

RESEARCH SEMINAR

**NEW SYNTHETIC APPLICATIONS OF
TRICHLOROMETHYLCARBINOLS
& SYNTHESIS OF SMALL MOLECULE
NATURAL PRODUCTS**

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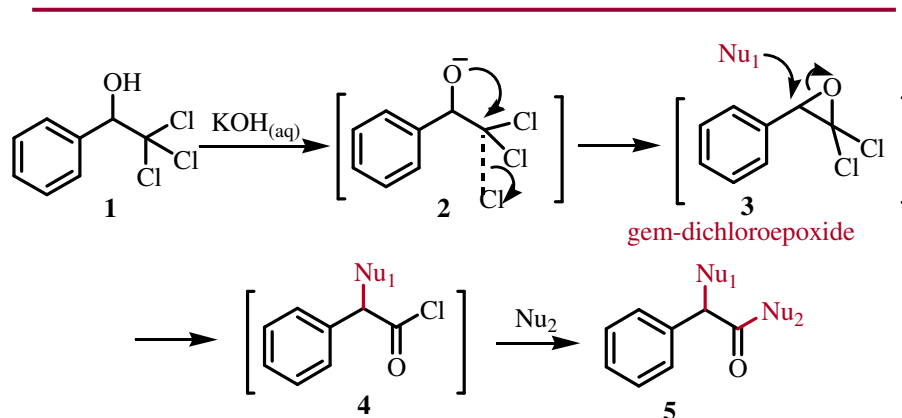
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NEW SYNTHETIC APPLICATIONS OF TRICHLOROMETHYLCARBINOLS

INTRODUCTION.

The Jocic reaction, the reaction of (trichloromethyl)carbinols (**1**) with aqueous hydroxide to provide 2-substituted carboxylic acids, was first reported in 1897.¹

Scheme 1. Mechanism of Jocic Reaction



The reaction has been studied with different nucleophiles by Reeve,² Corey,³ Link,³ Oliver⁴ and others.⁵ The mechanism involves deprotonation of the (trichloromethyl)carbinol (**1**) followed by intramolecular displacement of chloride affording a reactive 1,1-dichloroepoxide (**3**). Nucleophilic opening (with inversion of configuration) of dichloroepoxide gives the acyl chloride **4**. The resulting acid chloride, in turn, undergoes acylation with either a second or a tethered nucleophile, affording carboxylic acid derivatives (**5**) (Scheme 1). Protic solvents are required in the reaction. If the reaction is conducted in aprotic media, little or no conversion is observed. That dependence on a protic solvent implicates an S_N1-type mechanism in the formation of *gem*-dichloroepoxide (**3**), where substantial bond breakage between a chlorine atom and a carbon atom facilitates the intramolecular attack of the nucleophile.

¹ Jocic, Z. *Z. Zh. Russ. Fiz. Khim. Ova.* **1897**, 29, 97.

² (a) Reeve, W. *Synthesis* **1971**, 131-138. (b) Reeve, W.; Bianchi, R. J.; McKee, J. R. *J. Org. Chem.* **1975**, 40, 339-342. (c) Reeve, W.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem.* **1980**, 58, 485-493. (d) Reeve, W.; Steckel, T. F. *Can. J. Chem.* **1980**, 58, 2784-2788.

³ (a) Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, 109, 5551. (b) Corey E.J., Link, J.O. *J. Am. Chem. Soc.* **1992**, 114, 1906.

⁴ (a) Oliver, J. E.; Waters, R. M.; Lusby, W. R. (b) Khimian, A. P.; Oliver, J. E.; Waters, R. M.; Panicker, S.; Nicholson, J. M.; Klun, J. A. *Tetrahedron: Asymmetry* **1996**, 7, 37-40. (c) Oliver, J. E.; Schmidt, W. F. *Tetrahedron: Asymmetry* **1998**, 9, 1723-1728.

⁵ Mellin-Morlière, C.; Aitken, D. J.; Bull, S. D.; Davies, S. G.; Husson, H. -P. *Tetrahedron: Asymmetry* **2001**, 12, 149-155

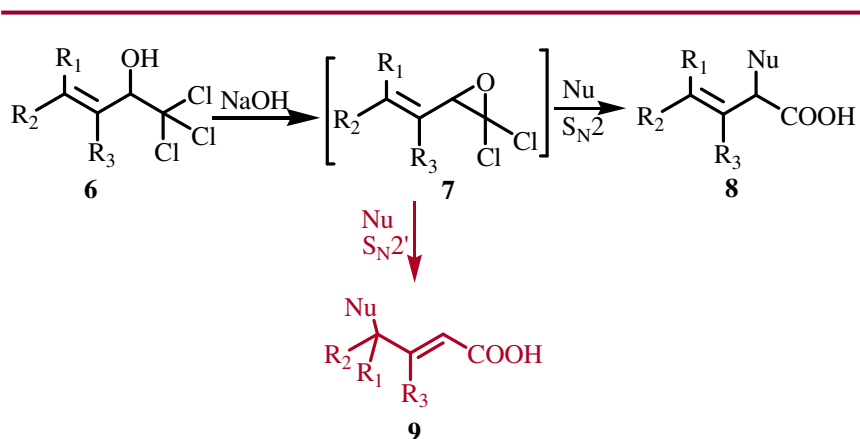
Three projects are discussed in this paper. The first two are studies of new types of Jovic reactions. Project I addresses the use of vinyl (trichloromethyl) carbinols in Jovic type reactions with various nucleophiles, and project II deals with the use of 4-trichloromethyl-2-oxetanones in the same type of reaction for the preparation of α,γ -disubstituted butyrolactones. Project III describes preparation of COX-2 inhibitor inotilone.

I. PREPARATION OF HETEROSUBSTITUTED ENOIC ACIDS

OBJECTIVES.

Reactions of alkenyl trichloromethyl carbinols (**6**) with nucleophiles have not been reported. It was decided that the reactivity of alkenyl trichloromethylcarbinols (**6**) in intermolecular reaction with an assortment of nucleophiles under basic conditions would be investigated. The main question to be answered was: what is the regioselectivity of nucleophilic additions with alkenyl *gem*-dichloroepoxides (**7**) in the Jovic-type reaction? Different nucleophiles could display a preference for either direct epoxide (**7**) substitution (S_N2 -type of the reaction), ultimately leading to β,γ -unsaturated α -substituted carboxylic acids (**8**), or proceed via an S_N2' pathway resulting in γ -substituted α,β -unsaturated enoic acids (**9**) (Scheme 2). In either case, the outcome would offer a convenient approach to disparate heterosubstituted unsaturated carboxylic acids (**8**, **9**), which are not readily accessible by conventional methods.

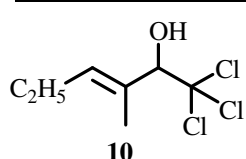
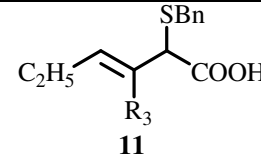
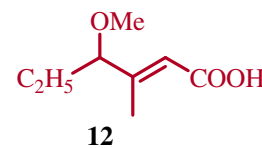
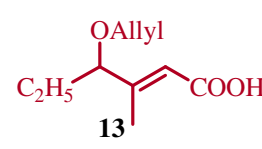
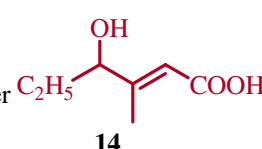
Scheme 2. Regioselectivity of Nucleophilic Addition to Alkenyl Substrates.



RESULTS AND DISCUSSION.

Vinyl trichloromethylcarbinols (**6**) were prepared by the procedure of Corey and Link⁶ using commercially available enals. The resulting trichloromethylcarbinols (**6**) featured a range of olefin substitutions and configurations. Unsaturated trichloromethylcarbinols (**6**) were allowed to react with a variety of nucleophiles in separate reactions. All substrates that were examined underwent facile nucleophilic substitution by both sulfur and oxygen nucleophiles (yields from 55 to >97%).

Table 1. Reactions of Trisubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles

Substrate	Conditions	Product	Yield
 10	BnSH MeOH	 11	85%
	MeOH	 12	76%
	AllylOH	 13	63%
	DME/water	 14	75%

Representative reaction results of trisubstituted, 1,2-disubstituted, and 1,1-disubstituted alkenyl trichloromethylcarbinols with various nucleophiles are presented in Table 1, 2, and 3, respectively.

It is noteworthy that when the reaction with the corresponding dichloroepoxide proceeded via S_N2' mechanism, *E*-substituted enoic acids (**9**) were formed with excellent diastereoselectivity. To verify this fact, the trichloromethyl carbinol formed from neral was used in the present work as a mixture of *E/Z* isomers. The reactions occurring via an S_N2'

⁶ (a) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, 33, 3435. .

pathway afforded (*E*)-olefin (**9**) exclusively. In no case did NMR analysis show *Z*-olefin formation in crude reaction mixtures.

Table 2. Reactions of 1,2-Disubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles.

Substrate	Conditions	X	16/17	Yield of major regioisomer
	MeOH	OMe	1.4:1	55%
	DME/MeOH	OMe	5:1	81%
	DME/H ₂ O	OH	1:2	64%
	AllylOH	OAllyl	>20:1	93%
	MeOH/BnSH	BnS	>20:1	64%

Table 3. Reactions of 1,1-Disubstituted Alkenyl Trichloromethyl Carbinols with Nucleophiles.

Substrate	Conditions	Product	Yield
	BnSH MeOH		78%
	MeOH		76%
	AllylOH		79%

CONCLUSION.

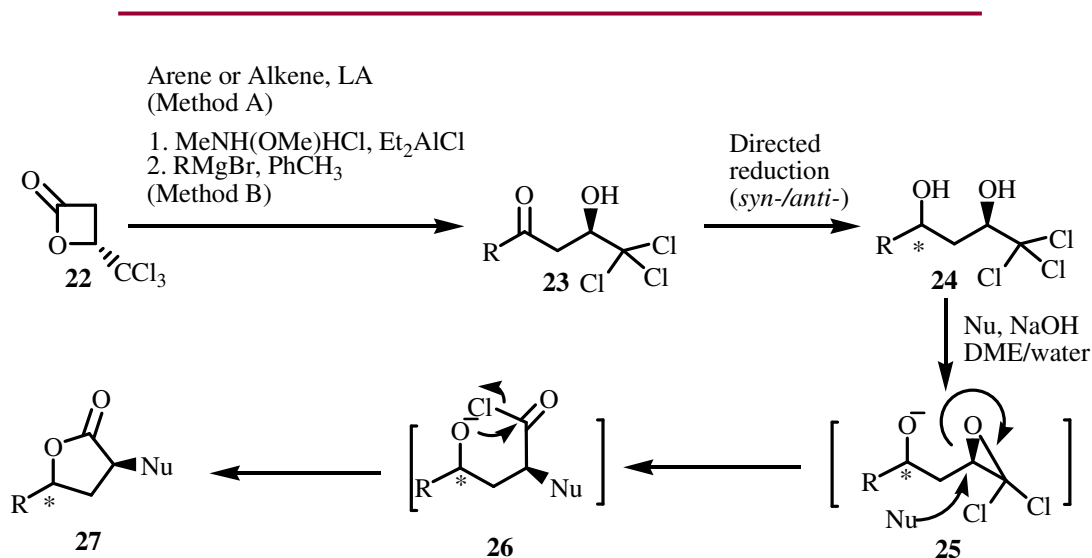
The new approach to γ -hydroxy- or alkoxy-(*E*)- α,β -enoic acids and α -thiophenyl- β,γ -unsaturated acids through trichloromethylcarbinols is both inexpensive and operationally simple. The reactions occurring via an S_N2' pathway afford (*E*)-olefins with excellent diastereoselectivity.

II. CONCISE APPROACH TO ASYMMETRIC α,γ -DISUBSTITUTED BUTYROLACTONES.

OBJECTIVES.

It was desired to develop a versatile approach to α,γ -disubstituted butyrolactones that serve as important intermediates in target-directed synthesis and asymmetric ligand generation. The route to asymmetric butyrolactones relies upon nucleophilic substitution of **25** followed by intramolecular cyclization of **26** (Scheme 3). The precursors to **25** are asymmetric diols (**24**) bearing two defined stereogenic centers. These are generated by directed reduction of the corresponding hydroxyketones (**23**) using Prasad's⁸ or Evans'⁹ conditions. Hydroxyketones (**23**), in turn, are formed from commercially available 4-trichloromethyl-2-oxetanone (**22**) or through the addition of the Weinreb amide to the excess of organometallic reagents.

Scheme 3. Approach to α,γ -Disubstituted butyrolactones.



RESULTS AND DISCUSSION.

To investigate the scope of the method the synthesis of functionalized 1,3-hydroxyketones (**23**) was required. 1,3-Hydroxyketones, possessing alkyl, aryl, allyl, vinyl, thienyl and ester substituents were synthesized from either 4-trichloromethyl-2-oxetanone (**22**) or the corresponded Weinreb amides. Subsequent directed reduction of prepared hydroxyketones (**23**) using Prasad's⁷ or Evans⁸ conditions afforded trichloromethyl-1,3-diols (**24**) bearing two defined stereogenic centers in excellent yields. Selectivity was ultimately achieved using either tetramethylammonium triacetoxymborohydride to give the *anti*-diol (99:1 selectivity) or borane-mediated reduction of the ketone to give *syn*-products (>9:1 selectivity).

Table 4. Directed Reductions of 1,3-Hydroxyketones.

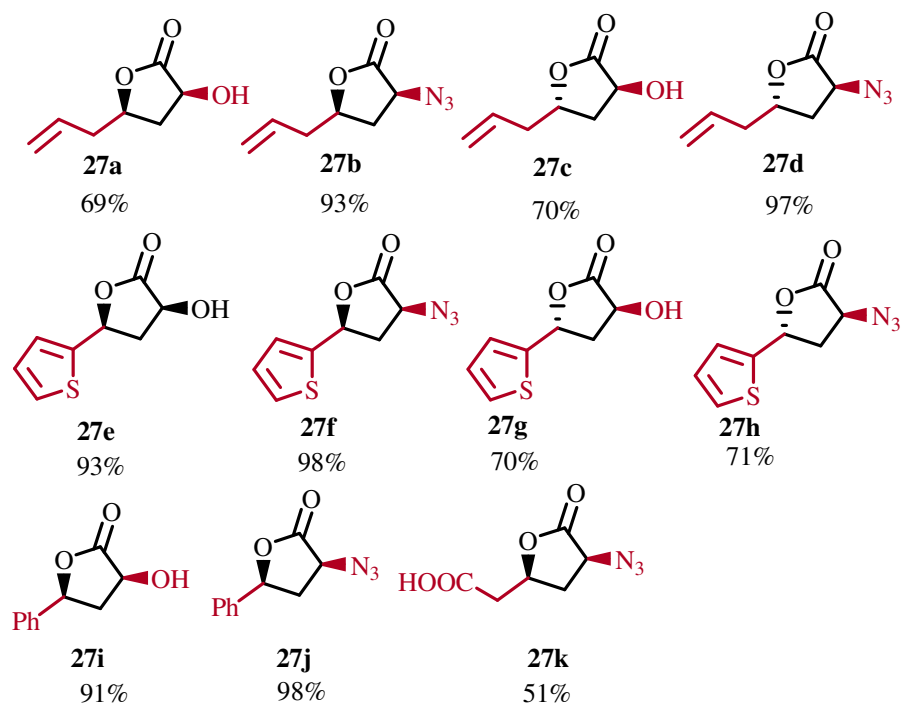
R=	<i>Anti</i> -reduction: <i>anti:syn ratio</i> Me ₄ N(OAc) ₃ BH/MeCN/AcOH/-40 ^o C	<i>syn</i> -reduction: <i>syn:anti ratio</i> NaBH ₄ /Et ₂ BOMe/THF/78 ^o C
Vinyl-	>99:1	>99:1
Allyl-	>99:1	92:8
Phenyl-	94:6	>99:1
Thienyl-	> 99:1	>99:1
tBuOC(O)-	90:10	>99:1

Treatment of asymmetric diols (**24**) with azide or hydroxide in a DME-water system generates asymmetric 2,4-disubstituted butyrolactones (**27**). While formation of butyrolactones from *syn*-diols takes place in uniformly high yields without epimerization, formation of butyrolactones (**27**) from *anti*-diols occurs with partial epimerization during either the reaction itself or the workup. Reaction conditions for the synthesis of butyrolactones (**27**) are being optimized.

⁷ Chen, K. -M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, 28(2), 155-158.

⁸ Evans, D. A.; Chapman, K. T.; Carreira, E. M., *J. Am. Chem. Soc.* **1988**, 110, 3560-3578.

Figure 2. Prepared Asymmetric Disubstituted Butyrolactones



Harzialactone A (**30**) is an antitumor marine metabolite isolated from a strain of *Trichoderma harianium* by Numata and coworkers.⁹ Mereyala et al.¹⁰ established this compound's absolute configuration and synthesized it from D-glucose (seven steps, 15% overall yield) and D-xylose (8 steps, 24 % yield).¹¹ It was also synthesized by Jian¹² in only 5 steps but in poor yield. We conducted a total synthesis of (-)-harzialactone A (Scheme 4), an antipode of the natural (+)-isomer, in only 4 steps, 55% overall yield, in just three days. This exemplifies the efficiency of our new protocol for the preparation of asymmetric 2,4-disubstituted butyrolactones (**27**). A natural Harzialactone A is also accessible by the same route using (S)-trichloromethyl-2-oxetanone as the starting material.

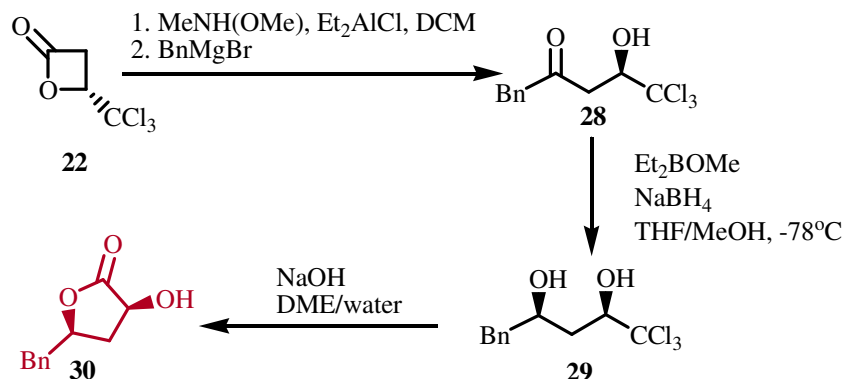
⁹ Amagata, T.; Usami, Y. Minoura, K. Ito T. Numata, A. *J. Antibiot.* **1998**, *51*, 33–40.

¹⁰ Mereyala, H.B.; Gadikota, R.R. *Tetrahedron: Asymmetry* **1999**, *10*, 2305–2306.

¹¹ Mereyala, H.B.; Joe, M.; Gadikota, R.R. *Tetrahedron: Asymmetry* **2000**, *11*, 4071–4081.

¹² Jian, Y.-J.; Wu, Y.; Li, L.; Lu, J. *Tetrahedron: Asymmetry* **2005**, *15*, 2649–2651.

Scheme 4. Preparation of Harzialactone.



CONCLUSION.

The method provides predictable access to any of the four stereoisomers by proper selection of the starting oxetanone and the conditions for *syn*- or *anti*-reductions. The work on this project is nearing completion.

III. TOTAL SYNTHESIS OF POTENT COX-2 INHIBITOR INOTILONE.

OBJECTIVES.

The class of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) showed efficacy in controlling inflammation, pain relief, and in inhibiting carcinogen-induced types of cancer.¹³ However, its mechanism of action remained unclear until Ferreira, Moncada and Vane demonstrated in 1971 that NSAIDs inhibit the biosynthesis of prostaglandins.¹⁴ The discovery that NSAIDs act by inhibiting the cyclooxygenase (COX) enzyme, involved in the generation of prostaglandins from arachidonic acid, provided an explanation of their therapeutic actions and established certain prostaglandins as important mediators of inflammatory diseases, maintenance, survival, and growth of cancer cells.^{15,16} Cyclooxygenase enzymes are known to be of three general classes: COX-1, COX-2 and COX-3, according to the structure of the cyclooxygenase. COX-1 is constitutively expressed in most tissues, whereas COX-2 is induced in connection with pathological

¹³Ahnen, D. J. *The European Journal of Surgery* **1998**, 582, 111- 114.

¹⁴Moncada, S.; Vane J. R. *Pharmacol Rev.***1979**,30, 271-331.

¹⁵Koki, A. T.; Leahy, K. M.; Masferrer, J. L. *Expert. Opin. Investig. Drugs*, **1999**, 8, 1623–1638.

¹⁶Seibert, K.; Zhang, Y.; Leahy, K.; Hauser, S.; Masferrer, J.; Isakson, P. *Adv. Exp. Med. Biol.*, **1997**, 400A, 167–170.

inflammatory sites, including human cancers.¹⁷ Recent studies have shown that the levels of COX-2, prostaglandins like PGF_{2a}, PGE₂ and their metabolites are elevated in certain cancers. The therapeutic effect to control growth of cancer tissues is based on the common ability of NSAIDs to inhibit the activity of COX enzymes. However, many of these drugs target COX-1 rather than COX-2 by binding reversibly or non-reversibly to the enzyme. Work over the past 5 years has shown that gastrointestinal ulceration, bleeding, renal damage, and platelet dysfunction are associated with the inhibition of COX-1. In particular, the more selective the drugs for COX-1, the greater the gastrointestinal side effects. In the late 90's, a new class of selective inhibitors of COX-2 or coxibs was developed as an alternative to traditional NSAIDs. Familiar example of coxibs include: Celecoxib (Celebrex®), Rofecoxib (Vioxx®), Valdecoxib (Bextra®) (Figure 3). The intended function of coxibs was to inhibit COX-2 with a little or no effect on COX-1. Coxibs are highly efficacious in pain and inflammation relief, but epidemiological studies prove that coxibs also serve as powerful chemopreventatives against a host of epithelial cancers including colorectal,¹⁸ breast,¹⁹ esophageal, lung, oral cavity, prostate and ovarian cancers.²⁰

However, recently it has become apparent that some coxibs, despite their promising and, in some cases singular, potential to inhibit cancer initiation or to reverse carcinogenesis, also increase the risk of serious cardiovascular events, including myocardial infarction, arrhythmias, congestive heart failure, and stroke.²⁰ Numerous clinical trials were conducted

¹⁷ Fu, J. Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, *265*, 16737–16740.

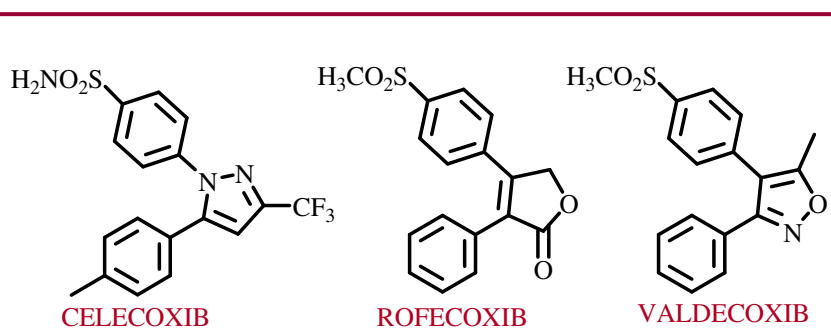
¹⁸ (a) Wiedmann, M. W.; Caca, K. *Curr. Cancer Drug Tar.* **2004**, *5*, 171-193. (b) Chun, K.-S.; Surh, Y.-J. *Biochem. Pharmacol.* **2004**, *68*, 1089-1100. (c) Samoha, S.; Arber, N. *Oncology* **2005**, *69*, 33-37. (d) Benamouzig, R.; Uzzan, B.; Little, J.; Chaussade, S. *Curr. Top. Med. Chem.* **2005**, *5*, 493-503. (e) Rodriguez-Moranta, F.; Castells, *Curr. Top. Med. Chem.* **2005**, *5*, 505-516. (f) Arber, N.; Levin, B. *Curr. Top. Med. Chem.* **2005**, *5*, 517-525. (g) Arber, N.; Eagle, C. J.; Spicak, J.; Rasz, I.; Petr, D.; Jan, H.; Zavoral, M.; Lechuga, M. J.; Gerletti, P.; Tang, J.; Rosenstein, R. B.; Macdonald, K.; Bhadra, P.; Fowler, R.; Wittes, J.; Zauber, A. G.; Solomon, S. D.; Levin, B. *N. Engl. J. Med.* **2006**, *355*, 2371-2373. (h) Arber, N.; Eagle, C. J.; Spicak, J.; Rasz, I.; Dite, P.; Hajer, J.; Zavoral, M.; Fowler, R.; Wittes, J.; Zauber, A. G.; Solomon, S. D.; Levin, B. *New Engl. J. Med.* **2006**, *355*, 885-895. (i) Bresalier, R. S. *Curr. Opin. Gastroen.* **2007**, *23*, 44-47.

¹⁹ (a) Davies, G. L. S. *J. Steroid Biochem.* **2003**, *86*, 495-499. (b) Bundred, N. J.; Barnes, N. L. P. *Brit. J. Cancer* **2005**, *93*, 510-515. (c) Uray, I. P.; Brown, P. H. *Expert Opin. Inv. Drug.* **2006**, *15*, 1583-1600.

²⁰ (a) Fitzgerald, G. A. *N. Engl. J. Med.* **2004**, *351*, 1709-1711. (b) Fitzgerald, G. A. *N. Engl. J. Med.* **2004**, *351*, 1709-1711. (c) Bresalier, R. S.; Sandler, R. S.; Quan, H.; Bolognese, J. A.; Oxenius, B.; Horgan, K.; *et. al. N. Engl. J. Med.* **2005**, *352*, 1092-1102. (d) Solomon, S. D.; McMurray, J. J.; Pfeffer, M. A.; Wittes, J.; Fowler, R.; Finn, P.; *et. al. N. Engl. J. Med.* **2005**, *352*, 1071-1080. (e) Nussmeier, N. A.; Whelton, A. A.; Brown, M. T.; Langford, R. M.; Hoelt, A.; Parlow, J. L.; *et. al. N. Engl. J. Med.* **2005**, *352*, 1081-1091.

for evaluation effects of the NSAIDs and coxibs on blood pressure and cardiovascular events.²¹ In 2004, Merck withdrew rofecoxib from the market after its Adenomatous Polyp Prevention on Vioxx (APPROVe) trial showed a 2-fold increase in cardiovascular risk with 25 mg/day of rofecoxib compared with placebo.²² This also has led to a withdrawal of Valdecoxib (Bextra®) from the market and raised a number of important issues including whether this risk is a class effect or limited to rofecoxib.²³

Figure 3. Representative Coxibs.



Recent studies indicate that cardiovascular risk originally ascribed to coxibs is not a class effect, and that the risk is actually associated with COX-2 independent inhibition pathways. This explains significant cardiovascular risk for patients taken Rofecoxib (Vioxx®) and Valdecoxib (Bextra®), while patients who taking Celecoxib exhibit a statistically insignificant increase in cardiovascular risk. Given the issues surrounding the clinical data for Celebrex® and Vioxx®, the development of second generation COX-2 inhibitors takes on extra importance.

Inotilone (Figure 4) was extracted from the fruiting body *Inonotus* sp. and exhibits significant inhibitory activities against key enzymes involved in inflammatory processes.²⁴ The compound was evaluated for its inhibitory activities in COX-1 and COX-2. The inhibitory potencies of inotilone, expressed as IC₅₀ values, are: 0.36 μM against COX-1, 0.03 μM against COX-2, and 0.08 μM for COX2/COX-1.¹⁹ Thus, its potency, selectivity, and low molecular weight made it an attractive target for further investigation.

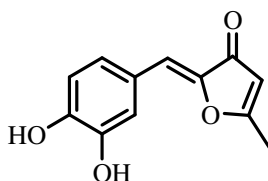
²¹ For a review see: White, W. B. *Curr. Rheumatology Rep.* **2007**, 36 and references therein.

²² Merck and Co Inc. Merck announces voluntary worldwide withdrawal of Vioxx [news release; September 30, 2004]. http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf.

²³(a) Topol, E. J.; Falk, G. W. *Lancet.* **2004**, 364, 639–640. (b) Horton, R. *Lancet.* **2004**, 364, 1995–1996. (c) Juni, P.; Nartey, L.; Reichenbach, S. *Lancet.* **2004**, 364, 2021–2029.

²⁴ Wangun, H. V. K.; Hartl, A.; Kiet, T. T.; Hertweck, C. *Org. Biomol. Chem.* **2006**, 4, 2545.

Figure 4. Potent COX-2 Inhibitor Inotilone.



RESULTS AND DISCUSSION.

The goal of the present work was to synthesize inotilone using an approach conducive to analog preparation. A facile preparation of alkylfuranones (**34**) was also necessary so that such derivatives could be rapidly constructed and attached to the aryl moiety. The method for preparation of alkylfuranones (**34**) from 1-halo-2,4-diones (**33**) was developed by Winkler.²⁵ The published route to 1-halo-2,4-diones (**33**) was unsatisfactory because the chloride (**33**) could be prepared in only poor yield (<40%). Kumler²⁶ described the method which has been developed for making α -iodo enols using iodine and hydrogen peroxide to form iodoenols in good yields. However, in the present work, direct iodination furnished an unacceptable mixture of sensitive regioisomeric iodo-2,4-diones. An attempt at regioselective bromination²⁷ of 2,4-pentanedione using hexabromocyclopentadiene resulted in an assortment of 1- and 3-bromoacetylacetone and polybrominated products that were difficult to separate.

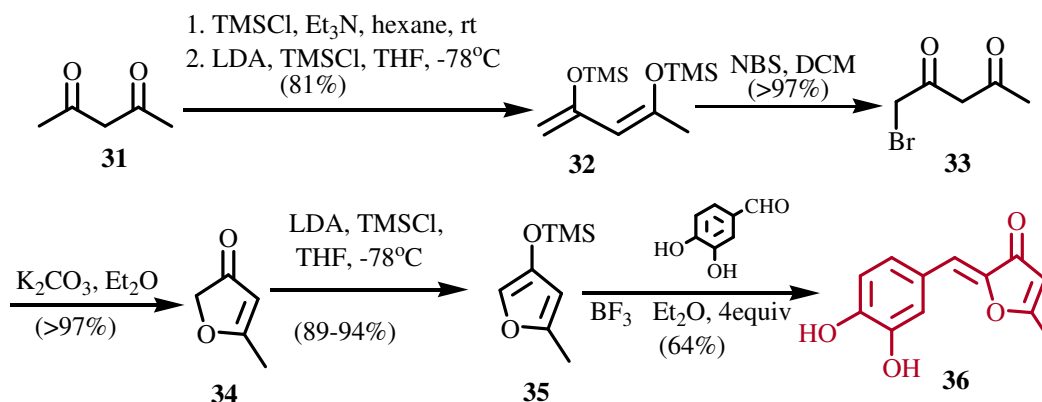
We developed a new approach to **33** via treatment of bis(silyl enol ether) (**32**) with NBS to afford the desired 1-bromo-2,4-pentanedione (**33**) in quantitative yield (Scheme 5). The reaction proceeds rapidly and is equally efficient on scales from 1 to 25 g. Attempts at cyclization of **33** using DBU proved problematic, primarily due to the moderate volatility of **34** and the arduous removal of the hydrophilic product from water during work-up. The cyclization with K_2CO_3 in ether was conducted. Rapid filtration of the crude reaction mixture through Celite and rotary evaporation of the filtrate at 23 °C provided pure **34** without the need for aqueous work-up or purification.

Scheme 5. Route to the Total Synthesis of Inotilone.

²⁵ Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, 7, 387-389

²⁶ Kumler, W. D. *J. Am. Chem. Soc.* **1938**, 60, 855-856.

²⁷ Magen, S.; Oren, J.; Fuchs, B. *Tetrahedron Lett.* **1984**, 25, 3369-3372.



The furanone (**34**) was subsequently treated with LDA and TMSCl to give **35**, which may be purified by simple distillation if desired. The Mukaiyama aldol reaction²⁸ between trimethylsilyloxyfuran **35** and 3,4-dihydroxy benzaldehyde was realized using 4.0 equiv of BF₃/Et₂O in THF at -30 °C. Elimination of the intermediate β -hydroxyl group occurs *in situ* or during work-up, because the crude reaction mixture shows no evidence of the hydroxyl functionality by ¹H NMR. It is noteworthy that the (*Z*)-alkene is the only observed isomer, presumably because of the destabilizing interaction between the furanone carbonyl and the aromatic C6 hydrogen in the (*E*)-diastereomer of 1. All characterization data and NOESY correlations of synthetic **36** coincide with those reported by Hertwick.²⁴

CONCLUSION.

In the present work, the first synthesis of potent COX-2 inhibitor inotilone was developed. The convergent route features a Mukaiyama aldol condensation that generates the target without the use of protecting groups or a separate dehydration step. During the total synthesis a superior regioselective preparation of 1-bromo-2,4-pentanedione involving a bis(silyl enol ether) and NBS was also achieved.

²⁸ M. Wadamoto, N. Ozasa, A. Yanagisawa, H. Yamamoto, *J. Org. Chem.*, **2003**, 68, 5593-5601.