Chemoselective Conversion of Biologically Sourced Polyols into Chiral Synthons

Highlighted article by L. L. Aducci, T. A. Bender, J. A. Dabrowski, M. R. Gagné

1,2-deoxyglucose

Si = SiMe₂Et

B(C₆F₅)₃ (5.0 mol%) HS/Me₂Et (2.5 equiv)

CH₂Cl₂, 25 °C, 4.5 h silyl deprotection

72% overall yield

3% overall yield

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Dear Readers,

Here we are at the end of another year. This December issue closes the 2015 volume of SYNFORM with an outstanding combination of top-notch articles covering very different areas of organic synthesis.

The first story offers an insight into the breakthrough methodology developed by M. Gagné (USA) who devised a straightforward way to convert renewable biomass (carbohydrates) into highly valuable chiral polyols that can be used as enantiopure building blocks in chemistry, including a number of previously undisclosed compounds. The second article covers a very interesting research published by E. Meggers (Germany) in the hot area of light-activated photo-redox catalysis, and specifically an enantioselective α-trichloromethylation of ketones carrying in α'-position a 2-imidazole or 2-pyridyl group catalyzed by a chiral iridium complex. The third contribution reports on a clever strategy developed by J. Zhou (Singapore) for achieving the direct stereocontrolled cyclopropylation of heterocycles from iodinated cyclopropanes by means of Pd catalysis.

This issue – and this year of SYNFORM – is closed by a Young Career Focus that comes from a Baltic Country, Lithuania, a perfect place for a magic Christmas atmosphere, and I. Cikotiene is our last protagonist. That’s all for SYNFORM 2015, let me just wish you all a fantastic festive period and a successful and healthy 2016.

Enjoy your reading!

Matteo Zanda
Chemoselective Conversion of Biologically Sourced Polyols into Chiral Synthons


While fine chemicals are critical building blocks for numerous materials, the majority are prepared from non-renewable petroleum-based feedstock. The synthesis of these compounds from renewable resources offers a more sustainable path but requires the development of new efficient synthetic methods capable of dealing with the inherent complexity of these feedstocks. "Biomass, including carbohydrates, offers a diverse array of highly oxygenated compounds, but their over-oxidation precludes their immediate adoption for industrial purposes," said Professor Michel Gagné from the University of North Carolina at Chapel Hill (USA). "Although significant developments have been made in the global deoxygenation of sugars to access biofuels, selective single C–O bond cleavage strategies have been limited to highly activated positions such as the anomeric or sterically accessible C6 positions in cyclic carbohydrates." Recently, Professor Gagné’s group found that the R3SiH/B(C6F5)3 catalytic system developed by the Piers group for reduction of carbonyl compounds converts biologically sourced polyols into otherwise difficult to access or brand new C6O compounds (Scheme 1).

Professor Gagné said: "For our initial foray into selective carbohydrate reduction we chose sorbitol, a reduced form of glucose, as our platform chemical." In the process the authors discovered that substrates may either be silyl-protected or remain as the parent alcohol, although in the latter case significant evolution of hydrogen gas occurs on hydrosilylation of the OH groups in situ. This method consequently requires higher equivalents of silane to accommodate the in situ protection. "When reducing the primary hydroxyl groups of sorbitol to generate the tetraol, we were surprised to isolate a triol as well (Scheme 1B)," says co-author Laura Adduci. "And furthermore, the reaction produced one diastereomer..."
of the triol preferentially. Our investigation of that process kicked off initial experiments for our current studies.” In most cases, when conditions were employed to promote multiple reductions, one secondary C–O bond was reduced selectively. But why? “The ‘aha’ moment came when we observed that reduction of galactitol furnishes a triol with inverted stereochemistry,” says co-author Professor Jennifer Dabrowski. “We hypothesized that inversion might occur under a regime where an annulative $S_N2$ displacement of the activated C–O bond takes place.” To investigate, the researchers conducted a series of mechanistic experiments by $^{13}$C NMR spectroscopy utilizing a silyl cation with the non-reducing $B(C_6F_5)_4$ counterion. By treating silyl-protected tetraols with stoichiometric amounts of $\text{[Me}_2\text{EtSi][B(C}_6\text{F}_5)_4]$ generated in situ, they were able to independently observe and characterize the proposed cyclic intermediates, selective reduction of which led to the observed products (Scheme 2B).

Interestingly, Professor Gagné and his co-workers noted that selectivity did not always follow known reactivity preferences for simple alcohols (i.e. $1^\circ > 2^\circ > 3^\circ$). In some instances they saw the predicted primary reduction product exclusively, while in others secondary C–O bonds were cleaved in the presence of primary C–O bonds, a reversal of previously observed trends (Scheme 2C). For example, reduction of 1,2-deoxyglucose furnished the 1,2,3-triol as the major product. “Although this was surprising at first,” said co-author Trandon Bender, “calling on cyclic intermediates and contrasteric charge analysis was the spoonful of sugar that helped this medicine go down.” The researchers found that the characterization of products was best accomplished at the alcohol stage; use of the solid state Dowex resin was a crucial deprotection strategy, as alternative standard methods proved challenging for the isolation of polyol material. When mixtures of polyols were formed and required separation, acetate protection was needed to furnish high yields of isolated products.

The success of this system towards selective defunctionalization led the group to investigate another class of biomass molecules, specifically the platform chemicals isosorbide and isomannide. These molecules are derived from sorbitol and mannitol, respectively, and offer the added benefit of requiring fewer silane equivalents to obtain the same extent of reduction. These substrates worked quite well under their catalytic system and also allowed them to prepare numerous products from two simple starting materials (Scheme 3). “One pretty sweet result is the ability to perform reductions at both secondary positions of isomannide to generate a 3,4-deoxy-

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Scheme 2 A) Formation of inverted triol from galactitol; B) Synthesis of a model for purported cyclic intermediates; C) Selective secondary C–O bond reduction of 1,2-deoxyglucose
tetraol in a single pot through thoughtful selection of the protecting and reducing silanes,” said Professor Dabrowski.

Professor Gagné concluded: “Whilst some of the products formed by this method are established fine chemicals, the majority of them are undisclosed and therefore offer the potential for new applications. Furthermore, the developed methodology opens new avenues of research to convert biomass into fine chemicals as the field of sustainable chemistry continues to expand.”

Scheme 3 Divergent reduction of dehydrated glucose and mannose

About the authors

Laura L. Adduci graduated from Brandeis University in Waltham, MA (USA) in 2009 with a B.S. in chemistry. She then began graduate studies in chemistry under the direction of Professor Michel R. Gagné at the University of North Carolina at Chapel Hill (USA), where she focused on selective carbohydrate transformations. Upon completion of her Ph.D., she accepted a position at Eastman Chemical Company in Kingsport, TN (USA). Her main interests involve characterization of small molecules and polymers.

Trandon A. Bender graduated from Weber State University in Ogden, UT (USA) in 2012 with a B.S. in chemistry. He then began his graduate studies under the tutelage of Professor Michel R. Gagné at the University of North Carolina at Chapel Hill (USA). His research focuses on deriving novel pathways for the selective reduction of carbohydrate and complex molecules through selective hydrosilylative processes. His interests include organometallics, organic synthesis, catalysis, and riding bikes.

Jennifer A. Dabrowski graduated from Le Moyne College in Syracuse, NY (USA) in 2007 with a B.S. in chemistry. She obtained her Ph.D. from Boston College (USA) in 2013. While in Professor Amir H. Hoveyda’s group she developed Cu–NHC–sulfonate complexes for catalytic enantioselective methods to form tertiary and quaternary C-based stereogenic centers. Dr. Dabrowski then joined the Gagné group at the University of North Carolina at Chapel Hill (USA) to pursue selective biomass conversion to fine chemicals. She is currently an Assistant Professor at Elon University (USA). Her interests include organometallics, organic synthesis, catalysis, and exploring new places.

Michel R. Gagné was profoundly influenced by his mentors, Professors Takats, Marks, Grubbs, and Evans. He is currently Mary Ann Smith Professor of Chemistry at the University of North Carolina at Chapel Hill (USA) and can only hope that he can similarly provide his own co-workers with the opportunities made available to him.
The activation of chemical reactions by visible light has attracted much interest over recent years. There are two key reasons for this: 1) visible light has been recognized as an abundant source of energy and is therefore in line with current interests of developing sustainable chemistry, and 2) visible-light activation provides a convenient tool for triggering single-electron transfer (redox chemistry) under mild conditions, thereby allowing exploitation of the useful reactivity of odd-electron species such as radical ions and radicals.

The group of Professor Eric Meggers at Philipps-Universität Marburg (Germany) has recently introduced a novel class of visible-light-activated asymmetric catalysts (Nature 2014, 515, 100; Chem. Eur. J. 2015, 21, 7355). In this ‘2-in-1’ design, a single and structurally surprisingly simple catalyst serves simultaneously as a photosensitizer and asymmetric chiral Lewis acid catalyst.

Haohua Huo, the first author on this new publication, said: “At the onset of the current study, we were seeking a useful application to demonstrate the merit of our asymmetric photoredox catalyst design and this culminated in the development of an enantioselective, catalytic trichloromethylation through visible-light-activated photoredox catalysis.” Their study was also inspired by elegant work from the Zakarian lab, which developed a diastereoselective redox-mediated haloalkyl radical addition to metal enolates (e.g. J. Am. Chem. Soc. 2010, 132, 1482).

Concerning the reaction mechanism, Professor Meggers explained: “The proposed mechanism involves the framed key intermediate iridium(III) enolate complex (Scheme), which is supposed to act as the chiral reaction partner for the electron-deficient trichloromethyl radical and, simultaneously, as the active photosensitizer.” Thus, according to Professor Meggers, the active photosensitizer is generated by coordination of the deprotonated substrate to the catalyst. This in situ assembly of the active photosensitizer is supported by a number of investigations, such as cyclovoltammetry and luminescence-quenching experiments. Professor Meggers continued: “This process can be classified as an electron-transfer-catalyzed reaction. It is overall redox-neutral. The role of an electron as a catalyst has been discussed recently by Studer and Curran (Nat. Chem. 2014, 6, 765).”

Professor Meggers remarked: “The use of light produces a complete switch in the reaction mechanism! When executed in the dark, a bromination product is formed, but in the presence of light only the trichloromethylation occurs.” A typical reaction setup is shown in the Figure, just to demonstrate that the equipment is available in every lab.

The enantioselectivities of this process are very high, in several cases ≥ 99%. The group found this to be intriguing, considering that the reaction proceeds through intermediate reactive trichloromethyl radicals. Furthermore, it demonstrates that the catalyst, in which the chirality is exclusively based on metal centrochirality, is configurationally absolutely stable.

Figure Exemplary photochemistry setup using a compact fluorescent lamp
Scheme Plausible mechanism for a combined photoredox and asymmetric catalysis with a chiral iridium Lewis acid photoredox sensitizer; light source: 20 W compact fluorescent lamp (CFL)
under the reaction conditions, something the group was not sure about at the onset of this project.

Professor Meggers concluded: “Looking from the viewpoint of the catalyst, we find it fascinating that the metal center serves multiple functions at the same time: it constitutes the exclusive center of chirality (only achiral ligands!), the catalytically active Lewis acid center, and additionally functions as the key component of the photosensitizer.”

Haohua Huo was born and raised in Guangdong (P. R. of China). He received his B.Sc. degree in chemistry from Xiamen University (P. R. of China) in 2009, and then continued to pursue his M.Sc. degree at the same university under the supervision of Professor Peiqiang Huang, where he finished the total synthesis of the natural product FR901483. In 2012, he joined the group of Professor Eric Meggers at the University of Marburg (Germany) as a Ph.D. student. His research in the Meggers laboratory focuses on asymmetric photoredox catalysis with novel chiral-at-metal complexes.

Chuanyong Wang was born and raised in Jiangsu Province (P. R. of China). He obtained his B.Sc. degree in 2010 from Nantong University (P. R. of China), and subsequently joined the research group of Professor Qi Shen at Soochow University (P. R. of China). He is currently a Ph.D. student at the University of Marburg (Germany) under the supervision of Professor Eric Meggers. His research interests are centered around asymmetric catalysis with chiral-at-metal rhodium(III) and iridium(III) complexes.

Klaus Harms received his Diploma in chemistry (Diploma thesis with Professor G. M. Sheldrick) in 1980 and a Ph.D. in natural sciences in 1984 under the direction of Professor L. F. Tietze at the University of Göttingen (Germany). Subsequently, he worked on a project in relation to ‘Patterson search methods’ (Dr. E. Egert, Professor G. M. Sheldrick) in Göttingen and since 1986 as a crystallographer in the ‘Sonderforschungsbereich 260’ at the University of Marburg (Germany). In 1991, he became a full member of the Central Laboratory of Crystallography at the Faculty of Chemistry at the University of Marburg. Since 2009, he is head of the X-ray laboratory. His research focuses on the crystal structure determination of inorganic, organometallic, organic, and bio-organic compounds, in particular on ‘problem structures’ showing disorder or twinning.

Eric Meggers was born and raised in Bonn (Germany). He received his Diploma in chemistry from the University of Bonn (Germany) in 1995 and a Ph.D. from the University of Basel (Switzerland) in 1999, under the guidance of Professor Bernd Giese. After postdoctoral research with Professor Peter G. Schultz at the Scripps Research Institute (La Jolla, USA), he became in 2002 an Assistant Professor in the Department of Chemistry at the University of Pennsylvania (USA). Since 2007, Eric Meggers has been Professor at the Department of Chemistry of the University of Marburg (Germany) and currently holds a secondary appointment as Professor at the College of Chemistry and Chemical Engineering of Xiamen University (P. R. of China). His research program currently focuses on aspects of metal-centered stereochemistry for applications in the life sciences and asymmetric catalysis.
Palladium-Catalyzed Direct Cyclopropylation of Heterocycles

Angew. Chem. Int. Ed. 2015, 54, 9601–9605

In 2014, Professor Jianrong (Steve) Zhou’s group at the Nan­yang Technical University in Singapore reported a palladium-catalyzed process for the alkylation of unsaturated heterocycles (Angew. Chem. Int. Ed. 2014, 53, 13573). The chemistry capitalized on Osborn’s initial discovery in the 1970s that phosphine complexes of Pd(0) react with alkyl halides to produce alkyl radicals via single-electron-transfer processes (J. Am. Chem. Soc. 1974, 96, 7145). Professor Zhou explained: “Under our conditions, the alkyl radicals that were involved in the catalytic bond formation can be trapped by TEMPO. The key step of direct radical addition to heteroarenes without intervention by metal catalysts was further supported by DFT calculations. Suitable substrates included many electron-deficient thiophenes, furans, pyroles, indoles and pyridines. About 90% of these alkylation products were new entities although they had simple structures. In many cases, good conjugate selectivity of addition was observed. That work was conducted in collaboration with Professor Hajime Hirao on DFT calculations and Professor Jean-Cyrille Hierso in France.”

Next, Professor Zhou and co-workers decided to investigate whether a similar radical process was possible by using cyclopropyl iodides together with heterocycles. “Compared with common cycloalkyl analogues, cyclopropyl radicals are known to be less nucleophilic and they added more slowly to electron-poor heteroarenes,” said Professor Zhou. “Cyclo­propyl rings are useful pharmacophores, since cyclopropyl rings are small and rigid and their ring substituents have specific orientations in space. They also have high built-in ring strains, which may prompt ring rupture. In the literature, very few methods existed that allowed incorporation of heteroaryl groups directly onto the three-membered rings when we initiated our study.”

Professor Zhou continued: “Our new method allowed an efficient cyclopropylation of various heterocycles such as oxazoles, thiazoles and caffeine. Our H/D exchange studies pointed to reversible deprotonation of heterocycles, such as oxazoles, by a base like NaOMe, even in the absence of a palladium catalyst. This finding led us to explore couplings of some electron-poor thiophenes, which have relatively acidic CH bonds with pKₐ values less than 30 in DMSO. Indeed, the reactions proceeded as we anticipated.”

However, to their surprise, when the Singapore-based researchers tested pure cis-2-phenylcyclopropyl iodide under the catalytic conditions at the end of the project, it led almost exclusively to a cis-coupling product. This result argued strongly against a radical pathway, as cyclopropyl radicals can undergo inversion of configuration with very low barriers.
(3–4 kcal/mol). Professor Zhou said: “Now, we believe that the catalytic cycle starts with a concerted oxidative addition of cyclopropyl iodides which is followed by fast transmetalation with anions of heterocycles formed in situ.” Suzuki reaction of cyclopropyl halides was previously reported by Charette to proceed with conservation of the configuration on the three-membered ring.

Professor Zhou concluded: “In retrospect, the main challenge in realizing this transformation was the side reactions lying outside the catalytic cycle, rather than a difficult step in the catalytic cycle. In fact, when the transmetalation step was slow, we found that the oxidative adduct, a cyclopropylpalladium complex, was prone to two side reactions, elimination to form 1,3-dienes and ring opening of cyclopropyl groups to form allylic radicals.”

About the authors

Xiaojin Wu was born in Yancheng (P. R. of China). He received his B.Sc. degree in chemistry at Soochow University in 2007 and his M.Sc. degree in Professor Shunjun Ji’s group in 2010. He then conducted his doctoral studies at the Nanyang Technological University (Singapore) in Professor Jianrong (Steve) Zhou’s group from 2010–2015. His thesis research focused on the palladium-catalyzed Heck reaction and alkylation of heteroarenes. He is currently a research fellow in Professor Jishan Wu’s lab at the National University of Singapore.

Chuan-Hu Lei was born in Sichuan (P. R. of China). He received his B.Sc. degree in chemistry from Beijing Normal University (P. R. of China) in 2008. Then he joined Professor Mei-Xiang Wang’s lab at the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) as a Ph.D. student and worked on tandem reactions between tertiary enamides and isonitriles for the efficient construction of azacycles. Since 2014, he has been working in Professor Jianrong (Steve) Zhou’s group at Nanyang Technological University in Singapore as a research fellow.

Guizhou Yue was born in Hubei (P. R. of China). From 2008–2011, he received Ph.D. training in the laboratory of Professor Bo Liu at Sichuan University (P. R. of China), working on the total synthesis of lindenane-type sesquiterpenoids. He began his independent research at the Sichuan Agricultural University (P. R. of China) in 2005 and was promoted to associate professor in 2013. His research focuses on the total synthesis of bioactive natural products and transition-metal-catalyzed reactions. In 2014/2015, he was a visiting professor in Professor Steve Zhou’s group under the support of Chinese Scholarship Council.

Jianrong (Steve) Zhou was born in Zhejiang (P. R. of China). He received undergraduate education and his Master’s degree at the National University of Singapore under the guidance of Professor Teck-Peng Loh. In 2000, he went to MIT (USA) and did his Ph.D. in Professor Gregory Fu’s lab where he developed cross-coupling reactions of alkyl halides. From 2005 to 2008, he was a postdoctoral researcher in Professor John Hartwig’s group at Yale University (USA) and later moved with him to the University of Illinois at Urbana (USA). In 2008, he started his independent career at Nanyang Technological University (Singapore) with a joint appointment as Singapore National Research Foundation Fellow. Steve’s research interests include transition-metal catalysis for fundamental bond-forming processes and mechanistic studies. He likes reading history and politics for leisure.
Young Career Focus:
Professor Inga Čikotienė (Vilnius University, Lithuania)

**Background and Purpose.** From time to time SYNFORM meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Inga Čikotienė (Vilnius University, Lithuania).

### Biographical Sketch

Inga Čikotienė was born in Vilnius (Lithuania) in 1979. She graduated with honors from Vilnius University in 2003 and obtained her PhD in chemistry at Vilnius University in 2006. After postdoctoral work at the Institute of Biotechnology (Lithuania), she returned to her alma mater as a lecturer, eventually being promoted to associate professor in 2009 and then to full professor in 2014. Her research interests include organic synthesis, investigations of reaction mechanisms, and medicinal chemistry. She has received several awards including Young Scientist awards and scholarships from Lithuanian Research Council, Lithuanian Academy of Science and Rector of Vilnius University.

**SYNFORM** What is the focus of your current research activity?

**Prof. I. Čikotienė** Currently, my group is working on the development of new synthetic methods and the investigation of reaction mechanisms. We are particularly interested in transformations of various functionalized alkynes and their use in the preparation of acyclic, carbocyclic or heterocyclic compounds. Transition-metal catalysis, Lewis acid or electrophilic mediation are generally used as tools for these transformations. Moreover, in some parts we are focusing on medicinal chemistry and the preparation of new antitumor compounds.

**SYNFORM** When did you get interested in synthesis?

**Prof. I. Čikotienė** During my undergraduate studies I was impressed by the theory of organic synthesis first. Then I joined an organic synthesis laboratory for the preparation of the final thesis for my bachelor’s degree and during work in the lab I understood that organic synthesis is a much richer and more elegant area than what is explained in general textbooks. I was impressed first by serendipitous findings during my research and I became curious to explain them all and to go deeper into understanding the reaction mechanisms and factors affecting the unprecedented outcome of some reactions. During my Master’s and PhD studies I was allowed to work independently and I am thankful to my former supervisor Dr. A. Brukstus for this possibility. I feel very lucky because I obtained a lot of surprising results in organic synthesis and the ability to explain the atypical reactions and reactivity modes was a great motivation and challenge for me.

**SYNFORM** What do you think about the modern role and prospects of organic synthesis?

**Prof. I. Čikotienė** Organic synthesis is an enormously growing field and it is useful for the preparation of a variety of materials (from natural products and biologically active compounds to chromophores or supramolecular units). New synthetic methods and tools are constantly being developed and may find application in the production of useful materials. A very important point is that organic synthesis is a unique scientific area by itself and is not just the mixing of two reagents with each other. A lot of unexplored areas still exist. I think that both rational design and serendipitous findings will constantly bring some novelties into modern synthetic approaches and understanding of reaction mechanisms. Undoubtedly, organic synthesis will stay important in the future.
Your research group is active in the areas of organic synthesis and medicinal chemistry. Could you tell us more about your research and its aims?

Prof. I. Čikotienė The main focus of our research lies on the development of new synthetic methods and the investigation of reactivity trends of some unsaturated compounds. Most attention is paid to the chemistry of propargylic substrates (esters, ureas, amides, carbamates, etc.) and their electrophile-mediated rearrangements in cyclization processes. Moreover, we have studied different intramolecular cyclizations and multicomponent processes of acetylenic aldehydes and acetylenic nitro compounds. N-Nitroso group assisted reactions of azines are also of particular interest. Thus, we are looking for an interesting chemistry and are investigating the synthetic potential of observed transformations. We have explored a number of new methodologies for the preparation of a variety of scaffolds.

We have also established some fruitful collaborations with biochemists, and general biological evaluation of our synthesized compounds using solid tumor or leukemic cancer cells, bacteria and fungi strains have been performed. The most active compounds are taken into more detailed studies and obtained SARs are used for the development of structures.

What is your most important scientific achievement to date and why?

Prof. I. Čikotienė This is difficult to answer, because each studied reaction has its own charm. One of the most exciting studies was the investigation of electrophile-induced rearrangements of propargylic esters leading to the formation of functionalized enones. We have shown that a 1,3-acyloxy shift in propargylic esters can be induced by some electrophiles (aldehydes, oxocarbenium ions, halonium ions) without the need for transition-metal catalysis. However, the reactions between propargylic esters and aldehydes were shown to proceed by either a classical alkyne–carbonyl metathesis route or an unprecedented addition–rearrangement cascade. Depending on the structure of the starting materials and the reaction conditions, the products of these reactions can be Morita–Baylis–Hillman (MBH) adducts that are unavailable by traditional MBH reactions or E- and Z-enones. Mechanistic studies of these reactions were performed by isotopic labeling experiments.

And of course, I hope that a lot of important achievements lie ahead of me.
Scheme 2

REFERENCES

Coming soon

- Literature Coverage
  Conversion of Amides into Esters by the Nickel-Catalyzed Activation of Amide C–N Bonds

- Literature Coverage
  Multimetallic Catalyzed Cross-Coupling of Aryl Bromides with Aryl Triflates

- Literature Coverage
  Iron-Catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes

Further highlights

- Synthesis  Review: Recent Advances in Catalytic Asymmetric Reactions of α-Quinone Methides
  (by Z. Wang, J. Sun)

- Synlett  Account: Developments inExternally Regulated Ring-Opening Metathesis Polymerization
  (by A. J. Boydston and co-workers)

- Synfacts  Synfact of the Month in category “Synthesis of Heterocycles”: Synthesis of Highly Functionalized Oxetanes

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