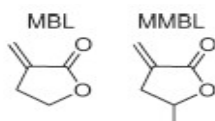


### 3-Methylene-2-Pyrrolidone(3M2P) and Related Monomer Chemistry

By: Robert B. Login rloginconsulting.com

“3M2P” are unique monomers that are not commercially available. I previously offered proposals that illustrate my ideas that can be downloaded below and also from my web page:

<http://rloginconsulting.com/joomla/images/SiteFiles/Patents/RCM%20Metathesis%20Polyfuranones%20and%20Polylactams%20and%20dendrimers%20combined.pdf>



Monomers MMBL and MBL are easily polymerized to very high MW by frustrated Lewis pair techniques but no mention of 3M2P by these techniques?

These lactams do polymerize with free-radical initiation.

<http://rloginconsulting.com/joomla/images/SiteFiles/Patents/combinedreport.3.pdf>

Iskander, G. M., Ovenell, T. R., & Davis, T. P. (1996). Synthesis and properties of poly (1-alkyl-3-methylene-2-pyrrolidone) s. *Macromolecular Chemistry and Physics*, 197(10), 3123-3133.

Heyns, I. M., Pfukwa, R., & Klumperman, B. (2016). Synthesis, Characterization, and Evaluation of Cytotoxicity of Poly (3-methylene-2-pyrrolidone). *Biomacromolecules*, 17(5), 1795-1800.

Heyns, I. M., Pfukwa, R., Bertossi, L., Ball, L. E., Kelland, M. A., & Klumperman, B. (2019). Thermoresponsive behavior of poly (3-methylene-2-pyrrolidone) derivatives. *European Polymer Journal*, 112, 714-721.

MBL and similar lactones are available from biomass and hence are renewable monomers, but so is 3M2P. All the references concerning FLP (and other methods of polymerization) show how MBL can readily be polymerized to very high MW narrow polydispersity polymers suitable as tough plastics that could replace petroleum based ones.

Kollar, J., Danko, M., Pippig, F., & Mosnáček, J. (2019). Functional Polymers and Polymeric Materials From Renewable Alpha-Unsaturated Gamma-Butyrolactones. *Frontiers in Chemistry*, 7.

Hu, L., Zhao, W., He, J., & Zhang, Y. (2018). Silyl Ketene Acetals/B (C6F5) 3 Lewis Pair-Catalyzed Living Group Transfer Polymerization of Renewable Cyclic Acrylic Monomers. *Molecules*, 23(3), 665.

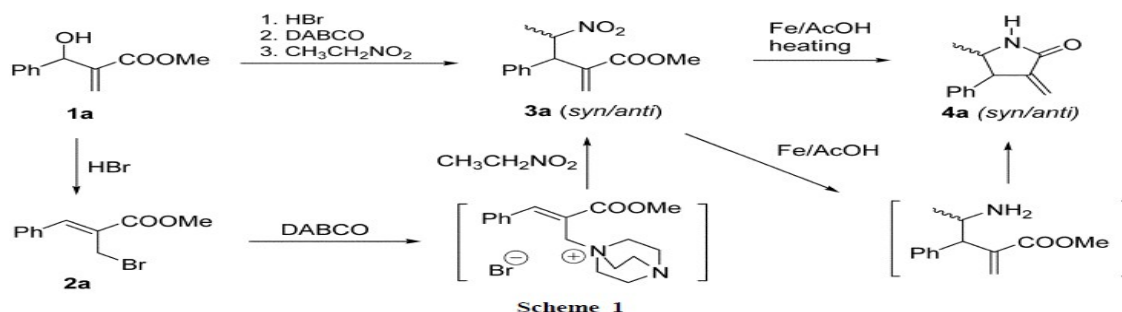
Hu, L., He, J., Zhang, Y., & Chen, E. Y. X. (2018). Living Group Transfer Polymerization of Renewable  $\alpha$ -Methylene- $\gamma$ -butyrolactones Using Al (C6F5) 3 Catalyzt. *Macromolecules*, 51(4), 1296-1307.

So why my interest in 3M2P? Because it is an alternate way to present the chemistry of PVP. Instead of the pyrrolidones lactam facing the polymer backbone, with P3M2P it would be the opposite. Also the pyrrolidones would, depending on tacticity, face each other resulting in unexpected complexation ability for iodine for example. Also tablet binding might be improved, so would utility as drug carriers etc.. PVP was once used as a blood plasma expander where an aqueous solution was used to prevent shock until blood could be administered. PVP proved to be difficult to eliminate and hence to be too toxic( this however was a function of MW with low MW being much better). P3M2P might be superior? 3M2P and related monomers could be copolymerized with a wide assortment of monomers.

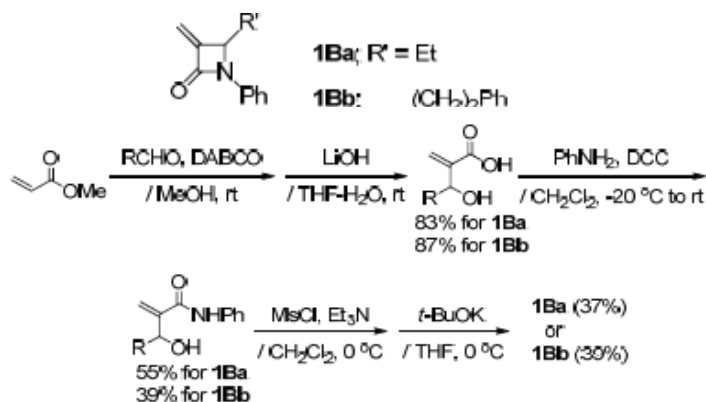
**I think the main issue holding back commercialization is a low cost synthesis route for commercial manufacture of these monomers.**

What follows is a brief review of the synthesis of 3M2P and related monomers. Note this review is not claimed to be complete.

Lee, K. Y., Lee, Y. J., & Kim, J. N. (2007). Synthesis of  $\beta$ ,  $\gamma$ -Disubstituted  $\alpha$ -Methylene- $\gamma$ -butyrolactams Starting from the Baylis-Hillman Adducts. *Bulletin of the Korean Chemical Society*, 28(1), 143-146.

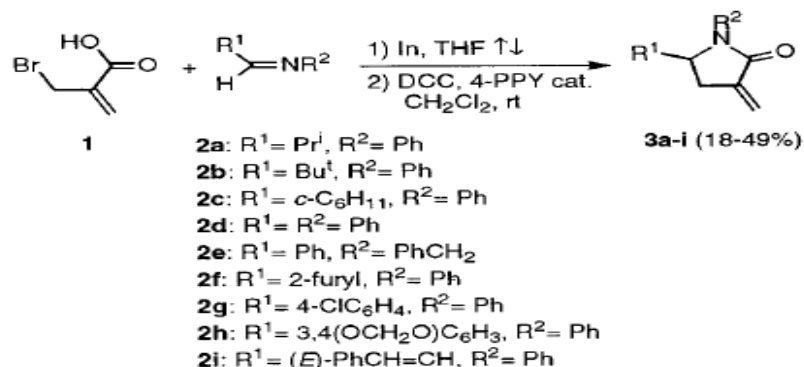


Takahashi, M., Sudo, T., Murata, Y., Sengoku, T., & Yoda, H. (2013). Synthetic Approach toward  $\alpha$ -Aminomethyl- $\gamma$ -butyrolactones from  $\beta$ -Lactam Synthons Elaborated by SmI<sub>2</sub>-mediated Reductive Coupling Reactions. *Natural product communications*, 8(7), 1934578X1300800709.

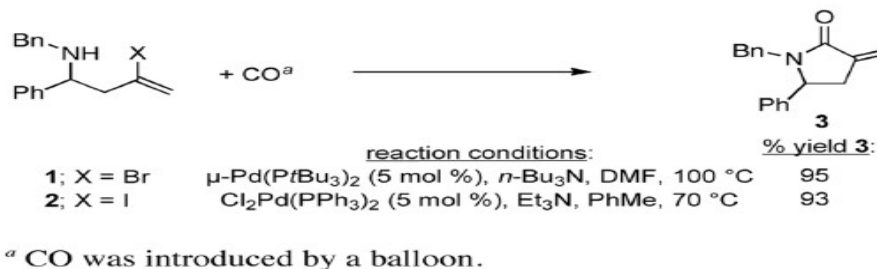


Choudhury, P. K., Foubelo, F., & Yus, M. (1999). Indium-Promoted Preparation of  $\alpha$ -Methylene- $\gamma$ -butyrolactams from 2-(Bromomethyl) acrylic Acid and Aldimines. *The Journal of organic chemistry*, 64(9), 3376-3378.

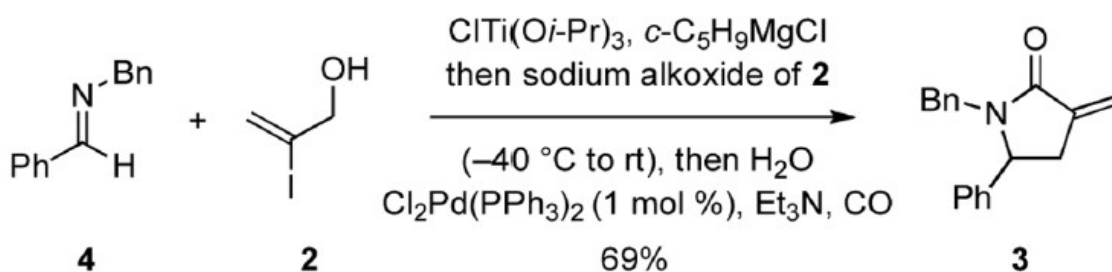
**Scheme 1**



Umemura, S., McLaughlin, M., & Micalizio, G. C. (2009). Convergent Synthesis of Stereodefined exo-Alkylidene- $\gamma$ -Lactams from  $\beta$ -Halo Allylic Alcohols. *Organic letters*, 11(23), 5402-5405.

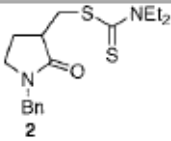
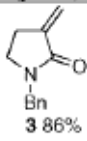


**Figure 4. Pd-catalyzed carbonylative cyclization**  
<sup>a</sup> CO was introduced by a balloon.

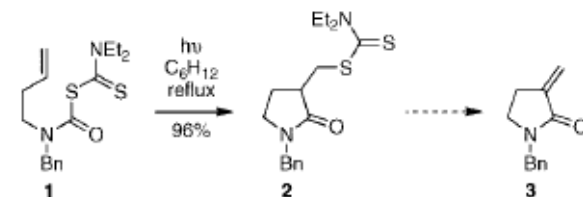


Ahmed, S., Baker, L. A., Grainger, R. S., Innocenti, P., & Quevedo, C. E. (2008). Thermal elimination of diethyldithiocarbamates and application in the synthesis of ( $\pm$ )-Ferrugine. *The Journal of organic chemistry*, 73(20), 8116-8119.

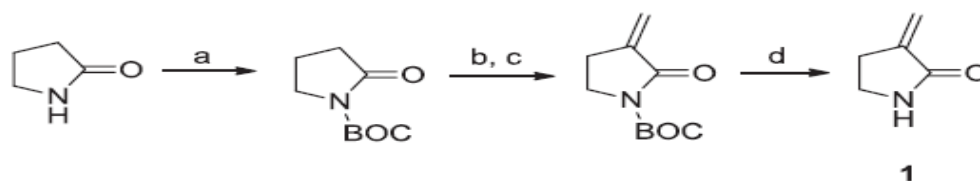
**TABLE 1. Thermal Elimination of Diethyldithiocarbamates<sup>a</sup>**

Entry	Dithiocarbamate	Time (h)	Alkene (yield <sup>b</sup> )
I		2	 3 86%

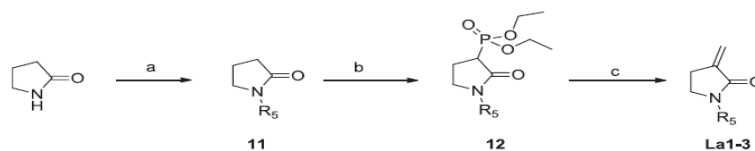
**SCHEME 1. Dithiocarbamate Group Transfer Carbamoyl Radical Cyclization and Proposed Elimination**



Delong, W., Lanying, W., Yongling, W., Shuang, S., Juntao, F., & Xing, Z. (2017). Natural  $\alpha$ -methylene- $\gamma$ -lactam analogues: Design, synthesis and evaluation of  $\alpha$ -alkenyl- $\gamma$  and  $\delta$ -lactams as potential antifungal agents against *Colletotrichum orbiculare*. *European journal of medicinal chemistry*, 130, 286-307.



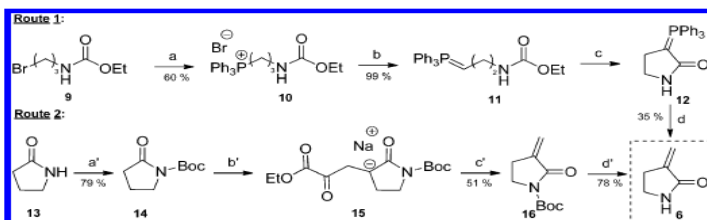
**Scheme 1.** Synthesis of  $\alpha$ -methylene- $\gamma$ -lactam. Reagents and conditions: a)  $\text{Boc}_2\text{O}$ , DMAP,  $\text{Et}_3\text{N}$ , DCM, r.t.; b) diethyl oxalate, NaH,  $\text{Et}_2\text{O}$ , 35°C; c) paraformaldehyde, DMF, 100°C; d) trifluoroacetic acid, DCM.



**Scheme 6.** Synthesis of N-substituted  $\alpha$ -methylene- $\gamma$ -lactam. Reagents and conditions: a) alkyl/benzyl bromide, NaH, THF, 0°C to r.t.; b) LDA, diethyl chlorophosphate, THF, -5°C to r.t.; c) paraformaldehyde, NaH, THF, 0°C to r.t..

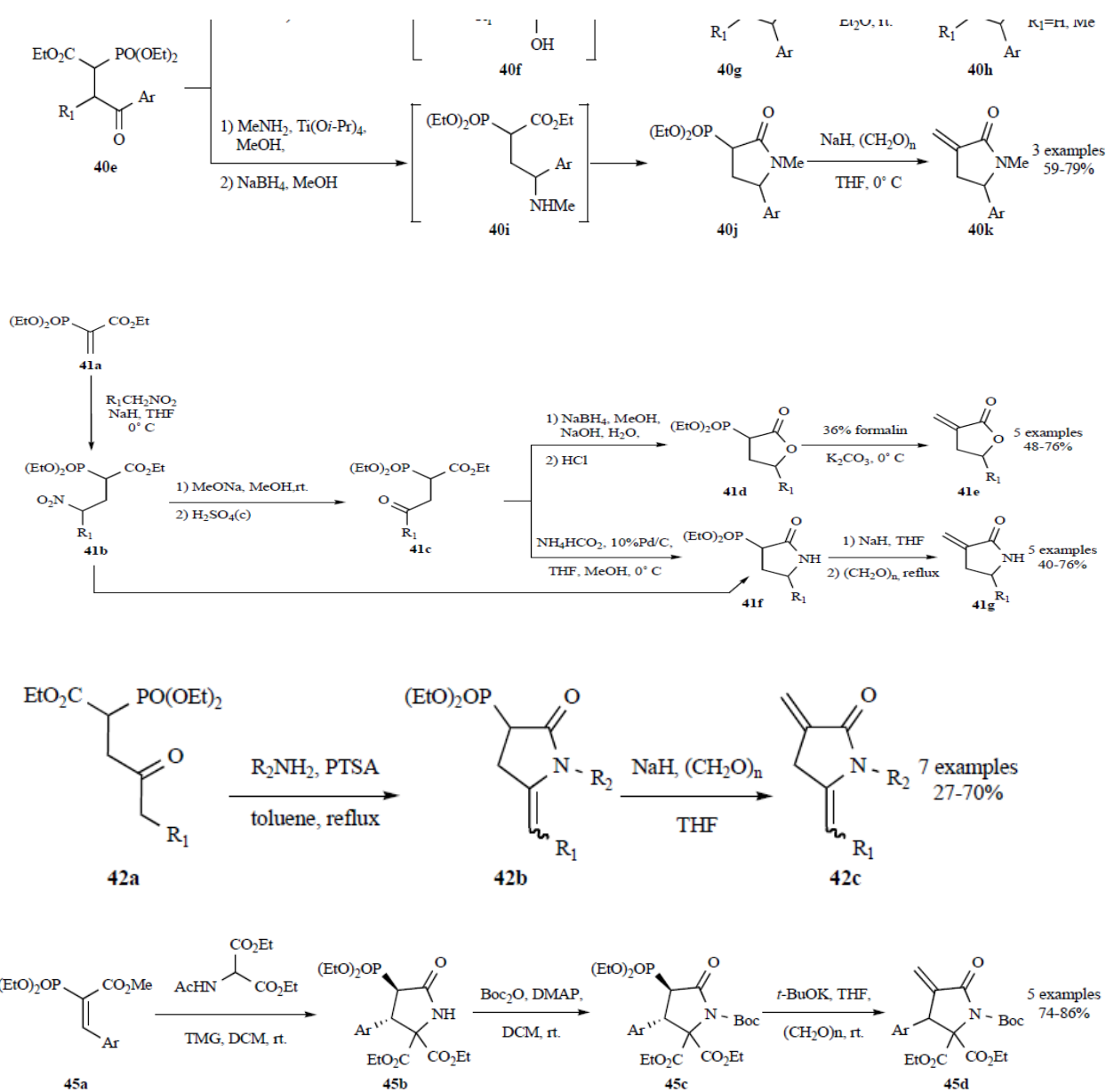
Heyns, I. M., Pfukwa, R., & Klumperman, B. (2016). Synthesis, Characterization, and Evaluation of Cytotoxicity of Poly (3-methylene-2-pyrrolidone). *Biomacromolecules*, 17(5), 1795-1800.

Scheme 1. Synthesis Routes for 3M2P<sup>42</sup>

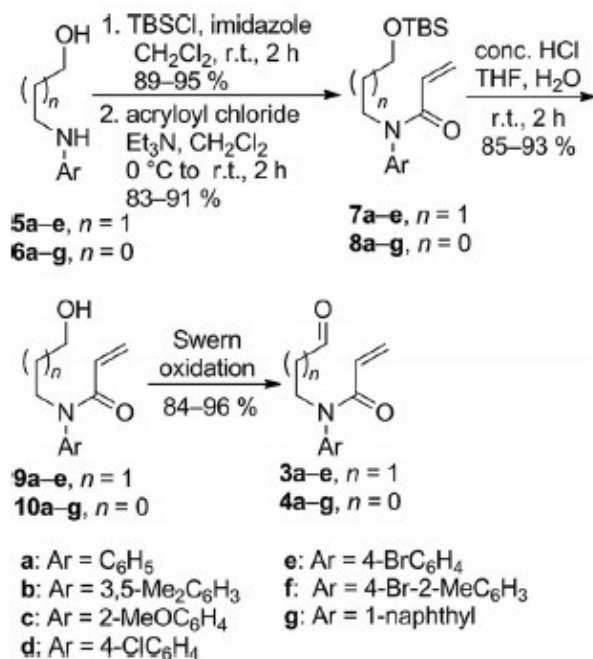


<sup>a</sup>Reagents and conditions: (a) PPh<sub>3</sub>, acetonitrile, 100 °C; (b) potassium *tert*-butoxide, toluene, r.t.; (c) 50 °C; (d) paraformaldehyde, toluene, 50 °C to r.t.; (a') di-*tert*-butyl dicarbonate, acetonitrile, 0 °C; (b') diethyl oxalate, sodium hydride, diisopropyl ether, 35 °C; (c') paraformaldehyde, dimethylformamide, 100 °C; (d') trifluoroacetic acid, dichloromethane.

A Bisceglia, J., & R Orelli, L. (2015). Recent progress in the Horner-Wadsworth-Emmons reaction. *Current Organic Chemistry*, 19(9), 744-775.



Basavaiah, D., Reddy, G. C., & Bharadwaj, K. C. (2014). The Acrylamide Moiety as an Activated Alkene Component in the Intramolecular Baylis–Hillman Reaction: Facile Synthesis of Functionalized  $\alpha$ -Methylene Lactam and Spirolactam Frameworks. *European Journal of Organic Chemistry*, 2014(6), 1157-1162.

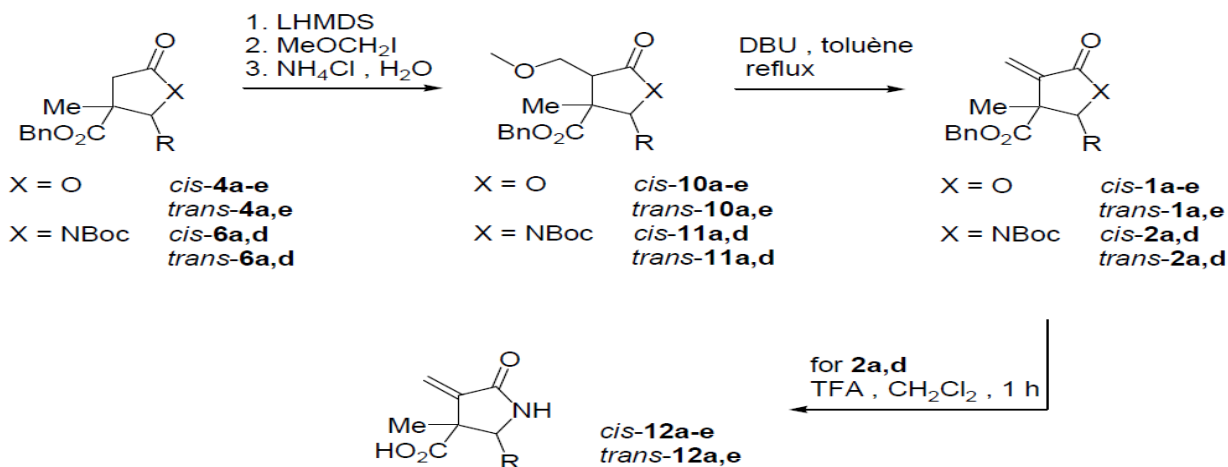


Scheme 2. Synthesis of acrylamide-aldehydes **3a-e** and **4a-g**. TBS = *tert*-butyldimethylsilyl.

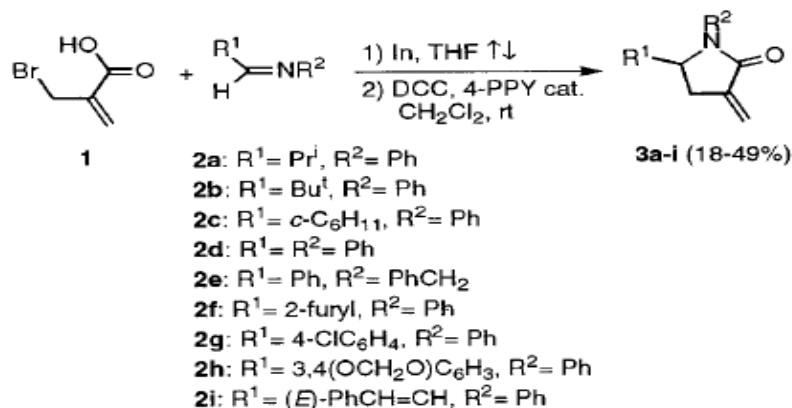
Table 3. Synthesis of  $\alpha$ -methylene  $\gamma$ -lactam derivatives **2a-g**.<sup>[a]</sup>

Entry	AA	Ar	Product <sup>[b]</sup>	Time [h]	Yield <sup>[c]</sup> [%]
1	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	<b>2a</b>	0.5	73
2	<b>4b</b>	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>2b</b>	1.5	67
3	<b>4c</b>	2-MeOC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	2.5	70
4	<b>4d</b>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2d</b> <sup>[d]</sup>	0.16	71
5	<b>4e</b>	4-BrC <sub>6</sub> H <sub>4</sub>	<b>2e</b>	0.16	69
6	<b>4f</b>	4-Br-2-MeC <sub>6</sub> H <sub>3</sub>	<b>2f</b>	1	72
7	<b>4g</b>	1-naphthyl	<b>2g</b>	1.5	70
8 <sup>[e]</sup>	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	<b>2a</b>	30	65 (10) <sup>[f]</sup>
9 <sup>[g]</sup>	<b>4a</b>	C <sub>6</sub> H <sub>5</sub>	<b>2a</b>	30	63 (5) <sup>[f]</sup>

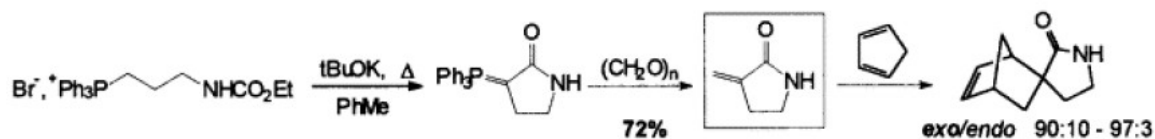
Liberge, G., Lebrun, S., Couture, A., & Grandclaudon, P. (2011, October). Convenient synthesis of functionalized  $\alpha$ -methylenebutano-4-lactams or lactones. In *15th Int. Electron. Conf. Synth. Org. Chem.* (Vol. 15). MDPI.



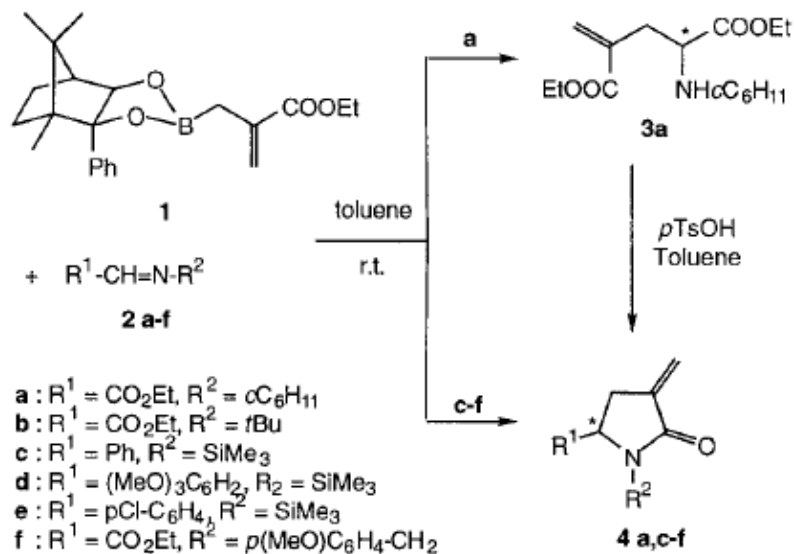
Choudhury, P. K., Foubelo, F., & Yus, M. (1999). Indium-Promoted Preparation of  $\alpha$ -Methylene- $\gamma$ -butyrolactams from 2-(Bromomethyl) acrylic Acid and Aldimines. *The Journal of organic chemistry*, 64(9), 3376-3378.



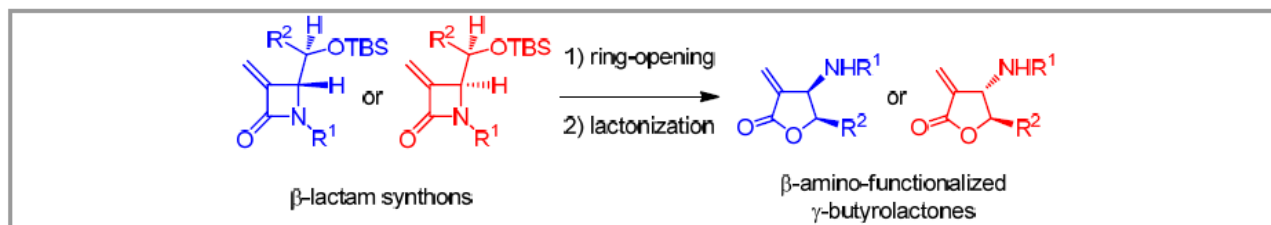
Fotiadu, F., Pardigon, O., Buono, G., Le Corre, M., & Hercouët, A. (1999). Efficient synthesis of 3-methylene-2-pyrrolidinone and highly exoselective Diels-Alder addition to cyclopentadiene. *Tetrahedron letters*, 40(5), 867-870.



Chataigner, I., Zammattio, F., Lebreton, J., & Villieras, J. (1998). Enantioselective Synthesis of  $\alpha$ -Methylene- $\gamma$ -Lactams. Nucleophilic Addition of a Chirally Modified  $\beta$ -Functionalized Allylboronate Reagent to Imines. *Synlett*, 9(03), 275-276.



Takahashi, M., Atsumi, J. I., Sengoku, T., & Yoda, H. (2010). Synthesis of  $\beta$ -amino-functionalized  $\alpha$ -exo-methylene- $\gamma$ -butyrolactones via a  $\beta$ -lactam synthon strategy. *Synthesis*, 2010(19), 3282-3288.



## A Method for the Synthesis of Unsaturated Carbonyl Compounds

Gary M. Ksander, John E. McMurry,\* and Mark Johnson

Thimann Laboratories, University of California, Santa Cruz, California 95064

Received July 26, 1976

Synthesis of Unsaturated Carbonyl Compounds


*J. Org. Chem.*, Vol. 42, No. 7, 1977 1183

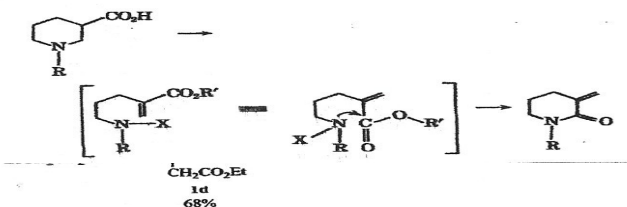
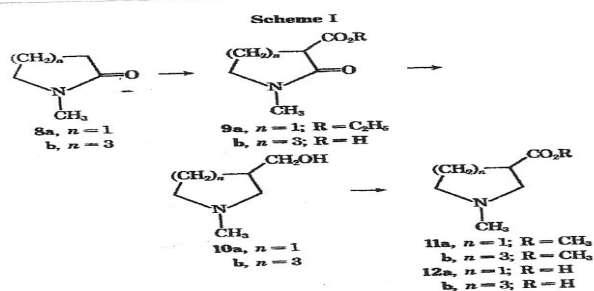
Table I (Continued)

Reaction	Carbonyl compd	Oxalyl derivative	(yield)	Aldehyde	Product	(yield)
22				$\text{CH}_2\text{O}$		(61)



Table I  
 $\alpha$ -Methylenelactam Rearrangement of 3-Carboxy-1-methylpyrrolidine, -piperidine, and -hexahydroazepine

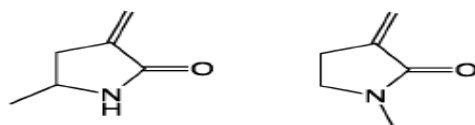
Compd	Reaction conditions <sup>a</sup>	Lactam	Yield, %	Products	Other	Yield, %
12a	Ac <sub>2</sub> O, K <sub>2</sub> CO <sub>3</sub>		95			



WO 2017/029630

PCT/IB2016/054940

5-Methyl-3-methylenepyrrolidone (A) and 1-methyl-3-methylenepyrrolidone (B), shown below, are derivatives of the lactam analogue of Tulipalin A.



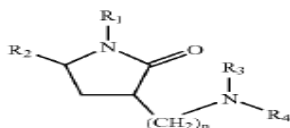
5-Methyl-3-methylenepyrrolidone (A) and 1-methyl-3-methylenepyrrolidone (B)

Both these monomers have been shown to undergo radical polymerisation (Ueda et al. *J. Polym. Sci. Polym. Chem. Ed.* 1983, 21, 1139; Van Beylen and Samyn, *Makromol. Chem.* 1990, 191, 2485). However, the polymer of compound (A), poly(A), is poorly characterized in terms of its solubility properties and its physical properties. Poly(A) is more hydrophilic than the polymer of compound (B), poly(B), and fairly soluble in organic solvents. The glass transition temperature ( $T_g$ ) of poly(A) is estimated to be less than that of poly(B), which has a  $T_g$  of 169 °C (Ishizone et al. *Macromol. Symp.* 2013, 323, 86). Poly(B) shows depolymerisation above 330 °C and is a semi-crystalline material (Ueda et al. *J. Polym. Sci., Part B: Polym. Phys.* 1983, 20, 1139). Poly(B) is water-soluble and also soluble in methanol, dichloromethane (DCM) and polar aprotic solvents at room temperature (similar solubility behavior to that of poly(*N*-vinylpyrrolidone) (PVP).

# US 2007/0172421 A1

## Jul. 26, 2007

(57) **ABSTRACT**  
The invention relates to compounds of formula (I)



Wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and n are as defined in the specification, to processes for their manufacture, to their use as pharmaceuticals, in diagnosis, as PET ligands and to pharmaceutical or diagnostic compositions comprising such compounds.

(12) **United States Patent**  
**Brandenburg et al.**

(10) **Patent No.:** **US 6,642,346 B2**  
(45) **Date of Patent:** **Nov. 4, 2003**

(54) **COATING COMPOSITIONS CONTAINING SUBSTITUTED AND UNSUBSTITUTED EXOMETHYLENE LACTONE OR LACTAM MONOMERS**

(75) **Inventors:** **Charles J. Brandenburg**, Wilmington, DE (US); **Randal D. King**, Kennett Square, PA (US); **Larry G. Oien**, Lapeer, MI (US); **Peter W. Uhlianuk**, Romeo, MI (US)

(73) **Assignee:** **E. I. du Pont de Nemours and Company**, Wilmington, DE (US)

(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/770,073**

(22) **Filed:** **Jan. 25, 2001**

(65) **Prior Publication Data**

US 2002/0010312 A1 Jan. 24, 2002

**Related U.S. Application Data**

(60) Provisional application No. 60/185,594, filed on Feb. 28, 2000.

(51) **Int. Cl.**<sup>7</sup> ..... **C08G 73/00**; C08G 63/08; C08F 224/00; C08F 226/00

(52) **U.S. Cl.** ..... **528/310**; 528/354; 528/318; 528/323; 528/359; 526/266; 525/410; 525/411; 525/413; 525/415

(58) **Field of Search** ..... 528/354, 310, 528/318, 323, 359; 526/266; 525/410, 411, 413, 415

(56) **References Cited**

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4,728,543 A 3/1988 Kurauchi et al.  
4,943,614 A \* 7/1990 Miyazaki et al. .... 525/117  
5,166,357 A 11/1992 Orlek et al.  
5,244,696 A 9/1993 Hazan et al.  
5,880,235 A 3/1999 Schwind et al. .... 526/868

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WO 00/35960 A2 6/2000

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Murray et al., Convenient Synthesis of  $\alpha$ -Epoxy lactones (4-oxo-1,5-dioxaspiro[2,4]heptanes and [2,5]Octanes), *Synthesis*, 1995, 35-38.

Martin et al., A New Method for the Synthesis of 960 - Methylenebutyrolactones, *Chemical Communications*, 1970, 27.

Mitsuru Ueda et al., Radical-Initiated Homo- and Copolymerization of  $\alpha$ -Methylene- $\gamma$ -Butyrolactone, *Journal of Polymer Science: Polymer Chemistry Edition*, vol. 20, 00, 2819-2828.

Copy of International Search Report dated 221/2001.

\* cited by examiner

*Primary Examiner*—P. Hampton-Hightower

(74) *Attorney, Agent, or Firm*—Steven C. Benjamin

(57) **ABSTRACT**

This invention is directed to a coating composition used for original equipment manufacturing or refinishing uses in the automotive industry, which coating composition utilizes an acrylic polymer which contains substituted or unsubstituted exomethylene lactones or lactams as a comonomer.

**United States Patent** [19]

Song et al.

[11] **Patent Number:** **5,035,884**[45] **Date of Patent:** **Jul. 30, 1991**[54] **METHYLENE PYRROLIDONE  
COPOLYMERS FOR CONTACT LENS AND  
PHARMACEUTICAL PREPARATIONS**[75] **Inventors:** Suk-Zu Song, Flanders; Surendra C. Mehta, Randolph; Kuchi S. Murthy, Morris Plains; Russell U. Nesbitt, Somerville; Mahdi B. Fawzi, Flanders, all of N.J.[73] **Assignee:** Warner-Lambert Company, Morris Plains, N.J.[21] **Appl. No.:** 480,431[22] **Filed:** Feb. 15, 1990**Related U.S. Application Data**

[62] Division of Ser. No. 347,630, May 5, 1989, Pat. No. 4,931,519, which is a division of Ser. No. 57,467, Jun. 2, 1987, Pat. No. 4,851,545.

[51] **Int. Cl.<sup>5</sup>** ..... A61K 31/785; G02C 7/04[52] **U.S. Cl.** ..... 424/78; 351/160 R; 424/81; 424/430; 424/435; 424/436; 424/449; 523/106; 523/111[58] **Field of Search** ..... 351/160 R; 424/78, 80, 424/81, 430, 435, 436, 449; 523/108, 106, 111[56] **References Cited****U.S. PATENT DOCUMENTS**

3,452,015	6/1969	Dillard	544/335
3,479,327	11/1969	Marijam	540/485
3,542,778	11/1970	Dillard	544/335
4,593,053	6/1986	Jevne	523/111
4,866,148	9/1989	Geyer	523/108

**FOREIGN PATENT DOCUMENTS**

70/3307 5/1969 South Africa .

*Primary Examiner*—Christopher Henderson  
*Attorney, Agent, or Firm*—Elizabeth M. Anderson[57] **ABSTRACT**

A new series of copolymers which are useful as coatings for solid dosage forms, for transdermal devices, for wound dressing materials, and for contact lenses. Also disclosed are methods for preparing monomers and polymers as well as pharmaceutical compositions containing such polymers.

**5 Claims, No Drawings****United States Patent** [19]

Song et al.

[11] **Patent Number:** **4,931,519**[45] **Date of Patent:** **Jun. 5, 1990**[54] **COPOLYMERS FROM  
N-ALKYL-3-ALKENYLENE-2-PYRROLI-  
DONE**[75] **Inventors:** Suk-Zu Song, Flanders; Surendra C. Mehta, Randolph; Kuchi S. Murthy, Morris Plains; Russell U. Nesbitt, Somerville; Mahdi B. Fawzi, Flanders, all of N.J.[73] **Assignee:** Warner-Lambert Company, Morris Plains, N.J.[21] **Appl. No.:** 347,630[22] **Filed:** May 5, 1989**Related U.S. Application Data**

[62] Division of Ser. No. 57,467, Jun. 2, 1987, Pat. No. 4,851,545.

[51] **Int. Cl.<sup>5</sup>** ..... C08F 26/06[52] **U.S. Cl.** ..... 526/258[58] **Field of Search** ..... 526/258[56] **References Cited****U.S. PATENT DOCUMENTS**

3,452,015	6/1969	Dillard	544/335
3,479,327	11/1969	Marijam	540/485
3,488,294	1/1970	Annand	526/258
3,542,778	11/1970	Dillard	544/335

**FOREIGN PATENT DOCUMENTS**

70/3307 5/1969 South Africa .

*Primary Examiner*—Christopher Henderson  
*Attorney, Agent, or Firm*—Elizabeth M. Anderson[57] **ABSTRACT**

A new series of copolymers which are useful as coatings for solid dosage forms, for transdermal devices, for wound dressing materials, and for contact lenses. Also disclosed are methods for preparing monomers and polymers as well as pharmaceutical compositions containing such polymers.

**1 Claim, No Drawings**

# United States Patent [19]

Song et al.

[11] Patent Number: 4,851,545

[45] Date of Patent: Jul. 25, 1989

[54] N-SUBSTITUTED-3-ALKYLENE-2-PYRROLIDONE COMPOUNDS

[75] Inventors: Suk-Zu Song, Flanders; Surendra C. Mehta, Randolph; Kuchi S. Murthy, Morris Plains; Russell U. Nesbitt, Somerville; Mahdi B. Fawzi, Flanders, all of N.J.

[73] Assignee: Warner-Lambert Company, Morris Plains, N.J.

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[51] Int. Cl.<sup>4</sup> ..... C07D 207/26

[52] U.S. Cl. .... 548/543

[58] Field of Search ..... 548/543

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Primary Examiner—Mary C. Lee

Assistant Examiner—Zinna Northington

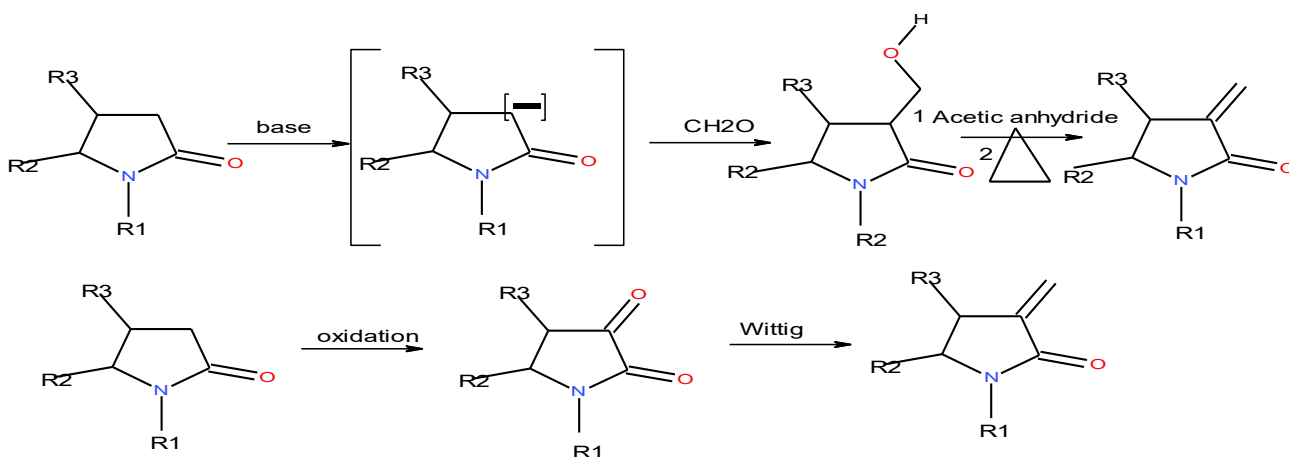
Attorney, Agent, or Firm—Elizabeth M. Anderson

## [57] ABSTRACT

A new series of copolymers such as N-isopropyl-3-methylene-2-pyrrolidone and 2-hydroxyethylmethacrylate which are useful as coatings for solid dosage forms, for transdermal devices, for wound dressing materials, and for contact lenses. Also disclosed are methods for preparing monomers and polymers as well as pharma-

As you can see “3M2P” has been of significant interest for a very long time. I think the above references gives one a good idea of its synthesis.

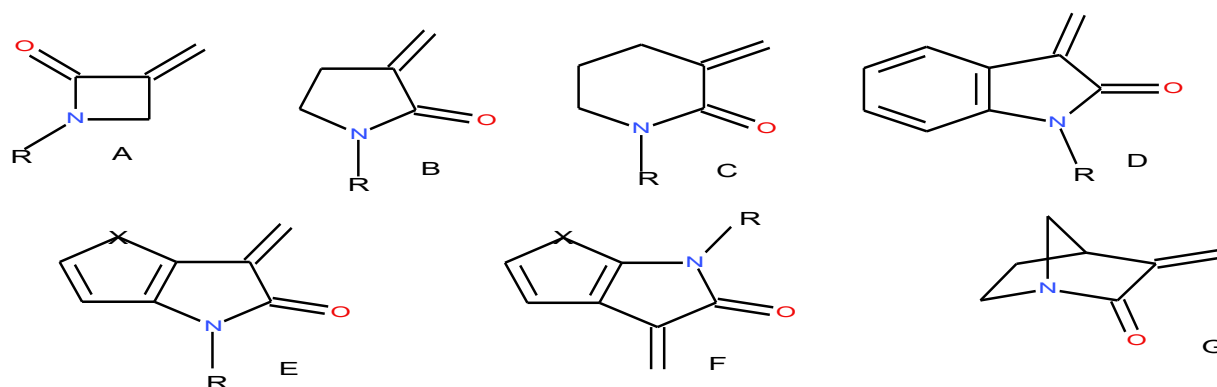
A problem with P3M2P itself is that it is very water soluble but it is insoluble in most organic solvents. Obviously one could prepare derivatives that would solve this problem.



Scheme 2: Simple ideas that I think are feasible. R1-3 could be anything and hence this chemistry seems very flexible. For example R1 could be ethylene dimethylamine or the corresponding quat.. P3M2P produces a very stiff film, perfect for hair-care products. R3 could be an activating EWG. etc Copolymers can enhance adsorption of dyes and

pigments for example in propylene and ethylene copolymers. Copolymers because of the great water solubility might be the basis of families of adhesives. Easy water removal suggest various mask applications. I could go on.

One of the most important features of this chemistry is that NMP and 2-Py are readily available commodity chemicals that could be converted to these valuable monomers by chemists with limited resources and capital.



Scheme 3: A few conceivable monomers besides B. I'm sure there are many more possibilities.

Thank you for reading these proposals.

Dr. Robert B. Login    [rloginconsulting.com](http://rloginconsulting.com)