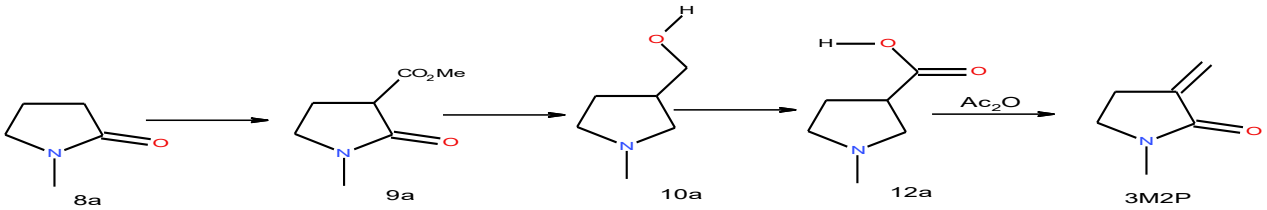
3-Pyrrolidinylcarboxylic acids(PCA)

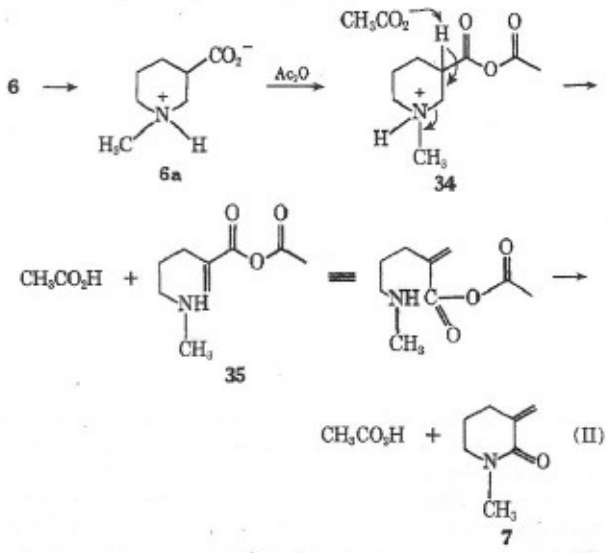
By: Robert B. Login rloginconsulting.com

During 1972 and 74, H. Rapoport et.al. explained in detail the amazing synthesis of this type of compound and its rearrangement to 3M2P.

Lee, D. L., Morrow, C. J., & Rapoport, H. (1974). . alpha.-Methylenelactam rearrangement. *The Journal of Organic Chemistry*, *39*(7), 893-902.



Treatment of the corresponding amides **8a** and **8b** with lithium diisopropylamide followed by the addition of diethyl carbonate or carbon dioxide yielded the carboxyl derivatives **9a** and **9b**, respectively. Lithium aluminum hydride reduction of the carboxyl and amide functions afforded the aminols **10a** and **10b**, and chromium trioxide–sulfuric acid oxidation of the alcohols gave acids **12a** and **12b**, purified *via* their respective methyl esters, **11a** and **11b**.



Scheme 1: Rapoport et. al. synthesis and rearrangement mechanism(1974). Although discovered earlier by others, Prof. Rapoport explained the mechanism of this rearrangement accurately, in great detail and should have his name associated with this rearrangement!

My proposal is based on the scheme 1 yield of 3-methylene-2- pyrrolidone(3M2P) being

95% in the final step(12a to 3M2P with acetic anhydride) which suggests that a cost-effective synthesis of 3-carboxy-1-methylpyrrolidine(PCA) would be very valuable. If cost-effective, it might make 3M2P a commercial success.

In my previous proposal I reviewed many references dealing with the preparation of 3M2P.

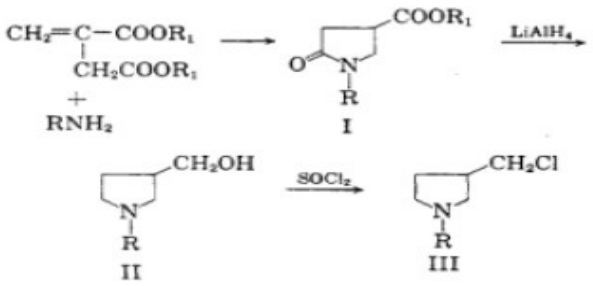
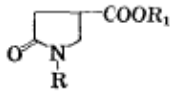


TABLE I

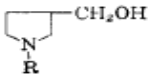
1-Substituted 5-Oxo-3-pyrrolidinecarboxylates



R	R_1	Procedure	B.P., Mm.	M.P.	n_D^{25}	Yield, %[f]
CH_3	CH_3	A	160–161, 18.0		1.4742	84
CH_3	C_2H_5	A	166–167, 19.0		1.4678	76
C_2H_5	CH_3	A	104–106, 0.13		1.4702	89
n-C_3H_7	CH_3	A	91.5–92, 0.08		1.4688	97
i-C_3H_7	CH_3	A	86–88, 0.06		1.4665	91
CH_2—$CHCH_2$	CH_3	A	178–179, 21.0		1.4829	96

TABLE II

1-Substituted 3-Pyrrolidinemethanols



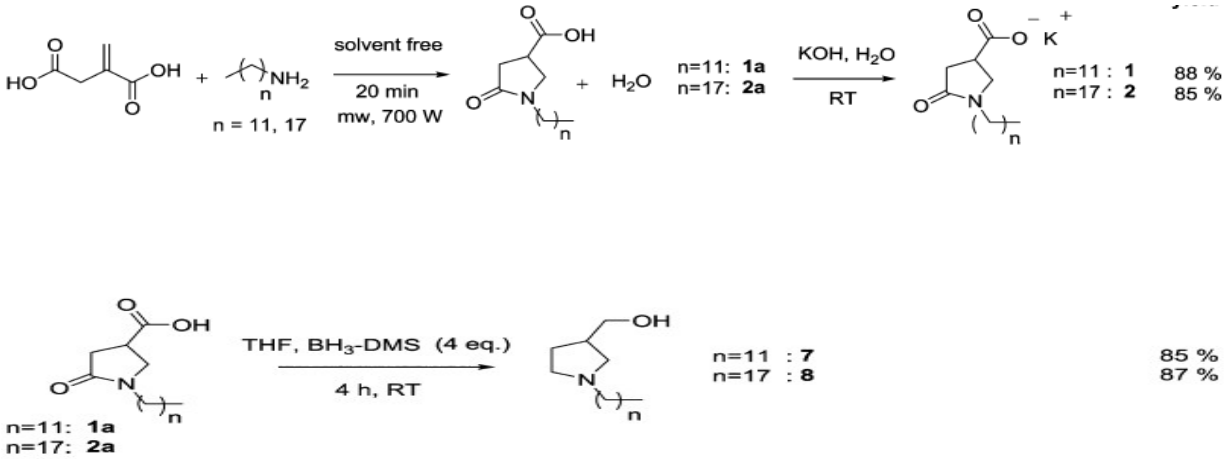
R	B.P., Mm.	n_D^{25}	Yield, %[d]	Formula
CH_3[a]	94–96.5, 15.0	1.4662	79	$C_6H_{13}NO$
C_2H_5	110–111, 20.0	1.4693	74	$C_7H_{15}NO$
n-C_3H_7	122–126, 24.0	1.4669	79	$C_8H_{17}NO$
i-C_3H_7	122–122.5, 24.0	1.4713	76	$C_8H_{17}NO$
CH_2=$CHCH_2$	122–124, 21.0	1.4822	69	$C_8H_{15}NO$
n-C_4H_9	130–131, 19.0	1.4672	79	$C_9H_{19}NO$
i-C_4H_9[b]	139.5–140.5, 36	1.4744	81	$C_9H_{19}NO$
Cyclohexyl	97–101, 0.06	1.5023	88	$C_{11}H_{21}NO$
$C_6H_5CH_2$	166–168, 12.0	1.5431	69	$C_{12}H_{17}NO$
o-$ClC_6H_4CH_2$	114–122, 0.06	1.5541	70	$C_{12}H_{16}ClNO$
$C_6H_5CH_2CH_2$	114, 0.05	1.5380	91	$C_{13}H_{19}NO$
3,4-di$CH_3OC_6H_3CH_2CH_2$	144–148, 0.06	1.5446	93	$C_{15}H_{23}NO_2$
C_6H_5	130–135, 0.05	1.5872	40	$C_{11}H_{15}NO$

Wu, Y. H., & Feldkamp, R. F. (1961). Pyrrolidines. I. 1-Substituted 3-Pyrrolidinylmethyl Alcohols and Chlorides1. *The Journal of Organic Chemistry*, *26*(5), 1519-1524.

With Rapoport's procedure, it looks like the itaconic route seems very reasonable. In addition, itaconic acid is prepared from bio-mass and would be a renewable green starting compound.

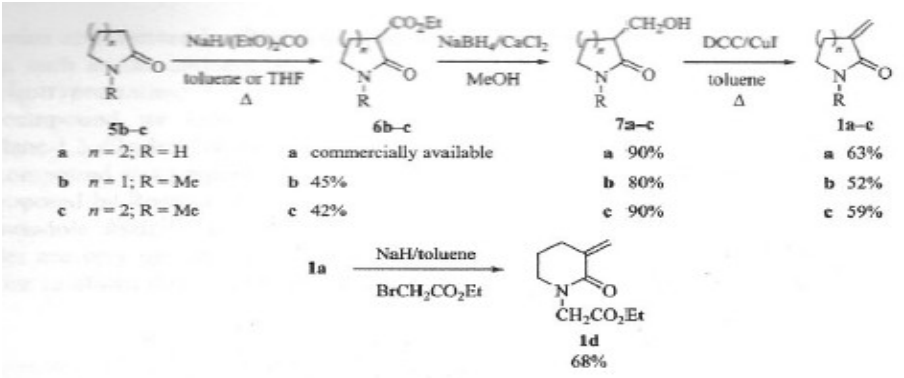
He, X., Alian, A., Stroud, R., & Ortiz de Montellano, P. R. (2006). Pyrrolidine carboxamides as a novel class of inhibitors of enoyl acyl carrier protein reductase from Mycobacterium tuberculosis. *Journal of medicinal chemistry*, *49*(21), 6308-6323.

Paytash PL, Sparrow E, Gathe JC. The reaction of itaconic acid with primary amines. J. Am. Chem. Soc 1950;72:1415–1416.



Malferrari, D., Armenise, N., Decesari, S., Galletti, P., & Tagliavini, E. (2015). Surfactants from itaconic acid: physicochemical properties and assessment of the synthetic strategies. *ACS Sustainable Chemistry & Engineering*, *3*(7), 1579-1588.

It seems to me that the itaconic route is the most convenient and possibly the most cost effective.

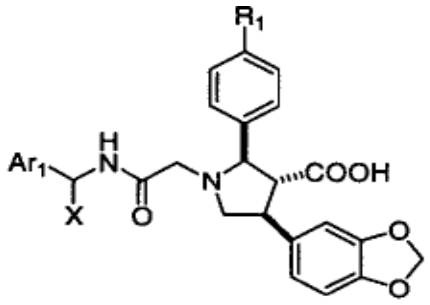


Loreto, M. A., Migliorini, A., Tardella, P. A., & Gambacorta, A. (2007). Novel Spiroheterocycles by Aziridination of α-Methylene-γ-and-δ-lactams. *European journal of organic chemistry*, *2007*(14), 2365-2371.

This paper shows an alternative to Ac2O.

The above is a review of the pyrrolidone route which is a three step synthesis as is the itaconic route. So this comes down to overall cost. The itaconic route also has the advantage of being green.

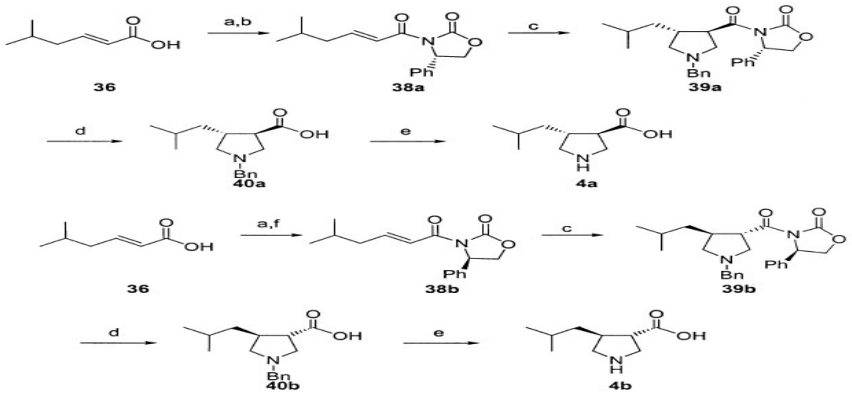
Review of additional 1-Substituted 3-Pyrrolidinylcarboxylic acids;
What follows are some of the literature dealing with PCA.



9 X = Ar_2
10 X = R_2

Liu, G., Kozmina, N. S., Winn, M., von Geldern, T. W., Chiou, W. J., Dixon, D. B., ... & Opgenorth, T. J. (1999).

Design, synthesis, and activity of a series of pyrrolidine-3-carboxylic acid-based, highly specific, orally active ETB antagonists containing a diphenylmethylamine acetamide side chain. *Journal of medicinal chemistry*, *42*(18), 3679-



Scheme 10. Synthesis of enantiomers **4a** and **4b**. (a) Oxalyl chloride, DMF, Toluene, rt; (b) NaH, (*S*)-4-phenyl-2-oxazolidinone (**37a**), THF, 0°C, 98% (two steps); (c) $Me_3SiCH_2N(Bn)CH_2OMe$, TFA, Toluene, 0°C, 62%; (d) LiOH, H_2O_2, THF–H_2O, rt, 78%; (e) H_2, 20%Pd/C, EtOH, 70%. (f) NaH, (*S*)-4-phenyl-2-oxazolidinone (**37b**), THF, 0°C, 98% (two steps).

Ling, R., Ekhato, I. V., Rubin, J. R., & Wustrow, D. J. (2001). Synthesis of 4-alkyl-pyrrolidine-3-carboxylic acid stereoisomers. *Tetrahedron*, *57*(30), 6579-6588.

Same workers but now on a patent:

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

(10) **Patent No.: US 6,245,801 B1**
(45) **Date of Patent: Jun. 12, 2001**

(54) **BRANCHED ALKYL PYRROLIDINE-3-CARBOXYLIC ACIDS**

(75) Inventors: **Justin Stephen Bryans**, Balsham (GB); **Ihoezo Victor Ekhato**, Ann Arbor, MI (US); **David Christopher Horwell**, Cambridge (GB); **Rong Ling**, Ann Arbor, MI (US); **Jean-Marie Receveur**, Cambridge (GB); **David Juergen Wustrow**, Ann Arbor, MI (US)

(73) Assignee: **Warner-Lambert Company**, Morris Plains, NJ (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.: **09/673,277**

(22) PCT Filed: **Aug. 11, 1999**

(86) PCT No.: **PCT/US99/18258**

§ 371 Date: **Oct. 13, 2000**

§ 102(e) Date: **Oct. 13, 2000**

(87) PCT Pub. No.: **WO00/15611**

PCT Pub. Date: **Mar. 23, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/100,156, filed on Sep. 14, 1998.

(51) **Int. Cl.**[7] **A61K 31/40**; A61P 25/08;

(58) **Field of Search** 548/572; 514/423

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,087,544 5/1978 Satzinger et al. .

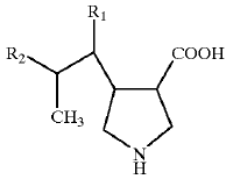
FOREIGN PATENT DOCUMENTS

96 06095 2/1996 (WO) .
96 15108 5/1996 (WO) .

Primary Examiner—Deborah C. Lambkin
Assistant Examiner—Andrea M D'Souza
(74) *Attorney, Agent, or Firm*—Elizabeth M. Anderson

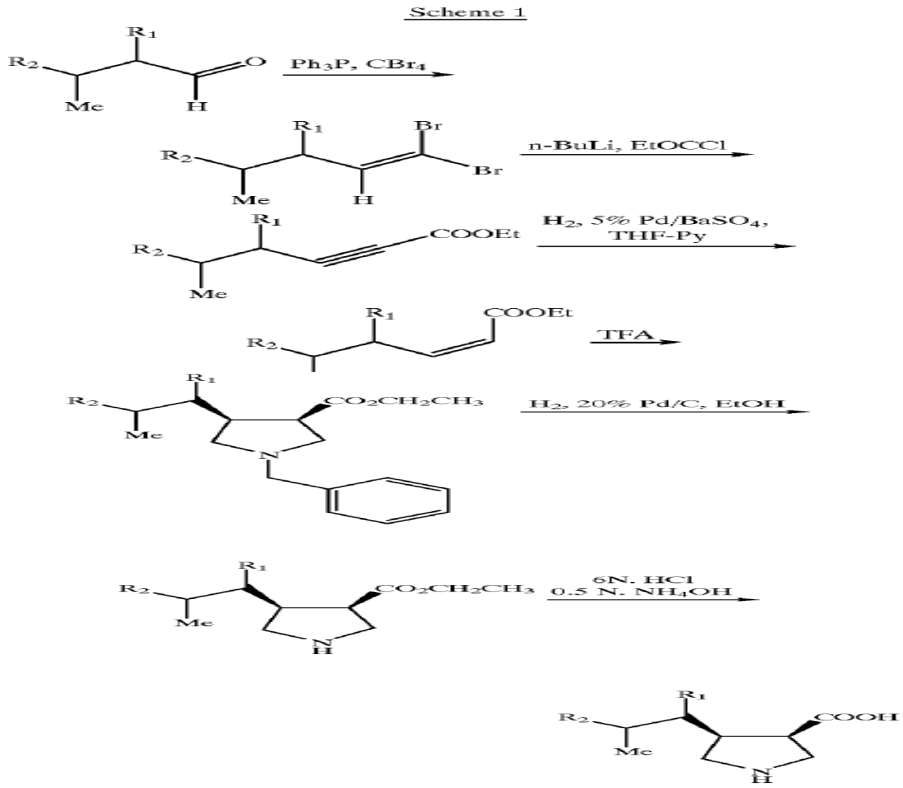
(57) **ABSTRACT**

(I)

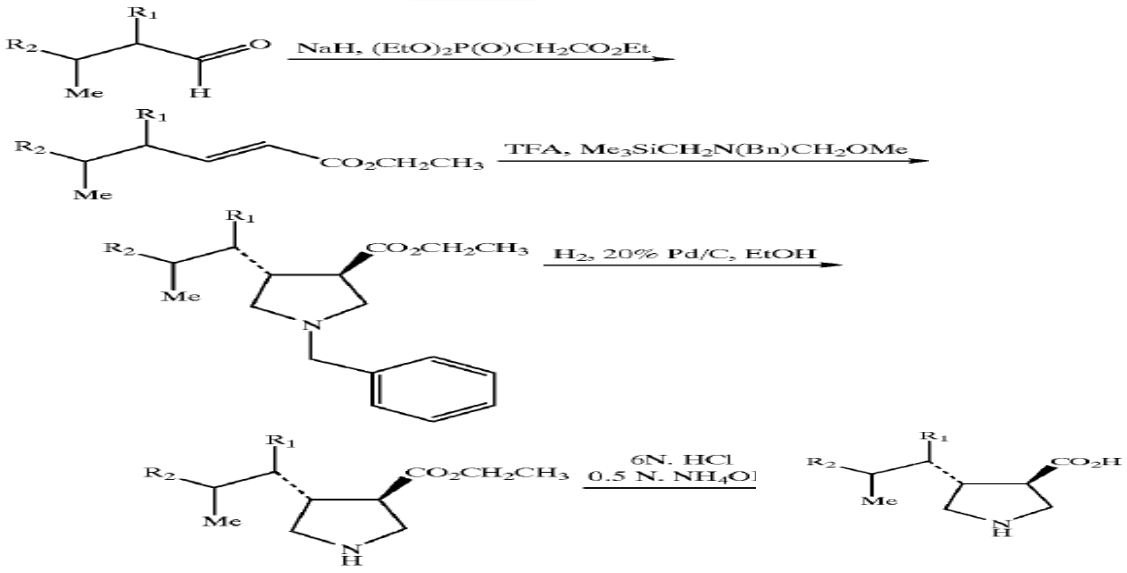


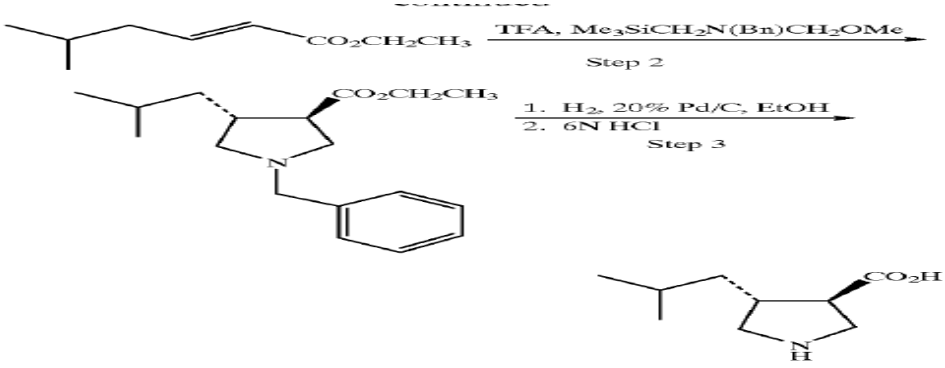
Branched alkyl pyrrolidines of formula (I) are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropatnological disorders. Processes for the preparation and intermediates useful in the preparation are also disclosed.

This patent describes several approaches to 3-carboxy derivatives:

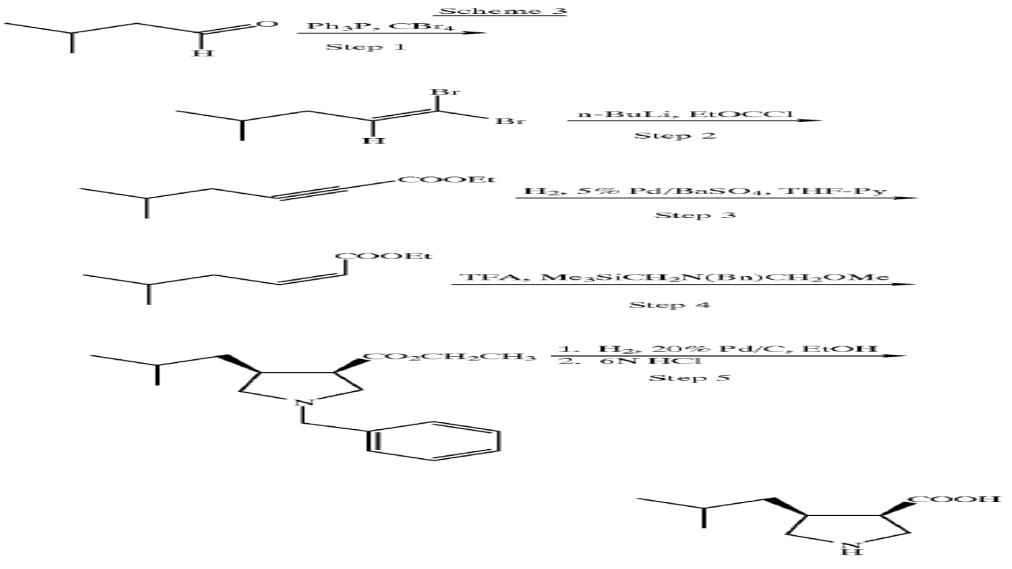


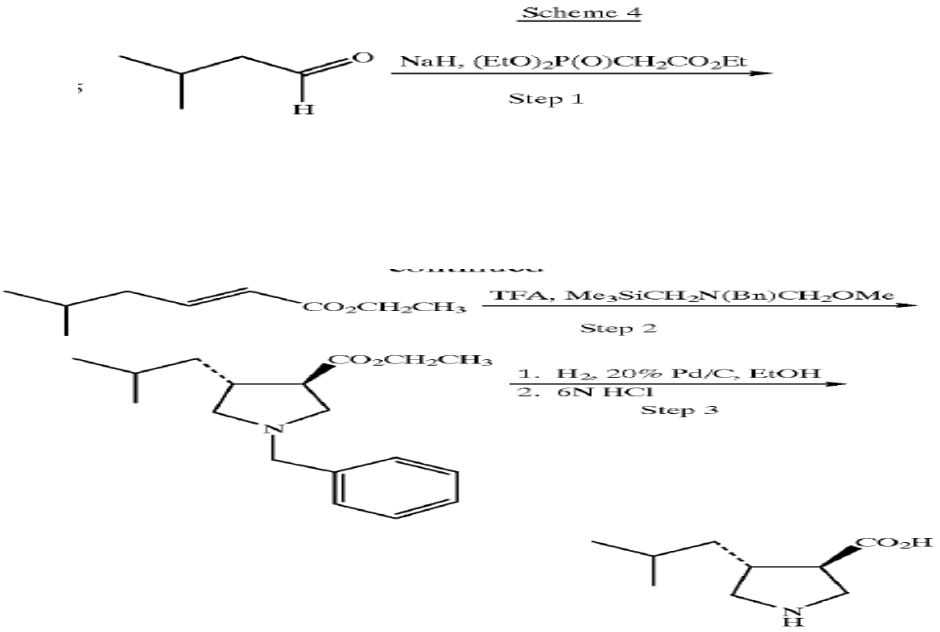
Scheme 2





Scheme 3





The problem here is the price of the above ylid.

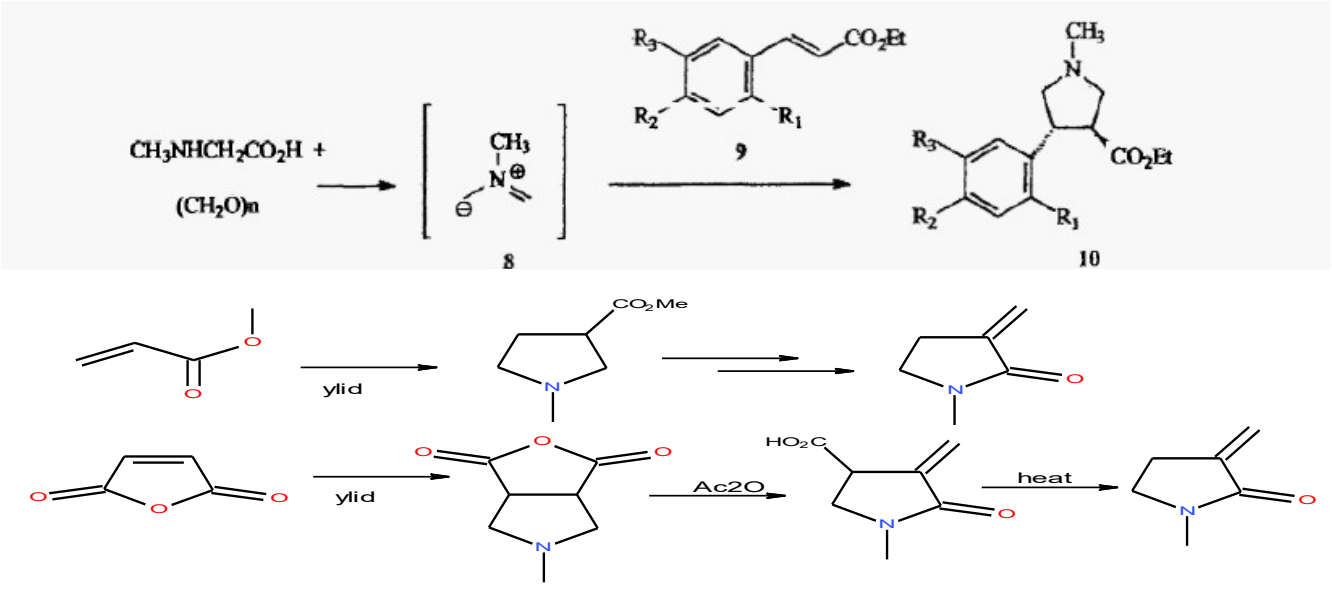
Also:

Chapman, K., Hale, J., Kim, D., Lynch, C., Shah, S., Shankaran, K., ... & Loebach, J. L. (2001). *U.S. Patent No. 6,248,755*. Washington, DC: U.S. Patent and Trademark Office.

Padwa, A., & Dent, W. (1987). Use of N-[(trimethylsilyl) methyl] amino ethers as capped azomethine ylide equivalents. *The Journal of Organic Chemistry*, *52*(2), 235-244.

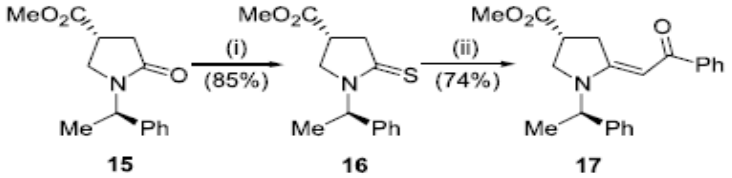
Pandey, G., Banerjee, P., & Gadre, S. R. (2006). Construction of enantiopure pyrrolidine ring system via asymmetric [3+ 2]-cycloaddition of azomethine ylides. *Chemical reviews*, *106*(11), 4484-4517.

A possible inexpensive ylid!

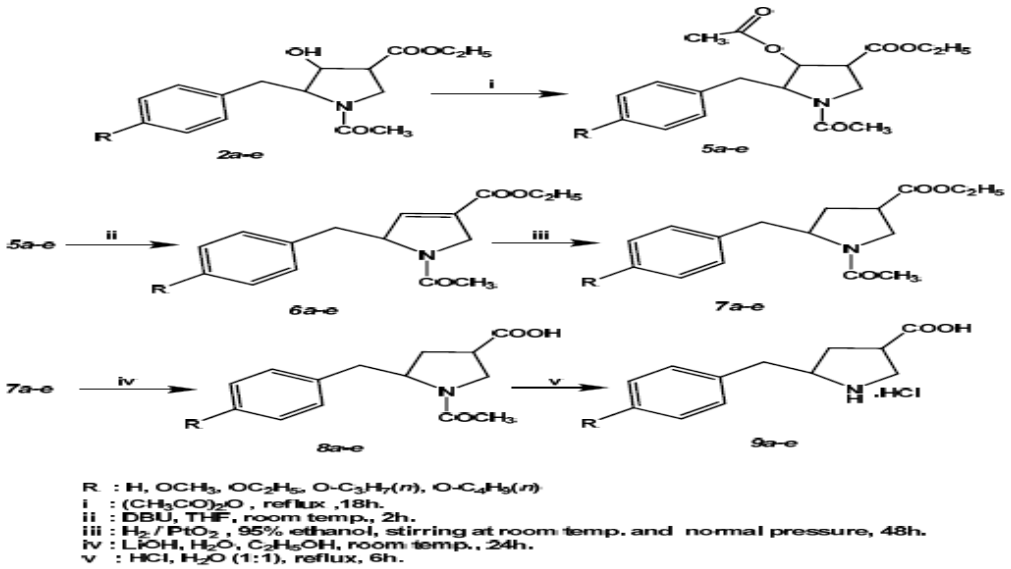


Scheme 2: The obvious reactions to form 3M2P

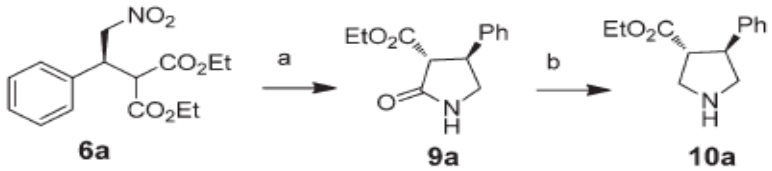
Nyerges, M., Virányi, A., & Tőke, L. (2003). A CONVENIENT SYNTHESIS OF PYRROLO| 3, 4-c| QUINOLINES. *Heterocyclic Communications*, *9*(3), 239-242.



Singh, R. K., Sinha, N., Jain, S., Salman, M., Naqvi, F., & Anand, N. (2005). A convenient and new approach to the synthesis of ω-heterocyclic amino acids from carboxy lactams through ring-chain-transformation. Part 2: Synthesis of (2R)-/(2S)-2-aminomethyl-3-(1-aryl-/1, 5-diaryl-1H-pyrazol-3-yl)-propionic acid. *Tetrahedron*, *61*(37), 8868-8874.

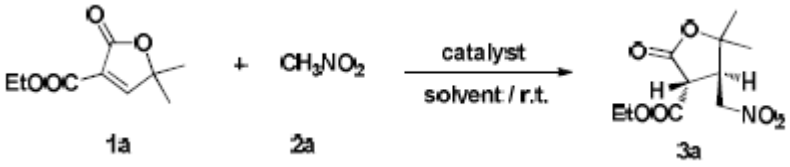


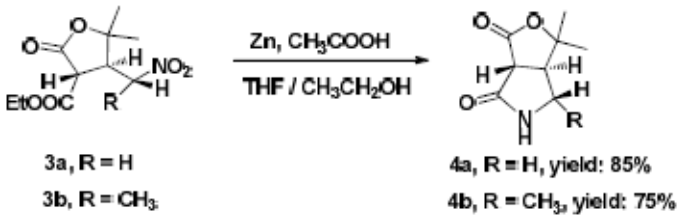
Aboul-Enein, M. N., El-Azzouny, A. A. E. S., Saleh, O. A., Nawwar, M. A. E. M., Ismail, M. A. E. H., Elsedeek, M. G. E. D., & Maklad, Y. A. (2010). Synthesis and preliminary biological screening of certain 5-aralkyl pyrrolidine-3-carboxylic acids as anticonvulsants. *European Journal of Chemistry*, *1*(2), 102-109.



Reagents: a) $NiCl_2 .6H_2O$ (1 equiv), $NaBH_4$ (8 equiv), MeOH, 0 °C-rt, 4 h; b) (i) $Et_3O^+BF_4^-$ CH_2Cl_2, rt, 14 h; (ii) $NaBH_3CN$, HCl (cat.), MeOH; 57% overall yield

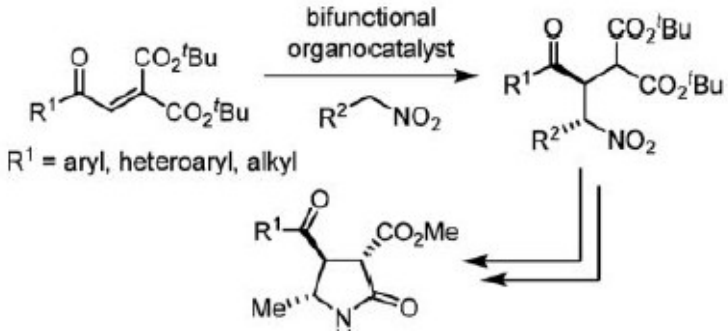
Hajra, S., Aziz, S. M., & Maji, R. (2013). Organocatalytic enantioselective conjugate addition of nitromethane to alkylidenemalonates: Asymmetric synthesis of pyrrolidine-3-carboxylic acid derivatives. *RSC advances*, *3*(26), 10185-10188.





Bai, Z., Ji, L., Ge, Z., Wang, X., & Li, R. (2015). Asymmetric Michael addition reactions of nitroalkanes to 2-furanones catalyzed by bifunctional thiourea catalysts. *Organic & biomolecular chemistry*, *13*(19), 5363-5366.

Note: I'm assuming that 4b can be reduced to a potential Rapoport rearrangement compound.

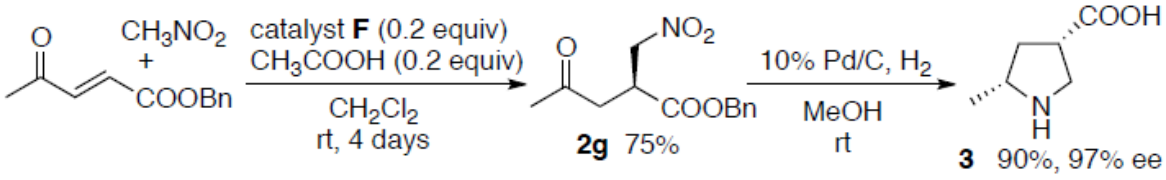


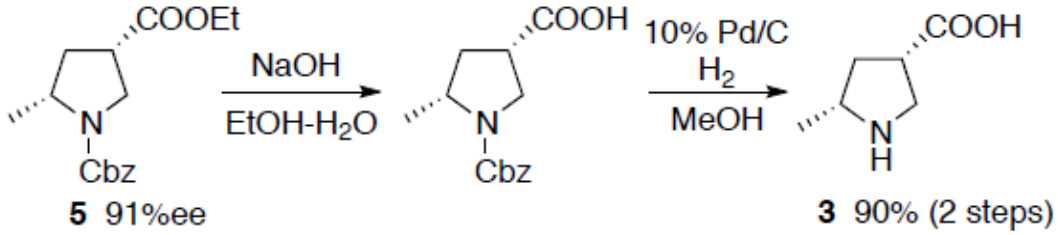
Horwitz, M. A., Fulton, J. L., & Johnson, J. S. (2017). Enantio-and Diastereoselective Organocatalytic Conjugate Additions of Nitroalkanes to Enone Diesters. *Organic letters*, *19*(21), 5783-5785.

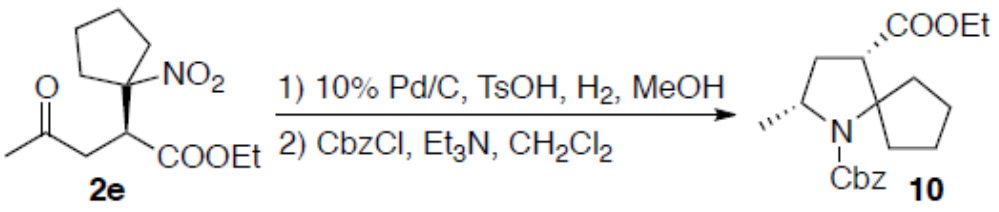
Here again reduction of the pyrrolidone should be possible.

5. Transformations of 2 to pyrrolidine-3-carboxylic acid and β²-amino acid derivatives

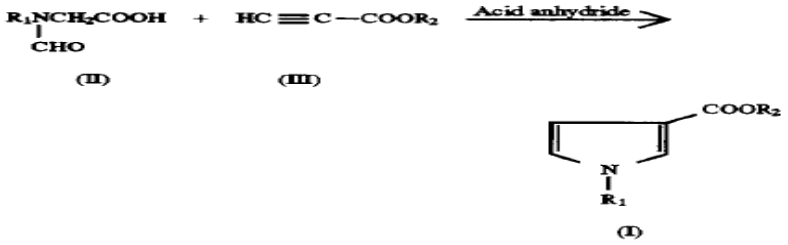
Synthesis of (3*S*,5*R*)-5-methylpyrrolidine-3-carboxylic acid (3) via 2g (Scheme 3)

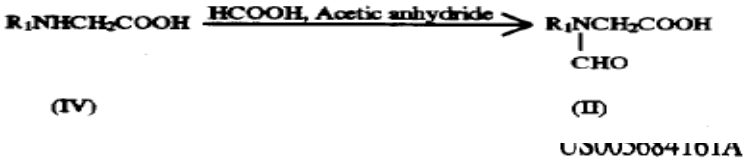






Yin, F., Garifullina, A., & Tanaka, F. (2017). Synthesis of pyrrolidine-3-carboxylic acid derivatives via asymmetric Michael addition reactions of carboxylate-substituted enones. *Organic & biomolecular chemistry*, *15*(29), 6089-6092.



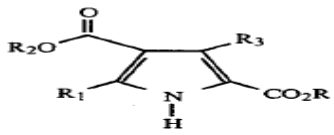


US005684161A

United States Patent [19] [11] **Patent Number: 5,684,161**

Imoto et al. [45] **Date of Patent: Nov. 4, 1997**

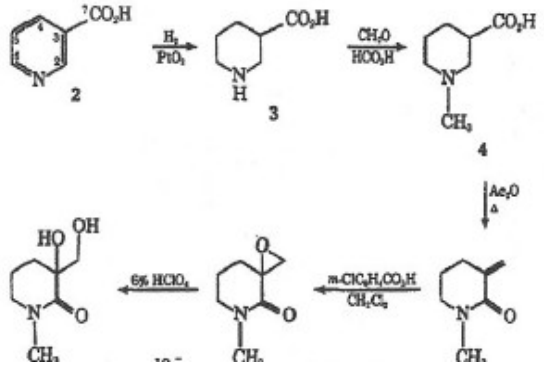
The carboxylic acids of formula II are prepared by hydrolysis of a corresponding ester of formula III



III

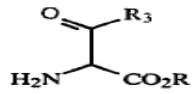
The cyclic α-ketoamide, 1-methyl-2,3-piperidinedione (**1**), was synthesized as shown in Scheme I. Nicotinic acid (**2**) was catalytically hydrogenated to quantitatively give **3**. Reductive methylation of **3** gave 1-methylnipecotic acid (**4**),[4] in quantitative yield, and **4** in refluxing acetic anhydride gave 1-methyl-3-methylene-2-piperidone (**5**)[5] in 93% yield. Epoxidation of

Scheme I



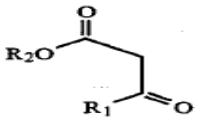
Rueppel, M. L., & Rapoport, H. (1972). Oxidation of. alpha.-ketoacyl derivatives. Rearrangement of pyruvates to malonates. *Journal of the American Chemical Society*, *94*(11), 3877-3883.

The esters of formula III are prepared by simple condensation of an amino ester of formula IV



IV

wherein R and R_3 are as defined above with a ketoester of formula V



V

United States Patent [19]
Schnettler et al.

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[45] **Date of Patent: Dec. 24, 1985**

[54] **PYRROLE-3-CARBOXYLATE CARDIOTONIC AGENTS**

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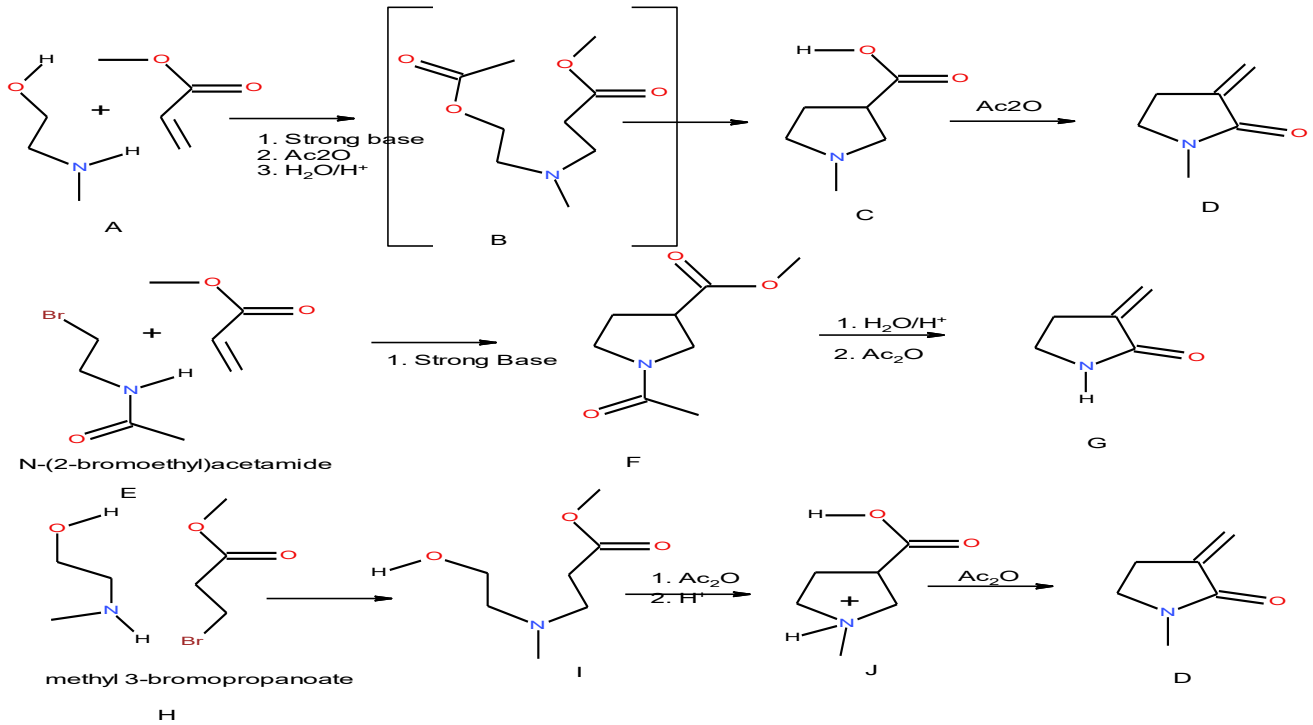
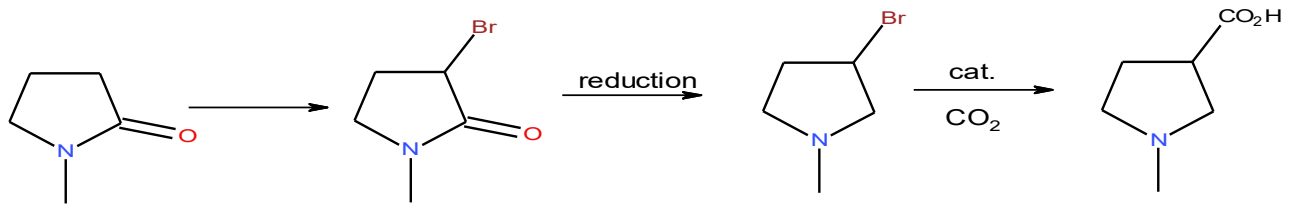
In some of the following schemes the free carboxylic acid and pyrrolidine are shown but in reality they sould be shown as the corresponding salts.



Scheme 3: Some ideas that if workable should be cost-effective. A-D employ inexpensive RM's. E-G might not work because the base can attack the bromine first but still worth a try? H-J here again the bromine might be a problem; however, if larger rings are desired this could be a possibility?



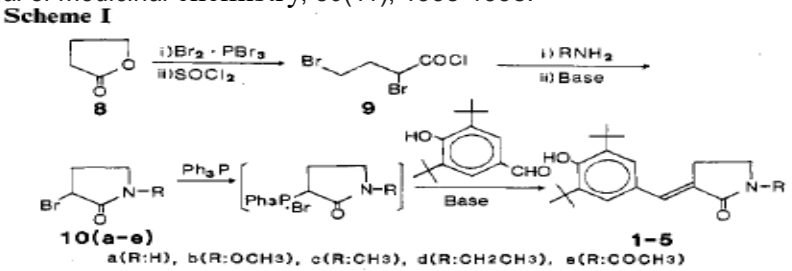
3-bromo-1-methyl-pyrrolidin-2-one

Scheme 4: Another suggested synthesis. Not sure if the Br would survive the reduction? See:

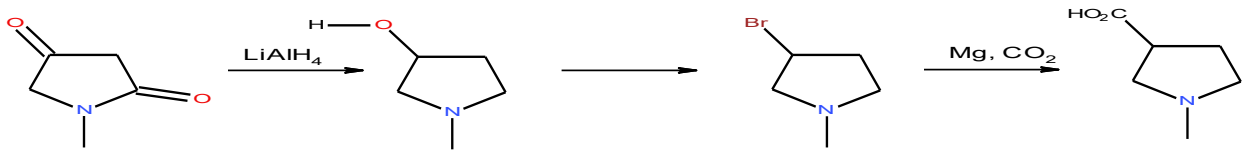
L Campbell, KG Pike, A Suleman, MJ Waring- US Patent 7,902,200, 2011 for Br derivative Ikuta, H., Shirota, H., Kobayashi, S., Yamagishi, Y., Yamada, K., Yamatsu, I., &

Katayama, K. (1987). Synthesis and anti-inflammatory activities of 3-(3, 5-di-tert-butyl-4-hydroxybenzylidene)

pyrrolidin-2-ones. *Journal of medicinal* chemistry, *30*(11), 1995-1998.



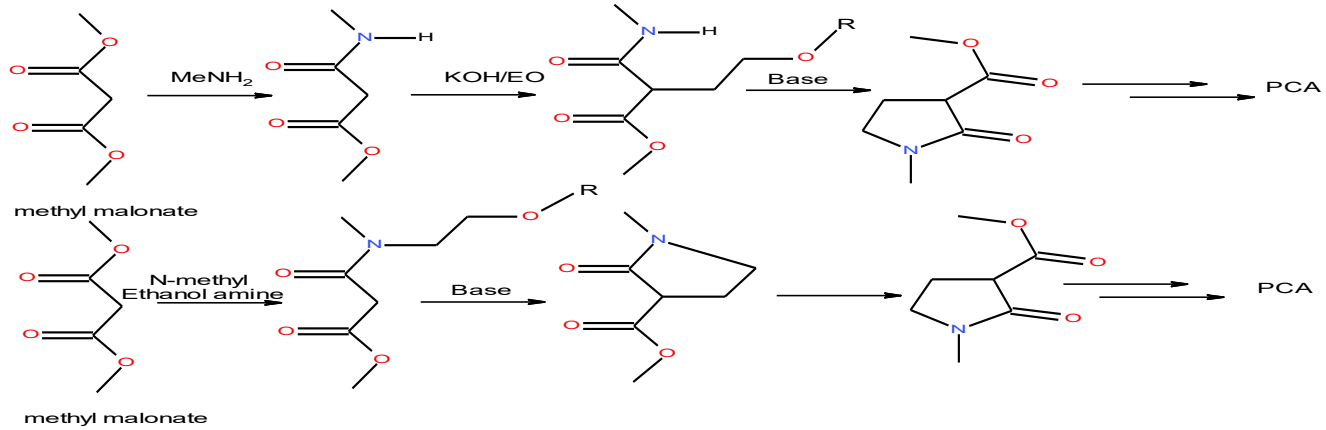
I would think there are simpler ways to synthesize the 3 Br derivative? However once in hand, the rest seems straight forward.



1-methylpyrrolidine-2,4-dione

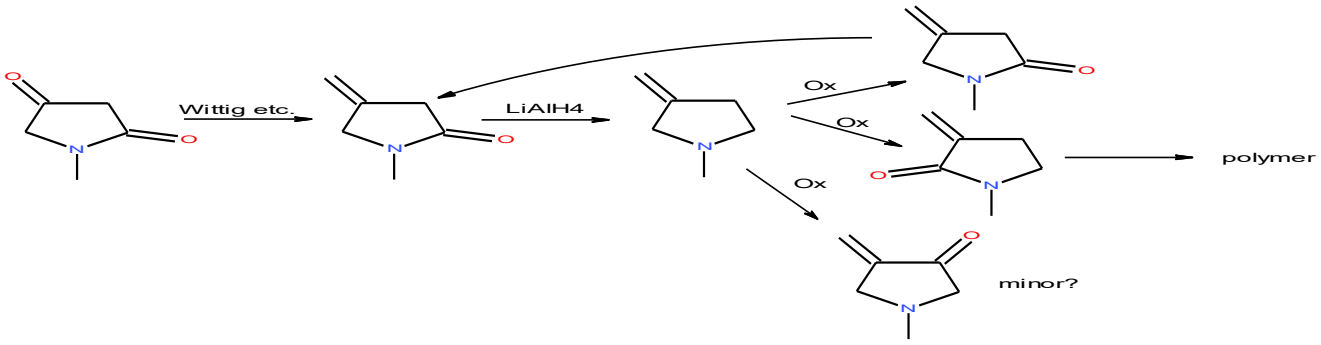
N-methyl Tetramic Acid

Scheme 5: Tetramic acids are readily prepared and should be an inexpensive route to PCA's.

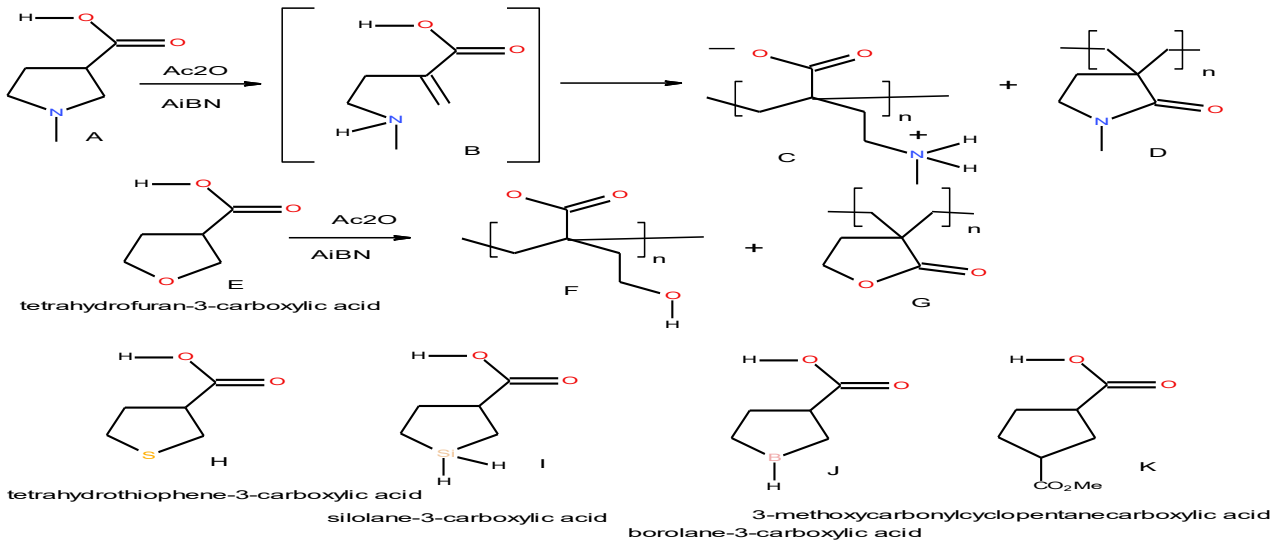


Scheme 6: I think if the above works, it would be a low cost route. The R groups can be selected from more active leaving groups should that be necessary. Conversion to PCA can be accomplished by the

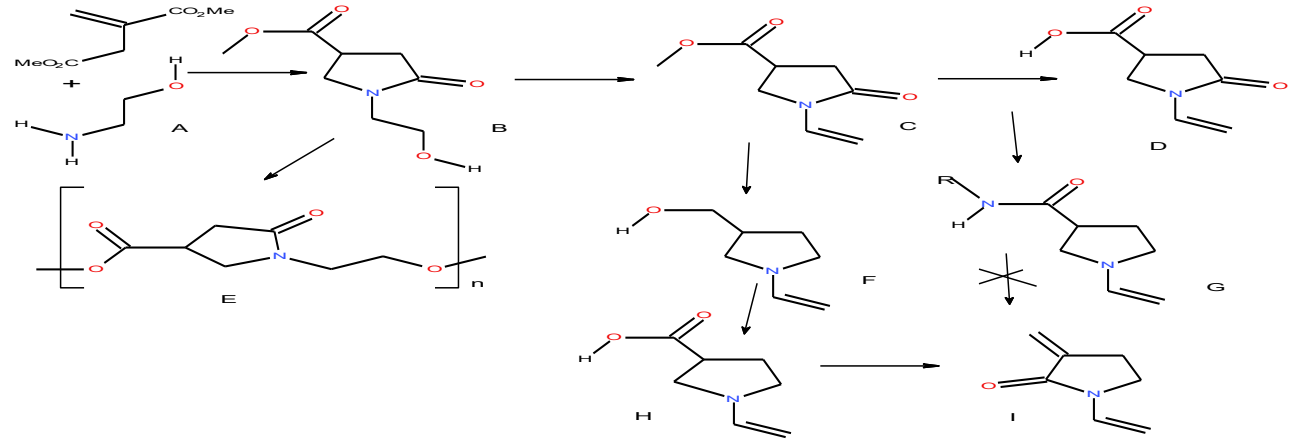
least expensive previously illustrated reductions.



Scheme 7: Tetramic acid can be treated with a Wittig etc to form the methylene. Reduction forms the pyrrolidine which can be oxidized to the starting compound or the product.

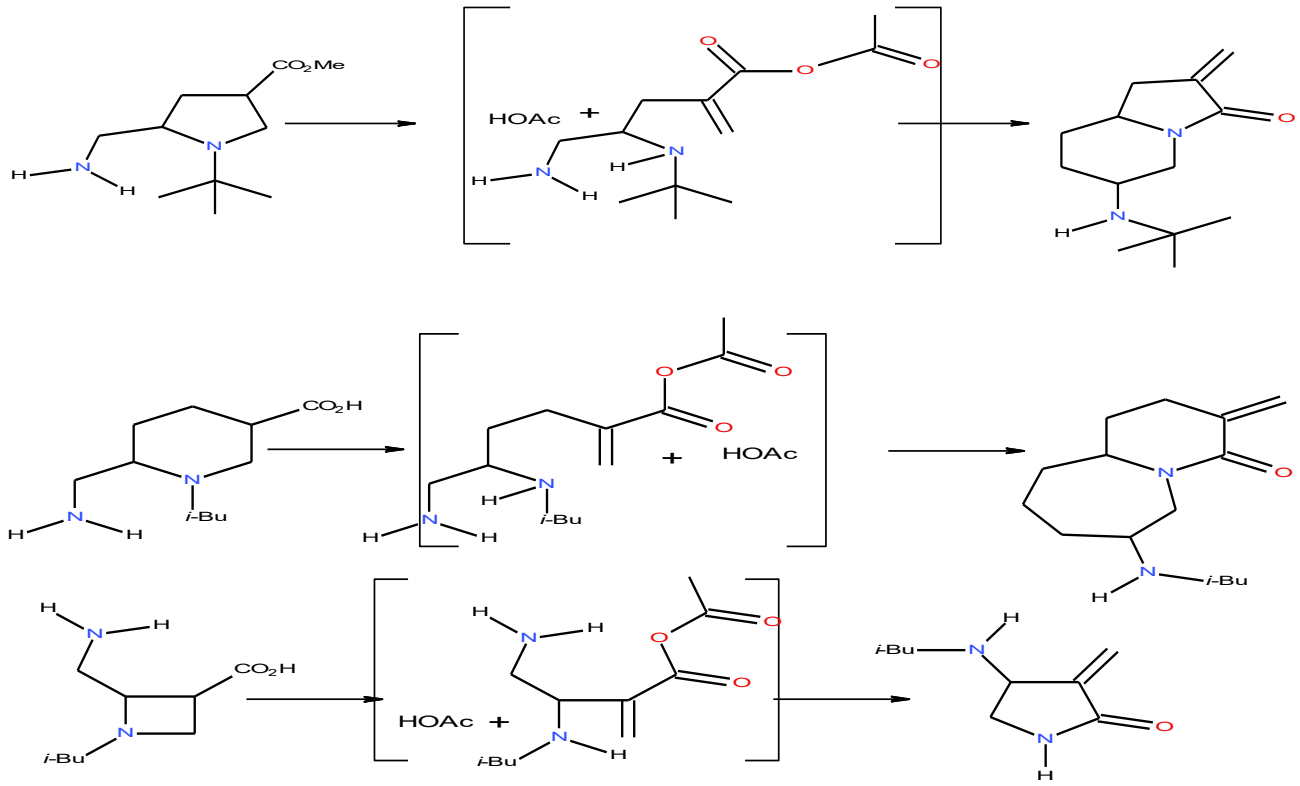


Scheme 8 :Here I present the possibility of trapping the intermediate B as a free radical polymerizeable monomer. Can C be the only product or is a mixture with D also produced? Can E also undergo this rearrangement? Compounds G-J are other rearrangement possibilities? I'm suggesting that B type intermediates have a life-time long enough for the above polymer possibilities.



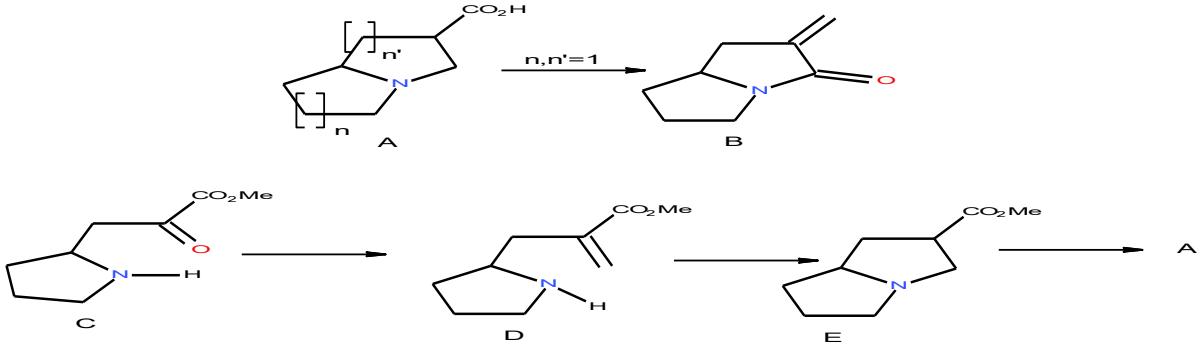
Scheme 9: Can itaconic acid react with ethanol amine resulting in C for example? It is known that B can be dehydrated to C. I think that G would not undergo the rearrangement? Can the N-vinyl

derivative survive the other reactions? “I” would afford an interesting crosslinker. Also the polyester E would be interesting as a biodegradable possibility?



Scheme 10: Can the pyrrolidine nitrogen be sterically blocked too favor another attached amine? Can this be applied to other diamines? Can the application of the Rapoport's rearrangement be expanded?

The potential flaw here is that the free amine can be attacked by acetic anhydride but it would inactuality be protected by nuetralizalization with acetic acid; however, the idea seems worth a try?



Scheme 11: Pyrrolizines, indolizine and related bicyclic ideas.

Thank you for reading these proposals!

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