IASOC XVI Proximity-induced Effects in Chemistry and Biology: From Conception to Discovery

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Stereo- and regiochemical control in bond formation



EXPLOITATION OF « EFFECTS »

INHERENT / IMPOSED

TOPOLOGY

- STEREOELECTRONIC
 SYMMETRY / ASYMMETRY
- STERIC BIAS
- CONFORMATION
- COORDINATION / CHELATION
- PROXIMITY / AFFINITY
- KINETIC / THERMODYNAMIC

Combining metal coordination, conformational bias topology, stereoelectronics , and C₂ symmetry in one reagent

Relevant chemistry in the Hanessian Group

Renin Inhibito J. Org. Chem. 2002, 67, 426

Morphinomimetic

Angew, Chem., Int. Ed.,

2001, 40, 3810;

J.Med.Chem. 2003, 46, 34

Chemical Diversity

Tubular Superstructure

J.Org.Chem. 2008, 73,1181

Website: http://osiris.corg.umontreal.ca

Drug Prototypes

Neuraminidas

Inhibitor

J. Am. Chem. Soc.

Asymmetric Synthesis

2002, 124, 4716

Chem 2000 65 5623

Chem. Eur. J.

2002. 8. 111

Chem. Rev. 1997, 97, 3161 J.Org.Chem. 2010, 75, 5601.

symmetric conjugate additio

asymmetric cyclopropanation

Natural Product Synthesis

2004 126 6064

Iolecular Recognition and Self-Assembly

1998, 120, 8569

2003 125 13784

Am. Chem. So

1995, 117, 7630

Carbohydrates/peptides

J. Org. Chem. 2002. 67. 3346



Early example of the use of 1,2-trans-diaminocyclohexane in asymmetric synthesis

with Delorme, D.; Beaudoin, S.; Leblanc, Y. J. Am. Chem. Soc. 1984, 106, 5754

Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161; Recent review: Focken, T.; Hanessian., S. *Beilstein J.Org.Chem.* **2014**, *110*, 1848

1

Targeted Drug Delivery

nanonolym

Chem.Med.Chem. 2009

Catalysis

99% ee

RNA Ligands and Antibiotics

2004 43 6735

Chem Comm. 2010.26.2013

006.8.478

000.2.297

CL, 2010. 20, 192

4 988

Design and reactivity of an asymmetric olefination reagent



with Delorme, D.; Beaudoin, S.; Leblanc, Y. J. Am. Chem. Soc. 1984, 106, 5754 with Bennani, Y. L. Chem. Rev. 1997, 97, 3161

Asymmetric conjugate additions: vicinal and off-template functionalization





with Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. J. Org. Chem. 1993, 58, 5032.





Asymmetric conjugate addition-alkylation in acyclic systems



with Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. J. Org. Chem. 1993, 58, 5032. with Gomtsyan, A. Tetrahedron Lett. 1993, 35, 7509. with Gomtsyan, A.; Malek, N. J. Org. Chem. 2000, 65, 5623.

Asymmetric sequential conjugate addition-alkylation



with Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. J. Org. Chem. **1993**, *58*, 5032; Gomtsyan, A. Tetrahedron Lett. **1994**, *35*, 7509; Gomtsyan, A.; Malek, N. J. Org. Chem. **2000**, *65*, 5623.

Asymmetric synthesis of trisubstituted cyclopropanes







with Andreotti, D.; Gomtsyan, A. R. J. Am. Chem. Soc. 1995, 117,10393









with Focken, T.; Mi, X.; Oza, R.; Chen. B.; Ritson, D. Beaudegnies, R. J. Org. Chem. 2010, 75, 5601

Total synthesis of Anthoplalone B



Stereocontrolled synthesis of disubstituted cis-aziridines





with Cantin, L.-D. Tetrahedron Lett. 2000, 41, 787; Moitessier, N.; Cantin, L.-D. Tetrahedron 2011, 37, 6885; Bennani, Y. Herve, Y. Synlett 1993, 35.

Deoxypropionate Units in Natural Products...



Synthetic approaches: Mori; Enders; Wipf, Feringa; Negishi (ZACA)

Proximally-assisted 'secondary carbon S_N2 displacement'

Concept:



with Dehoff, B.; Cooke, N.; Sakito, Y., *J. Am. Chem. Soc.* **1990**, *112*, 5276 with Thavonekham. B.; Dehoff, B.;.*J. Org. Chem.* **1989**, *54*, 5831 **4**

Conformation design of 2,4-dimethylpentane subunits

Observation: "The stereochemical memory in most polymerizations is in the asymmetric unit closest to the end of the growing 91% 76% 58% chain, and supports the 1,3-asymmetric induction hypothesis for stereospecific polymerization " Me Me Me Me Me Me Me Me A virtual diamond lattice model Isotactic **Syndiotactic** • 2,4-Dimethylpentane unit can serve as inductor group to control conformation of neighboring dimethylpentane segment. • True only if the inducing dimethylpentane segment is **isotactic**, not when it is syndiotactic. Conformation preference decreases upon extension of molecular skeleton. Leitereg, T. J.; Cram, D. J. J. Am. Chem. Soc. 1968, 90, 4011 Hoffmann, R. W. et al. Angew. Chem. Int. Ed. Engl. 2000, 39, 2054 Models for 1,2-Induction



with Sumi, K. Synthesis 1991, 1083

with Wang, W.; Gai, Y.; Olivier, E. J. Am. Chem. Soc. 1997, 119, 10034 with Gai, Y.; Wang, W. Tetrahedron Lett. 1996, 42, 7473

Asymmetric Cuprate Addition-Hydroxylation Strategy in **Synthesis of Natural Macrolide Antibiotics**



with Wang, W.; Gai, Y.; Olivier, E. J. Am. Chem. Soc. 1997, 119, 10034 with Ma, J.; Wang, W. J. Am. Chem. Soc. 2001, 125, 10200





Extended deoxypropionates in natural products





Doliculide

with Mascitti, V.; Giroux, S. PNAS, **2004**, 101, 11996



with Yang, H.; Schaum, R. J. Am. Chem. Soc. 1996, 118, 2507.

Design of a novel secondary structure scaffolding device: induction of a reverse turn in tetrapeptides by incorporating a β-amino acid and stereocontrolled free radical α-substitution reactions in peptide motifs



with Yang, H.; Schaum. R. J.Am. Chem. Soc. 1996, 118, 2507. with Yang, H. Tetrahedron Lett. 1997, 38, 3155.

Chance observation

1,2 -trans (R,R)-Diaminocyclohexane (DACH) as a ligand in asymmetric synthesis



NMR of crude product showed new entity

with Meffre P., Girard M., Beaudoin S., Sanceau J. Y., Bennani Y., J. Org. Chem. 1993, 58, 1991.

What is the nature of the "complex"?



withSimard M., Roelens S., JAmChemSoc. 1995, 117, 7630. with Saladino, R., Margarita, R., Simard, M. Chem. Eur. J. 1999, 5, 2169. Saladino, R., Hanessian S. In Crystal Design: Structure and Function, "Molecular Recognition and Self-Assembly Between Amines and Alcohols (Supraminols)", Chapter 2, Ed. G.R. Desiraju, John Wiley, 77-151 (2003).

Benzene Reflux (R,R) (R,R) (S,S) complex 67% ee

Kawashima M., Hirayama A., Chem. Lett. 1991, 763. Hanessian S. et al., unpublished observations



The power of observation and open-eyed serendipity: Supramínols





Objective: beta sheets with *bis*- D,L- tripeptides anchored on 1,2-*trans*-DACH Superstructures



with Vinci, V.; Fettis, K.; Maris, T.; Viet. M.T.P, J.Org.Chem. 2008, 75, 2581

Self-embracing peptide arms



X-ray structure of an individual 1*R*,2*R*- DACH-bis-tripeptide showing intramolecularly H-bondec strands that cross over each other like the self-embracing arms of Fogatier's statue of Spartacus. Side-chains and hydrogen atoms (except those attached to nitrogen) have been omitted for clarity. Two distinct but similar conformations A and B are observed in the crystal; only one is shown.

X-Ray Crystal Superstructure



Left. View along the c-axis of a 2 × 2 × 2 array of unit-cells of the packing in structure of the DACH-bis-tripeptide displayed in red with the included $CHCl_3$ and benzene molecules shown as sphere of van der Waals radii. Right. View of one column along the a-axis showing the stacking of alternating DACH-bis-tripeptide 13 conformers A (green) and B (purple) with the included $CHCl_3$ and benzene molecules shown as sphere of van der Waals radii.

1,2-(R,R) DACH vs 1,2- (S,S) DACH anchored tripeptides



with Vinci, V.; Fettis, K.; Maris, T.; Viet. M.T.P., J.Org.Chem. 2008, 75, 2581

Catalytic Diastereoselective Friedel-Crafts Alkylation: Toward beta-amino-1,1'-diarylmethanes



See also: Olah, Bach, Prakash, Lautens, Beller, Rueping for related systems; Diarylmethanes review: Ameen, D.; Snape, T.J. *Med. Chem. Commun.*, **2013**, *4*, 893 Friedel-Crafts review: Rueping, M.; Nachtsheim, B.J. *Beilstein J. Org. Chem.*, **2010**, 1.

Acyclic conformationally controlled benzylic substitution: Diarylmethanes with a phenethylamine pharmacophore



- D. Welch, W. M. Jr.; Harbert, C. A.; Koe, B. K.; Kraska, A. R. US patent 4.536.518 (1985).

Diastereoselective benzylic arylation



^oRatios were determined by ¹H NMR analysis of the crude materials and yields were obtained after purification. ^bFull conversion was achieved within 30 min with 10 mol % of Bi(OTf)₃ in MeNO₂ ^cOver 95% of the starting material **1** was consumed within 45 min, to give **3** with 10 mol % of $Bi(OTf)_3$ in MeNO₂ ^dSFC separation and ¹H NMR of the pure sample of **3** gave a ratio of 9:1. ^eThe crude ¹H NMR spectrum showed a 9:1 ratio of the regioisomer.

with Chénard, R.; Org.Lett. 2014, 16, 2668

Kinetic diastereomer differentiation



with Chénard, R. Org.Lett. 2014, 16, 2668

¹H NMR time course



Biaryl formation rediscovered



For related work, see:

Jimenez-Oses, G.; Brockway, A. J.; Shaw, J. T.; Houk, K. N. J. Am. Chem. Soc. 2013, 135, 6633. Fuson, R.C.; Speck, S.B. J. Am. Chem. Soc. 1942, 64, 2446 41

Natural products: the providers, the healers, and the enticers



1,4-aromatic substitution of o-methoxyphenyl 2-alkyl ketones



with Grelier, G.; Chénard, E.,; Büschleb, M. (manuscript submitted)

The 'academic' Synthetic Chemist's Dilemma

- 1. Which molecule should I synthesize (The What of Synthesis)
- 2. Incentives, reasons, and rationales for synthesis (The *Why* of synthesis)
- 3. How can I make sure I have an efficient and viable route ? (The *How* of synthesis)
- 4. Where and with what do I begin? (The *journey*, or climb to the summit)
- 5. Will I get there ?



Satratoxin H (Household mold)

Nymania 1 (Anti-proliferative activity) 11

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Total Synthesis of Pactamycin

What and why ?

Isolation

Isolation and biological activity:

 Isolated in 1961 from Streptomyces of pactum by scientists at the former Upjohn Company.

Ме он

 Proposed structure of pactamycin was reported in 1970 and corrected in 1972 with help of X-ray crystallographic studies.

Wiley, P. F., et al. J. Org. Chem. 1970, 35, 1420.

Bhuyan, B. K., et al. Antimicrob. Agents Chemother., **1961**, 184. Argoudelis, A. D., et al. Antimicrob. Agents Chemother., **1961**, 191

Structure:

Me The enterprise of synthesis: definition

 An undertaking, especially one of some scope, complication, and risk
 Willingness to undertake new ventures

Biology

- Exhibits activity against Gram positive and Gram negative bacteria.
- Potent in vivo and in vitro cytotoxic effects as well as antimicrobial activity.
- Potent protein synthesis inhibitory activity in prokaryotes as well as in eukaryotes.
- Unfortunately toxic....

Major challenge: *How* to orchestrate the sequence and types of reactions ? A proximity effects nightmare



with Vakiti, R.R.; Dorich, S.; Banerjee, S.; Lecomte, F.; Del Valle, J. R.; Zhang, J.; Deschesnes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497: *J.Org.Chem.* **2012**, *77*, 9458; see also Johnson, J. et al. *Science*, **2013**, *340*, 180

Proximity in Nature:Small molecules meet the ribosome

Duchamp, D. J., et al. American Crystallographic Association Meeting. 1972, April, p. 23.





• Aromatic stacking in pactamycin mimics two consecutive mRNA bases. Pactamycin displaces mRNA in the E-site, preventing movement through the 30S subunit.



Co-crystal structure of 6-demethyl salicylyl pactamycin with RNA



Uncovering new activities with pactamycin analogs

Pharmacophore modulations

Urea analogs with new pharmacophores





Antibacterial, antitumor, and antimalarial activity

with Vakiti, R.R.; Kumar, A.; Dorich, S.; Lavallee, C. *Bioorg. Med. Chem.* **2013**, *21*, 1775

Magnetically-induced drug targeting with Ultrasmall Superparamagnetic Iron Oxide Nanoparticles (USPIONs): A Brave New Nano World of Magic Bullets



Reviews:

*Goya, G.F., et al. "Magnetic Nanoparticles for Cancer Therapy" *Current Nanoscience*, 2008, 4, 1-16. *Cho, K., et al."Therapeutic Nanoparticles for for Drug Delivery in Cancer" *Clin. Cancer Res.* 2008, *1*, 1310-1316. *Parveen, S., Sahoo, K. "Polymeric Nanoparticles for Cancer Therapy". *J.Drug Targeting* 2008, *16*, 108-123. *Juillerat-Jeanneret, L. in *Nanomaterials for Cancer Therapy*, Kumar, C.S.S.R. ed. Wiley-VCH, Weinheim, 2006, Vol.6, pp 199-232.

*Gupta, A. K., Gupta, M. "Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications" *Biomaterials*, 2005, *26*, 3995-4021.

*Kobayashi, T., et al. "Medical Application of Functionalized Magnetic Nanoparticles" J. Biosci. Bioeng. 2005, 100, 1-11.

*Rabinow, B.E. "Nanosuspensions in Drug Delivery" Nature Rev. Drug Discov. 2004, 3, 785-796.



Efficient USPIONs uptake by Me 300 cells



Hierarchical Surface Assembly of Camptothecin (CPT)-USPIONs



Drug loading on amino PVA: 24%



Malayamycin A: the glycosyl cyanide route



Malayamycin A



with Marcotte, S.; Machaalani, R.; Huang, G. *Org. Lett.* **2003**, *5*, 4277-4280.

with Huang, G.; Chenel, C.; Machaalani, R.; Loiseleur, O. J. Org. Chem. **2005**, 70, 6721.

Proximity-induced mild tetrazole formation !!!



with Simard, D.; Deschênes-Simard, B. Org. Lett., 2008, 10, 1381.

Azide and tetrazole in the same natural product?!!!!

Questions of the day:

- 1. Are there natural products that contain an azide group
- 2. Are there natural products that contain a tetrazole ring



If your answer is yes, suggest a biosynthetic pathway, if your answer is no.....





6-Azidotetrazolo[5,1-a]pht halazine (C₈H₄N₈) mp 140°C

Occurrence: Toxic secondary metabolite in Dinoflaggelate

Gymnodinium breve

Isolation and structure:

Bilayet-Hossain, M.; van der Helm, D.; Sanduja, R.; Alam, M. Acta Cryst. 1985, C41, 1199-1202.

Fact: synthesis preceded isolation!





- A. Stollé, R.; Storch, H. J. Prakt. Chem. 1932, 135, 128.
- B. Reynolds, G.A.; Van Allan, J. A.; Tinker, J.F. J. Org. Chem. 1959, 24, 1205.

Tetrazole Reviews

General Reviews

Yet, L. "Five membered ring systems: with more than one N atom." *Progress in Heterocyclic Chemistry*, **2003**, *15*, 206-229.

Butler, R. N. "Tetrazoles" Comprehensive heterocyclic chemistry, 1996, 4, 621-678, 905-1006.

Wittenberger, S. J. "Recent developments in tetrazole chemistry. A review." Org. Prep. Proceeed. Int. 1994, 26, 499.

Medicinal Chemistry Reviews

Herr, R. J. "5-Substituted 1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods." *Bioorganic & Medicinal Chemistry*, **2002**, *10*, 3379-3393.

Zabrocki, J.; Marshall, G. R. "The 1,5-disubstituted tetrazole ring as a cis-amide bond surrogate." *Methods in Molecular Medicine*, **1999**, *24*, 417-436.

Relevant publications on tetrazoles from the Hanessian group

with Simard, D.; Deschênes-Simard, B. Org. Lett., 2008, 10, 1381.

with Simard, D.;;Deschênes-Simard, B.; Chenel, C.; Haak, E. Tetrahedron 2009, 65, 656