



**Trip Report:  
7<sup>th</sup> Annual Florida Heterocyclic Conference  
Gainesville, Florida  
March 12 – 15, 2006**

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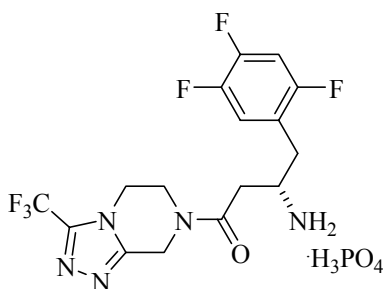
***Abstract:** This conference was organized by ARKAT-USA and sponsored by IUPAC. The conference included a total of 12 plenary lectures, 4 short talks, 14 invited lectures and poster session. A short course in heterocyclic chemistry was taught as a separate session by Professors Alan Katritzky (University of Florida), Eric F. V. Scriven (University of Florida), and Gordon Gribble (Dartmouth College, Hanover, NH).*

Below are presentation abstracts and a list of topics presented during the conference. A copy of the program is available for review for anyone at AMRI.

Plenary lecture were presented on the following topics:

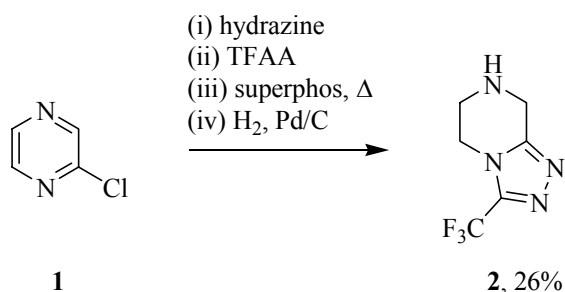
1. William Dolbier, Crow Professor, University of Florida, USA “*New Synthetic Methods for Fluorinated Aromatics and Heterocycles*”
2. Greg Fu, MIT, USA “*Asymmetric Catalysis with Planar-Chiral Heterocycles*”
3. Bruce Ganem, Roessler Professor, Cornell, USA “*Multiple Component Condensations*”
4. Thomas Hoye, University of Minnesota, USA “*Methods for Heterocycle Synthesis and Structure Determination*”
5. Bruce Maryanoff, Distinguished Fellow, J & J Pharmaceuticals, USA “*Pyridine-Containing Macrocycles from the Cobalt-Mediated [2+2+2] Cycloadditions*”
6. Goverdhan Mehta, Director, Indian Institute of Science, Bangalore, India “*Total Synthesis of Bioactive Natural Products*”
7. Manfred Reetz, Max-Planck-Institute fur Kohlenforschung, Germany “*Novel Combinatorial Approaches to Asymmetric Catalysis*”
8. Richard Taylor, University of York, UK “*Tandem Approaches to Heterocyclic Synthesis*”
9. Barry Trost, Tamaki Professor, Stanford University, USA “*The Impact of New Synthetic Methodology on the Synthesis of Heterocycles*”
10. R. P. Volante, Process Research, Merck Research Laboratories, USA “*Practical Synthesis of Heterocyclic Drug Candidates*”

Synthesis of heterocyclic drug candidates was demonstrated by an example of efficient asymmetric synthesis of a diabetes triazole-derived drug candidate (Figure 1).



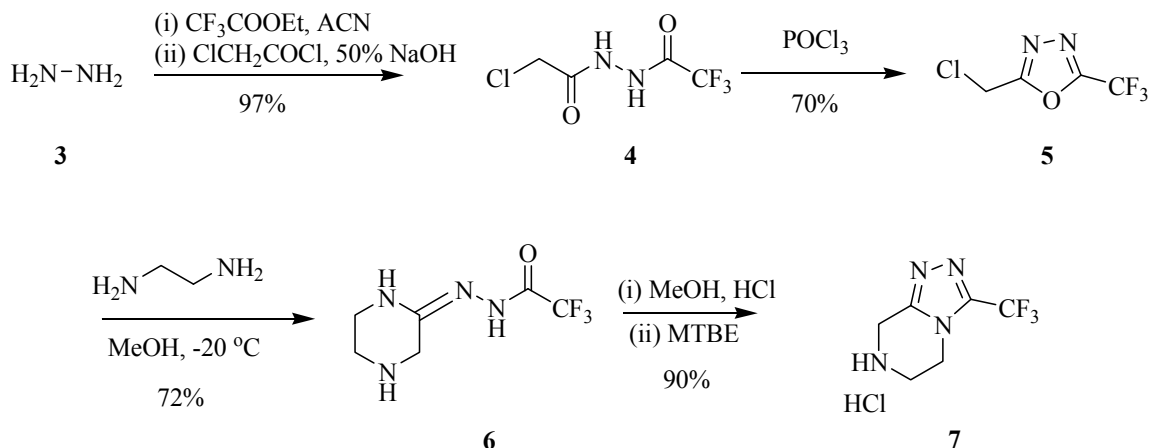
**Figure 1**

Original synthetic route during medicinal chemistry optimization included four step procedure (Scheme 1) with expensive and hazardous reagent to afford final compound in 26% overall yield.



**Scheme 1**

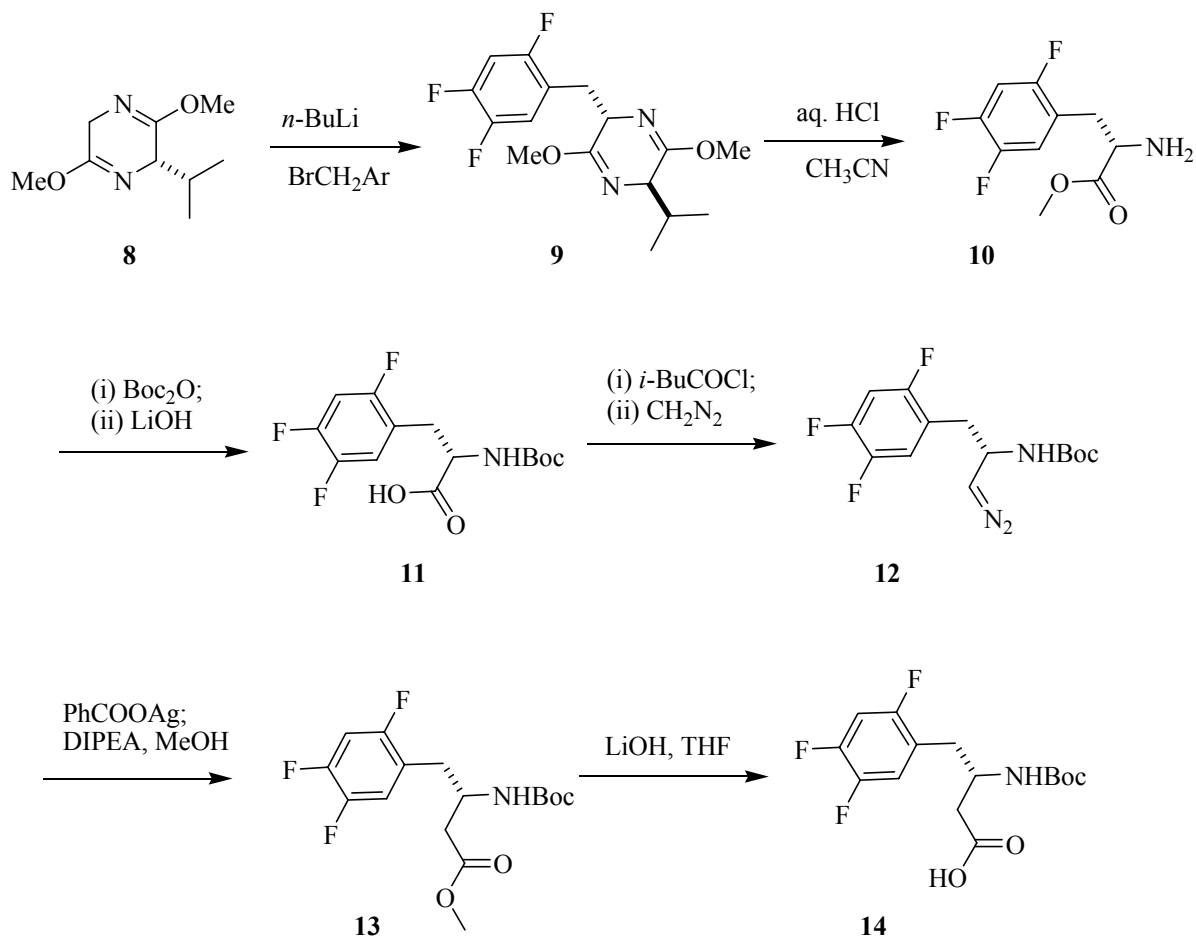
Alternative route, involving synthesis of oxadiazole intermediate **5**, was proposed (Scheme 2).



**Scheme 2**

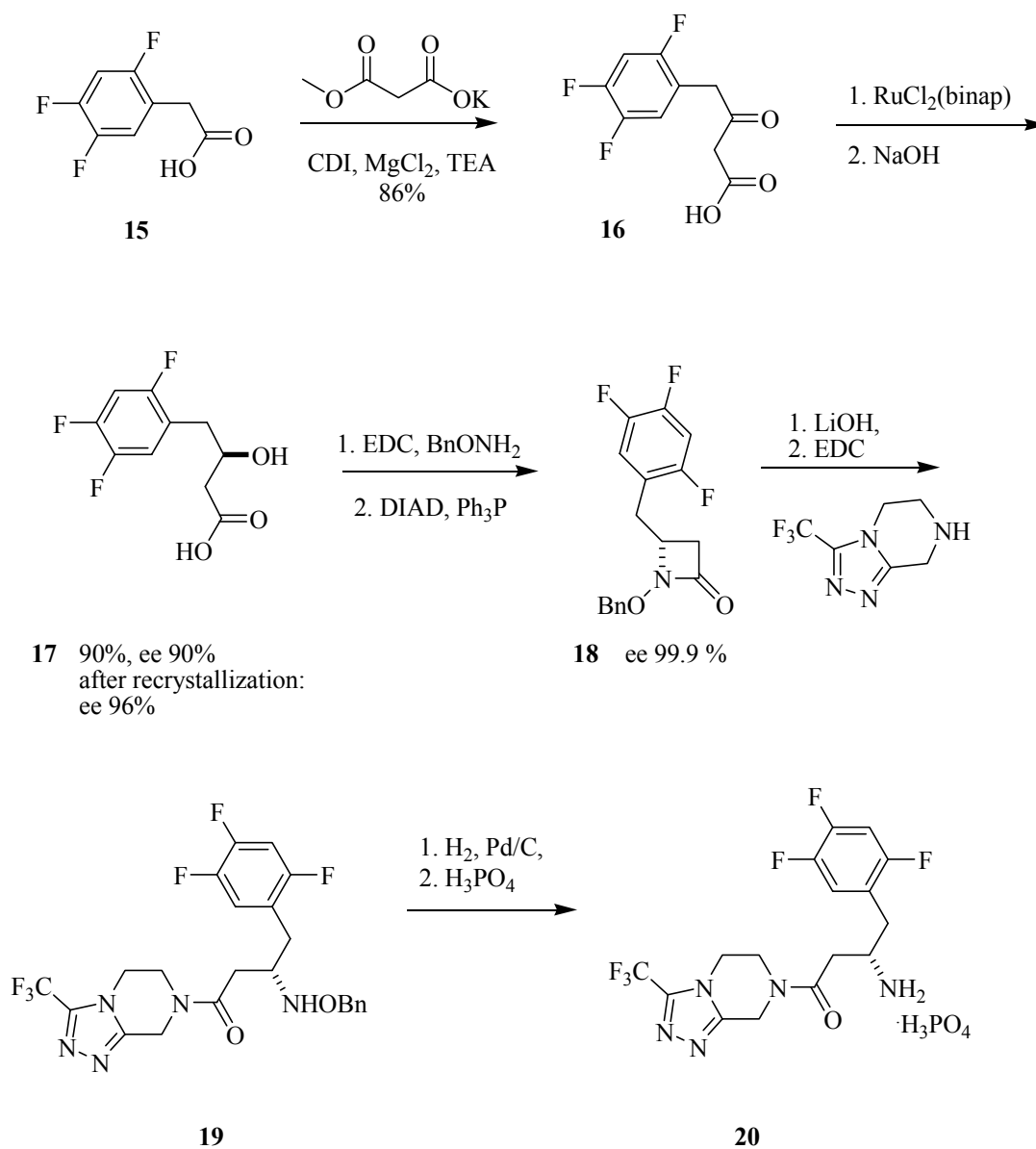
This route does not have safety issues, yielded overall 49% of the product, and resulted in tenfold reduction in cost. Over 1 metric ton of the product was prepared within 1 year.

Second part of the project included synthesis of  $\beta$ -amino acid counterpart (Scheme 3).



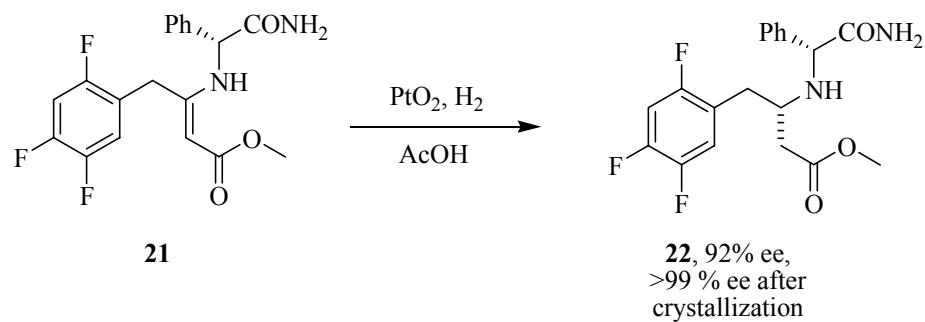
### Scheme 3

First generation process research preparation of the final product (Scheme 4) included preparation of enantiomerically pure  $\beta$ -hydroxyacid **17**, followed by the synthesis of cyclic lactam **18**, acylation and deprotection (Scheme 4). Such process had nine chemical steps, involved two crystallizations for *ee* upgrade, was expensive as it involved Noyori hydrogenation and two EDC couplings. Mitsunobu reaction was undesirable due to waste disposal issues. More efficient process for manufacturing was required.

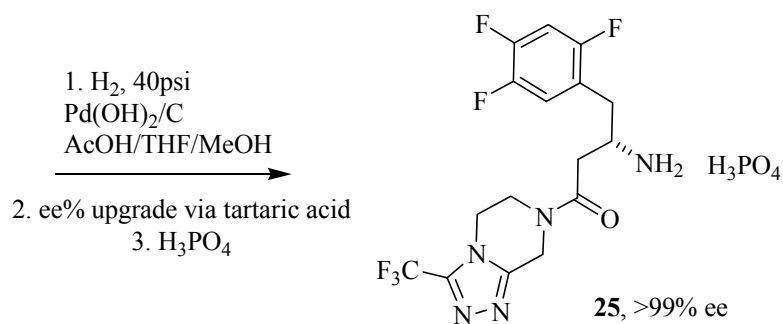
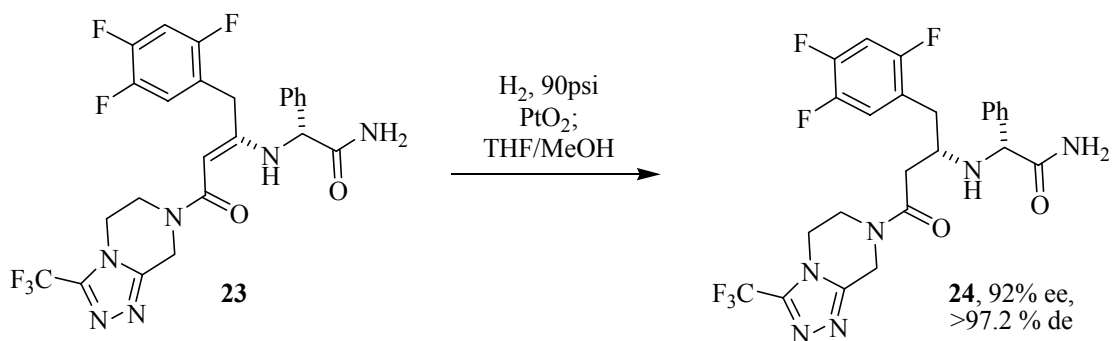


Scheme 4

Alternative approaches included diastereoselective reduction of model compound (Scheme 5) and of triazole intermediate (Scheme 6).

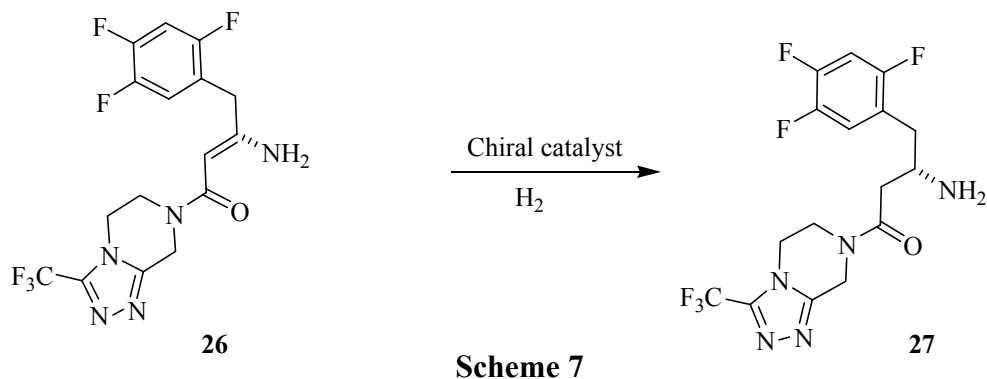


Scheme 5

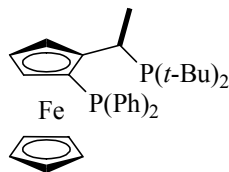


Scheme 6

In the search for an ultimate synthetic scheme a direct asymmetric hydrogenation of enamine was successfully attempted. This is the first example of the process of unprotected enamine (Scheme 7).

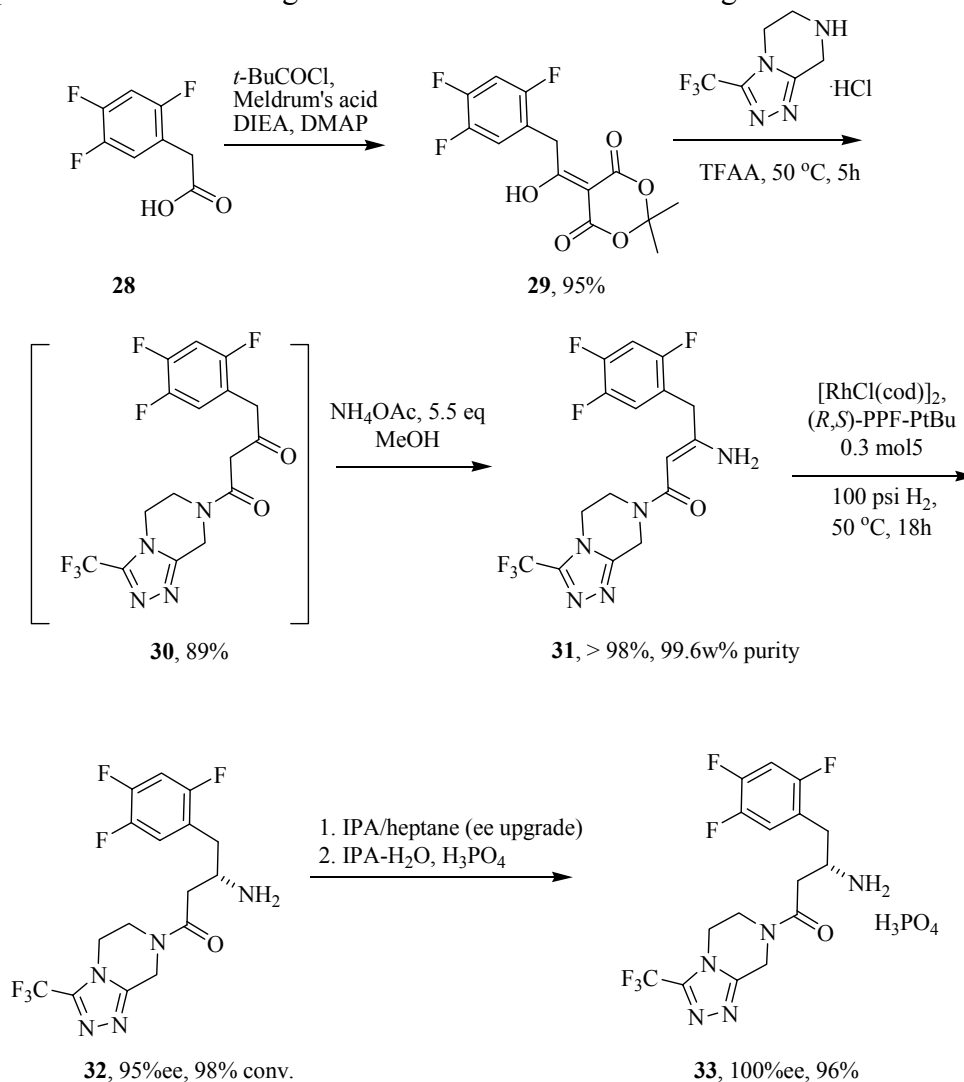


The process was further optimized using different catalysts. The best result (99% conversion and 95% ee) was achieved for catalytic system *t*-BuJOSIPHOS (Figure 2) and Rh(cod)CF<sub>3</sub>SO<sub>3</sub>. After process optimization it was proved that ee is independent of pressure, and the catalyst loading was reduced to 0.15 mol% at 250 psi.



**Figure 2**

The final route, “enamine amide through process” (Scheme 8) is based on a novel and robust chemistry, provides atom- and step-economy. It is economically viable, and has significant economic potential. Over 2000 kg of material have been made using this route.



Scheme 8

11. Dave Wustrow, Ann Arbor Laboratories, Pfizer, USA “*Heterocyclic Bioisosteres in CNS Drug Discovery*”

12. Hisushi Yamamoto, Compton Professor, University of Chicago, USA “*Recent Advances in Asymmetric Nitroso Diels-Alder Reaction*”

Invited lectures included the following topics:

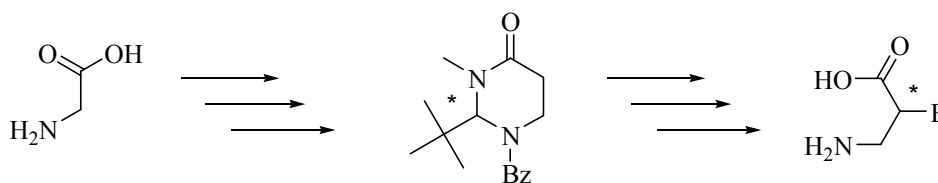
1. Prof. Eusebio Juaristi, Centro de Investigación y de Estudios Avanzados del I. P. N., México  
Centro de Investigación y de Estudios Avanzados del I. P. N., México  
“*Synthesis of 2-Substituted-5-halo-2,3-dihydro-4(H)-pyrimidin-4-ones and Their Derivatization to Potential Precursors of  $\alpha$ -Substituted  $\beta$ -Amino Acids Utilizing the Sonogashira Coupling Reaction*”

Chiral glycine enolates were first proposed for the preparation of enantiomerically pure  $\alpha$ -substituted  $\alpha$ -amino acids by Seebach and coworkers (Scheme 9) [Weber, *Helv. Chim. Acta*, 1987, 70, 237].



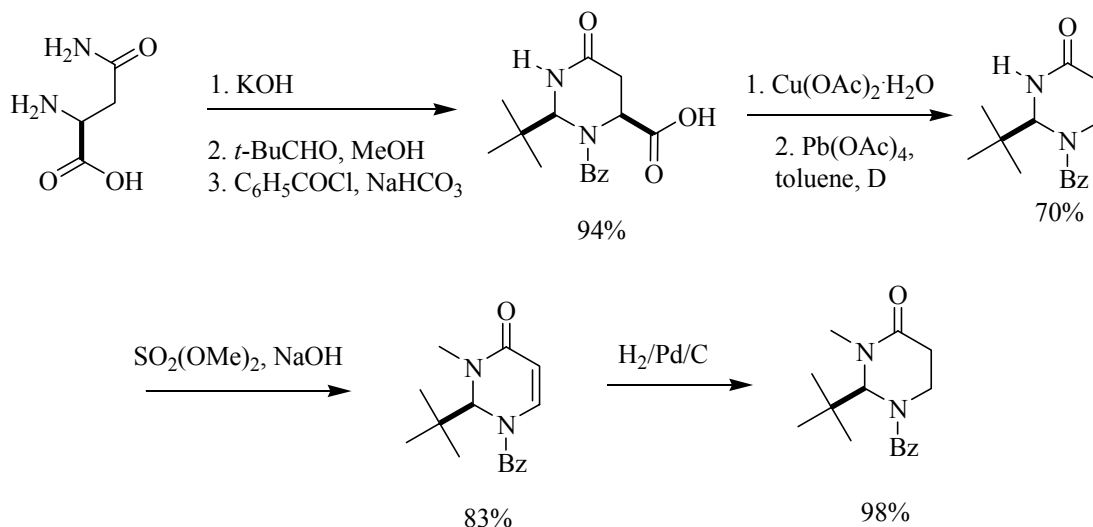
**Scheme 9**

The goal of the study was to find synthetic routes for the preparation of  $\alpha$ -substituted  $\beta$ -amino acids from  $\beta$ -alanine according to the general Scheme 10.



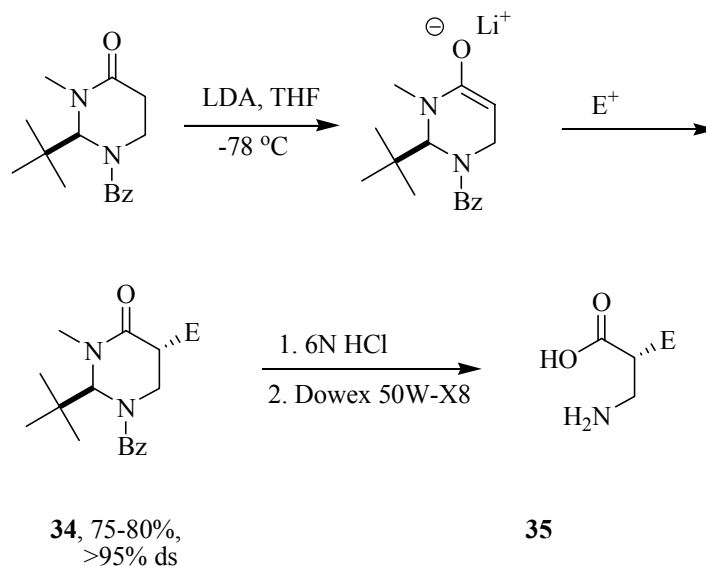
**Scheme 10**

Enantioselective synthesis of starting pyrimidinone was achieved in four synthetic step as depicted in Scheme 11.



**Scheme 11**

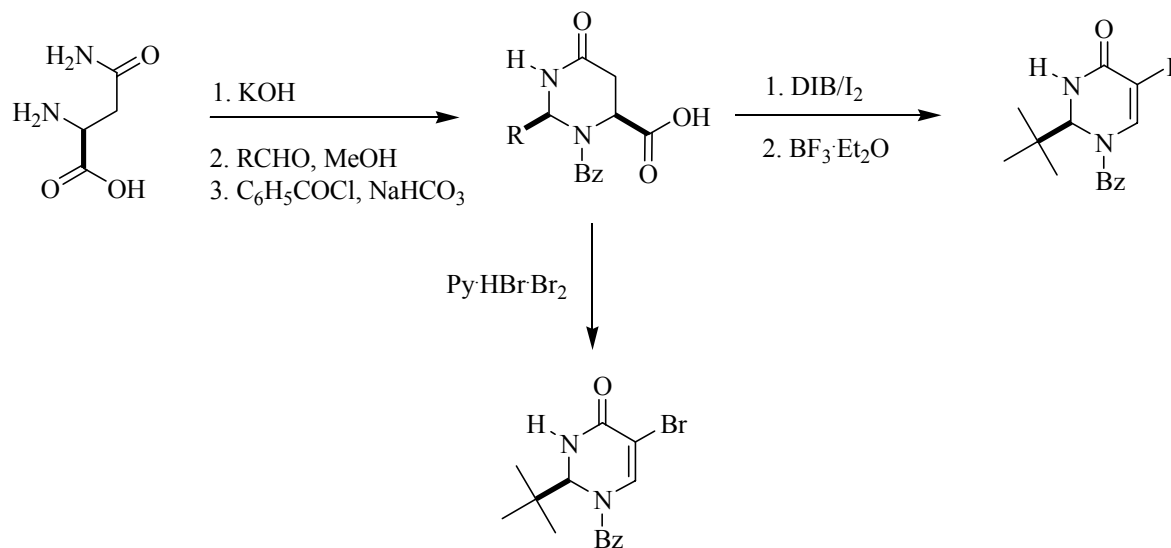
Further lithiation and reaction with electrophiles afforded corresponding (*S*)-1-benzoyl-2-*tert*-butyl-3-methyltetrahydropyrimidin-4(1H)-ones **34**, which can be easily hydrolyzed to the desired amino acid **35** (Scheme 12).



**Scheme 12**

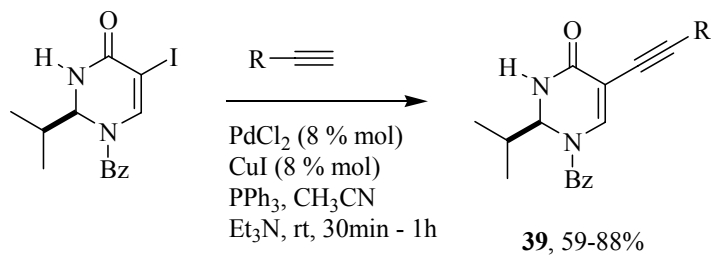


This sequence was further used for the preparation of enantiomerically pure iodoenones and bromoenones (Scheme 15).



**Scheme 15**

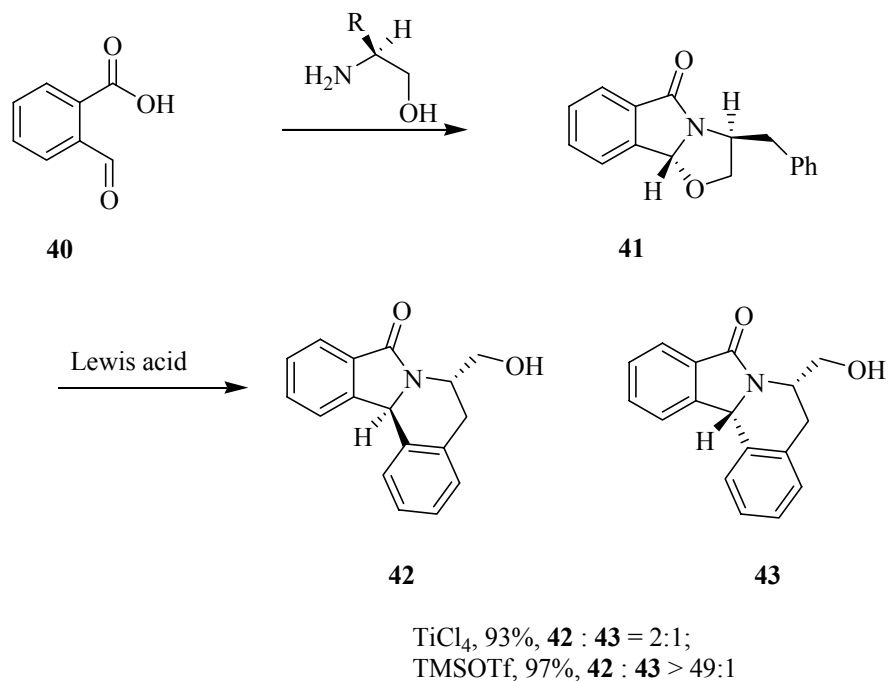
Sonogashira reaction of iodoenones with terminal alkynes results in the corresponding alkyne derivatives **39** in moderate to good yields (Scheme 16).



**Scheme 16**

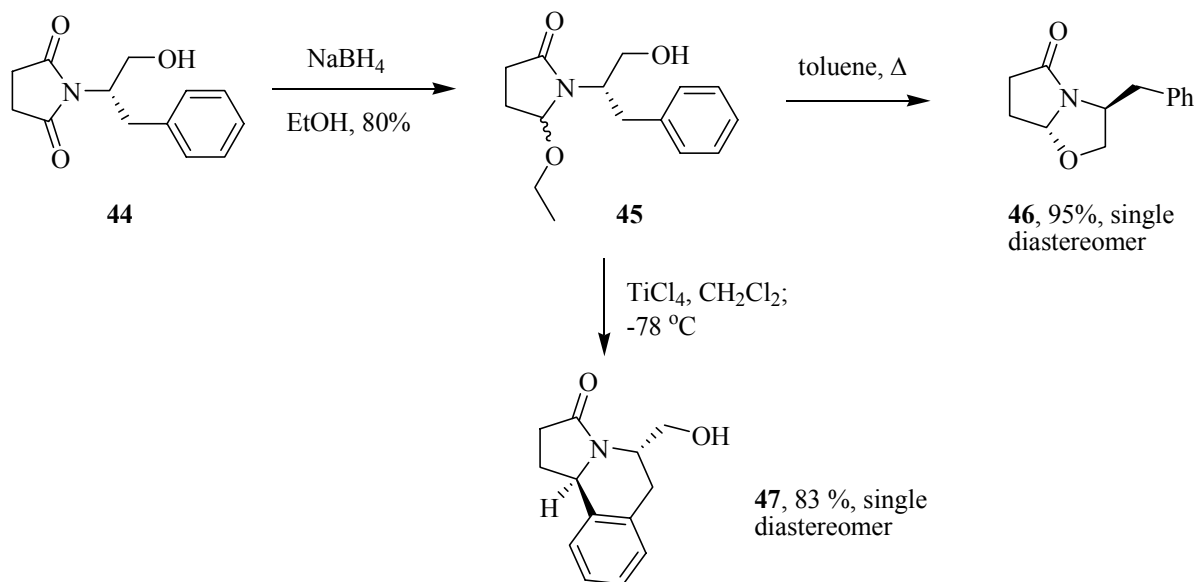
2. Dr. Steven M. Allin, Department of Chemistry, Loughborough University, UK “A new approach for the stereoselective synthesis of some complex alkaloids”

A highly diastereoselective synthesis of chiral ring-fused isoindolinone products, the skeleton of which is common to many naturally occurring and biologically active compounds, is achieved in two synthetic steps from readily available precursors *via* an *N*-acyliminium ion cyclization reaction of an isoindolinone substrate (Scheme 17).



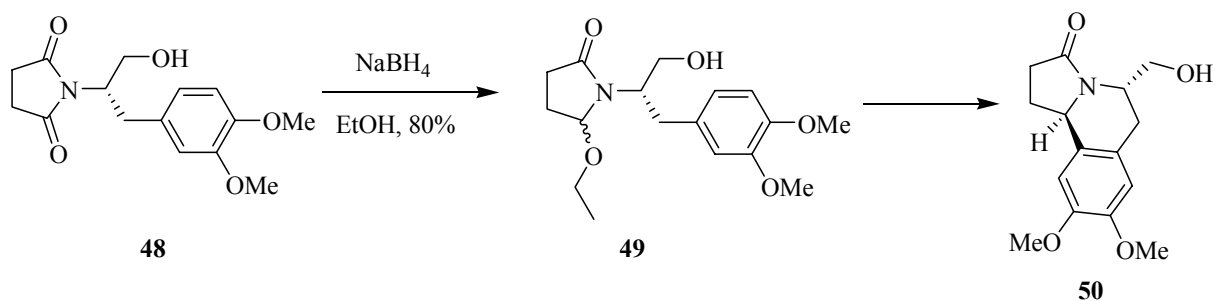
**Scheme 17**

This methodology was further applied to the synthesis of several alkaloids. Model reactions were performed starting from phenylalaninol (Scheme 18).



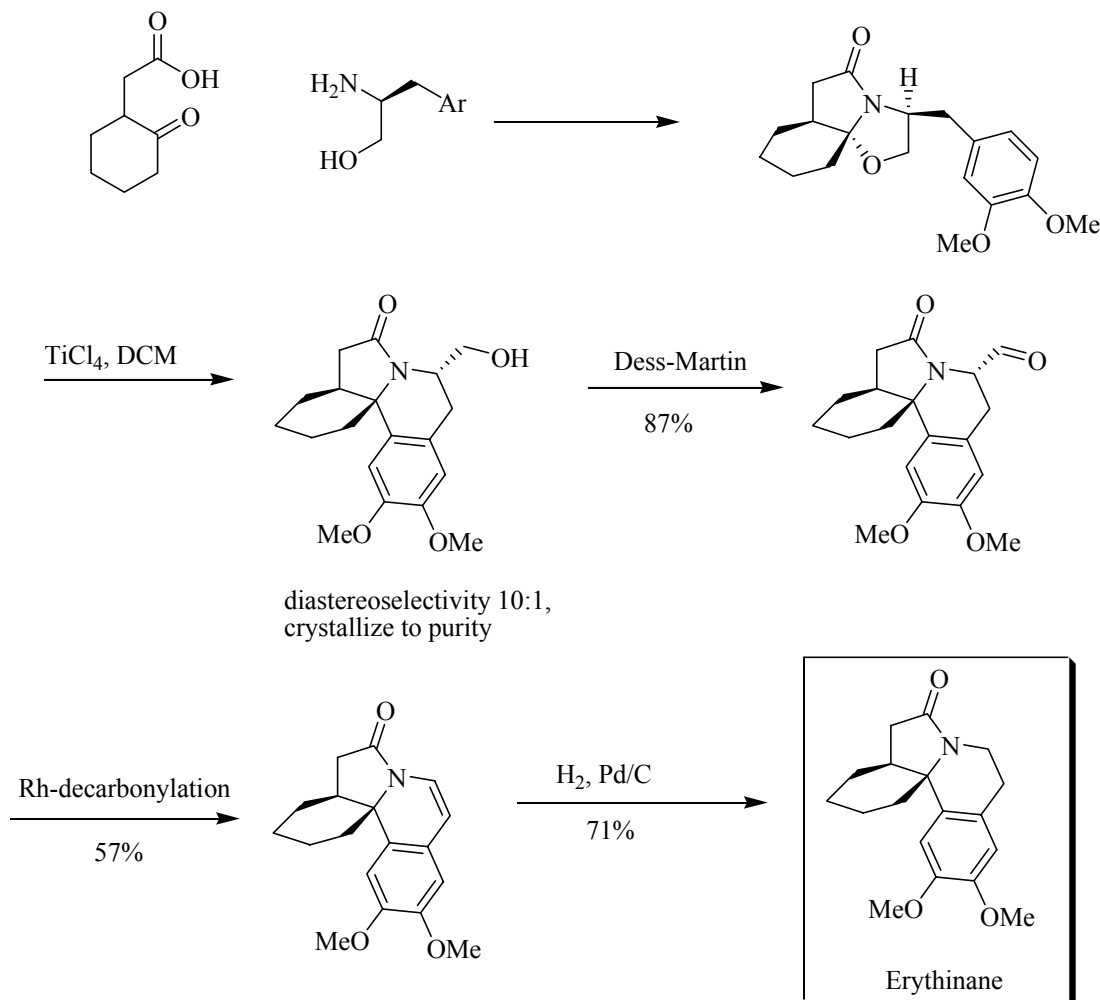
**Scheme 18**

Similar synthetic sequence (Scheme 19) resulted in the synthesis of hydroxymethyl derivative of (+)-crispine A, a pyrrolo[2,1-*a*] isoquinoline alkaloid with anti-tumor activity isolated in 2002.

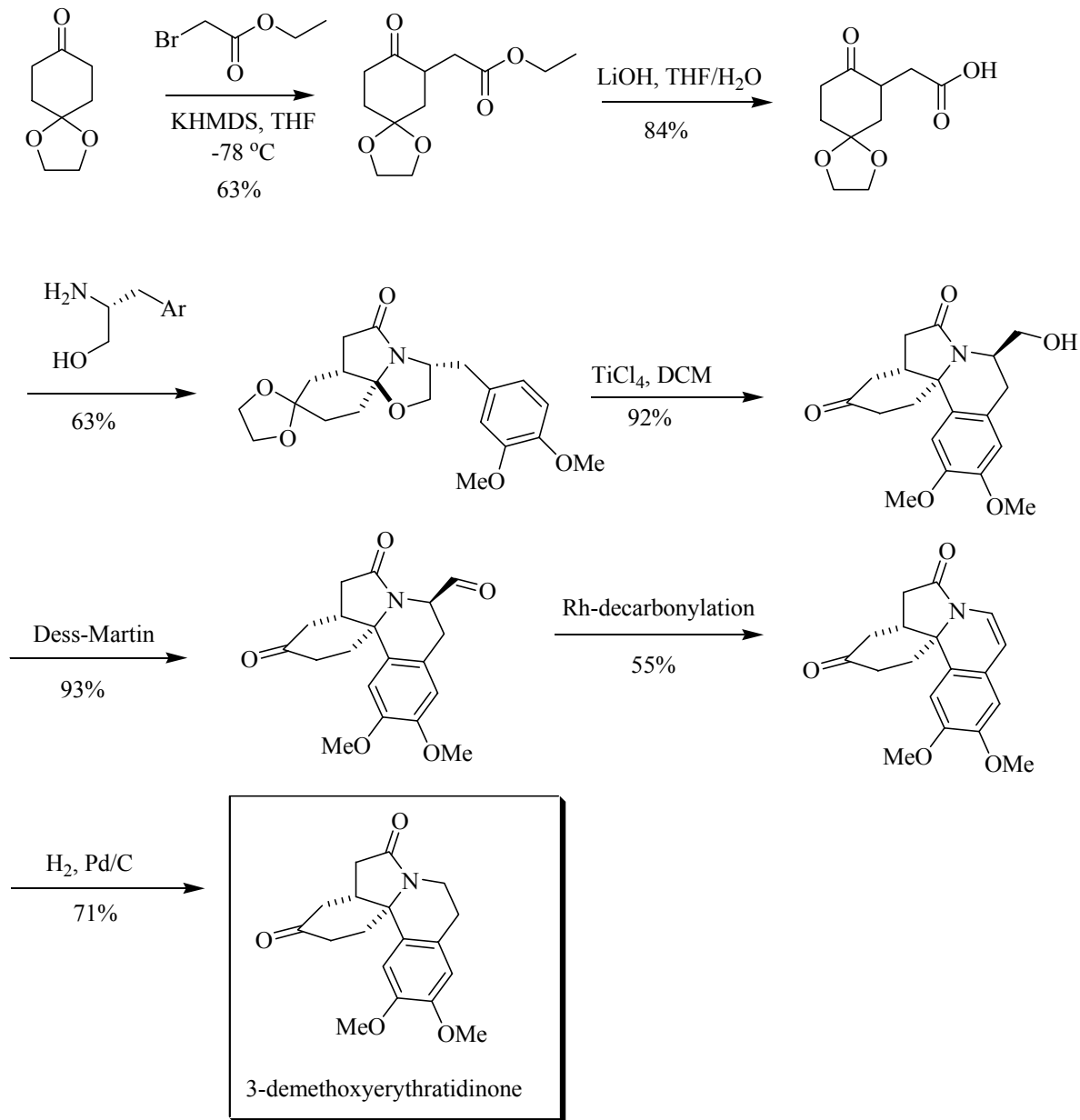


**Scheme 19**

Next target was synthesis of Erythinane. Functionalized substrate approach was used contrary to previously reported methathesis methodology. Removal of hydroxymethyl group included Dess-Martin oxidation, Rh-catalysed decarbonylation and final reduction of the double bond (Scheme 20).

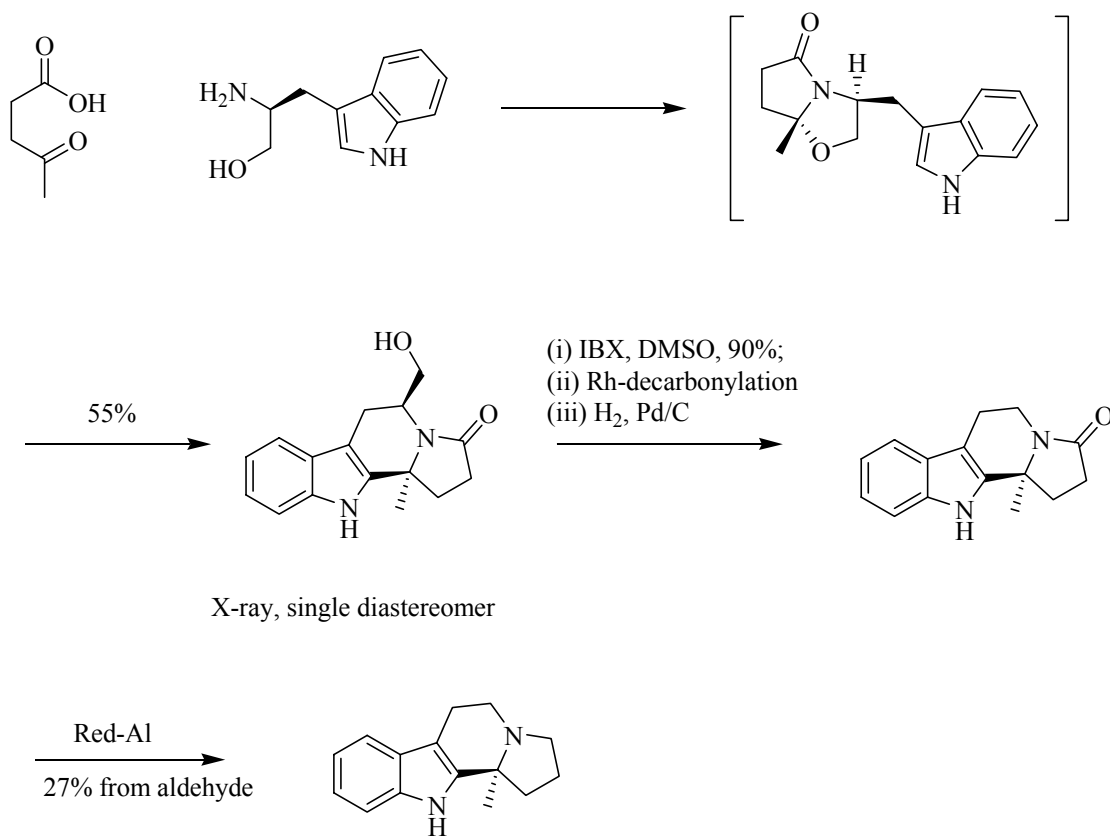
**Scheme 20**

It was further extended to the synthesis of 3-demethoxyerythratidinone (Scheme 21), a member of the *Erythrina* family of alkaloids, which display curare-like and hypnotic activity. It was isolated from *Erythrina lithosperma* in 1973. Despite being structurally one of the simplest of the *Erythrina* class of alkaloid, it was not until 1984 when the first total synthesis, in racemic form, of this natural product was reported.

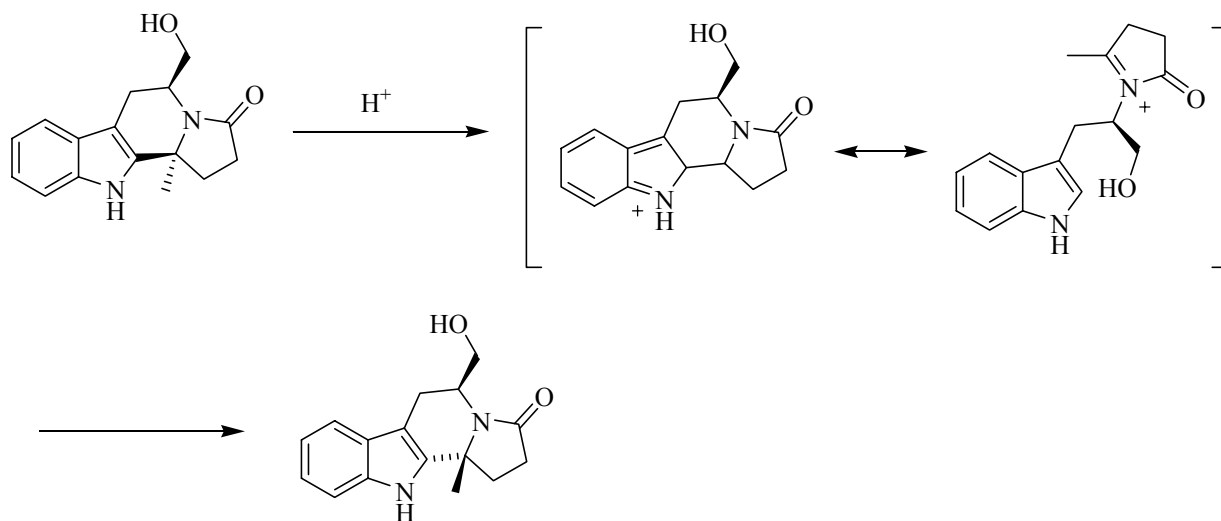


Scheme 21

This synthetic strategy provided a novel, facile and stereoselective approach to the indolizino[8,7-*b*]indole ring system from a readily available, chiral template (Scheme 22). Such ring systems are of interest to the pharmaceutical industry having been used as intermediates in the preparation of diuretic compounds, and are also known to exhibit analgesic and anti-inflammatory activity. Functionalised templates have been shown to act as  $\beta$ -turn mimics and display high binding affinity and selectivity for CCK<sub>1</sub> receptors.

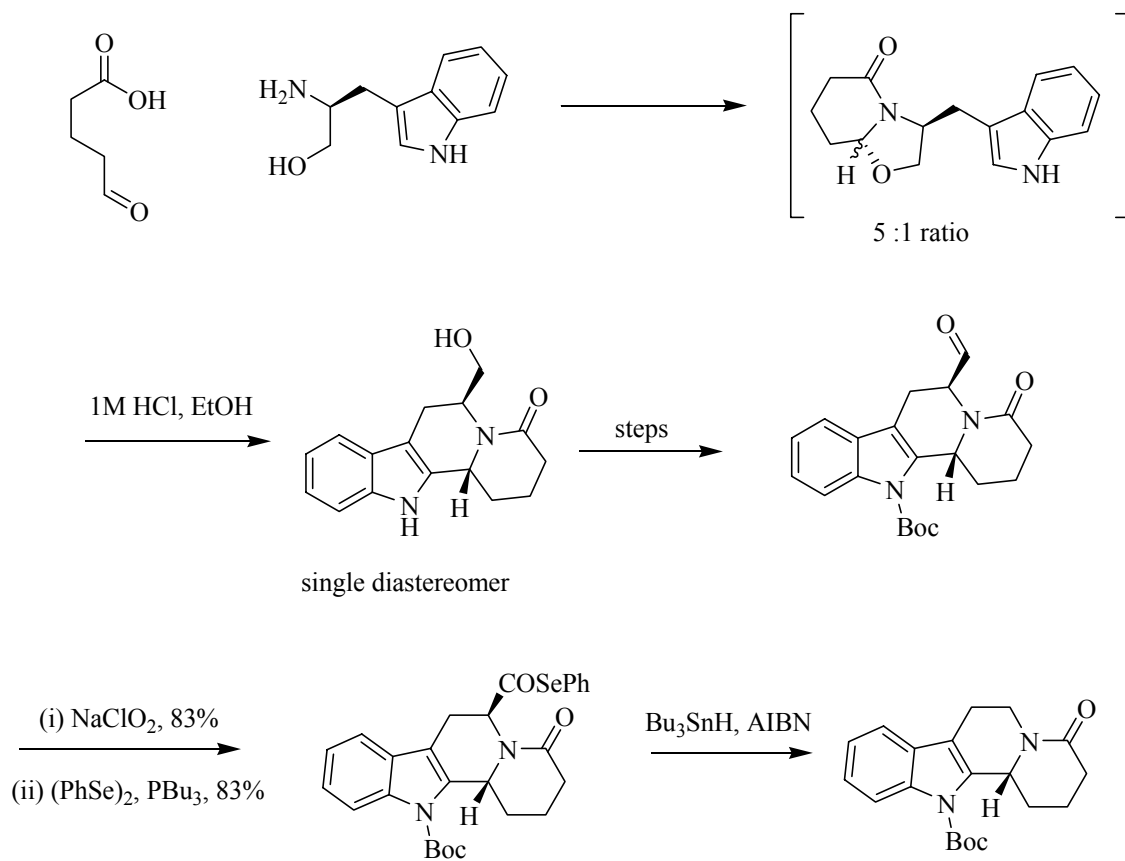
**Scheme 22**

Another enantiomer of hydroxymethyl derivative was obtained by TFA-induced epimerization (Scheme 23).

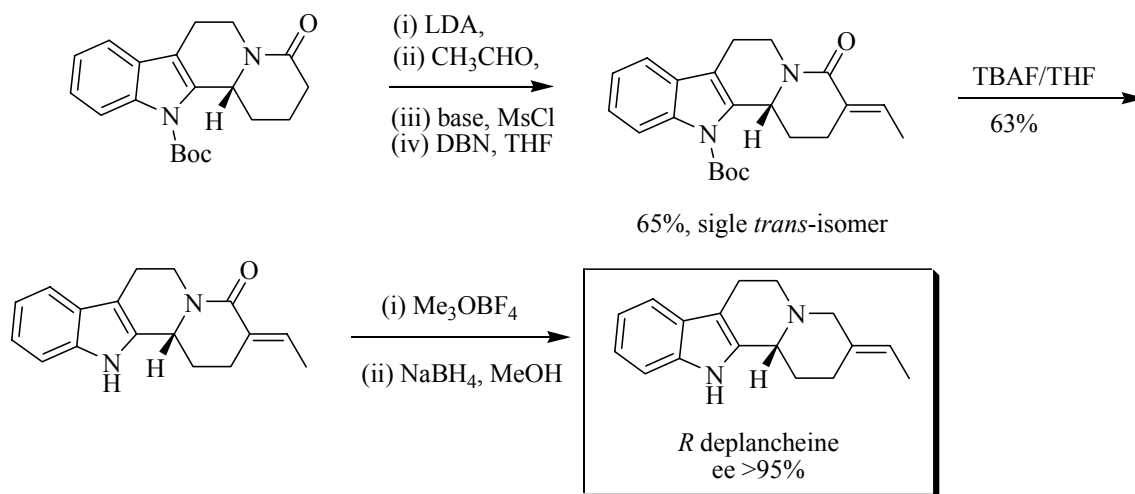


**Scheme 23**

A novel, facile and highly stereoselective approach to the indolo[2,3-*a*]quinolizine ring system was also reported (Scheme 24). The potential for application of this methodology to natural product synthesis was demonstrated through conversion of the template to a simple indole alkaloid with high enantiomeric purity. A new strategy of hydroxymethyl group removal was also proposed.

**Scheme 24**

Reaction sequence was further continued to synthesize R deplancheine.



**Scheme 25**

3. Dr. Wim De Borggraeve, Katholieke Universiteit Leuven, Leuven, The Netherlands “*Synthesis and functionalisation of 3,5-dichloro-2-(1H)-pyrazinones and applications in the development of secondary structure mimics*”
4. Dmytro O. Tymoshenko, Albany Molecular Research, Inc. “*Probing Chemical Space: Enhancing Lead Generation and Optimization via Highthroughput Heterocyclic Synthesis*”
5. Rainer Beckert, Institut für Organische und Makromolekulare Chemie, Friedrich-Schiller-Universität Jena, Jena, Germany “*New Reversible Two-Electron Redox Systems Based on Cross-Conjugated Cycloamidines*”
6. Ken Turnbull, Wright State University, Dayton, OH “*Manipulations with Sydnones*”
7. Saverio Florio, Università degli Studi di Bari, Italy “*Lithiated Oxiranes: Synthetic Utility*”
8. Gloria Inés Yranzo, Universidad Nacional de Córdoba, Córdoba, Argentina “*Flash Vacuum Pyrolysis of some 2,3,4A,5,8,8A-Hexahydro-Quinazolin-4(1H)-Ones. The First Mechanistic Study*”
9. Virinder S. Parmar, University of Dehli, Dehli, India “*Studies on Novel Heterocyclic Compounds*”
10. Kenneth Nicholas, University of Oklahoma “*Indole Synthesis via Nitro- and Nitrosoarene Annulation with Alkynes*”
11. H.G.Raj, V. P. Chest Institute, University of Dehli, Dehli, India “*Oxygen Containing Heterocyclic Compound*”
12. Ralph Nicholas Salvatore, Center for Green Chemistry, Dana-Farber / Harvard Cancer Center, University of Massachusetts “*An Experiment and Highly Efficient Method for the Reduction of Nitrogen Heterocycles*”

13. J. A. Dixon, FMC Corporation “*Synthetic Approaches to Tetrahydroquinoline Ecdysone Agonists*”

14. Viktor V. Zhdankin, University of Minnesota “*Chemistry of Hypervalent Iodine Heterocycles*”

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The following short talks were presented at the conference:

1. G. Verniest and N. De Kimpe, Ghent University, Belgium “*Synthesis of 5-halogenated 2(5H)-furanones via ring transformation of cyclobutenediones*”

2. Shiva K. Agarwal, Dabur Research Foundation, Sahibabad, India “*Betulinic Acid Derivatives: Synthesis And Their Cytotoxicity*”

3. El-Dusouqui, Kuwait University “*Contribution to Hydrazonal and Benzotriazole Chemistry*”

4. Rienzi Luisi, Università degli Studi di Bari, Italy “*On the Lithiation of Arylaziridines*”.