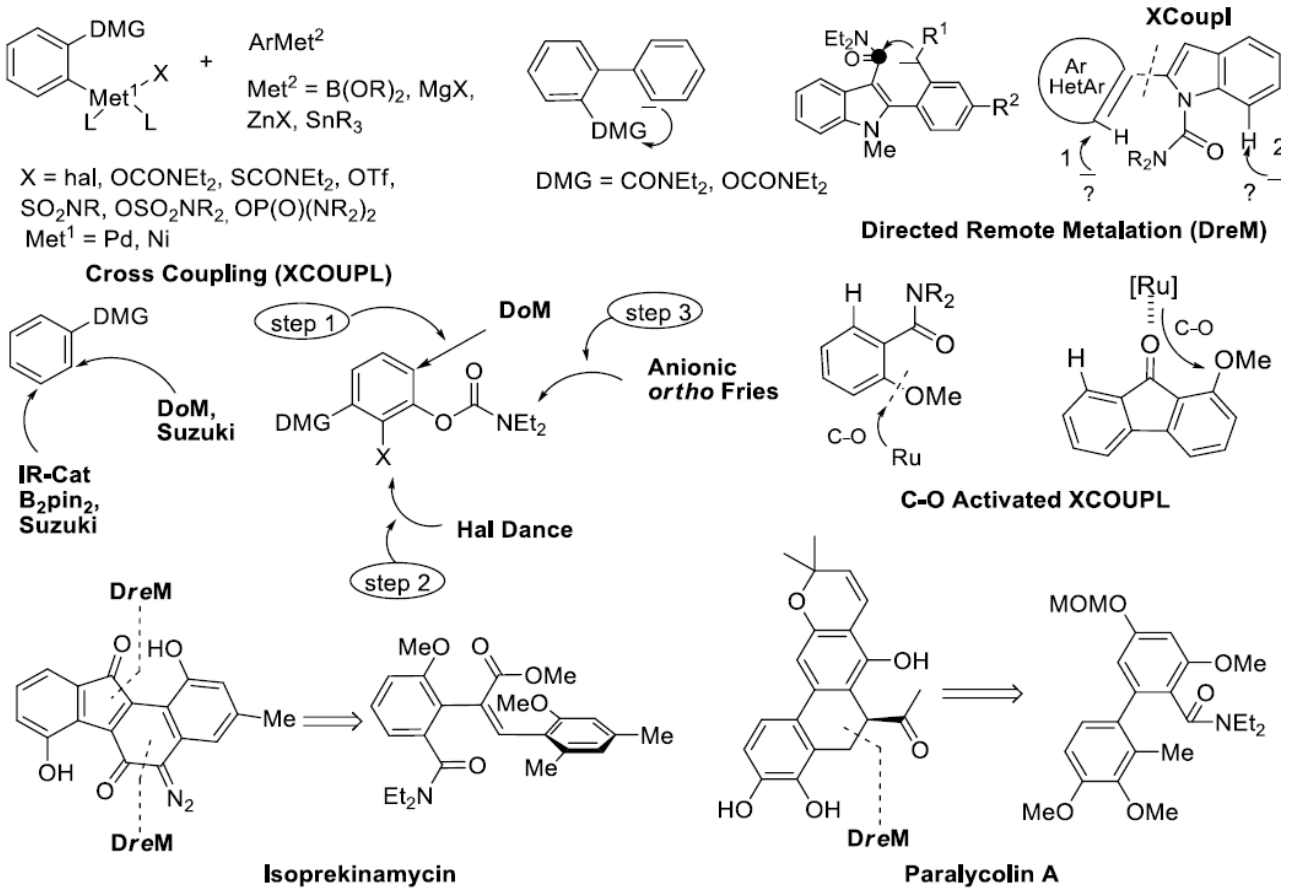
Snieckus@chem.queensu.ca

"Before the advent of DoM, the preparation of contiguously substituted (e.g. 1,2-, 1,2,3- or 1,2,3,4-) aromatic compounds, using the directing effect of the various substituents in S_EAr reactions was a major challenge and required many steps to accomplish".

Kürti, László, Czakó, Barbara
Strategic Application of Named Reactions in Organic Synthesis, Elsevier, Amsterdam, 2005, p 420

The Directed ortho Metalation (DoM) reaction, discovered by Wittig and Gilman over 70 years ago and propelled into prominence by Hauser, Beak, Christensen, Gschwend, Meyers, Muchowski, and others, is now beginning to infiltrate undergraduate organic texts and is increasingly practiced on mg to metric ton scales, e.g. Sustiva™ (Dupont-Merck → BMS, anti-AIDS), Silthiofam™ (Monsanto, fungicide). The link of transition metal catalyzed reactions (e.g. Heck, Suzuki, Sonogashira, Grubbs) to DoM is providing the synthetic chemist with a variety of effective combined protocols and is also finding application on large scale, e.g. Losartan™ (BMS, anti-inflammatory).

The common theme in our laboratories is the invention and development of new DoM aromatic chemistry, separate and linked to transition metal catalyzed processes, and their demonstration in bioactive molecule, natural product, and materials construction. A selection of these themes (below) including new departures into Ir, Rh, and Ru catalyzed DoM-enhancing connections will be described.



Hartung, C.G., Snieckus, V. In Astruc, D. Ed. *Modern Arene Chemistry*, Wiley-VCH; New York, **2002**, pp 330; Whistler, M.C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; Anctil, E. Snieckus, V. In Diederich, F., de Meijere, A. Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed., **2004**, pp 761; Macklin, T.; Snieckus, V. In Dyker., G. Ed. *Handbook of CH Transformations*, **2005**, Wiley-VCH, New York, pp 106; *Palladium-Catalysed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize*. Johansson Seechurn, C.C.C., Kitching, M.O., Colacot, T.J., Snieckus, V., *Angew. Chem. Int. Ed.*, **2012**, *51*, 5062.

The Ideal Synthesis, Step Economy And Function Oriented Synthesis: First-In-Class Strategies For Treating AIDS, Resistant Cancer And Alzheimer's Disease

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My group is interested in solving molecular problems in chemistry, biology, medicine, imaging and materials research. An emphasis is placed on the design and synthesis of molecules with function (therapeutic, diagnostic, imaging, catalytic), appropriately termed "*function oriented synthesis*" (*Nature* **2009**, 460, 197-201; *Accts. Chem. Res.* **2008**, 40-49; *Proc. Natl. Acad. Sci.* USA **2011**, 6721-6726). Through function- and synthesis-informed design, we seek to develop agents to eradicate HIV/AIDS (Science **2008**, 649-652; *Nature Chemistry* **2012**, 705-710), to overcome resistant cancer – the major cause of chemotherapy failure (*PNAS* **2008**, 12128-12133; *Gynecologic Oncology* **2012**, 118-123) and to treat cognitive dysfunction including Alzheimer's disease (*Neurobiology of Disease* **2009**, *34(2)*, 332-339). "Function" is also manifest in the design of new catalysts (*Angewandte Chemie Int. Ed.* **2012**, *51(11),* 2736-2740). An emphasis is also placed on the development of new reactions and multicomponent reactions (lead ref: *J. Am. Chem. Soc.*, **2012**, *134* (26), 11012–11025), including arene-alkene photocycloadditions and metal-catalyzed [4+4], [4+2], [3+2], [5+2], [6+2], [5+2+1], [4+2+1], [4+2+2], [2+2+2], [2+2+2+2] and [5+2+1+1] cycloadditions, that allow for the *step- and time-economical*, if not *ideal*, synthesis of targets of value. In 1985 (*Tetrahedron Lett.* **1985**, 2625), we first defined "*ideal syntheses [as] those in which the target molecule is assembled from readily available starting materials in one simple, safe, economical, and efficient operation.*" This lecture will describe the role of synthesis, new reaction design, time- and step-economy, and function oriented synthesis in studies directed at as yet unsolved but highly significant therapeutic problems.

Short Oral Communications

Enantioselective modification of oxindole derivatives: aminooxygenation and syntheses of spirooxindoles

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The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA
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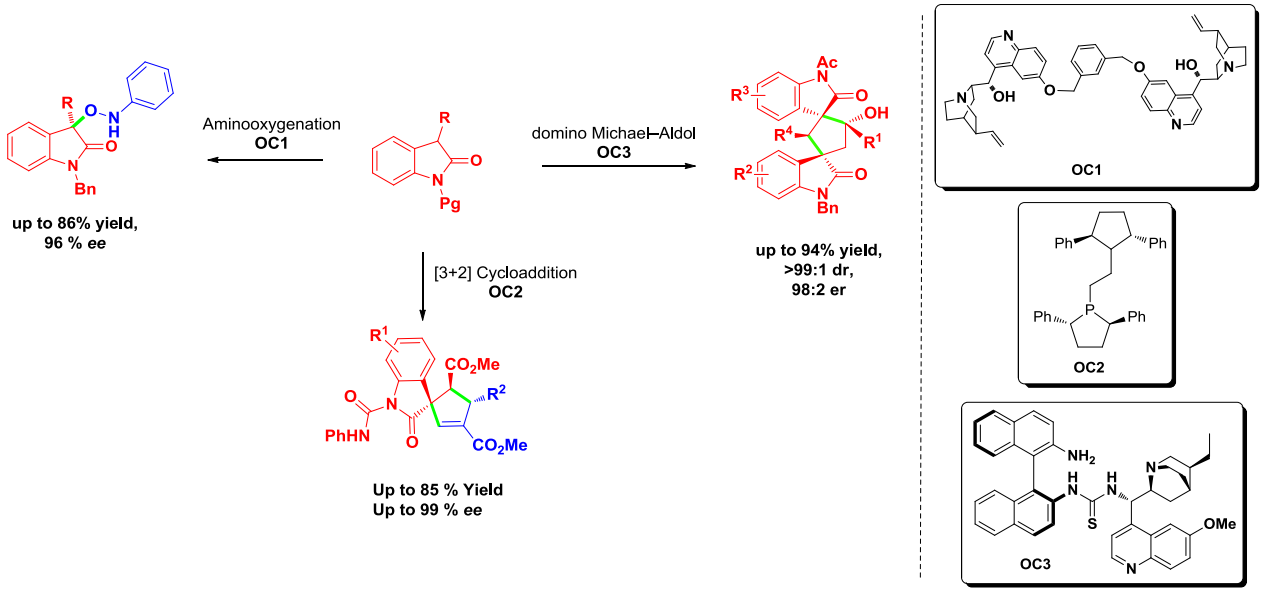
2-Oxindoles are a structural framework of several alkaloid natural products and compounds of known biological activity. Hence, huge efforts have been recently done in order to develop new synthetic routes for the asymmetric preparation and modification of such structures.[1] 3-Hydroxyoxindoles, spirocyclopenteneoxindoles and bispirooxindoles have been prepared in excellent yields and enantioselectivities, by using different types of organocatalysts such as a dimeric quinidine derivative (OC1),[2] a phosphine (OC2)[3] or a multifunctional organocatalyst (OC3),[4] respectively. Recent efforts for the development of new tools for the asymmetric modification of 2-oxindoles and derivatives will be presented.



1. a) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *early view*, DOI: 10.1002/adsc.201200808.; b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104–6155.
2. Bui, T.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2010**, *132*, 5574–5575.
3. Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675.
4. Tan, B.; Candeias, N. R.; Barbas, C. F. III *Nature Chem.* **2011**, *3*, 473–477.

Allylative 5-*endo-trig* cyclization: mechanistic insights and applications

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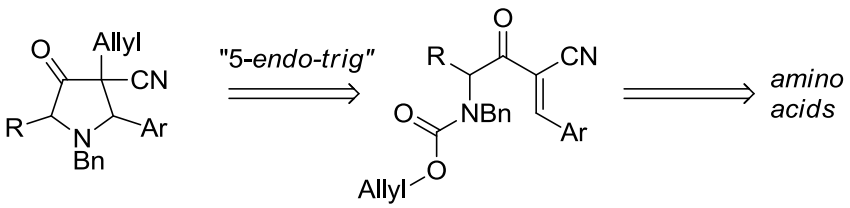
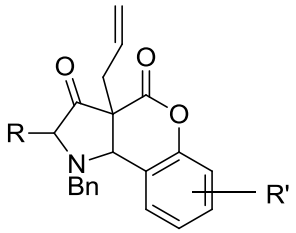
Recently, we reported a paper on a novel diastereoselective allylative palladium catalyzed 5-*endo-trig* annulation, which uses the allyloxycarbamate protecting group as the allyl cation source.[1] In this communication we wish to present our progress towards the unveiling of the underlying reaction mechanism.



We have also started to extend this methodology to construct more complex systems. To this end, the facile synthesis of novel pyrrolidinocoumarins (example below) is also discussed.



1. Karjalainen, O. K.; Nieger, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2551-2554.

Cross-Dehydrogenative Couplings between Indoles and β -Keto Esters: Mechanistic Evidence from Kinetic Isotope Effects

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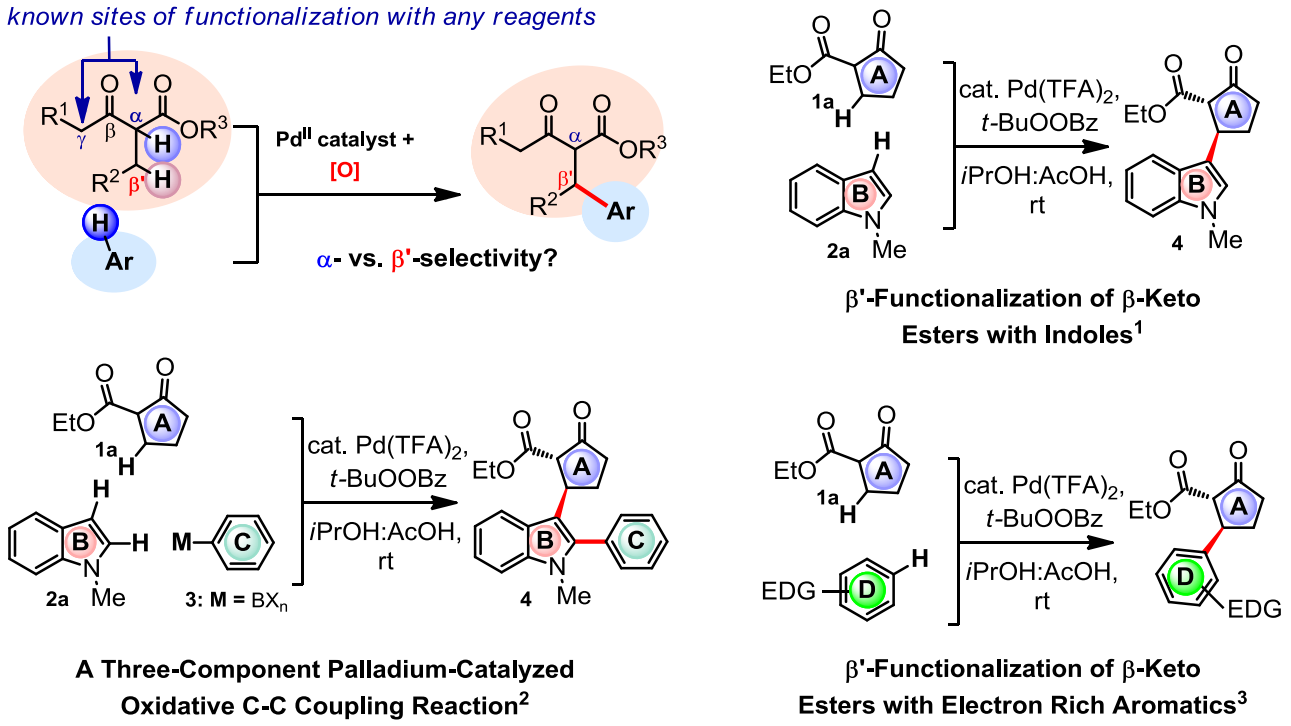
We have recently developed several palladium-catalyzed cross-dehydrogenative coupling reactions to β'-functionalize the β-keto esters with different substrates, including a three-component oxidative C-C coupling reaction.[1-3]



In this communication we discuss the detailed reaction mechanism of the cross-dehydrogenative coupling and present evidence for the mechanism based on kinetic isotope effects.

1. Leskinen, M. V.; Yip, K.-T.; Valkonen, A.; Pihko, P. M. *J. Am. Chem. Soc.* **2012**, *134*, 5750−5753.
2. Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4818–4822.
3. Yip, K.-T.; Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Chem. Eur. J.* **2012**, *18*, 12590–12594.

Short and modular approach to lepadin alkaloids

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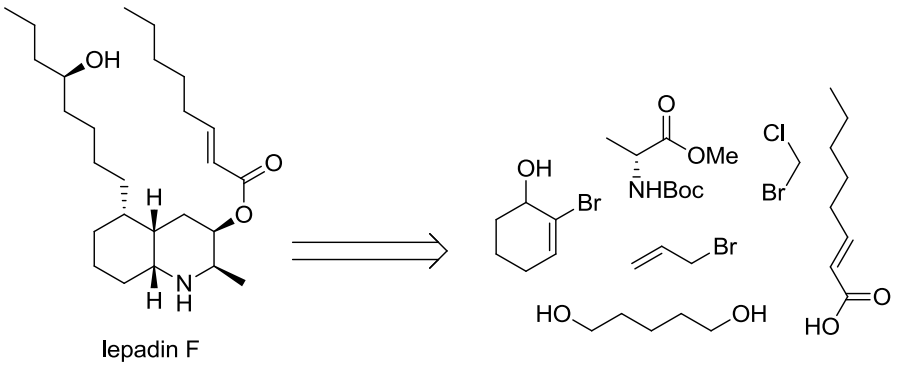
Lepadins form one of four groups of biologically distinct decahydroquinoline alkaloids. There are three stereochemical groups of lepadin alkaloids. Current state of the art strategies for lepadin alkaloid synthesis require 18-38 steps. None of these syntheses can provide practical access to lepadins to support further biological studies. Owing to our interest in C-18 aminoalcohol natural product chemistry we decided to make our contribution to decahydroquinoline alkaloid research and choose lepadins as suitable targets. During lepadin alkaloid synthesis studies we have developed a unified strategy with the aim to access complete stereochemical complexity of these natural compounds in a step economic and modular fashion.



lepadin F

In this presentation all details on the development of short synthetic sequences to lepadin alkaloids including the advancement of several new methodologies during various stages of synthetic routes will be discussed.

Posters

Komppa Symposium
JUNE 24 - 26, 2013, ESPOO, FINLAND

Synthesis Towards Mucosin and Dictyosphaerin

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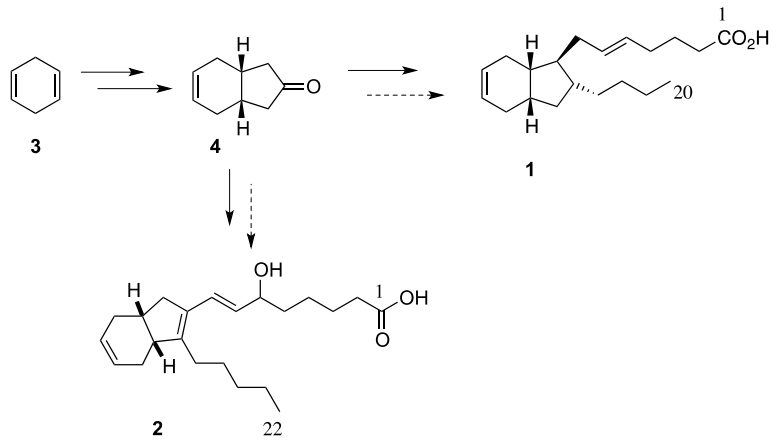
Mucosin (1), isolated from a Mediterranean sponge, and dictyosphaerin (2), isolated from a marine green alga from southern Australia, have prostaglandin-like structures as seen in **Fig. 1.** [1,2]

However, they differ from typical prostaglandins by having a bicyclic[4.3.0]nonane skeleton containing *cis*-fused hydrogens and varying side-chain lengths. We wanted to make a general route to these and similar compounds.

Currently, we are starting with 1,4-cyclohexadiene (3), to form a bicyclic *meso*-ketone (4) in a three-step synthesis, has proved successful and in good yields by simple reactions and commercially available reagents.

Following on from this, we have done subsequent asymmetry reactions, employing a chiral base, to add the side chains with the right stereochemistry.

Fig. 1:



1. Casapullo, A. Scognamiglio, G. Cimino, G. *Tetrahedron Letters*, **1997**, *38*, 3643-3646
2. Rochfort, S. J. Watson, R. Capon, R. J. *J. Nat. Prod.* **1996**, *59*, 1154-1156

Synthetic studies towards protectin D1

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Norway
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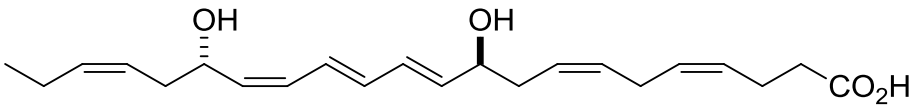
Protectin D1 (**1**) is an endogenous metabolite of docosahexaenoic acid (DHA) with potent anti-inflammatory properties in vivo. The protectin family of oxygenated metabolites shares a characteristic triene moiety, varied patterns of hydroxylation, as well as potent biological effects observed in their ability to protect against several human ailments.[1]

The presentation will give a summary of our synthetic studies towards protectin D1 (**1**).



Protectin D1 (**1**)

1. Mukherjee, P. K.; Marcheselli, V. L.; Serhan, C. N.; Bazan, N. G. *Proc. Natl. Acad. Sci.* **2004**, *101*, 8491–8496.

Studies Towards the Total Synthesis of Ophiodilactones A and B

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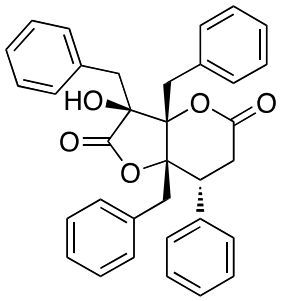
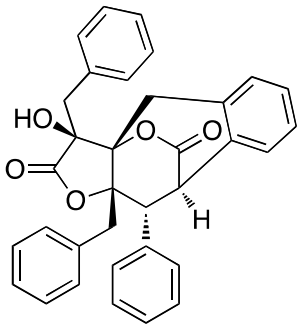
In 2009, Matsunaga *et al.* reported the isolation of the tetrameric phenylpropanoids ophiodilactones A (**1**) and B (**2**) from the brittle star *Ophiocoma scolopendrina*. Both compounds show cytotoxic activity against P388 murine leukemia cell lines.[1] The γ,δ-dilactonic core structure is uncommon in nature and synthetic examples of similar skeletons are rare in literature.[2-4] The intriguing architecture combined with the biological activity of **1** and **2** triggered our interest and motivated us to start a program directed towards their total synthesis.



1



2

Key challenges of the synthesis are the four contiguous stereogenic centers, the unusual dilactone skeleton and the α-arylated lactone in compound **2**. We will present our recent efforts towards the total synthesis of the ophiodilactones A and B.

1. Ueoka, R.; Fujita, T.; Matsunaga, S. *J. Org. Chem.* **2009**, *74*, 4396–4399.
2. Borsche, W. *Chem. Ber.* **1916**, *49/II*, 2538–2546.
3. Kapferer, T.; Brückner, R. *Eur. J. Org. Chem.* **2006**, *9*, 2119–2133.
4. Hatakeyama, S.; Matsubara, T.; Takahashi, K.; Ishihara, J. *Heterocycles* **2012**, *86*, 155–158.

Electronic Regioselectivity of Diarylalkynes in Cobalt Mediated Pauson-Khand Reaction

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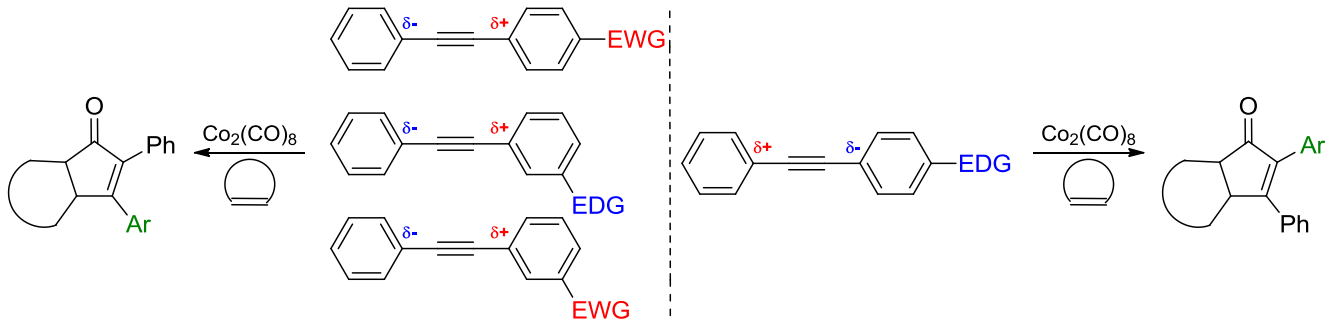
Finland
erika.fager-jokela@helsinki.fi

Both steric and electronic factors of substituted alkynes are known to guide α/β-cyclopentenone regioselectivity in the cobalt mediated Pauson-Khand reaction (PKR). In its synthetic applications, the steric factors often override or render possible electronic effects. This study examined alkyne dependent electronic regioselectivity of cyclopentenone formation in PKR with norbornene and sterically equivalent, but electronically unsymmetrical, *meta*- and *para*-substituted diarylethynyls in order to unveil the role of electronic effects alone.[1] In agreement with the literature reports, EDG *para*-substituted aryls, to some extent, favoured cyclopentenone α-position, while the EWG substituted aryls correspondingly preferred the β-regioisomer. Both EWG and EDG *meta* substituted aryls preferred β-regioselectivity. Computational investigations at the DFT level revealed a correlation between NBO charges and the regioselectivity. Overall, the results suggest that the polarity of an alkyne dictates the regioselectivity in the absence of steric effects.



1) Fager-Jokela, E.; Muuronen, M.; Patzschke, M.; Helaja, J. *J.Org. Chem*. **2012**, *77*, 9134-9147.

TOWARDS THE TOTAL SYNTHESIS OF CALYCULIN C:

STUDIES FOR THE PREPARATION OF C1-C9 TETRAENE MOIETY

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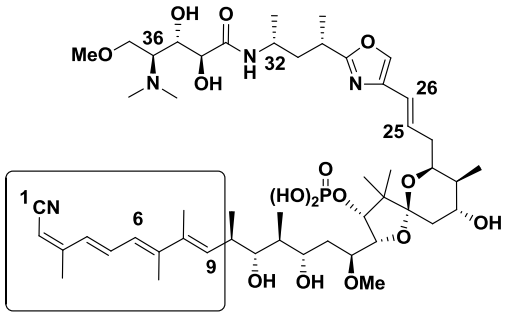
Calyculin C is a member of a secondary metabolite polyketides family, first isolated from the marine sponge *Discodermia calyx* by Fusetani *et al.*[1] Calyculins are potent inhibitors of serine/threonine protein phosphatases PP1 and PP2A. Due to the lack of knowledge of the exact function of these enzymes, the discovery of small molecule inhibitors has proven to be valuable for a better understanding of the biological processes mediated by protein phosphorylation.[2]



Calyculin C

It was our desire to design a convergent approach to Calyculin C which easily lent itself to the synthesis of a myriad of analogues to probe the biological role of PP1 and PP2A. Our group has previously reported the synthesis of the other fragments of the natural product.[2] The goal of the current study is to develop a new and more efficient synthesis for the C1-C8 fragment. Our progress towards this moiety is described.

1. Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem*. **1988**, *53*, 3930.
2. Sheppeck, II, J. E.; Gauss, C.-M.; Chamberlain, R. *Bioorg & Med. Chem. Lett.* **1997,** *5,* 1739.
3. Fagerholm, A.E.; Habrant, D.; Koskinen, A.M.P. *Mar. Drugs*. **2010**, *8*, 122.

Asymmetric iodolactonization catalyzed by a dinuclear zinc complex

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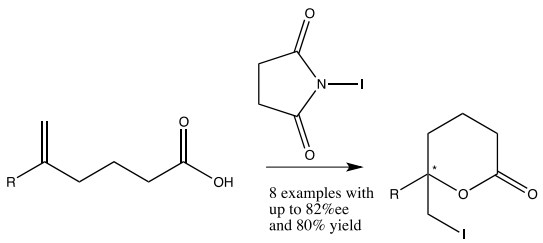
Catalytic enantioselective iodolactonization is an attractive route to stereochemically-defined lactones that can serve as key intermediates in the synthesis of biologically active compounds[1]. Despite growing interest in this area[2], successful examples of this transformation, with levels of enantioinduction higher than 90-95%, are still limited[2a,c] which leave room for further investigation. In connection with our ongoing projects in natural product synthesis, we are interested in an efficient catalyst system for this type of reaction. Our attention was particularly driven towards *bis*-ProPhenol Trost ligand complexes, which are known to be useful in a rich variety of asymmetric transformations[3] such as aldol condensations, Henry reactions, Michael additions, alkylations, Mannich-type reactions amongst others.

Herein, results of our study on enantioselective iodolactonization reactions catalyzed by a dinuclear zinc *bis*-ProPhenol Trost ligand complex are presented.



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Progress Towards the Total Synthesis of Jiadifenolide

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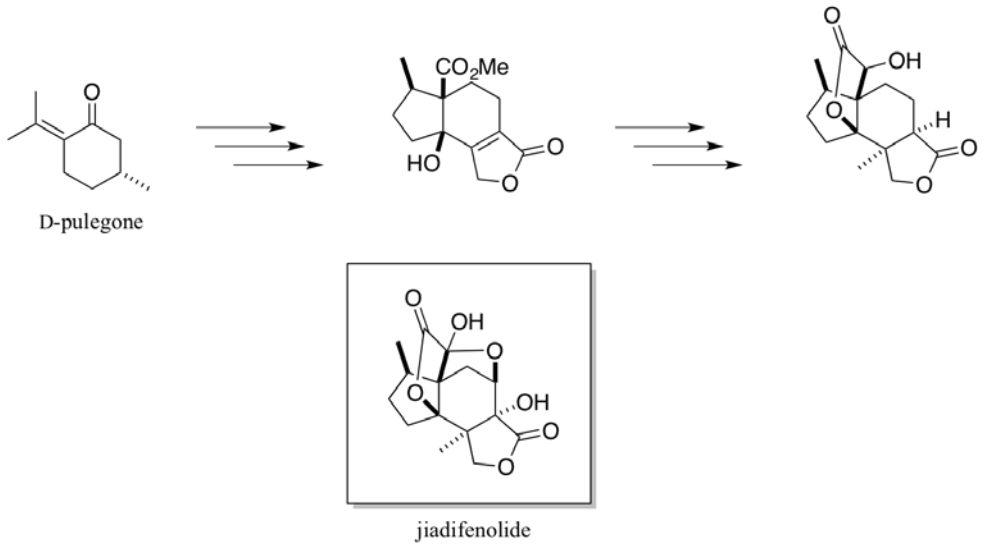
The progression of Alzheimer's, Parkinson's, and Huntington's disease have been linked to decreased neurotrophic support. Therefore, neurotrophins have been selected as candidates for a successful therapeutic strategy aimed at controlling these medical challenges.[1] An attractive approach is based on the search for orally bioavailable small organic molecules that could mimic or enhance neurotrophin (e.g. *nerve growth factor*) action.



In search for such compounds, some majucin-type *seco*-prezizaanes, found in the pericarps of *Illicium majus*, have shown to exhibit neurotrophic activity at very low concentrations.[2] We will present our results towards the total synthesis of its most active member, jiadifenolide.

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2. Fukuyama, Y.; Huang, J.-M. *Studies in Natural Products Chemistry*, Elsevier **2005** Vol. 32.

Total synthesis of ferrocenestrone

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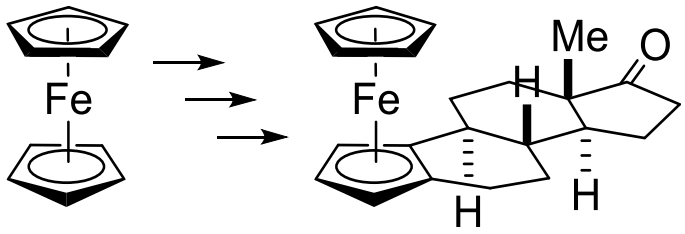
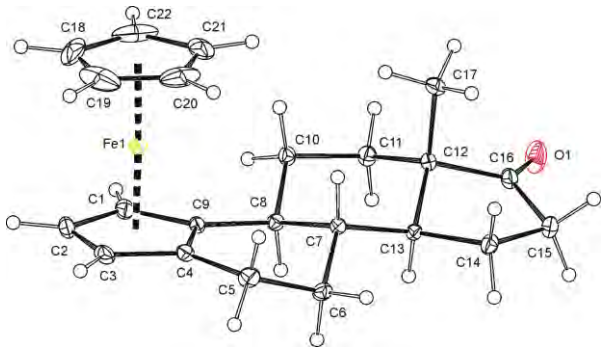
Ferrocene conjugates with various types of biologically active compounds such as saccharides, steroids or peptides have been studied intensively in the last few years for their interesting properties, compared to the model compounds.[1] Ferrocifen may serve as a notable example of an interesting new substance. It is a ferrocene containing derivative of tamoxifen with potential effect in treatment of breast cancer.[2]

Although several conjugates of steroids with ferrocene have been prepared, the cyclopentadienyl ring has not been the integral part of the steroid skeleton in any of them. With regard to our recent results concerning new synthesis of estrone[3] and hoping to simulate the biological effects of ferrocifen, we decided to address the synthesis of first such steroid – ferrocenestrone, an analogue of estrone containing ferrocene in place of the aromatic A-ring. Various transition-metal mediated procedures were applied during synthesis of this first metallocene-based steroid derivative.[4]





1. Stepnicka P. *Ferrocenes: Ligands, Materials and Biomolecules*, John Wiley & Sons Ltd: Chichester, **2008**.
2. Schatzschneider U.; Metzler-Nolte N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1504-1507.
3. Herrmann P.; Budešínský M.; Kotora M. *J. Org. Chem*. **2008**, *73*, 6202-6206.
4. Hessler F.; Císařová I.; Sedlák D.; Bartůněk P.; Kotora M. *Chem. Eur. J.* **2012**, *18*, 5515-5518.

Chemoenzymatic formal synthesis of *ent*-codeine via nitrone cycloadditions and/or radical cyclizations

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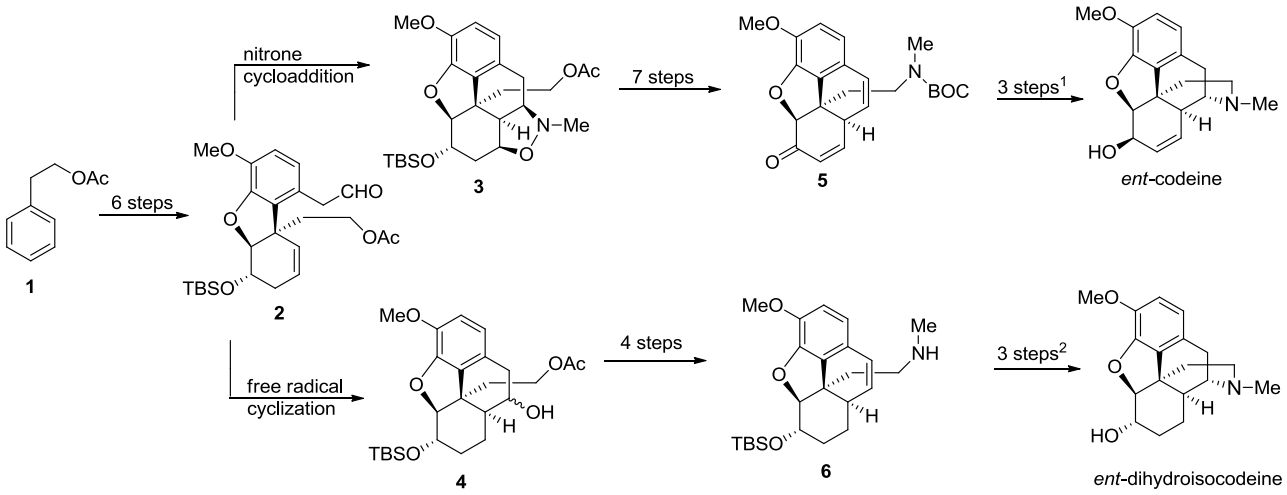
A formal synthesis of ent-codeine was achieved using cycloaddition of nitrone derived from aldehyde **2**, which was prepared *via* the toluene dioxygenase-mediated dihydroxylation of 2-phenyl ethanol *O*-acetate **1** by whole-cell fermentation with *E. coli* JM109(pDTG601A). Similarly, **2** can be converted to **4** *via* SmI_2-mediated free radical cyclization as the key step. Details of these two syntheses will be presented.



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2. Ichiki, M.; Tanimoto, H.; Miwa, S.; Saito, R.; Sato, T.; Chida, N. *Chem. Eur. J.* **2013**, *19*, 264.

Novel regioselective nitration of the chlorin ring: utilizing of chlorophyll derivatives as anion sensor probes

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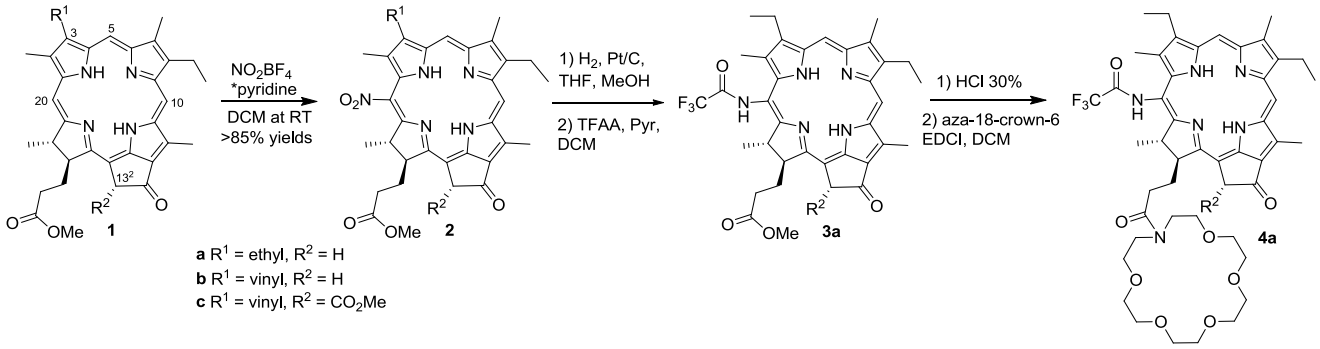
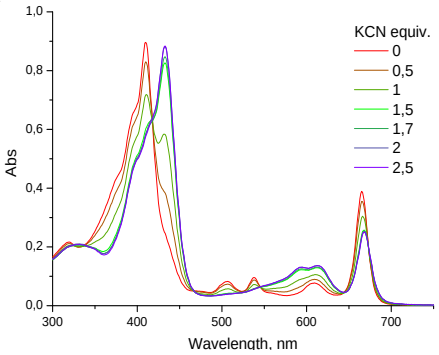
Based on Olah's reagent, NO_2BF_4*pyridine complex,[1] a novel soft method for selective chlorin ring nitration at 20 position was developed giving excellent yields. Subsequently, the nitro group was converted to TFA-amide in order to introduce sensing moiety into chlorin core ring. To achieve tight binding of ions with potassium counter-ions the molecule was further equipped with aza-18-crown-6 moiety.[2]



Synthesized molecules were tested as colorimetric sensors for variety of anions at μM level. Response of **3a** towards CN^- and F^- in different solvents was studied.[2] In order to figure out the possibility of utilizing **4a** as a selective KCN sensor, dependence of the sensing and discrimination between CN- and F- in systems with different DMF:H_2O ratio was studied.[2]



UV changes upon addition of KCN to **4a**.

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2. Iashin, V. A.; Koso, T. V.; Stranius, K.; Muuronen, M.; Heikkinen, S.; Kavakka, J.; Tkachenko, N. V.; Helaja, J. *RCS Adv.* **2013**, in press.

Synthesis of Heterocycles via Ru-Catalyzed Tandem RCM/Isomerization Sequences

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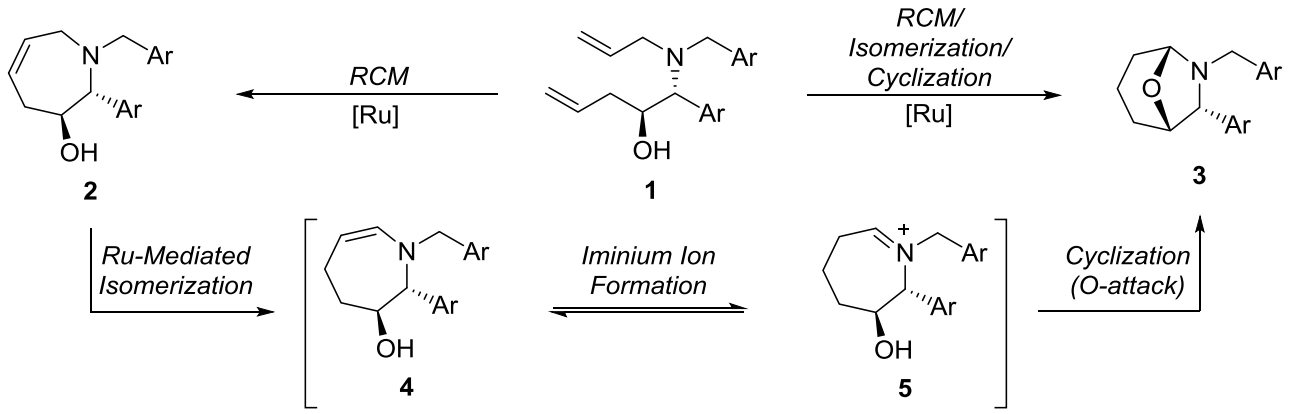
Ruthenium-catalyzed ring-closing metathesis (RCM) and isomerization reactions are powerful tools for the generation of structurally diverse small molecules. We here wish to report the development of a novel tandem RCM/isomerization/cyclization sequence. From a common *anti*-amino alcohol diene precursor **1**, biologically intriguing tetrahydroazepines **2** and oxazabicyclooctanes **3** were selectively synthesized,[1] and some of the factors influencing the rate of the reaction pathways were elucidated. Selected applications of the synthetic methodology to other ring systems will also be presented.



1. Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E. *ACS Comb. Sci.*, **2012,** *14*, 253-257.

Chirospecific synthesis of phenethylamine derivatives

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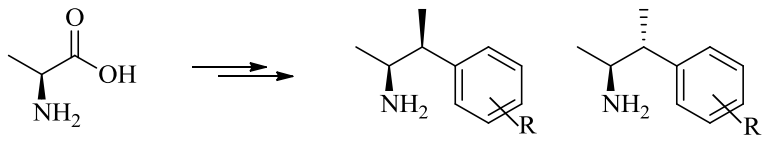
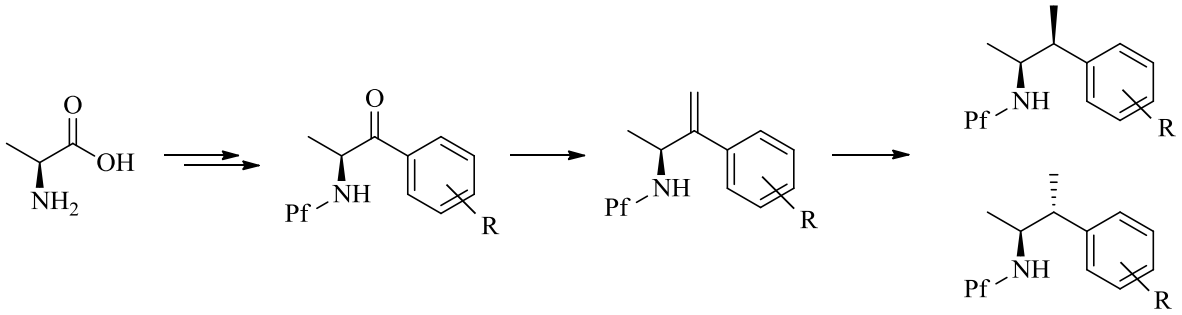
In this work, a series of phenethylamine derivatives were made starting from L-alanine.



Phenyl-9-fluorenyl (Pf) was used as the amine protecting group, which ensured the enantiopurity in the reaction steps.[1]



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Solid-supported synthesis of multipodal scaffolds for glycotargeting

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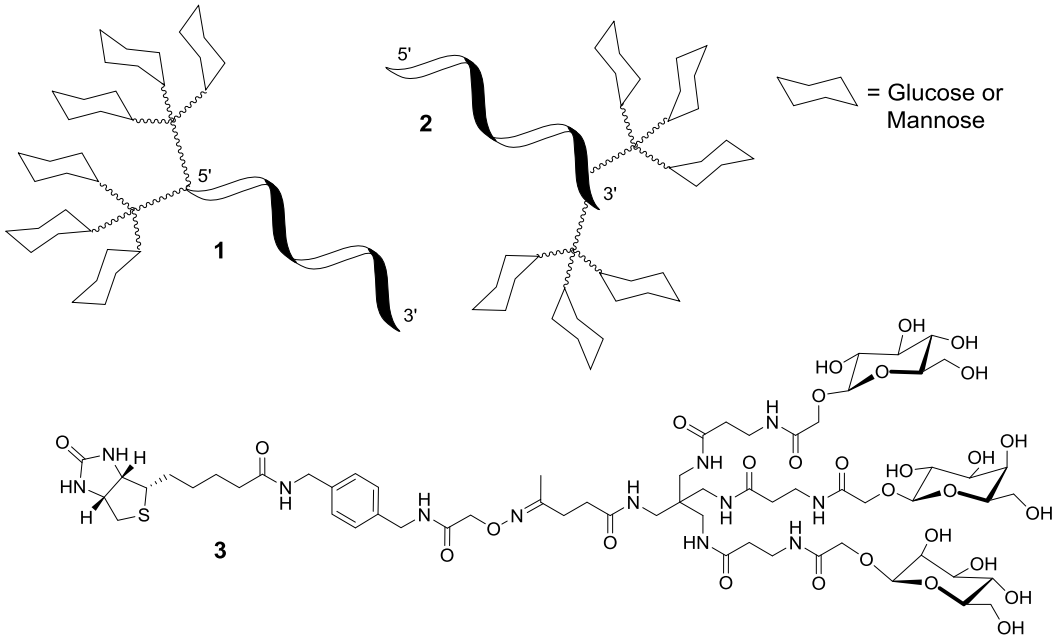
Interactions between carbohydrates and proteins are responsible for the initiation of numerous physiological processes. Synthetic glycoclusters are potential tools for the modification and utilization of these carbohydrate recognition events. Applications include e.g. cell specific targeting of oligonucleotide drugs, blocking of microbial infections and detection of cancer. Multivalency is generally needed for high affinity and specificity. We have synthesized diverse multipodal scaffolds to build homotypic and heterotypic glycoclusters. These clusters were further conjugated with oligonucleotides (**1**, **2**)[1] or peptide structures (**3**)[2]. Conjugations were based on click and oximation ligations and peptide couplings on solid support.



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Synthesis of 7-substituted 3-*β*-D-ribofuranosyl-3*H*-imidazo[1,2-*i*]purines

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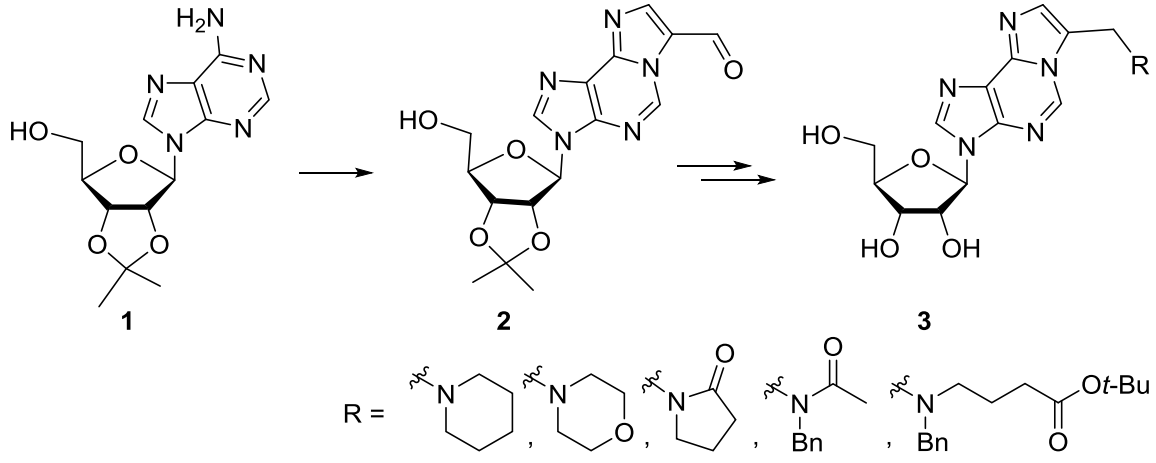
Purine nucleosides and their congeners have found numerous applications in medicinal research. Although a wealth of structural analogs has been synthesized and studied, there is a constant need for further modifications. Therefore, a method for the solution phase synthesis of 7-substituted 3-*β*-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purines has been devised.[1] This is an extension of our previous studies on solid-supported synthesis of 3-substituted 3*H*-imidazo[2,1-*i*]purine-7-carbaldehydes[2] and 4(5),1',5'-trisubstituted 2,4'-biimidazoles[3]. The compounds were prepared in a few steps from a common intermediate, 3-(2',3'-*O*-isopropylidene-*β*-D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde (**2**), obtained by reacting 2',3'-*O*-isopropylideneadenosine (**1**) with bromomalonaldehyde (Scheme 1). The formyl group of **2** was reductively aminated with piperidine, morpholine, benzylamine, or *tert*-butyl 4-aminobutanoate. The resulting secondary amines were then either acetylated, lactamized or alkylated reductively yielding products **3** after deprotection.



Scheme 1. General overview of the syntheses.

1. Karskela, T.; Klika, K. D.; Lönnberg, H. *Collect. Czech Chem. Comm.* **2011**, *76*, 1043–1054.
2. Karskela T., Lönnberg H.; *Org. Biomol. Chem.* **2006**, *4*, 4506–4513.
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α-Substituted Acroleins – Novel Substrates For The Organocatalytic Mukaiyama–Michael Reaction

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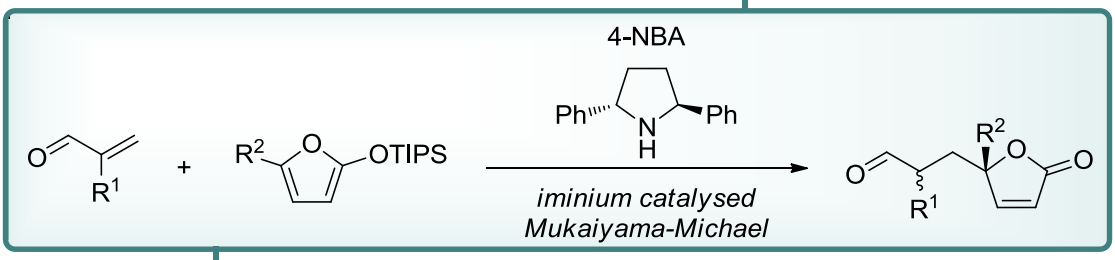
α-Substituted acroleins are typically known to be unreactive substrates in secondary amine catalysed reactions.[1] We have developed a new methodology to expand the scope of the organocatalyzed Mukaiyama-Michael reaction to include these substrates, and have also applied the methodology in natural product synthesis.[2]



R^1 = H, alkyl, OR
R^2 = H, Me

- typically 95:5 to 97:3 *er*
- 53-90% yield
- separable diastereomers when R^1 = alkyl, OBn

1) a) Kunz, R. K.; MacMillan, D. W. C. J. Am. Chem. Soc. 2005, 127, 3240-3241. b) Kravina, A. G.; Mahatthananchai, J.; Bode. J. W. Angew. Chem. Int. Ed. 2012, 51, 9433-9436.

2) Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. Org. Lett. 2012, 14, 1086-1089.

2,2-Disubstituted 4-acylthio-3-oxobutyl groups as esterase- and thermolabile protecting groups of phosphodiesters

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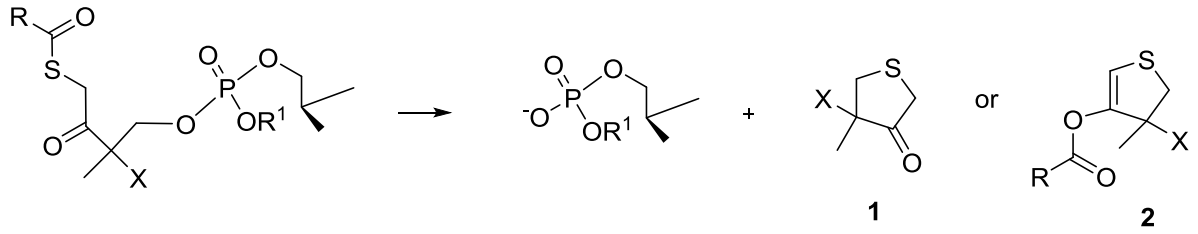
The applicability of 2,2-disubstituted 4-acylthio-3-oxobutyl groups as esterase- and thermolabile protecting groups for phosphodiester linkages was studied.[1] Appropriately protected nucleoside 5′-methyl phosphates and bis(2′-*C*-methyluridin-5′-yl) phosphate were prepared as model compounds and their enzymatic and non-enzymatic deprotection was followed at pH 7.5 and 37 °C. The removal of the protecting groups takes place by intramolecular cyclization with the release of the phosphodiester. Enzymatic deacylation by carboxyesterases triggers the departure of the protecting group as 4,4-disubstituted dihydrothiophen-3(2*H*)-one (**1**). In the case of the non-enzymatic deprotection, the acyl group migrates from the sulfur atom to C3-*gem*-diol obtained by hydration of the keto group and the exposed mercapto group attacks on C1 resulting in departure of the protecting group as 4,4-disubstituted 3-acyloxy-4,5-dihydrothiophene (**2**). The rate of the non-enzymatic deprotection depends on both, the electronegativity of the 2-substituents and the size of the 4-acylthio groups, while the rate of the enzymatic deprotection was mainly tuned by the nature of the acyl group.



R^1 = Me, 2′-C-methyluridin-5′-yl
R = Me, Ph, t-Bu
X = Me, CO_2Et

1. Kiuru, E.; Ahmed, Z.; Lönnberg, H.; Beigelman, L.; Ora, M. *J. Org. Chem.* **2013**, *78*, 950-959.

Synthesis of Chiral ionic liquids and salts

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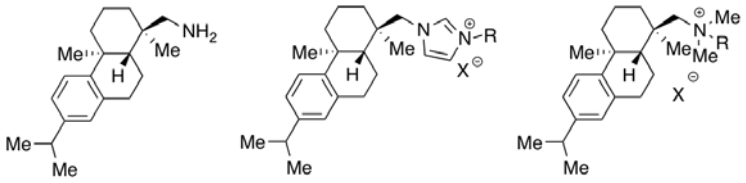
We have synthesised several novel chiral ionic liquids/salts from chiral compound derived from softwood rosin. Our starting material, (+)-dehydroabietylamine (Fig. 1(A)), is easily isolated from readily available mixture of amines derived from rosin.[1]

Since (+)-dehydroabietylamine has been known to have chiral recognition abilities towards carboxylic acids,[1] due to its backbone structure, we considered it can be useful starting material for creating novel chiral ionic liquids/salts. Those materials could be utilised in an analytical application for chiral analytes, e.g. in a chiral NMR recognition. Our attention is focused on synthesising chiral ammonium, imidazolium and guanidinium salts/ionic liquids derived from (+)-dehydroabietylamine (Fig. 1(B) and (C)).



(A) (B) (C)

1. W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, 1965, **30**, 2072.

Synthesis towards 1,2,3,4-Tetrahydro-β-Carbolines and their Open-Chained Analogues from Amino Acids

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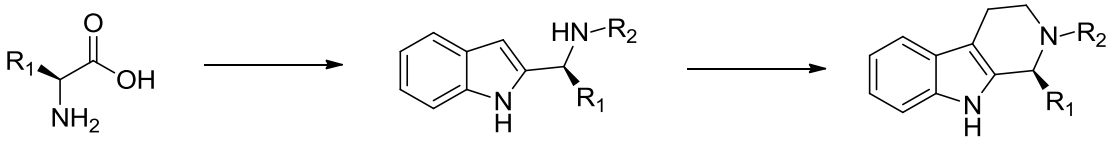
A novel synthesis towards 1,2,3,4-tetrahydro-β-carbolines and their open-chain analogues is reported. In this synthesis stereochemical information is passed to the end product by the use of chiral amino acids as starting materials. It is an appealing alternative to inducing chirality to achiral molecules as many starting materials such as amino acids, sugars and terpenes in the so called "chiral pool" are readily available and inexpensive. The challenge in this approach is the epimerization of the stereocenter in the α-carbon of the amino acid. This is avoided by exploiting 9-phenyl-9-fluorenyl (Pf) group to both protect the amine and the labile stereocenter – a method that has been increasingly applied in the amino acid chemistry since originally introduced in 1980's [1].

This work highlights the applicability of reported synthesis route to various amino acids including alanine, serine, proline and phenylalanine.



1. a) Bradley, D. C; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239; b) Karppanen, E. J.; Koskinen, A. M. P. *Molecules* **2010**, *15*, 6512.

Synthesis of Clathrodin Analogues

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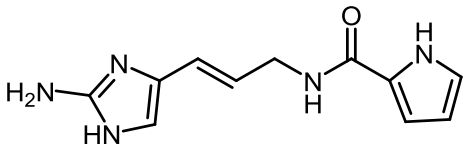
The methanol extracts of the Caribbean sea sponge *Agelas clathrodes* have shown weak antibacterial and cytotoxic activity and a marine alkaloid clathrodin was isolated from the sponge.[1] Several 2-aminobenzothiazole and benzimidazole analogues based on the clathrodin structure have been synthesized. For the 2-aminobenzothiazole analogues a convenient four-step synthesis route was developed. The benzimidazole analogues were obtained by a three-step synthesis. The compounds were submitted to antibacterial and antiviral screening. One 2-aminobenzothiazole derivative showed moderate antiviral (Hepatitis C virus (HCV) replicon model) activity.



Clathrodin

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4-Acetylthio-2,2-dimethyl-3-oxobutyl Group as Thermolabile Protecting Group for Oligomeric Phosphodiesters

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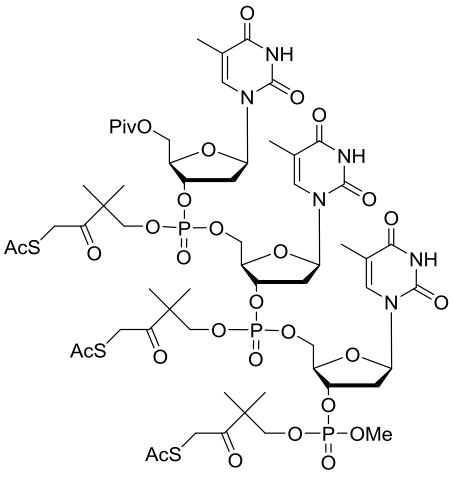
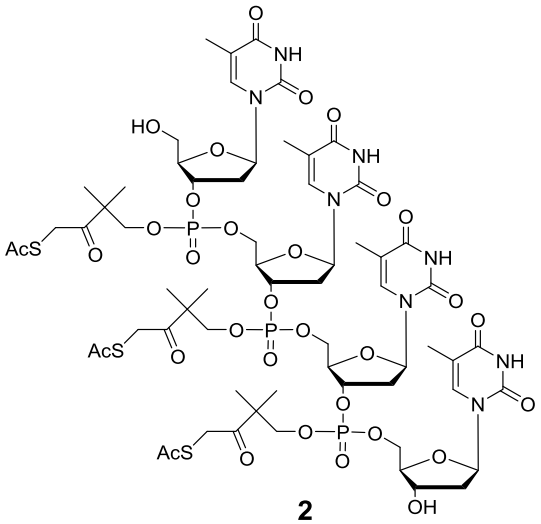
4-Acetylthio-2,2-dimethyl-3-oxobutyl group has been studied as phosphate protecting group for oligomeric phosphodiesters. The protecting group is esterase-labile and, moreover, it will undergo thermolytic cleavage in case the enzymatic reaction becomes too slow.[1] With oligomeric phosphodiesters this feature is important, since the removal of this type of biodegradable protecting groups by esterases becomes slow upon accumulation of negative charge on the substrate.[2] 4-Acetylthio-2,2-dimethyl-3-oxobutyl protected TpTpTp trimer (**1**) and TpTpTpT tetramer (**2**) were synthesized as model compounds and both the enzymatic and non-enzymatic removal of the phosphate protecting groups at 37°C and pH 7.5 will be studied.



1



2

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Total synthesis of Harmicine

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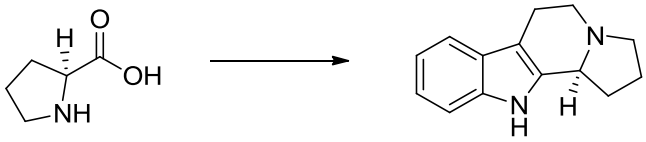
Chiral pool synthesis using amino acids as starting materials has a long history in synthetic organic chemistry. However, the inherent acidity of the α-proton in the useful synthetic intermediates of e.g. chiral α-amino-aldehydes, α-amino-ketones and α-amino-esters can easily cause epimerization of products and/or starting materials. To circumvent this limiting factor the 9-phenyl-9-fluorenyl (Pf) group was introduced in amino acid protecting group chemistry during the 1980's, not only for amine protection but also as a mean to protect the sensitive stereocenter.[1]

Here is reported a novel route to access the 1,2,3,4-tetrahydro-β-carbolines scaffold using Pf-protecting group chemistry. Harmicine, a natural product isolated from the plant *Kopsia griffithii*, was synthesized, starting from proline, in order to showcase the applicability of this synthetic strategy.[2]



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New kind of bifunctional cooperative hydrogen bond catalysts

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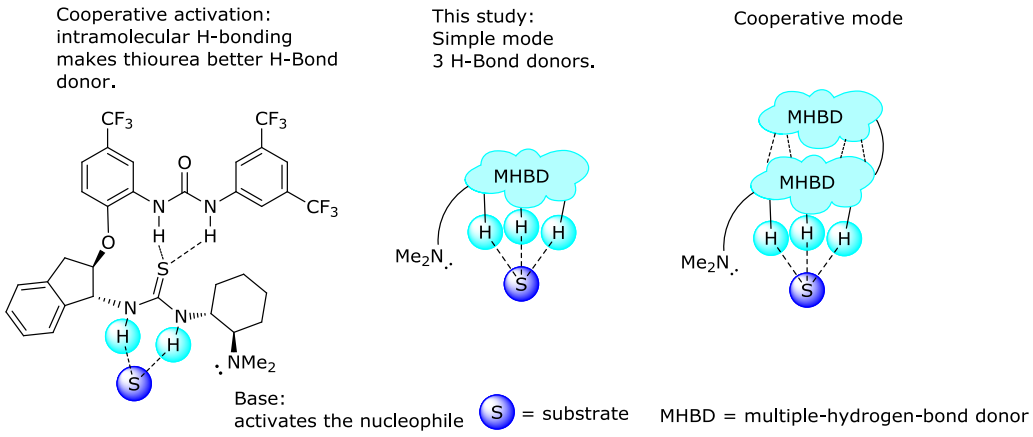
Bifunctional organocatalysts containing Brønsted-basic amine and (thio)urea moiety in the same molecule have been succesful catalysts for many enantioselective reactions.[1]Mannich reactions between dialkyl malonates and aromatic imines are promoted with simple Takemoto[2] and Soós[3] type of catalysts but less reactive aliphatic imines are typically unreactive with these catalysts. When using (thio)urea catalysts containing cooperative intramolecular hydrogen bonds also these aliphatic imines become viable substrates for the reaction.[4]

The purpose of this study is to design new kind of bifunctional hydrogen bond catalysts and use them in a variety of hydrogen bond activated reactions which require enolization of the nucleophile.[5]Afterwards these catalysts will be activated via intramolecular hydrogen bonds in a cooperative manner.



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Solid-Phase Synthesis of Doxorubicin Derivatives: Towards Cell-based On-Bead Screening

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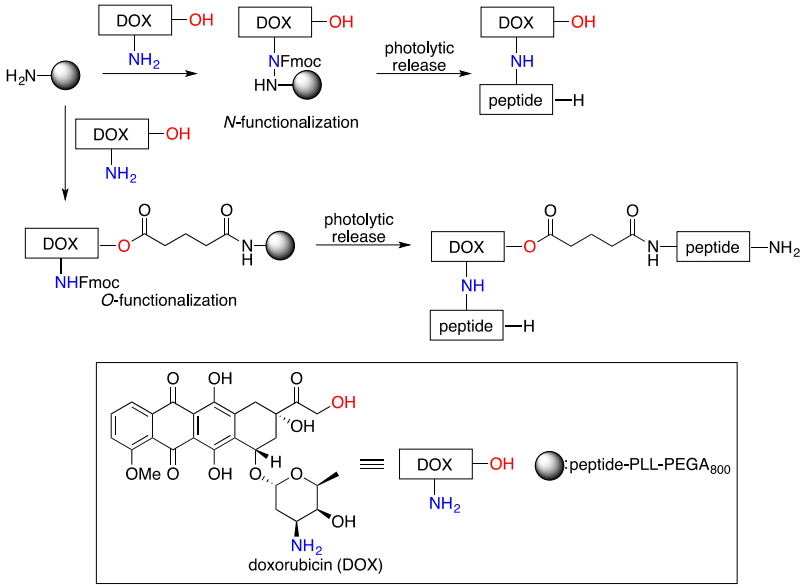
Doxorubicin (DOX) is a valuable drug for the treatment of breast cancer, liver cancer and soft-tissue sarcomas. However, its clinical application is limited by its dose-related, toxic side effects, such as cumulative cardiotoxicity. Efforts have therefore been made to create less toxic derivatives of DOX. The aim of this study was to develop a platform technology for the integrated chemical synthesis and cell-based screening of DOX derivatives. Relatively harsh conditions are often required to liberate a target molecule from the solid support which is problematic for complex natural products like DOX. In order to circumvent these issues, and to provide a biocompatible release platform, the present technology relies on the application of novel photolabile linkers.

The primary amine and primary alcohol are two obvious sites for structural modification of DOX. Along these lines, we successfully developed strategies for the selective synthesis (and release) of otherwise quite sensitive DOX-peptide conjugates at both the N- and O-positions. In this way, pharmacologically promising DOX-derivatives could be synthesized in good yields and purities applicable to biological screening assays.



Theoretical study on gold(III) assisted cis-trans isomerisation - A dual activation

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An important goal of computational chemistry is to provide theoretical insight for mechanistic steps that cannot be directly studied experimentally. We have found a *cis-trans* isomerisation to be a key step in gold(III) catalysed conversion of enyneamines to cyclopentadienes.[1,2] Here comprehensive computational studies are presented to support our hypothesis on reaction involving dual gold(III) activation.[3] Five different pathways were studied for this step at DFT and CASSCF/NEVPT2 levels. Pathway including two gold(III) moieties was found to be most probable with low activation energy barrier whereas other pathways were disclosed due to high activation energy barriers or experimental data.

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3. Muuronen, M.; Wirtanen T.; Patzschke, M.; Helaja J. *Manuscript in preparation*

Design of Bifunctional Cooperative Hydrogen Bond Catalysts

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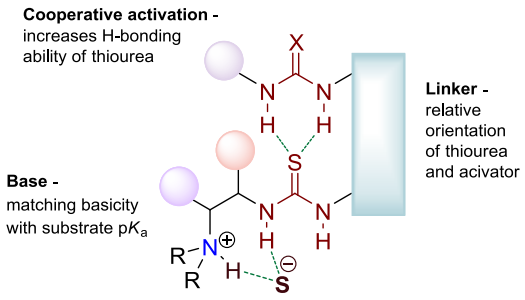
Bifunctional thiourea–Brønsted base catalysts have been found effective in a variety of 1,2 and 1,4-addition reactions which require enolization of the nucleophile.[1] Although simple bifunctional catalysts[2] provide good yields and enantioselectivities in many cases, the substrate scope is still fairly limited. Cooperative activation[3] of bifunctional thiourea catalysts was found to improve the catalytic activity in enantioselective Mannich reactions.[4] Structure of the linker affected the angle between urea and thiourea planes, and the distance between urea and thiourea moieties. This was found to correlate with the catalytic activity and enantioselectivity in Mannich reactions between aliphatic imines and malonates. The modularity and the convergent synthesis of the catalysts allow further tuning of the activity.



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Synthesis of bis(azacrown) conjugates of 2′-*O*-methyl oligoribonucleotides

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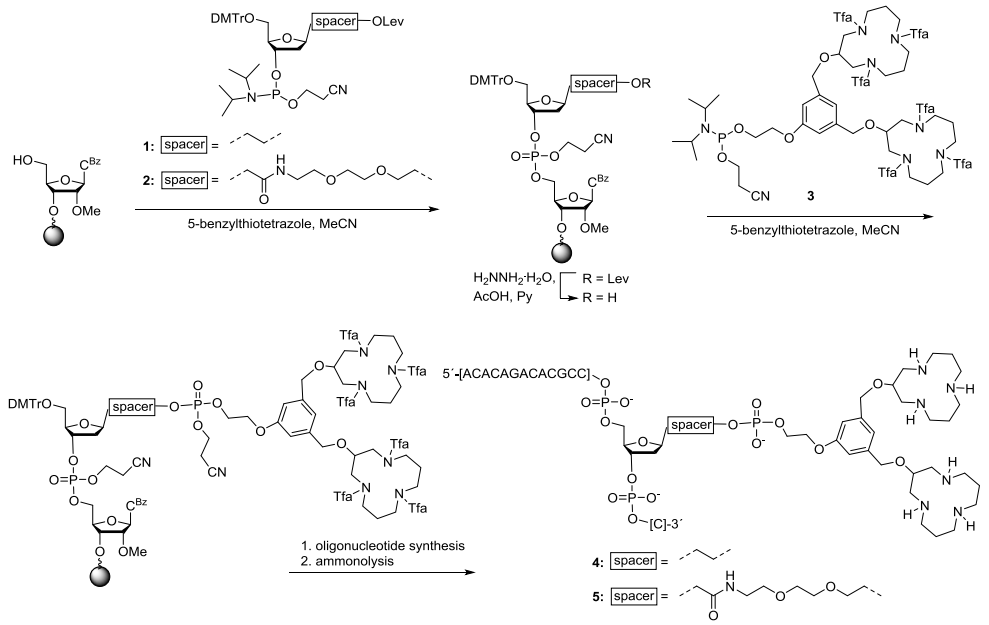
Conjugates of 2′-*O*-methyl oligoribonucleotides carrying 3,5-bis[(1,5,9-triazacyclododecan-3-yloxy)methyl]phenyl cleaving agent near the 3′-terminus were synthesized by the conventional phosphoramidite chemistry.[1] For this purpose, the non-nucleosidic building blocks **1** and **2** varied with length of the spacer and bis(azacrown) building block **3** were prepared and attached on support to the 2′-*O*-methyl oligoribonucleotide.



The ability of the Zn^{2+} complexes of the conjugates **4** and **5** to cleave a complementary RNA target was investigated. The present study is aimed at elucidate if, in synergy with the sequence recognition by a 2′-*O*-methyl oligoribonucleotide probe, two azacrowns attached in the vicinity act cooperatively, the one recognizing the uracil base of the target and the other one cleaving the phosphodiester bond of the target. Quite unexpectedly, the catalytic activity was not enhanced compared to the discrete Zn^{2+} complexes of bis(azacrown) ligands, although the azacrown really recognized the uracil base of the target.

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Synthesis and properties of ferrocene- and ruthenocene-appended chlorin derivatives

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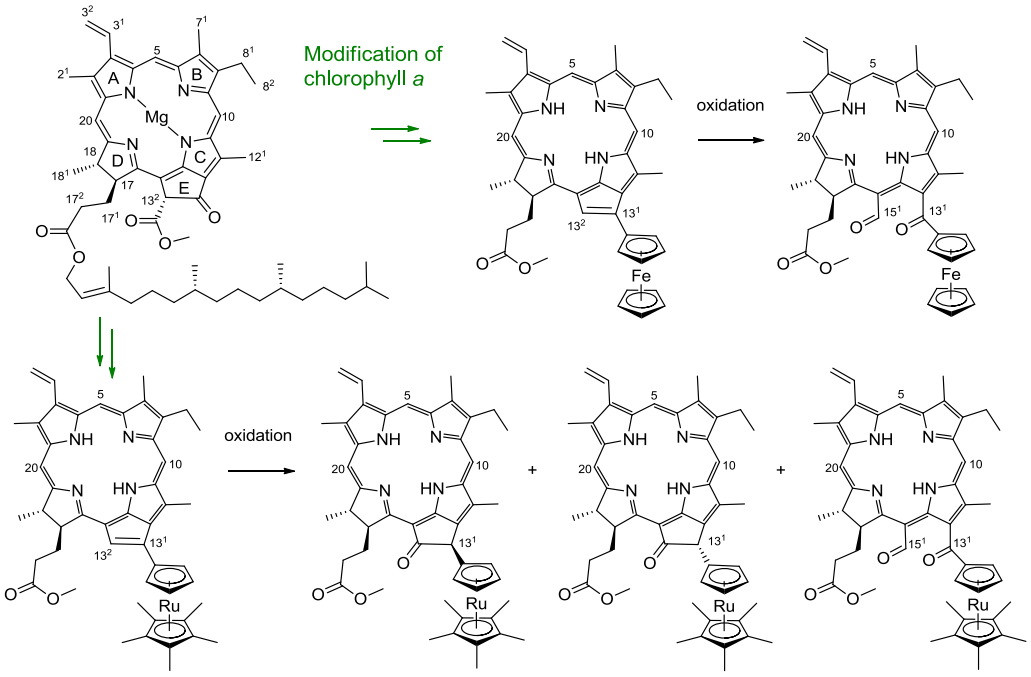
Chlorophyll *a* was separated from *Spirulina pacifica* and successfully modified to the first reported metallocene-appended chlorin derivatives, in which metallocene (either [Fe(η^5-C_5H_5)$_2$] or [Ru(η^5-C_5H_5)(η^5-C_5Me_5)]) is located in the 13^1-position of the chlorin macrocycle.[1] These conjugated metallocene-chlorins oxidize spontaneously under air to certain oxidation products depending on the type of metallocene attached to the aromatic chlorin macrocycle. The novel chlorin-metallocenes were characterized by NMR and MS spectroscopy and investigated photophysically.



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Progress towards synthesis of resolvin D1

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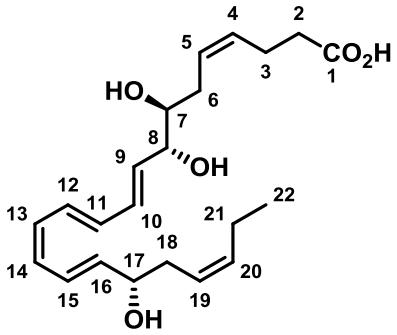
Resolvins are a class of endogenous metabolites acting as lipid mediators for the resolution of acute inflammation.[1] They originate from *in vivo* oxidation of polyunsaturated ω-3 fatty acids. Depending on whether the resolvins originate from docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), they can be subdivided into a D-series and an E-series.[2] Each of the resolvins demonstrate potent stereospecific action in the nanomolar range.[3]

We are currently targeting resolvin D1, which is a C22 trihydroxy polyunsaturated fatty acid derivative. From a synthetic point of view, the most challenging structural features of resolvin D1 are the C7-C8 *anti*-diol and the C11-C16 *E*,*Z*,*E*-triene.



Resolvin D1

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Synthesis of tetrahydro-β-carbolines via metal-catalyzed cross-coupling/isomerization/cyclization reactions

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The tetrahydro-β-carboline skeleton (Figure 1) is found in many natural products and synthetic compounds associated with a range of pharmaceutically relevant properties [1-2].

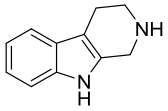
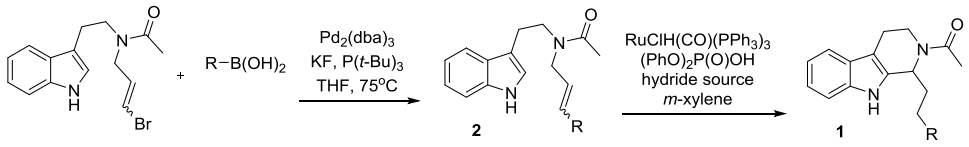


Figure 1: The tetrahydro-β-carboline skeleton.

We now wish to present a new method for the synthesis of substituted tetrahydro-β-carbolines with the general structure **1** (Scheme 1).[3-4] The key transformation comprises a Ru-catalyzed isomerization of the double bond of allylic tryptamine derivatives (**2**) to the corresponding enamides. Subsequent protonation leads to the formation of tetrahydro-β-carbolines through Pictet-Spengler type cyclization reactions.



Scheme 1: Preparation of tetrahydro-β-carbolines via cross-coupling/isomerization/cyclization reactions.

Several substrates (**2**) have been synthesized for this study via Suzuki cross-coupling reactions (Scheme 1). The conjugation of the double bond (R = Ar) renders the isomerization particularly challenging. A range of conditions and hydride sources have been investigated to optimize the reaction, and selected results will be presented.

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Towards the total synthesis of (+)-Sieboldine A

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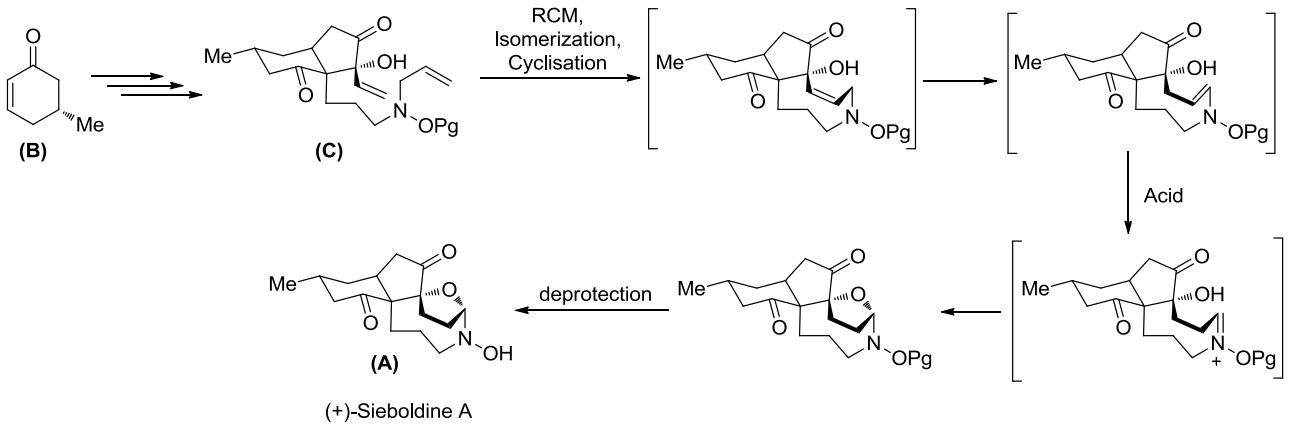
The plant family *Lycopodium* is well known for producing a variety of structurally diverse alkaloids of biological interest. One of these alkaloids, (+)–Sieboldine A (**A**), was isolated in 2003 from *Lycopodium Sieboldii,* and shown to have high inhibitory activity against acetylcholinesterase [1] making it a candidate for treatment of Alzheimer's disease. From a chemical point of view (+)–Sieboldine A, presents a challenging target for total synthesis, with its tetracyclic skeleton containing five stereocenters of which two are quaternary.

We envision the assembly of this complex tetracyclic compound from the much simpler bicyclic compound (**C**) through a ruthenium catalyzed ring closing methathesis, isomerization, and cyclisation tandem sequence, developed in the Nielsen group at DTU Chemistry [2]. The first goal of the project is the synthesis of the precursor (**C**) for the tandem sequence. This is currently well under way from the easily available chiral cyclohexenone derivative (**B**).



References

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Towards the total synthesis of aspergillides A and B.

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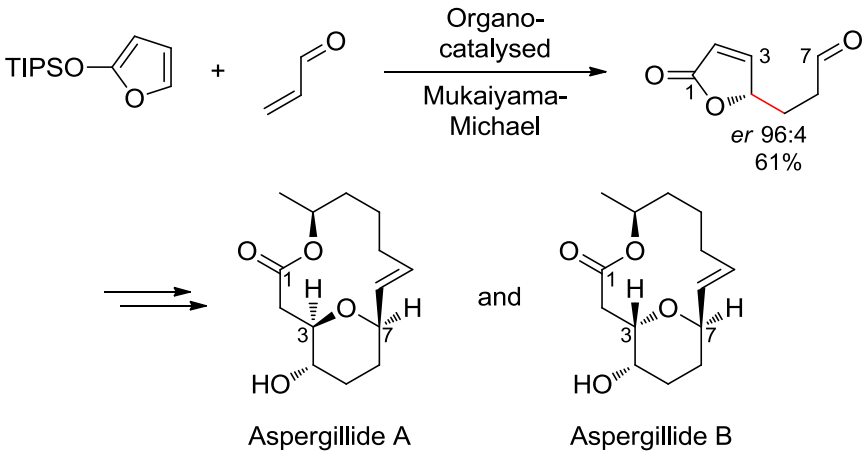
The aspergillides are structurally novel natural products first isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313. The core structure of the molecules consists of a 14-membered macrolactone ring incorporating a trisubstituted di- or tetrahydropyran ring. The compounds are highly cytotoxic (LD_{50} values of 2.0–71 µg/mL) towards mouse lymphocytic leukaemia cells (L1210).[1]



Applying a highly enantioselective Mukaiyama–Michael reaction methodology developed in the group[2] as the starting point, the total synthesis of aspergillides A and B has been attempted. Studies towards the total synthesis of these natural products will be presented.

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Synthesis and deuterium labelling of plant and mammalian lignans

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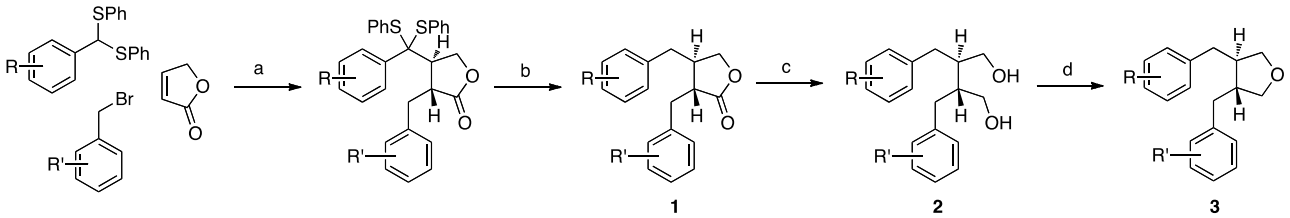
Lignans are a large class of secondary metabolites widely encountered in the plant kingdom. They possess a range of biological activities, and e.g. certain current anticancer drugs are chemical derivatives of the plant lignan podophyllotoxin. Due to their ubiquitous presence, lignans are included in our daily diet. After finding new lignans also in human fluids, resulting from metabolic conversion of dietary lignans, the research activity around lignans has grown rapidly. Various sophisticated analytical methods are needed to study and analyse lignans. However, these methods often suffer from a lack of reference materials. Synthetic methods for authentic standards and isotopically labelled analogues are therefore required.

In our laboratory we have been studying a versatile route to synthesise the lignan skeleton from readily available starting materials. The route is flexible in controlling the relative and absolute stereochemistry and the nature of the aryl substituents. Moreover, various lignan classes **1**–**3** are available by modifying the oxidation levels of the aliphatic moiety.



Reagents and conditions: a) i. *n*-BuLi, THF, –78 °C, ii. butenolide, THF, –78 °C, iii. DMI, benzyl bromide, THF, –78 °C; b) Raney-Ni, EtOH, rf; c) $LiAlH_4$, THF; d) HCl, MW.

We have also developed a fast and efficient method using 35 % DCl in D_2O to deuterate the reactive aromatic sites of lignane-9,9'-lactones **1** and 9,9'-epoxylignanes **3** to achieve stable and isotopically pure (over 90 % exchange of protons) deuterated derivatives.

Preparation and characterization of a sol-gel ω-transaminase catalyst for (*S*)-amine production

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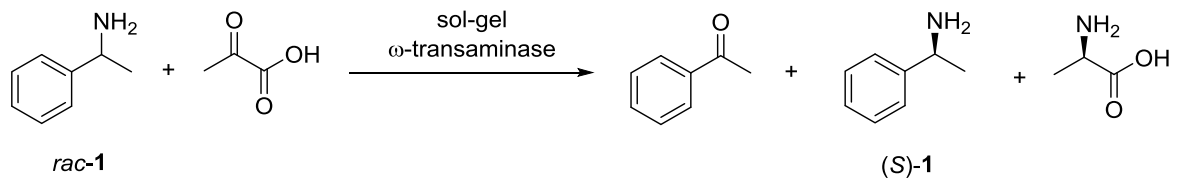
ω-Transaminases catalyze the pyridoxal-5'-phosphate -mediated transfer of an amino group between an amine and a ketone without the requirement of adjacent carboxylic acid moiety, a necessity with other transaminases. ω-Transaminases have a relatively broad substrate specificity which enables the preparation of diverse unfunctionalized amines at high enantiomeric purity through kinetic resolution and asymmetric synthesis.

Development and optimization of a sol-gel entrapment method for a (*R*)-selective ω-transaminase from *Arthrobacter sp*. KNK168 is presented. The focus of the method development was on improving operational and storage stability, and reaction efficiency. The prepared sol-gel ω-transaminase catalysts were characterized in terms of immobilization degree, loading capacity and ability to catalyze the kinetic resolution of racemic 1-phenylethylamine (*rac*-**1**) in an aqueous reaction system. With the optimized sol-gel catalyst at hands the substrate scope of the method was studied with a range of primary amines. Finally, the synthetic potential of the sol-gel ω-transaminase catalyst was investigated in successive preparative reactions performed under reaction conditions enabling high reaction efficiency.



rac-**1** (*S*)-**1**

Mechanistic investigation of the thermal isomerization of monooctylammonium tartrate

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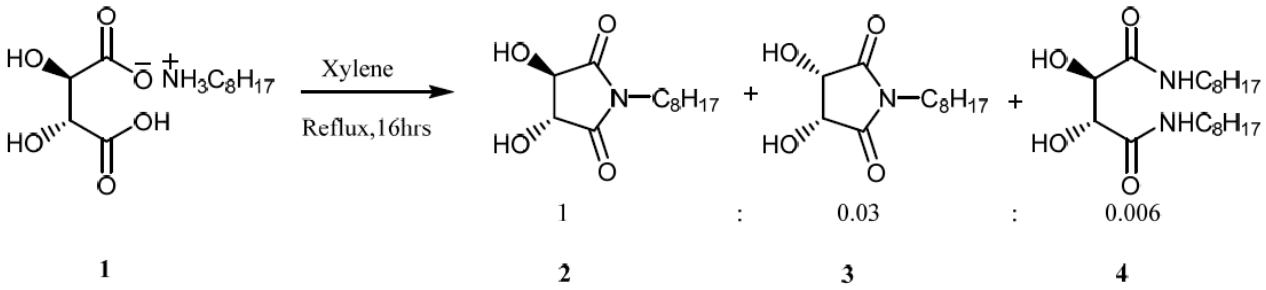
Tartaric acid coupled with an amine in a nonpolar aprotic solvent at high temperature leads to a mixture of isomerization products.[1] Refluxing (2*R*,3*R*)-monooctylammonium tartrate **1** in xylene affords a mixture of octyltartaramides **2**, **3** and **4**. The mechanism for the reaction is assumed to involve ketene[2] and ionic pair intermediates.[3]



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

The poster will present experimental and calculated support for the presence of two nondistinguished mechanistic pathways.

(1) Carlsen, P.; Villa Gonzalez, S.; *Arkivoc* **2011**, *9*, 325.
(2) Villa Gonzalez, S.; Carlsen, P.; *Eur. J. Org. Chem.* **2007**, 3495.
(3) Cram, D. J.; Gosser, L.; *J. Am. Chem. Soc.* **1964**, *86,* 5445.

Synthesis of Analogs of 2-Methoxyestradiol as Potential Anticancer Agents

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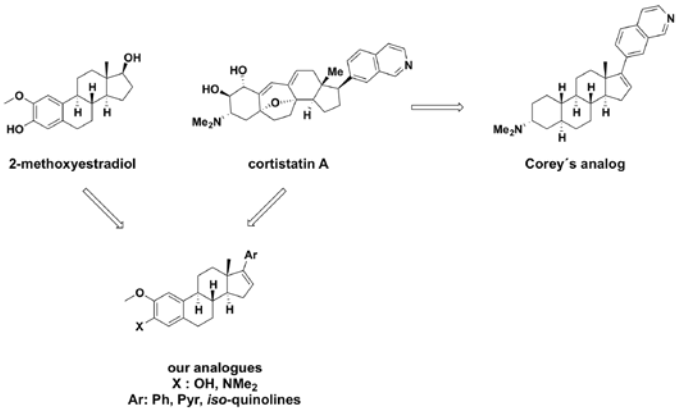
The steroidal alkaloid cortistatin A, isolated in 2006 from the marine sponge *corticum simplex*, exhibits potent cytotoxic and anti-angiogenetic effects.[1] Similarly, 2-methoxyestradiol (2-ME), an endogenous metabolite of estrogen, also exhibits cytotoxic and anti-angiogenetic effects as well as tubulin inhibition.[2] Consequently, both cortistatin A and 2-ME are interesting lead compounds for the development of new anticancer agents.[3]



Taking advantage of the known structure-activity relationship (SAR) described for cortistatin A and 2-ME, our effort towards the preparation of 2-ME analogs will be presented.

1) S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku, M. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3148-3149.
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3) B. Czakó, L. Kürti, A. Mammoto, D. Ingber, E. J. Corey, *A J. Am.Chem. Soc.* **2009**, *131* 9014-9019; (b) For a review of SAR on 2-Me, see A. O. Mueck, H. Seeger, *Steroids* **2010,** *75*, 625-631.

Synthesis Towards Mucosin

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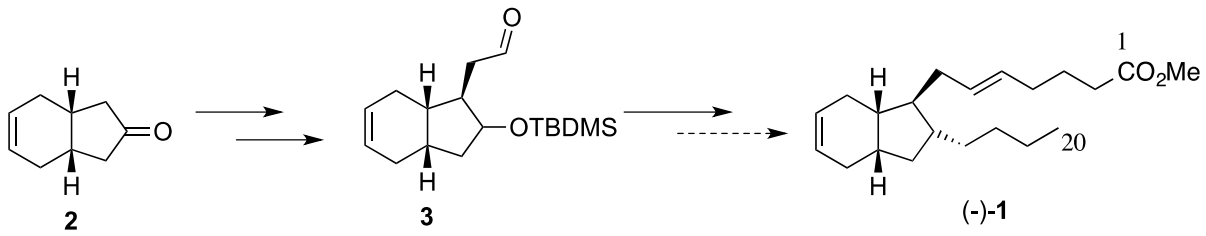
We have been working on a method to synthesize mucosin (**1**), isolated from a Mediterranean sponge, *Reniera mucosa*.[1] The structure is similar to the structure of prostaglandins, but it differ from typical prostaglandins by having a bicyclic[4.3.0]nonane skeleton. So far only one, very recent paper describe a synthesis of **1**.[2]

Currently we are working on the side chain containing the carboxylic acid. So far we have reacted a meso-ketone (**2**) via Claisen condensation, protected the ketone, oxidized the ester to the aldehyde succeeded by Wittig olefinations. The reactions are simple and straightforward. The synthesis will give the racemic mixture, but in principle resolution should give both enantiomers.

Our group are currently also working on the syntheses of dictyosphaerin a similar compound, starting with the same starting material (please see a separate poster).



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C_2-Symmetric bicyclo[3.3.1]nonadiene derivatives as chiral ligands for Rh-catalyzed asymmetric 1,4-addition reactions

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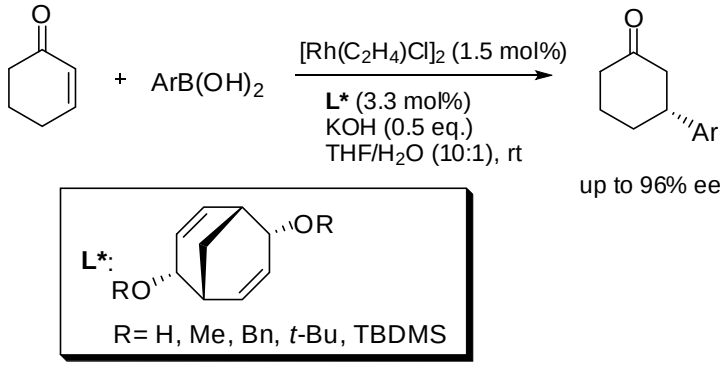
Chiral dienes have been recently recognized as effective ligands for rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents.[1] The chiral diene-rhodium complexes frequently display catalytic activity and enantioselectivity higher than that of chiral phosphine complexes for the aryl transfer to α,β-unsaturated compounds. Herein we present the synthesis of new C_2-symmetric bicyclo[3.3.1]nona-3,7-diene-2,6-diol derivatives and their use in the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to enones.



Bicyclo[3.3.1]nonadienes, which can be easily obtained in a few synthetic steps from enantiomerically pure (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione, were found to be efficient ligands for Rh-catalyzed asymmetric addition of arylboronic acids to cyclohexenone, furnishing the corresponding 3-arylcyclohexanones in excellent yields and enantioselectivity up to 96% ee.

Acknowledgement: This research is funded by the European Social Fund under the Global Grant measure (VP1-3.1-ŠMM-07-K-01-030).

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Glyceric acid esters of methyl α-D-glycosides by lipase-catalysis

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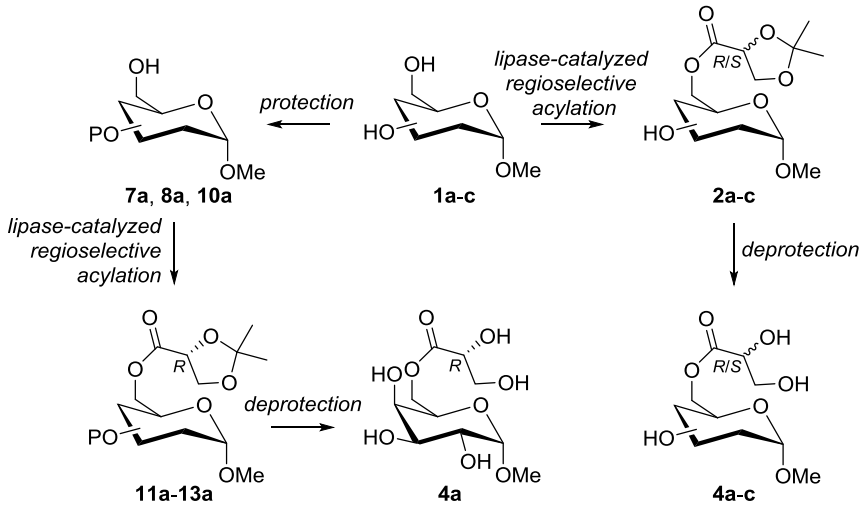
The regioselective synthesis of glyceric acid esters of methyl α-D-galacto-, -gluco- and –mannopyranosides (**1a-c**, respectively) with isopropylidene-protected methyl (*R*)- and (*S*)-glycerates [(*R*)- and (*S*)-**5**] via lipase-catalysis is presented.[1] The formation of the corresponding 6-*O*-acylated (**2a-c**) and 2,6-di-*O*-acylated products (**3a** and **3b**) is studied, and removal of the isopropylidene protection from the acyl moiety of **2a-c** yields the title compounds (**4a-c**). The combination of *Thermomyces lanuginosus* lipase (as the commercial Lipozyme TL IM preparation) for the regioselective acylation and an acidic resin in methanol for the deprotection step proved to be successful. In addition, the use of partially protected methyl α-D-galactopyranosides (**7a**, **8a** and **10a**) to enhance the solubility and thus the overall reaction of the sugar substrates is examined.



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Komppa Symposium
JUNE 24 - 26, 2013, ESPOO, FINLAND

Novel tautomeric switch molecules based on 4-hydroxyquinoline derivatives

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Keto-enol-type tautomeric switches have remained to date a rather rare class of molecular switches. This somewhat unexpected, while the proton shift connected with equilibrating tautomerism is a fairly general phenomenon in organic chemistry. Therefore, we could conceive that there is a class of little-explored, conceptually novel, tautomeric switch molecules with significant supramolecular and biomimetic potential. The transformation of a tautomer molecule to a molecule which tautomeric states controlled by an external input is challenging.[1] In practice, this requires intelligent molecular design enabling molecules to receive a control input and convert it to an energetically favored tautomeric state. Novel tautomeric switches based on 4-hydroxyquinoline derivatives have been demonstrated.[2] 4-Hydroxyquinoline equipped with coordinative side arms was synthesized to assess either O- or N-site selective chelation by metal cations. In the case of the monodentate arylimino group, O-chelation of the metal ions and the freezing of tautomerism have been shown. In the case of bidentate ligands, NMR studies have indicated that both Cd^{2+} and Zn^{2+} ions afford N-site chelation, coexisting with tautomeric switching from 4-hydroxyquinoline to quinolin-4(1H)-one. To verify this, UV-Vis monitored metal ion titrations have been demonstrated and the results implied similar structural changes. Additionally, fluorescence measurements indicated that the metal triggered tautomeric switching is associated with the signaling properties of the compound. Several metal-free and chelated 4-hydroxyquinoline X-ray-resolved structures are presented to support the solution studies.

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Preliminary optimisation steps of a formal synthesis towards Calyculin C

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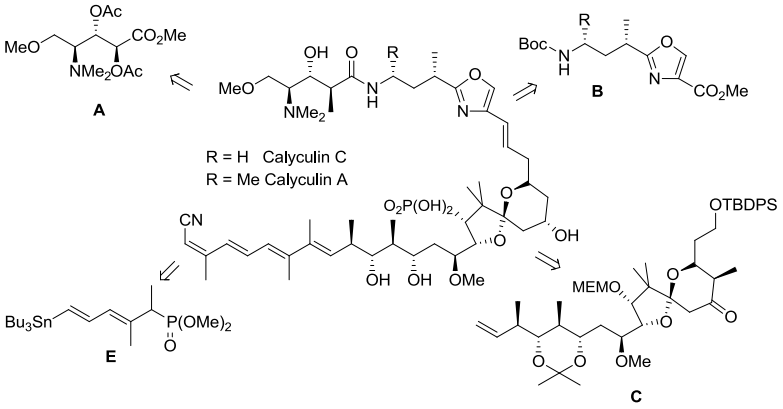
The present study is part of a long project in the group dedicated to the development of a total synthesis to Calyculin C. Calyculins are a class of eighteen highly cytotoxic polyketides isolated as structurally new secondary metabolites from the marine sponge Discodermia calyx. Calyculin C and A are the most abundant and differ only by a methyl group. Their ability to inhibit PP1 and 2A protein phosphatases, the enzymes that catalyze the protein phosphorylation, renders them potential target-molecules for drug-design concerning a number of human diseases. The architecturally complex structure of Calyculins along with their biological activity has attracted the interest of synthetic chemists.

Scheme 1



A formal synthesis leading to four major fragments-precursors of Calyculin C was previously developed by the group. Currently, only Calyculin A is commercial available, however in milligram quantities, whereas the previously described syntheses report a maximum overall yield of 0.9 %. Consequently, main priority is the optimisation of the developed synthetic paths to provide a robust and easy to scale-up total synthesis, producing target molecule in considerable quantities efficiently, cost-effectively and environmentally benign. Initial approaches towards this direction, focused on fragment C, are disclosed here. Focal point is: 1) the use of low-cost, environmental- and user-friendly reagents and conditions easily applicable on an industrial scale, 2) the optimisation of the inefficient steps in terms of reaction yield and time using also green chemistry techniques such as microwave irradiation and flow synthesis and 3) the improvement of isolation and purification procedures.

1. Fagerholm, A. E. ; Habrant, D. ; Koskinen, A. M. P. *Mar. Drugs* **2010**, *8*, 122–172.

Asymmetric Iodolactonization Utilizing Chiral Squaramides

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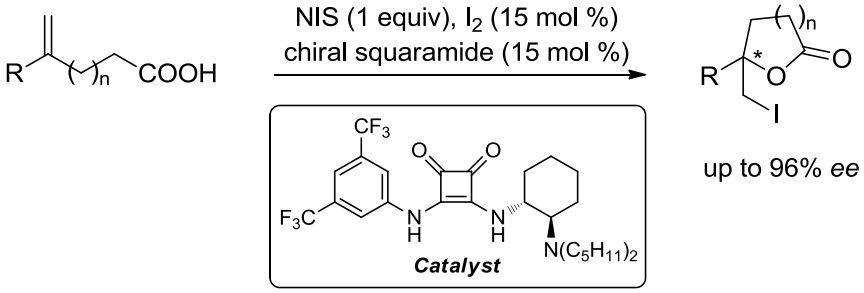
The development of reliable and highly enantioselective iodolactonization protocols affording synthetically valuable non-racemic iodolactones has proven a challenge. Currently, only a limited number of reports deal with the aspect of catalytic asymmetric iodolactionization.[1]

We have investigated the asymmetric iodolactonization of γ- and δ-unsaturated carboxylic acids in the presence of chiral squaramide organocatalysts. The cyclization of 5-arylhex-5-enoic acids to the corresponding iodolactones were achieved with up to 96% *ee*.[2] By this protocol, unsaturated carboxylic acids are converted enantioselectively to synthetically useful δ-lactones in high yields. Apparently, both hydrogen bonding and aryl/aryl interactions are important for efficient stereodifferentiation.



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2. Tungen, J. E.; Nolsøe, J. M. J.; Hansen, T. V. *Org. Lett*. 2012, *14*, 5884

Stereoselective 1,4-Hydrosilylation of Acroleins with Heterogeneous Palladium.

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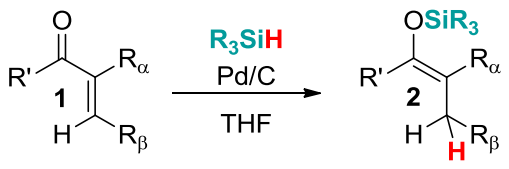
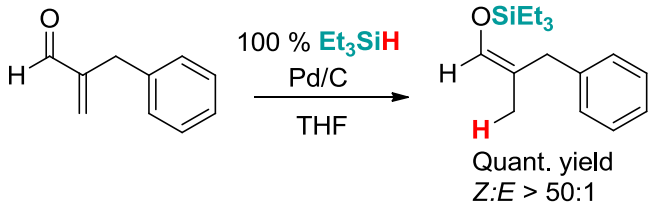
Stereoselective reductions of α,β-unsaturated carbonyl compounds **1** are highly important reactions in organic synthesis due to the high utility of stereodefined enolsilanes **2** as nucleophiles.[1] Previously we have developed a very convenient *in situ* palladium nanoparticle catalyzed protocol for accessing enolsilanes **2** as a single isomer.[2] Here we present an improved method, which same reaction can be done with palladium on charcoal (Schemes **a** and **b**). In order to understand the mechanism and to rationalize the selectivities, we are studying the reaction using first-principle calculations based on density functional theory of the elementary reaction steps.

Scheme a:



Scheme b:



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New Methodology for Selective Acetylation of Primary Amino Groups

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Selective acetylation of primary amino groups is a useful method in synthetic organic chemistry as well as in medicinal chemistry. These kind of acetylation reactions of primary amines with esters are already known but have required the use of catalysts or reagents such as pincer-ruthenium complex[1], nitrogen heterocyclic carbenes[2] and manganese (III) bis(2-hydroxyanil)acetylacetonato complex[3]. As the catalysts commonly used in the acetylation of amines, can be expensive, toxic and difficult to prepare and/or isolate the catalyst from the reaction.

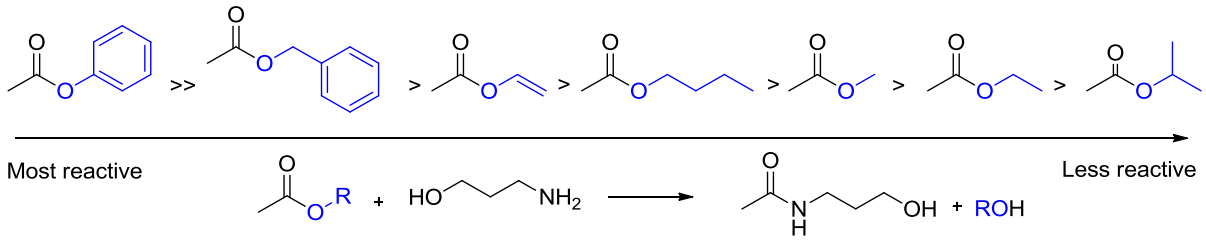

Figure 1. The reactivity of different acetates with primary amino group determined in this study.

We have recently developed a new methodology for selective acetylation of primary amino groups without the requirement of any catalysts (Figure 1). Briefly, phenyl acetate has been demonstrated for the first time to be a new highly selective acetylating agent in acetonitrile in room temperature at 30 min. Our reaction shows high selectivity for primary -NH_2 groups over primary -OH or secondary -NH groups. Moreover, it is very efficient way to synthesize diacetylated polyamines, the natural products of polyamine acetylating enzyme, without any additional step(s), and thus, simplifies the synthesis of these compounds.

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Synthesis of Aza- and Thio-Analogues of Annonaceous Acetogenins

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Four aza- and two thio-analogues of acetogenins (Figure 1) were synthesized in an enantioselective manner following a convergent synthesis route, which allows facile variation in the stereochemistry and of the aza- and thio-fragments in the compound.[1] Two remote stereocenters in the analogue were set via hydrolytic kinetic resolution of terminal bis-epoxides.[2] As annonaceous acetogenins are naturally occurring cytotoxic compounds with an interesting selectivity towards cancerous cells,[3] the bioactivities of the synthesized analogues were also evaluated.

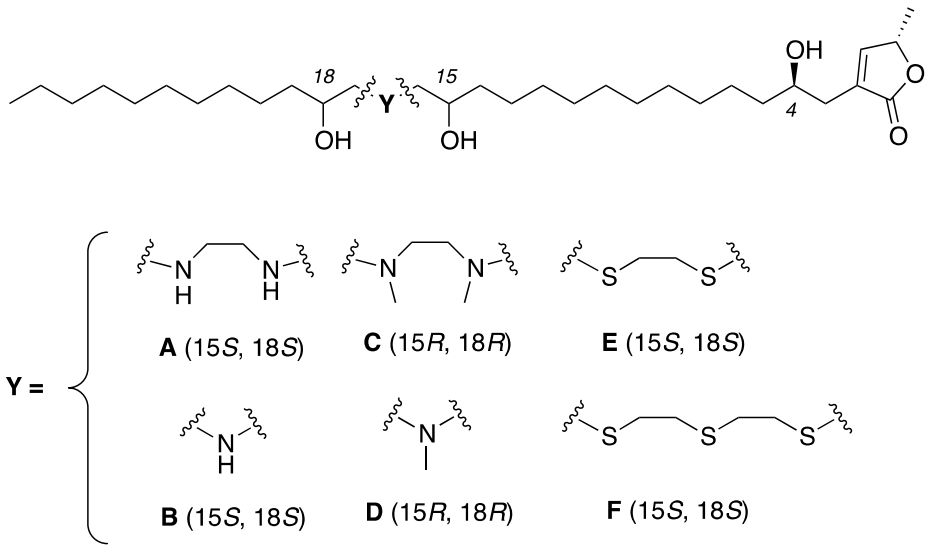

Figure 1. Synthesized aza- and thio-analogues.

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Au(III)-catalysed cyclopentadiene synthesis with chirality transfer

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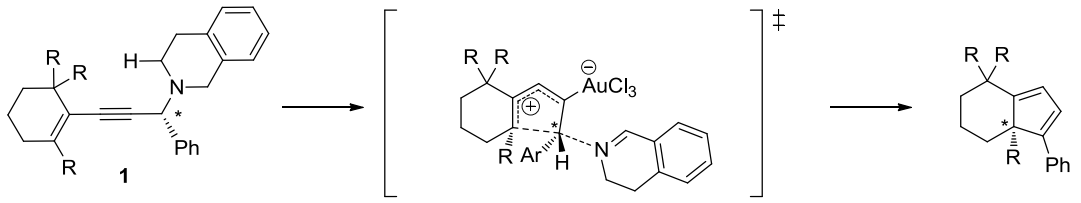

Yield: **23** - **75** %
up to **98 %** transfer of chirality

In our previous work we have reported a novel Au(III)-catalysed synthetic route to cyclopentadienes from enyneamines. However, the reaction seemed to suffer from rather modest yields. [1] In the present work, we have optimized the reaction conditions for the above conversion, and considerably improved the yields. Moreover, we established center-to-center chirality transfer and investigated the scope and mechanism of the reaction. [2] Our study revealed that the method gives access to a range of cyclopentadienes bearing chiral tertiary or quaternary carbon. Experimental values for enantioselectivity were found to be in excellent agreement with computationally calculated values. Computational and mechanistic studies also suggest that the *cis-trans* isomerisation, a key step in the reaction mechanism, is achieved by dual gold activation.

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2. Wirtanen, T.; Muuronen, M.; Melchionna, M.; Patzschke, M.; Helaja J. *Manuscript in preparation*

Asymmetric synthesis of 7'-hydroxybutyrolactones

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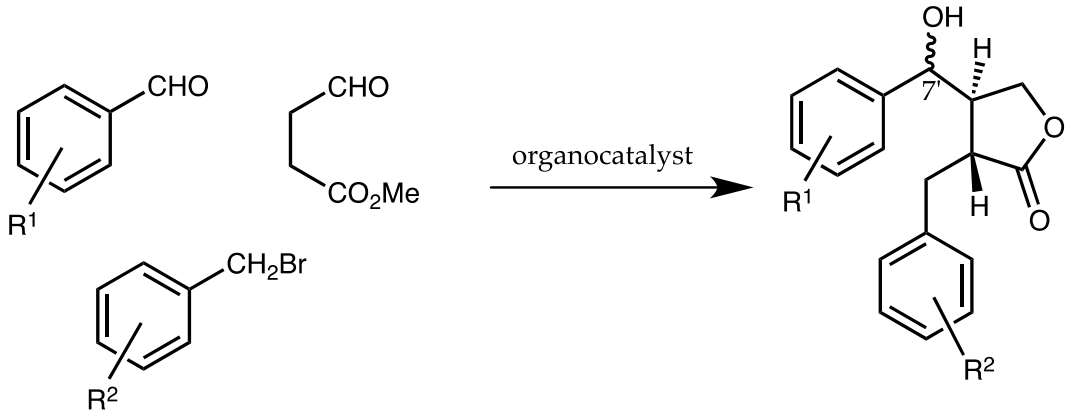
Lignans naturally exist in many plant species. They are presently studied by many researchers due to their biological activities, such as anticancer, antitumor, and immunosuppressive activity.

Our research group has previously reported asymmetric synthesis and stereochemistry of series of lignan compounds. In the synthesis, we have utilized 5-(-)-menthyloxybutenolide as a chiral auxiliary for Michael addition-alkylation to obtain 7'-hydroxylignano-9,9'-lactones.[1]

In this study, we are employing organocatalyzed aldol reaction to achieve enantiopure 7'-hydroxybutyrolactones.



7'-hydroxybutyrolactone

R^1=OH/OMe/H

R^2=OH/OMe/H

1) Barbara Raffaelli, Kristiina Wähälä and Tapio Hase. *Org. Biomol. Chem.*, **2006**, *4*, 331-341.

Towards organocatalytic enolization reactions

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The main goal of this study is develop novel enantioselective organocatalysts capable of direct enolization as a model for enolizing enzymes. Enolizing enzymes are a subclass of powerful metabolic enzymes. Some of them (e.g. thiolase, citrate synthase, triosephosphate isomerase etc.) are capable of direct enolization of carbonyl compounds such as thioesters and ketones under benign, aqueous conditions. Enzymatic enolization is a stereoelectronically controlled process where hydrogen bonds stabilize different states of reaction forming an oxyanion hole in the active site of enzyme. One of the key ideas behind this work is to study how these stereoelectronic effects in the oxyanion hole contribute to efficiency of enolizing enzymes. In this poster we will present design, synthesis and the main results of experimental and theoretical studies of the small molecule oxyanion hole mimics (Figure 1).

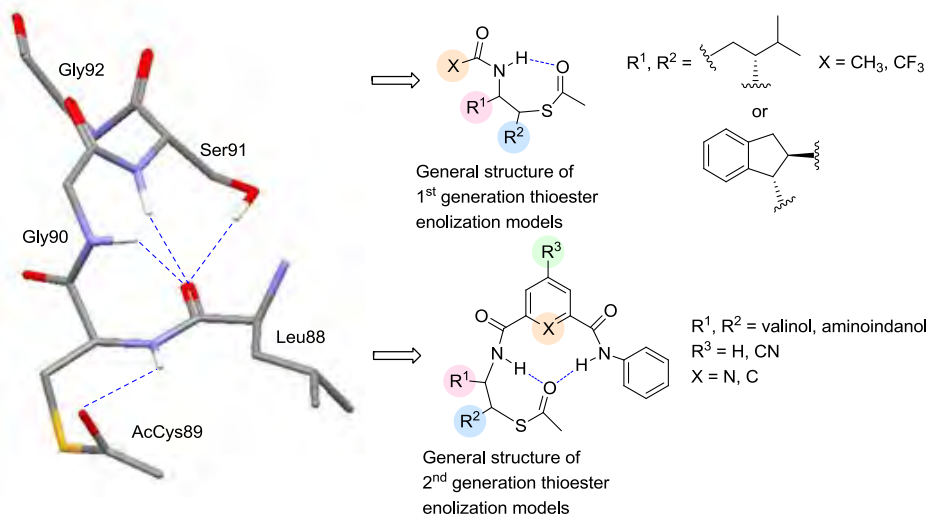

Figure 1. General design of the small molecule oxyanion hole mimics based to thiolase β-turn (2nd oxyanion hole molecular model).

Synthesis and *in vitro* biological evaluation of new oxysterols as liver X receptor modulators.

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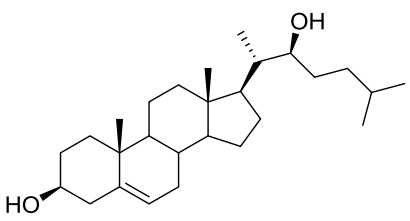
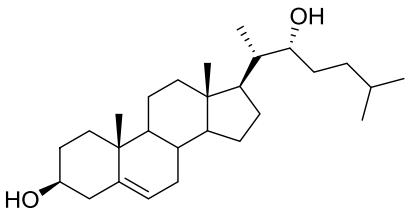
The liver X-receptors (LXRα and β) have been implicated in multiple diseases such as diabetes and obesity.[1] In order to further study the effect of selective activation of the LXR receptors, there is a need for analogues of the endogenous LXR antagonist 22(*S*)-hydroxycholesterol (22SHC)

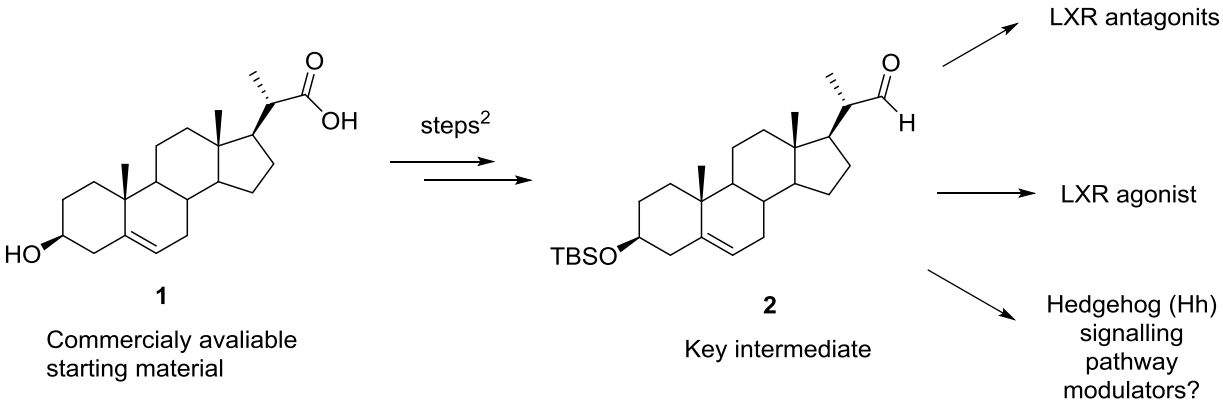


22SHC
LXR antagonist



22RHC
LXR agonist

This presentation will focus on the stereoselective synthesis of such analogues and the synthetic planning of potential LXR ligands shown below. The design of the new ligands synthesised is based on the best hits from a molecular modelling experiment and will also be briefly described.



1
Commercialy avaliable starting material

2
Key intermediate

1. R. Geyeregger, M. Zeyda M, T. M. Stulnig, *Cell Mol Life Sci.* **2006** *63*, 524–539.
2. G. Guerlet et al., *Bioorg. Med. Chem. Lett.* **2011** *21*, 3608–3612.