Project Prospect

Introducing semantics into chemical science publishing

Richard Kidd

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Aims of Project Prospect

- Preserve authors' science
- Capture the science as XML
- Apply ontologies to find meaning
- Make it part of the publishing process
- Provide new views to readers
- Computer-readable chemistry

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Meaningful searches

Why is it hard for chemistry?

- Searching
  - Free text or proprietary
- Related articles
  - No standards

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Introduction

The generation of bespoke pseudopeptide sequences that exhibit highly ordered secondary and tertiary structures in both solution and solid phase has developed into a highly competitive field of research in recent years, with the ability to predict the conformation of a given peptide sequence from knowledge of its primary structure an elusive goal. While much effort has been directed towards understanding the factors that control the secondary structure of α-peptides, the utility of peptides incorporating the β-amino acid structural motif has recently been investigated widely, most notably by Seebach[1] and Gellman.[2] For instance, Gellman *et al.* have shown that β-peptides derived from *trans*-2-aminocyclopentanecarboxylic acid (transpentacin) **1** adopt a helical stucture in both the solid state and in solution,[3] while Fülop *et al.* have shown that homo-oligomers of *cis*-2-aminocyclopentanecarboxylic acid (cispentacin) **2** form a sheetlike secondary structure in solution (Fig. 1).[4] The ability of mixed α,β-peptides containing both α-amino and β-amino acid derivatives to adopt a preferred conformation in solution has also been reported recently.[5]

We have shown extensively that the conjugate addition of lithiumamides derived from α-methylbenzylamine to α,β-unsaturated acceptors may be used for the asymmetric synthesis of β-amino acid derivatives.[6] This methodology has recently been utilised for the synthesis of (1*R*,2*S*,3*R*)-3-methylcispentacin **5** in >98% de and 98 ± 1% ee and (1*S*,2*S*,3*R*)-3-methyltranspentacin **7** in >98% de and 97 ± 1% ee by the kinetic resolution of *tert*-butyl (*RS*)-3-methylcyclopentene-1-carboxylate **3** with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (Scheme 1).[7]

The protocol that we use to understand fully the stereoselectivity observed in these kinetic resolution reactions

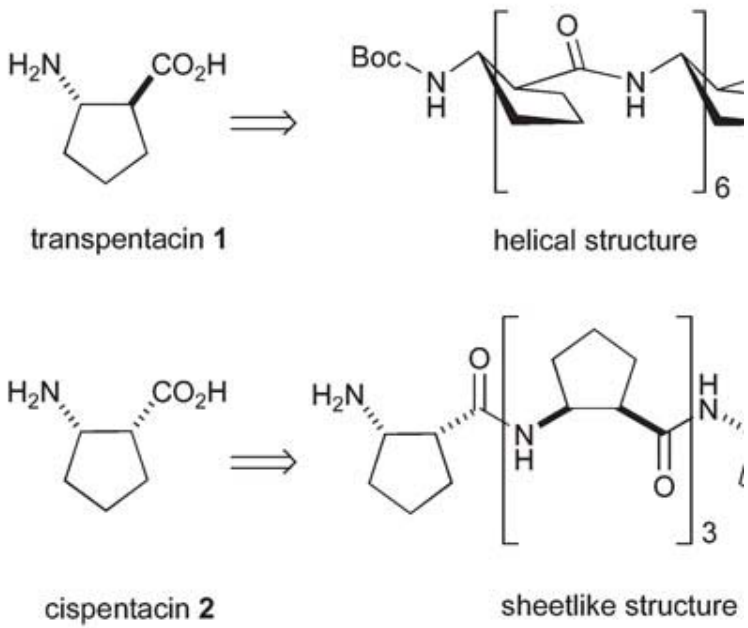

Fig. 1 Secondary structure of poly homo-pe

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Systematic name

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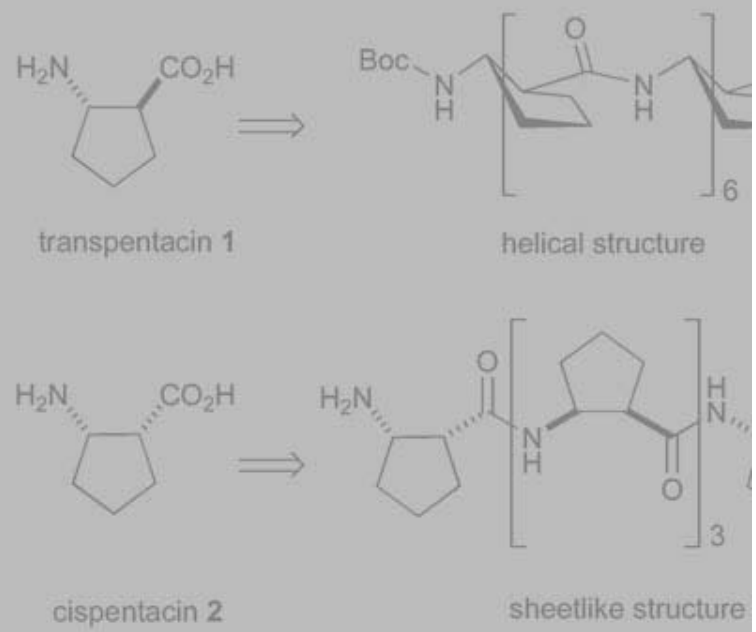

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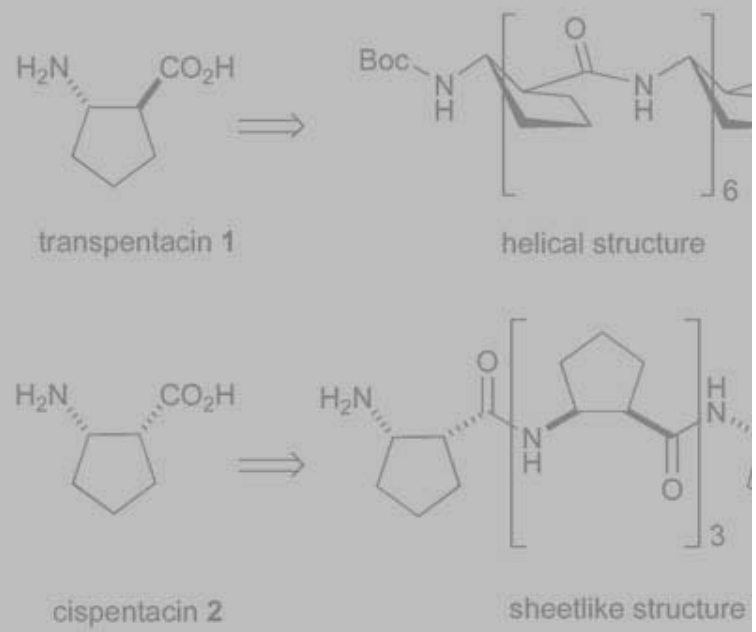

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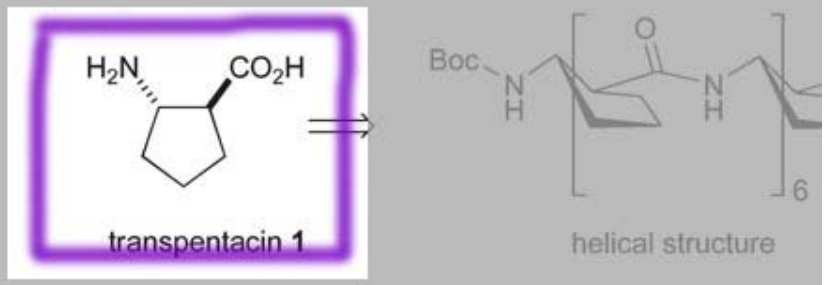

2D structural diagram

cispentacin 2 sheetlike s

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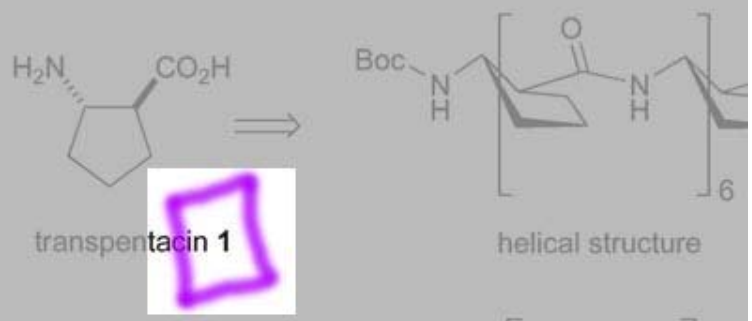

boldface numbers

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The Prospect model

- Enhance existing publications
- Build straight into existing workflow
- Reduce problems with introducing separate product

- Marked small molecule libraries…
  …lysyl oxidase in zebrafish notochord morphogenesis

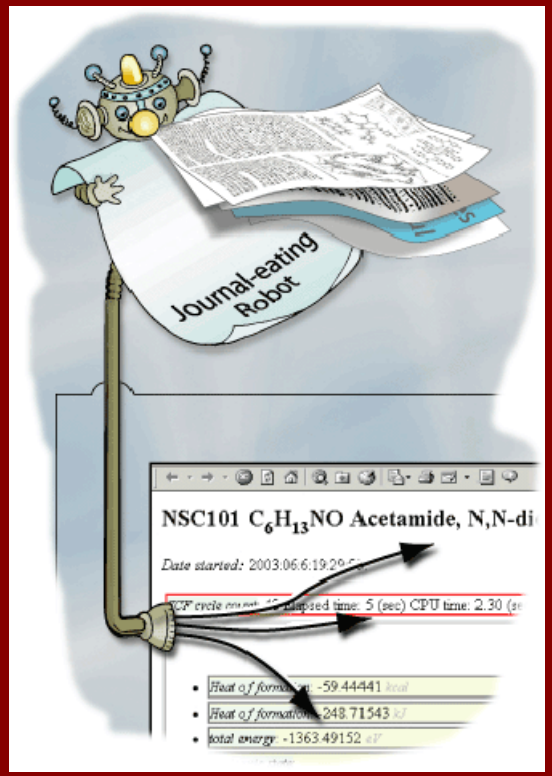
How?

- Collaborations
  - Unilever Centre/Computer Lab
  - Others
- Technology
  - OSCAR text mining
  - Standards
  - Workflow
  - RSS feeds

OSCAR text mining

Open Source Chemical Analysis Routines

- University of Cambridge: Chemistry (Unilever Centre) –Computer Lab collaboration
- SciBorg
- Analyses single words and short chemical-looking phrases to determine structure
- Attaches structures to text
- Extended to subjects



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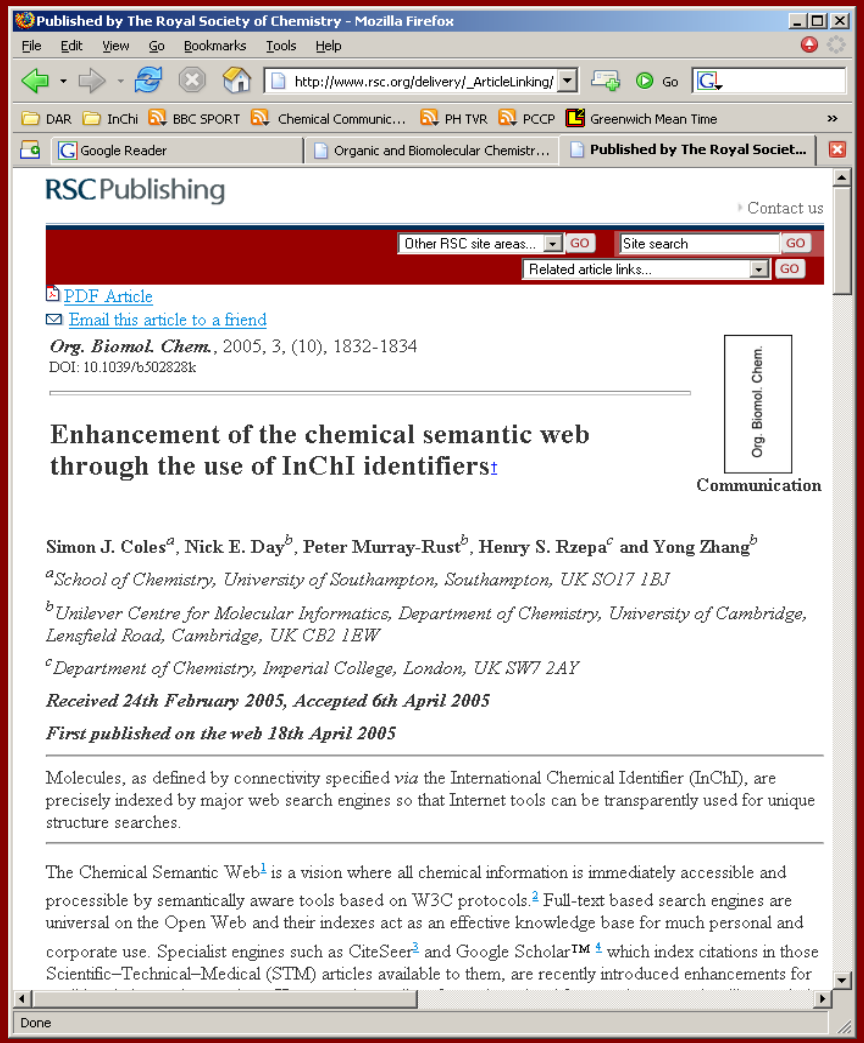
InChI

- IUPAC International Chemical Identifier
- InChI=1/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3
- Machine readable
- InChIkey RYYVLZVUVIJVGH-UHFFFAOYAW



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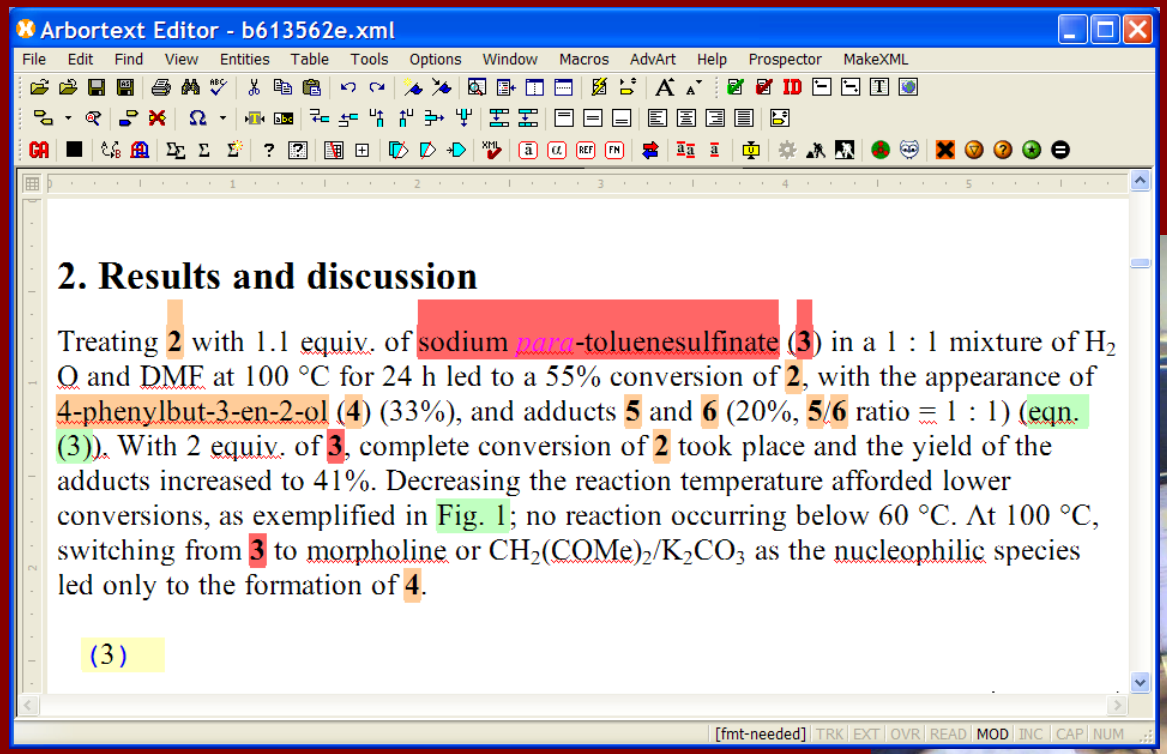
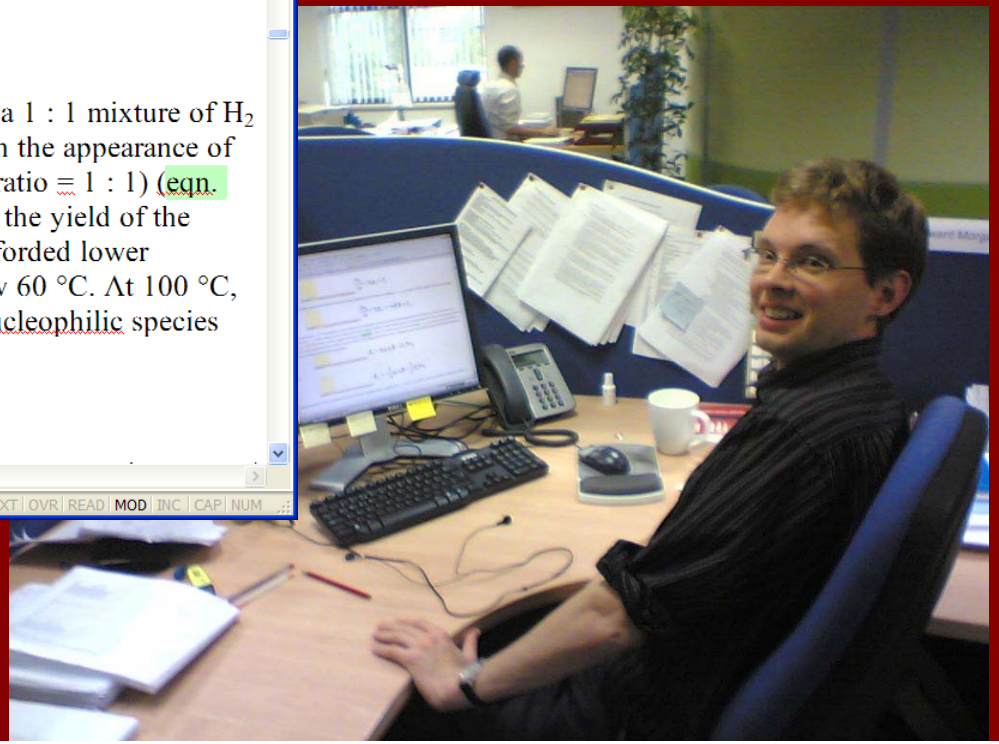
Subject terms

- Open Biomedical Ontologies
  - Gene Ontology (GO)
  - Sequence Ontology (SO)
  - Cell Ontology (CL)
- IUPAC Gold Book
  - Dictionary of chemical terminology

RSC Publishing process

- Editing
- Mining
- Add & Tidy





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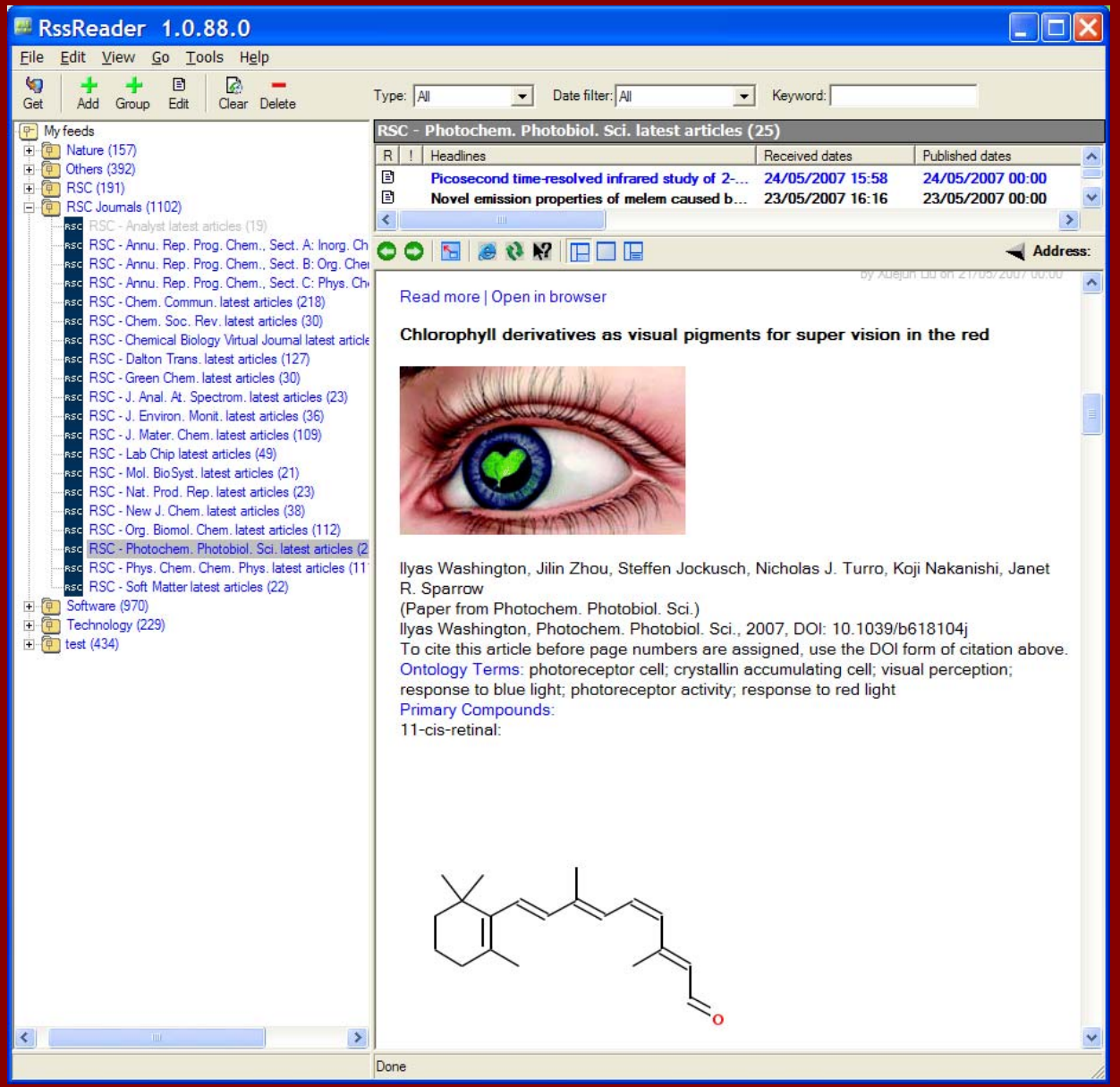
Enhanced RSS feeds



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Problems?

- Significant manual QA required
  - and old data even harder
- Ontology development required in many areas
- Wider adoption and interlinking required to maximise benefits

New data standards

- Experimental data checker
  - Validation
  - Visualisation
- Role for society publishers

2-Methyl-2-hydroxymethyl-2,5-dihydrofuran **9** (50 mg, 0.51 mmol) was oxidised using OsO_4, TMEDA to yield the crude products [6 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (petrol-EtOAc, 4 : 1) to afford the pure title compound as a colourless oil (116 mg, 83%); ν_{max} (film)/cm^{-1} 2977, 2929, 1746, 1374, 1230, 1046; δ_H (300 MHz; $CDCl_3$) 5.43 (1H, q, *J* 5), 5.17 (1H, d, *J* 5), 4.26-4.09 (3H, m), 3.89 (1H, dd, *J* 10 and 5), 2.10 (6H, s), 2.08 (3H, s), 1.36 (3H, s); δ_C (75 MHz; $CDCl_3$) 170.6, 169.8, 169.5, 80.8, 76.2, 71.2, 68.9, 65.3, 22.3, 20.6, 20.4, 18.3; Found (CI) 292.1392, $C_{12}H_{22}NO_7 + NH_4$ requires 292.1396.

***anti*-2-Methyl-2-(acetoxymethyl)tetrahydrofuran *anti*-15**

2-Methyl-2-hydroxymethyl-2,5-dihydrofuran **9** (50 mg, 0.51 mmol) was oxidised using UpJohn conditions to yield the crude products [2 : 1 (*anti* : *syn*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (petrol-EtOAc, 4 : 1) to afford the product mixture as a colourless oil (110 mg, 79%) as an inseparable mixture of isomers (*anti* major compound); ν_{max} (film)/cm^{-1} 2989, 2944, 1746, 1379, 1232, 1046; δ_H (300 MHz; $CDCl_3$) 5.46-5.39 (1H, m), 5.26 (1H, d, *J* 6), 4.26-3.85 (4H, m), 2.11 (3H, s), 2.10 (6H, s), 1.26 (3H, s); δ_C (75 MHz; $CDCl_3$) 170.4, 169.8, 169.6, 81.2, 72.7, 71.9, 69.3, 67.9, 20.7, 20.5, 20.4, 18.3; Found (CI) 292.1400, $C_{12}H_{22}NO_7$ requires 292.1396,

***syn*-1,2,4-Triacetoxycyclohexane *syn*-16**

Cyclohex-3-en-1-ol **11** (50 mg, 0.51 mmol) was oxidised using OsO_4, TMEDA to yield the crude mixture of products [3 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (EtOAc) to afford a colourless oil (121 mg, 92%) as an inseparable mixture of isomers; mixture: ν_{max} (film)/cm^{-1} 2953, 1745, 1370, 1235, 1028; *syn*-**16** δ_H (300 MHz; $CDCl_3$) 5.17-5.11 (1H, m), 4.84-4.72 (2H, m), 2.04 (3H, s), 1.98 (3H, s), 1.86 (3H, s), 2.05-1.45 (6H, m); δ_C (75 MHz; $CDCl_3$) 170.1, 170.0, 169.9, 69.5, 69.3, 67.9, 31.4, 25.3, 24.7, 21.1, 20.9, 20.8; *anti*-**16**; δ_H (300 MHz; $CDCl_3$) 5.08-5.01 (1H, m), 4.81-4.67 (2H, m), 1.99 (9H, s), 2.05-1.45 (6H, m); δ_C (75 MHz; $CDCl_3$) 170.3, 170.2, 170.1, 69.7, 68.8, 68.6, 31.8, 25.9, 25.3, 23.6, 21.1, 20.9; mixture Found (CI) 276.1437, $C_{12}H_{22}NO_6$ requires 276.1447.

***anti*-1,2,4-Triacetoxycyclohexane *anti*-16**

Cyclohex-3-en-1-ol **11** (50 mg, 0.51 mmol) was oxidised using UpJohn conditions to yield the crude mixture of products [1 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (EtOAc) to afford the product mixture as a colourless oil (115 mg, 88%) as an inseparable mixture of isomers; All data are consistent with *syn*- and *anti*-**16** prepared previously.

***syn*-1,2,4,5-Tetraacetoxycyclohexane *syn*-17**

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*"My first forays show [Project Prospect is] **brilliant**. [It's] great to see the compounds and have machine readable SMILES and InChIs"*

*"Your new system is **very impressive**, I am sure it will become very useful to a large community"*

*•It is **great and exciting**!! Just from the very few minutes I looked into it I realized its great potential and immediately ran to show it to my students!"*

*"This is **a fantastic resource** for the community, and a great use of the GO and SO. Nice work"*

*"I have … found it **very intuitive/ straightforward** to use.[I] believe that it will make the manuscript even more appealing to readers."*

"It is fantastic. I've just seen the future of the journal"

Ed Pentz

Executive Director, CrossRef

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What's unique?

- Technology
  - Semantic enrichment
    - Compounds
    - Ontology terms
  - Enhanced RSS feeds
- Implementation across existing portfolio
  - Incorporation into workflow
  - Shows the possibilities for structured science

Future for RSC Project Prospect

- Experimental data
- Linguistics
- Extensive linking
- Other subject areas
- E-books, databases and backfile
- Peer review
- Prospect services

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