



**Trip Report:  
ACS National Meeting  
Washington, DC  
August 28 – September 5, 2005**

**Ulhas Bhatt, Ph.D.**

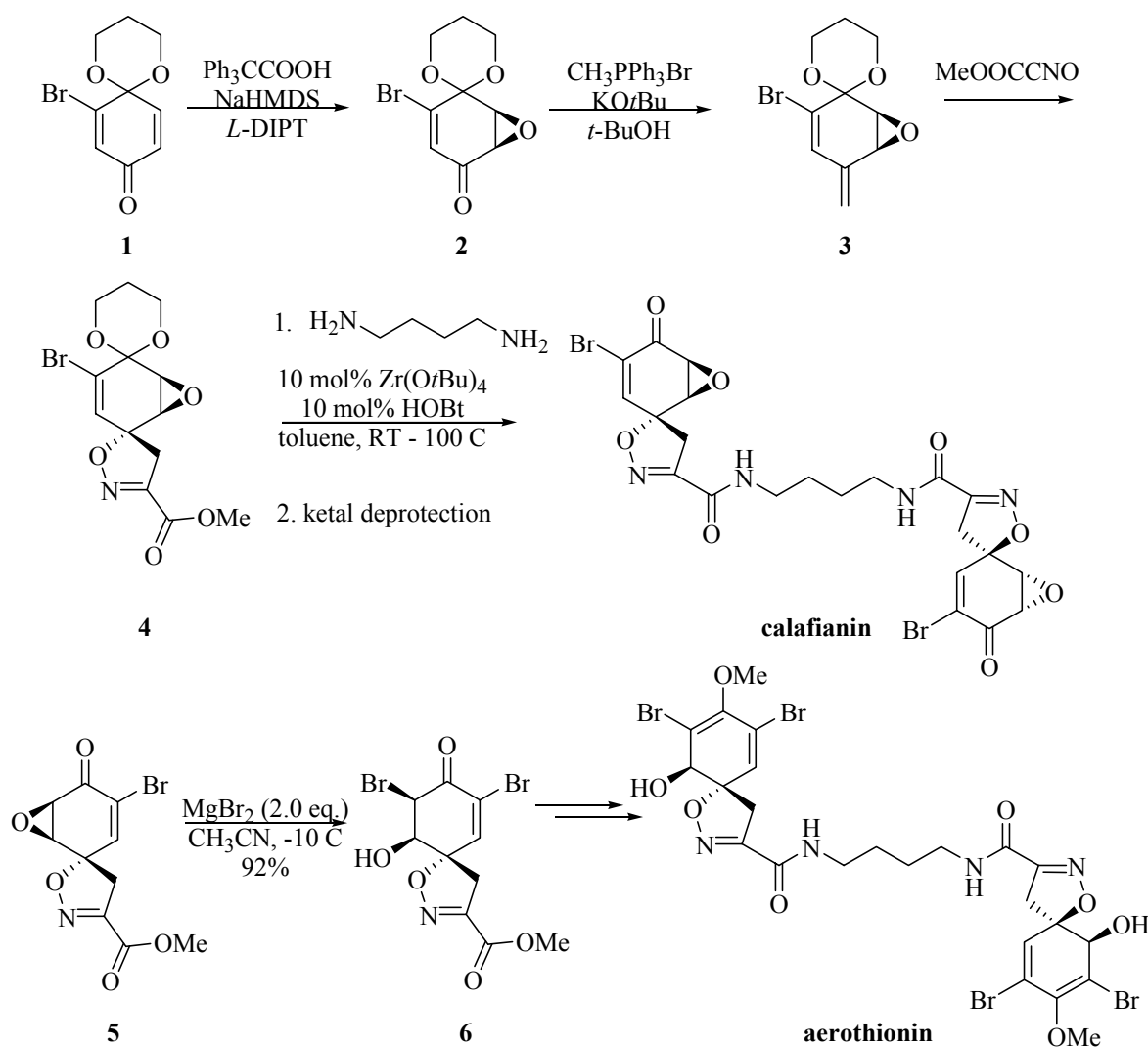
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***Abstract:** The ACS National Meeting was a five day event. The conference covered all aspects of chemistry. I will highlight the key issues of some of the presentations and posters that I attended. Overall, the symposium was a nice opportunity to hear current research being done in both academia and industry in the broad areas of drug discovery and organic chemistry.*

**“Studies toward the asymmetric synthesis of the spiro-isoxazole natural products,”**  
*S. Bardhan, D. C. Schmitt, J. A. Porco Jr. (Boston University).*

S. Bardhan described the progress made in the laboratories of Prof. Porco Jr. towards the asymmetric synthesis of spiro-isoxazole natural products. The presentation focused on two specific natural products in this class of natural products – calafianin and arothionin. Their synthetic strategy as described below in Scheme 1. A *L*-DIPT mediated asymmetric epoxidation of compound **1** produced epoxide **2** that was converted to the corresponding alkene **3** via a Wittig reaction. Alkene **3** was transformed to the isoxazole compound **4** via a 3 + 2 cyclization. Ester **4** was then directly converted to the dimeric amide by reacting it with 1,4-diaminobutane in presence of catalytic amounts of zirconium-*O*-*tert*-butoxide and hydroxybenzotriazole in toluene. This direct conversion of an ester to an amide was based on methodology developed in their laboratories and has been described recently in a publication (*J. Am. Chem. Soc.* **2005**, *127*, 10039). The final deprotection of the ketal then provided the natural product, calafianin.

The presentation also described efforts towards the synthesis of arothionin, another natural product containing the spiro-isoxazole ring system. Epoxide **5** was converted to the *syn* bromoalcohol **6** by using 2 equivalents of magnesium bromide. The amide bond formation methodology described above was again used to produce arothionin.

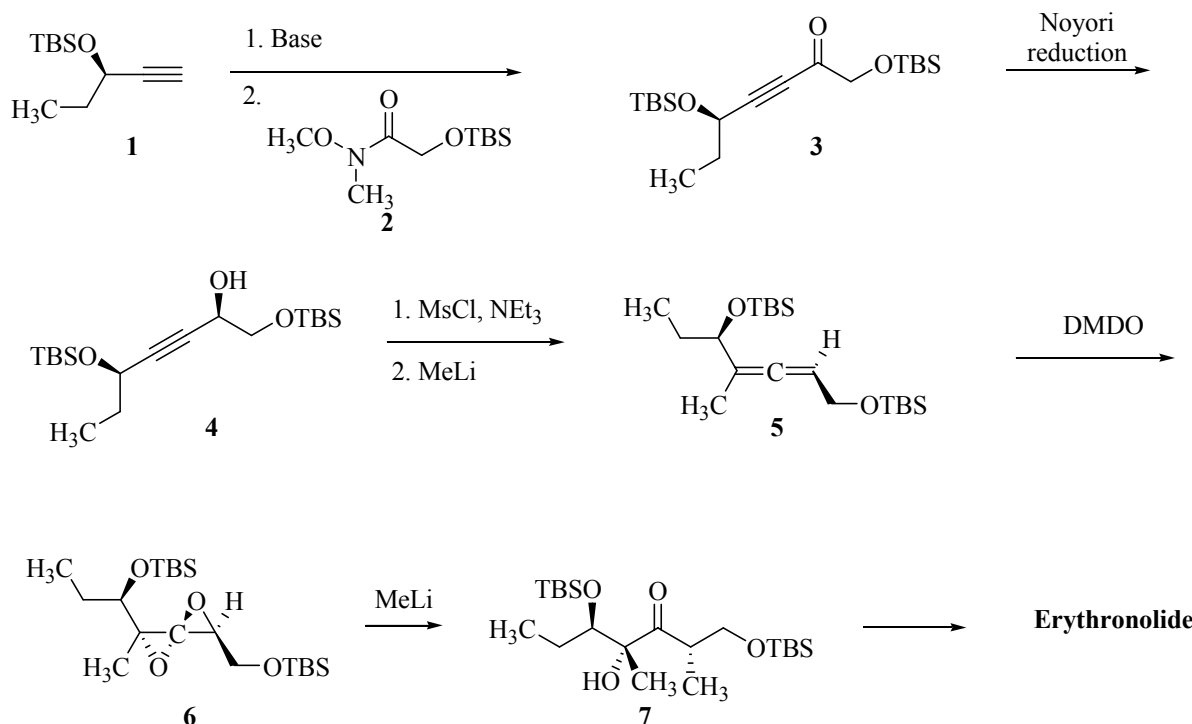
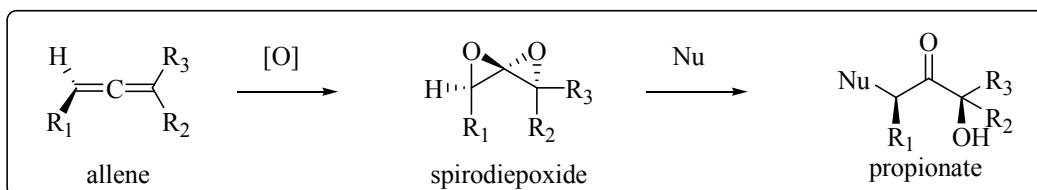




### “Spirodiepoxides: Applications and mechanisms,”

*L. J. Williams (The State University of New Jersey, Rutgers).*

Prof. Williams gave an excellent presentation on his groups efforts directed at the use of spirodiepoxides in the stereoselective synthesis of polypropionate fragments. These spirodiepoxides are generated by stepwise stereoselective bisepoxidation of an allene substrate. These are readily opened by nucleophiles thereby providing easy access to functionalized polypropionate fragments found in many natural products. His talk also described the synthesis of erythronolide based on this work.



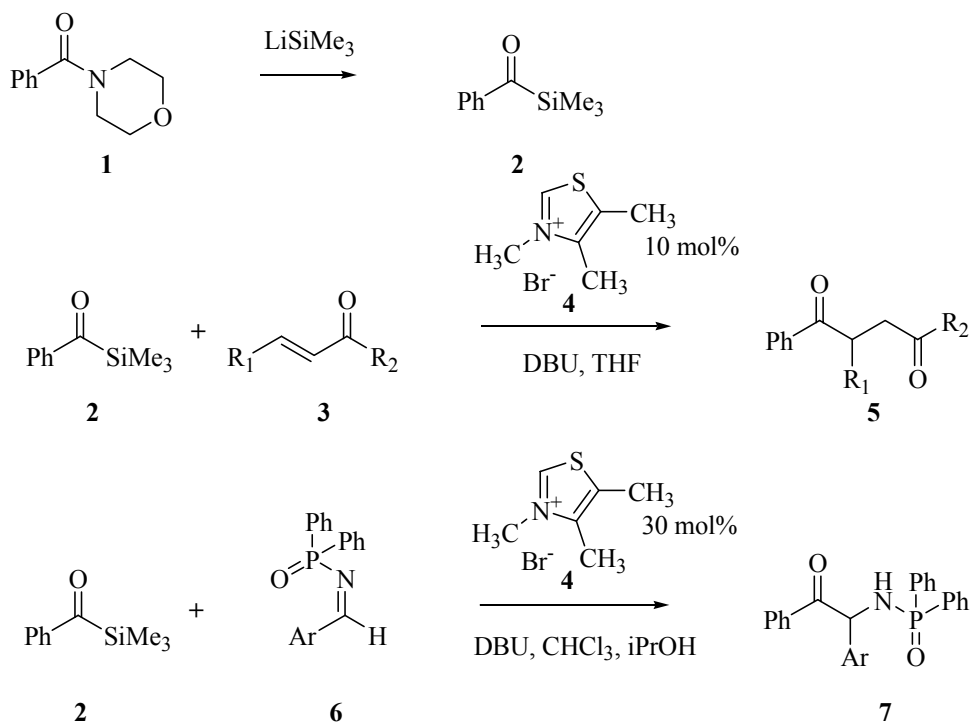
The synthesis began with the reaction of the anion of **1** with Weinreb amide **2** to produce ketone **3**. Asymmetric reduction using Noyori's catalyst system produced alcohol **4** that was converted to its corresponding mesylate whose reaction with methyl lithium gave allene **5**. The reaction of allene **5** with dimethyldioxorane produced the spirobisepoxide **6** stereoselectively, whose reaction with methyl lithium gave the key fragment **7**. This fragment was then utilized to produce erythronolide.

### “Catalytic carbonyl anion additions to activated alkenes,”

*K. A. Scheidt (Northwestern University).*

Prof. Scheidt described the reactions of acyl silanes with conjugated acceptors using thiozolium salts as catalysts.

He showed that commercially available thiozolium salt **4** was identified as the catalyst of choice for the reaction of acyl silanes (produced by reacting lithium trimethylsilane with corresponding morpholino ketones) with alpha-beta unsaturated ketones to produce the corresponding alpha-gamma diketones. These reactions proceeded best when DBU was used as the base and THF as the solvent. He provided several examples to demonstrate the scope of the reaction. He then described the reaction of acyl silanes with protected imines to provide beta-keto amines using the same thiozolium salt as the catalyst. Various electron withdrawing and donating groups were utilized for the scope of these reactions and the products were obtained in 60-90% yields.

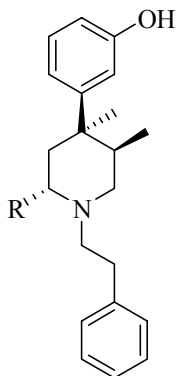


**“Synthesis and SAR of a new series of 2 $\alpha$ -substituted trans-4,5-dimethyl-4-(3-hydroxyphenyl)piperidines as  $\mu$ -Selective Opioid Antagonists,”**

*Allan Goodman et al. (Adolor Corporation).*

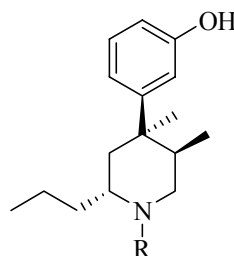
In this poster presentation, scientists from Adolor Corporation described the synthesis of new series of 2 $\alpha$ -substituted trans-4,5-dimethyl-4-(3-hydroxyphenyl)piperidines as  $\mu$ -selective opioid antagonists. Their SAR focused on (a) the 2- $\alpha$  position of the piperidine ring (Table 1), and (b) the attachment on the nitrogen of the piperidine ring (Table 2).

**Table 1**



(A): 2- $\alpha$  position of the piperidine ring

#	R	Ki ( $\mu$ ) (nM)	Ki ( $\kappa$ ) (nM)	Ki ( $\delta$ ) (nM)
1	H	1.9	17	33
2	Me	15	100	65
3	Et	75	710	680
4	<i>n</i> Pr	20	110	120
5	<i>i</i> Pr	270	>1000	>1000
6	<i>n</i> Bu	110	200	580
7	CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	780	510	>1000
8	CH <sub>2</sub> CH <sub>2</sub> NHCOCH <sub>3</sub>	190	620	>1000
9	CH <sub>2</sub> CH <sub>2</sub> NHCOC <sub>6</sub> H <sub>5</sub>	59	200	710
10	CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub>	>1000	>1000	>1000
11	Ph	280	290	260
12	Bn	290	920	800
13	CH <sub>2</sub> CH <sub>2</sub> Ph	160	790	610
14	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Ph	230	260	320

**Table 2**

(B): attachment on the nitrogen of the piperidine ring

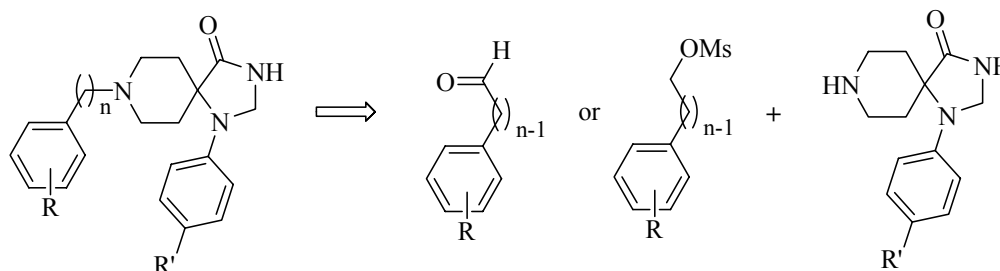
#	R	Ki ( $\mu$ ) (nM)	Ki ( $\kappa$ ) (nM)	Ki ( $\delta$ ) (nM)
15	H	560	690	>1000
16	Bn	700	360	880
17	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Ph	19	74	180
18	Me	520	220	>1000
19	Et	410	270	>1000
20	<i>n</i> Pr	430	360	>1000
21	<i>n</i> Bu	550	610	>1000
22	<i>n</i> Pen	380	570	>1000
23	<i>n</i> Hex	47	150	340
24	<i>n</i> Hep	13	57	80

The study showed that only small linear alkyl groups (e.g. methyl, propyl) were tolerated at the 2 $\alpha$ -position of the piperidine ring of this series. 2 $\alpha$ -substitution also led to decreased selectivity for the  $\mu$  versus  $\delta$  and  $\kappa$  receptors. The highest  $\mu$  *in vitro* antagonist activity was observed in the 1-heptyl-2 $\alpha$ -propyl-piperidine derivative **24**.

**“Design, Synthesis and Biological Evaluation of  $\mu$  Opioid Selective Biaryl-substituted 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one Derivatives,”**

*Alfonzo D. Jordan et al. (Johnson & Johnson).*

In this poster presentation, scientists from Johnson and Johnson described a series of triazaspiro compounds exhibiting selective binding to the  $\mu$ -opioid receptor subtype. Screening of the JNJ corporate library revealed two compounds (**2** and **3**) that showed selectivity towards the  $\mu$ -opioid receptor. Both these compounds contained the 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one subunit. This prompted the start of a program to prepare a series of similar compounds and evaluate them for potential therapeutic utility in pain relief.



OPIOID RECEPTOR FOR SUBTYPE BINDING, $K_i$ 's (nM)							
Cmpd #	n	R	R'	$\mu$	$\delta$	$\kappa$	NOP
2	1	H	H	3.66	3979	239.6	72.3
3	2	H	H	0.34	112.4	74.0	151.7
5	1	2-(3-thienyl)	H	0.22	120.2	0.90	3.4
7	1	3-(3-thienyl)	H	5.4	302.5	85.81	944
8	1	4-(3-thienyl)	H	32.5	510.5	391.2	>5000
10	1	2-(2-thienyl)	H	0.21	19.53	0.81	4.9
11	2	2-(2-thienyl)	H	0.53	173.8	5.57	8.9
12	3	2-(2-thienyl)	H	5.43	302.5	32.52	5.7
19	4	2-(2-thienyl)	H	2.46	296.3	133.6	79.5
22	1	2-(2-thienyl)	F	0.30	49.87	1.11	11.5
23	1	2-(2-furanyl)	H	0.25	150.5	2.76	3.6
24	1	2-(2-thiazoyl)	H	3.02	1314	20.96	108

The 8-(heteroaryl)phenalkyl 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one derivatives were evaluated for their binding affinity at all four opioid receptors. For comparison purposes, opioid

binding affinity data for the HTS lead compounds **2** and **3** are also included. In general, the new compounds showed greater potency at the MOP receptor versus the DOP, KOP and NOP receptors. Four of the compounds displayed subnanomolar affinities against MOP while the rest showed activity in the 2-34 nM  $K_i$  range. The position of substitution of the thienyl group on the phenyl ring resulted in an effect on MOP with 2-(3-thienyl) (compound **5**) being the most potent (0.22 nM MOP  $K_i$ ). In comparison, the 3-(3-thienyl) (compound **7**) and 4-(3-thienyl) (compound **8**) derivatives displayed lower binding affinities of 5.4 nM and 32.5 nM  $K_i$ 's respectively. The enhanced affinity of compound **5** was attributed to the 2-(3-thienyl)benzyl group's ability to access a more bioactive conformation of the MOP receptor that compounds **7** and **8**. Cometta-Morini et al. have suggested based on computational studies, that there are four structural elements necessary for the  $\mu$ -receptor recognition to spiropiperidine ligands related to **5**.<sup>1</sup> The proposed pharmacophore model include a protonated nitrogen center, a proton acceptor center (carbonyl group), a  $\pi$ - $\pi$  stacking center (ring B), and a lipophilic ring A appended off the piperidine ring.

The synthesis of these compounds was performed by reacting commercially available spiropiperidine compound 1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, with either suitably substituted aryl aldehydes under reductive amination conditions, or with suitable substituted aryl mesylates under alkylating conditions.

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<sup>1</sup> Cometta-Morini, C.; Maguire, P. A.; Loew, G. H. *Mol. Pharmacol.* **1992**, *41*, 185-196.  
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