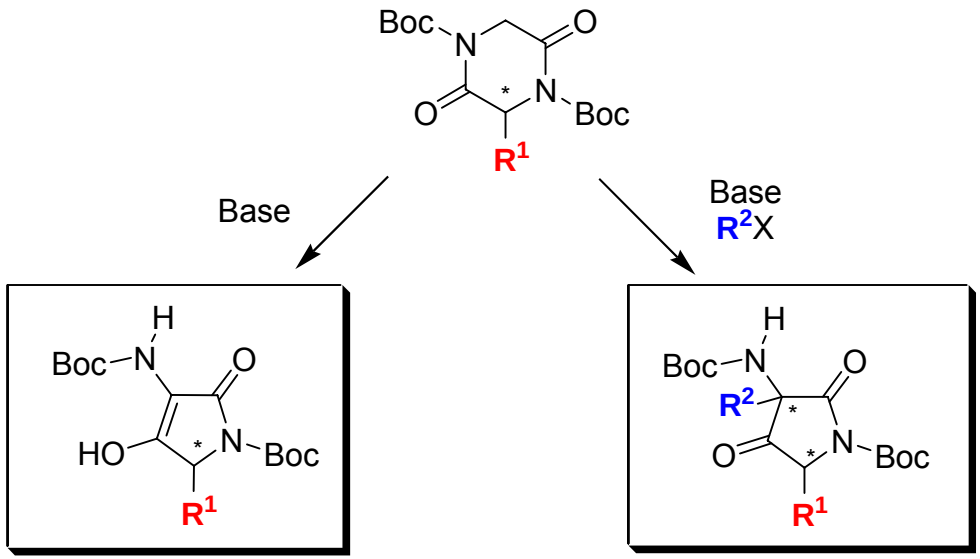
Transannular Rearrangement of Activated Lactams: Stereoselective Synthesis of Substituted Pyrrolidine-2,4-diones from Diketopiperazines

Daniel Farran, Isabelle Parrot, Jean Martinez, Georges Dewynter
Angew. Chem. Int. Ed. 2007, early view

Current Literature Presentation
Shuli Mao
09/15/07

Transannular Rearrangement of Activated Lactams (TRAL): A Serendipitous Finding

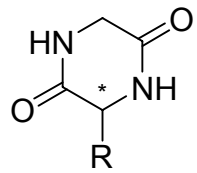


G. Dewynter, D. Farran, J. Martinez, Patent No. 0753973, deposited March 21, **2007**.

Outline

- Biological Activities and Synthesis of 2,5-DKPs
- Biological Activities and Synthesis of Pyrrolidine-2,4-diones
- Title Paper
- Summary and Future Directions

2,5-Diketopiperazines(DKPs)

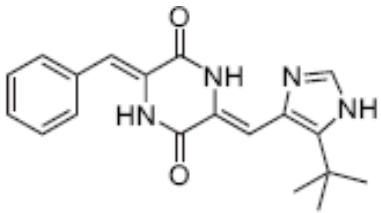


Characteristics:

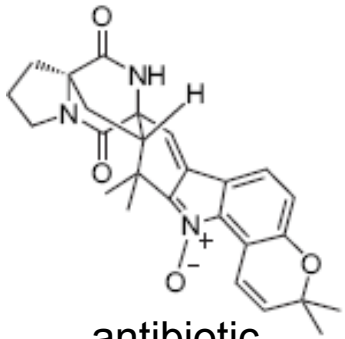
1. *The smallest cyclic peptide derived from the folding head-to-tail of a linear dipeptide*
2. *Structure is rigid and can be chiral molecule and can be functionalized*

Biological Activities:

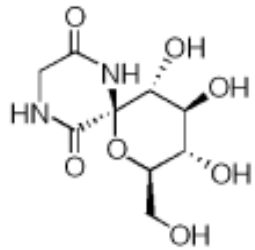
Inhibition of plasminogen activator inhibitor-1 (PAI-1), alteration of cardiovascular and blood-clotting functions, activity as antitumor, antiviral, antifungal, antibacterial agents etc.



antitumor activity (IC_{50}:4.3-18nM); being test in preclinical studies



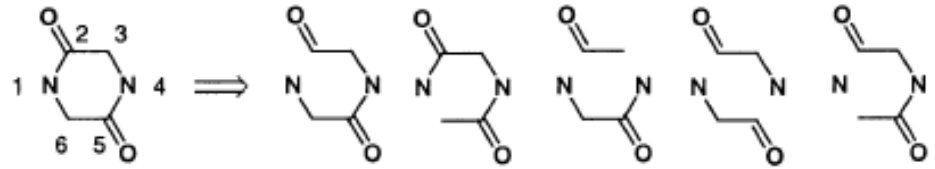
antibiotic



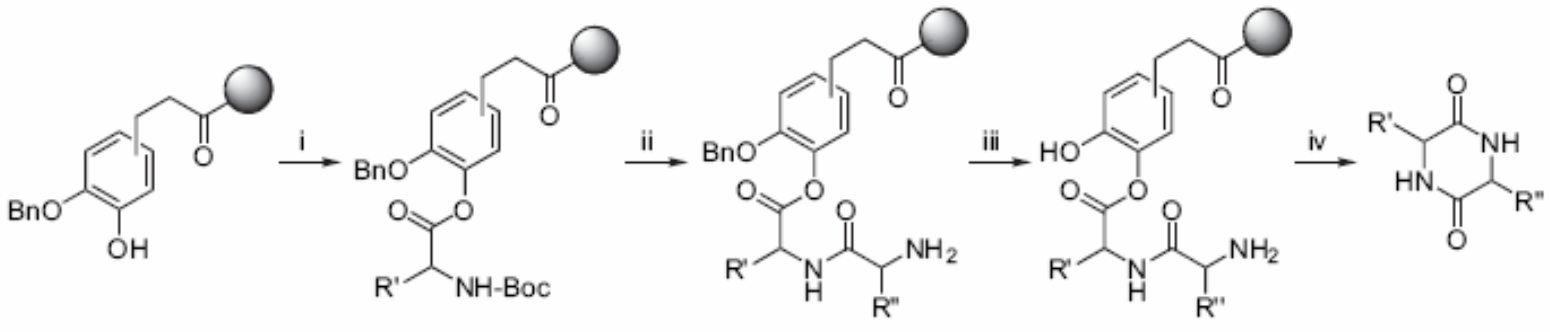
Inhibition of glycogen phosphorylase

Reviews:(a) “Diketopiperazines: biological activity and synthesis” Martins, M. B.; Carvalho, I. *Tetrahydron* **2007**, *63*, 9923. (b) “Recent advances in the synthesis of diketopiperazines” Dinsmore, C. J.; Beshore, D. C. *Tetrahydron* **2002**, *58*, 3297. (c) “Diketopiperazines in peptide and combinatorial chemistry” Fischer, P. M. *J. Pept. Sci.* **2003**, *9*, 9.

Synthesis of 2,5-Diketopiperazines



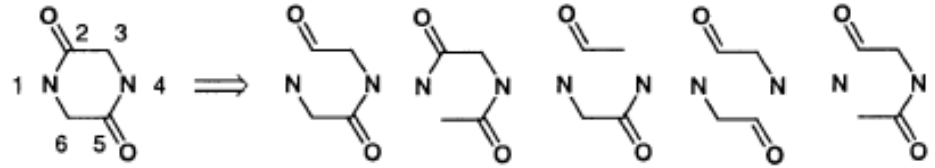
(a) Intramolecular formation of N1-C2



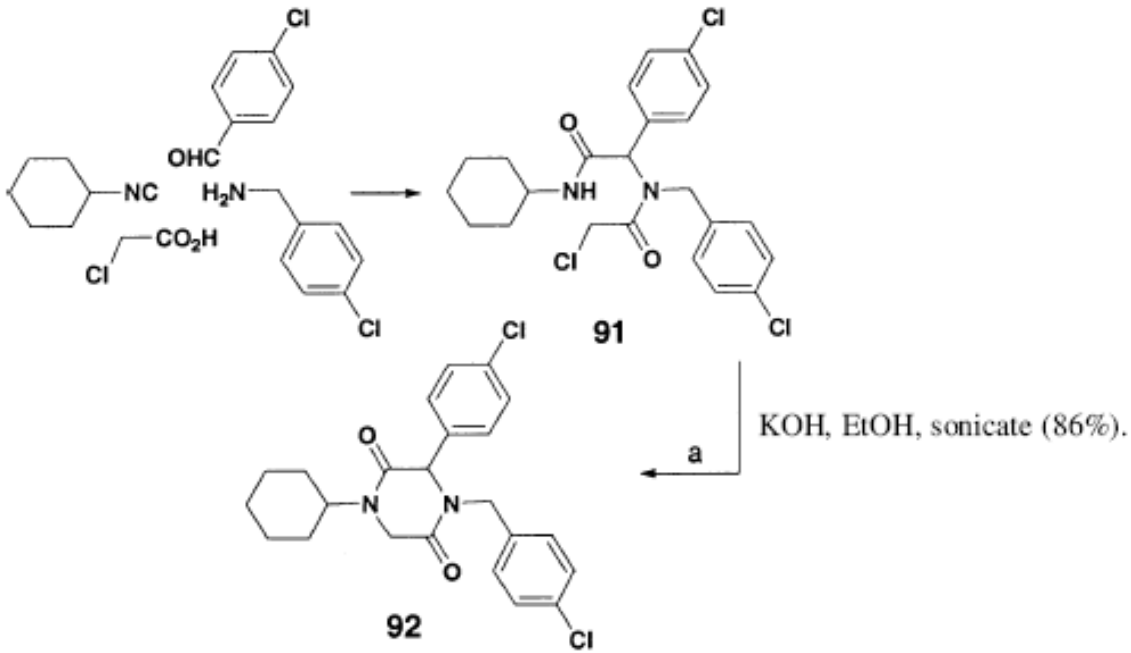
(i) Boc-AA–OH, DIC, DIEA; (ii) Boc-based solid-phase peptide synthesis; (iii) TFMSA, TFA; (iv) DIEA.

(1) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1138.
(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Mol. Divers.* **2000**, *5*, 289.

Synthesis of 2,5-Diketopiperazines

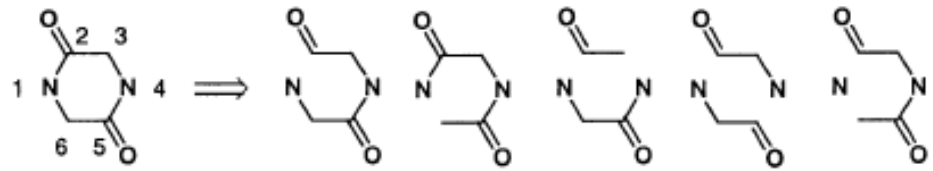


(b) Intramolecular formation of N1-C6

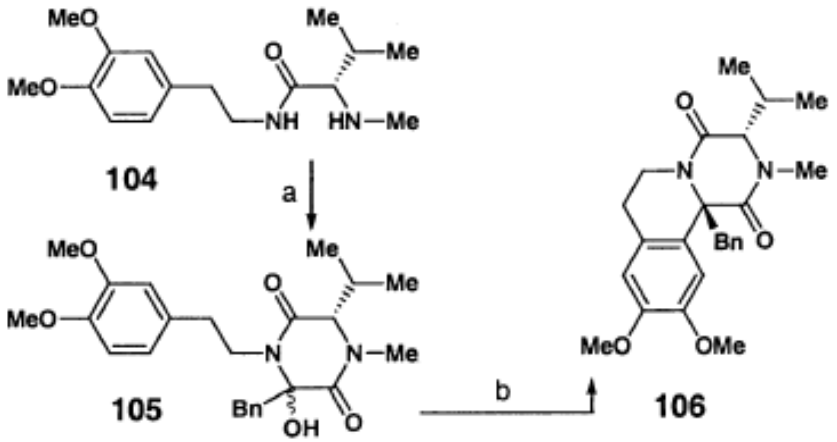


Marcaccini, S.; Pepino, R.; Pozo, M. A. *Tetrahedron Lett.* **2001**, *42*, 2727.

Synthesis of 2,5-Diketopiperazines

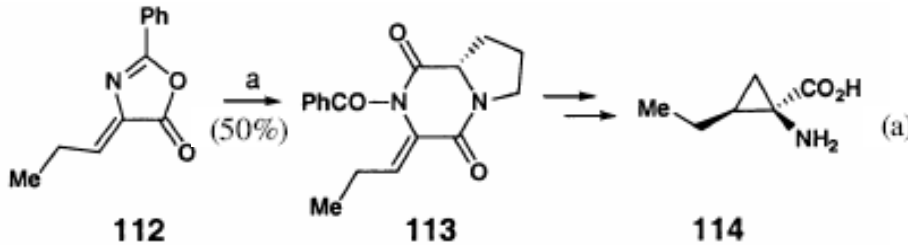


(c) Tandem formation of N1-C2/C3-N4



(a) $PhCH_2COCO_2H$, BOP, Et_3N, ACN (70%); (b) HCl, MeOH (>95%).

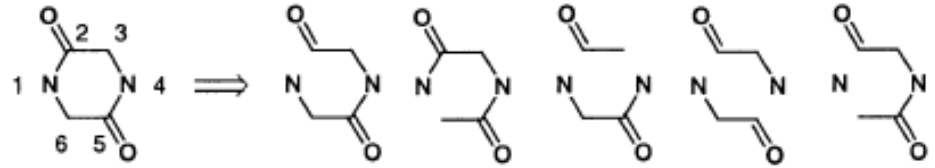
(d) Tandem formation of N1-C2/N4-C5



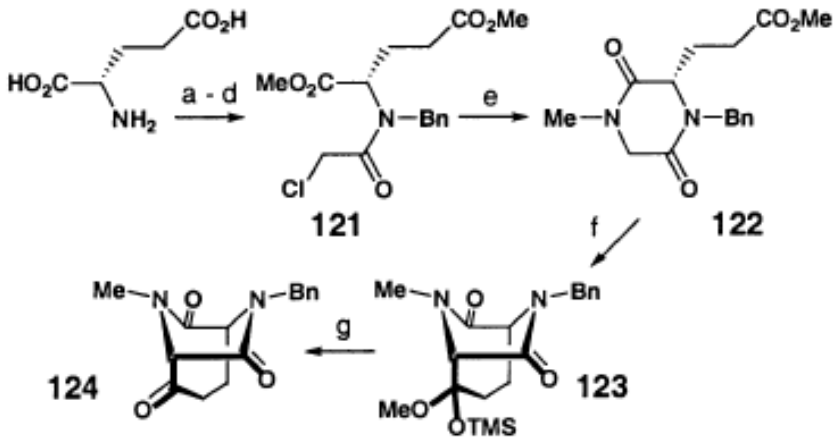
(a) (*S*)-Proline, NaOH, H_2O/Me_2CO, then Ac_2O

(1) Zawadzka, A.; Leniewski, A.; Maurin, J. K.; Wojtasiewicz, K.; Czarnocki, Z. *Org. Lett.* **2001**, *3*, 997. (2) Alcaraz, C.; Herrero, A.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1992**, *33*, 5605.

Synthesis of 2,5-Diketopiperazines



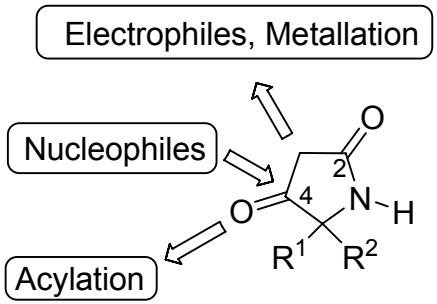
(e) Tandem formation of C2-N1-C6



Scheme 39. *Reagents*: (a) TMSCl, MeOH; (b) PhCHO; (c) $NaBH_4$; (d) $ClCH_2COCl$; (e) $MeNH_2$ (87%); (f) LiHMDS, THF, then TMSCl; (g) TsOH, THF/H_2O (82%).

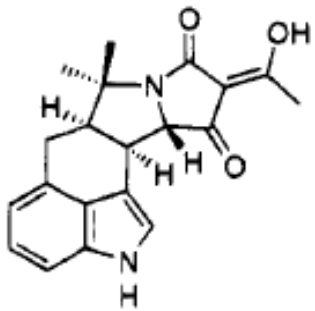
Weigl, M.; Wünsch, B. *Org. Lett.* **2000**, *2*, 1177.

Pyrrolidine-2,4-diones (Tetramic Acids)



- 3-Acyl derivative of tetramic acid (common)
- 4-*O*-alkyl ether derivative of tetramic acid (less common)

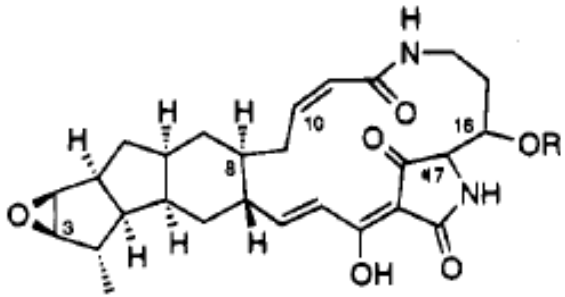
Spectrum of biological activity: antibiotic, antiviral, antiulcerative, cytotoxicity, mycotoxicity, tumor inhibition and fungicidal action



α-Cyclopiazonic acid

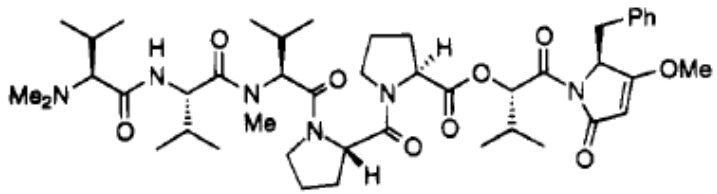
very toxic (LD_{50}:2-6 $mgkg^{-1}$)

potent inhibitor of calcium uptake and Ca^{2+}ATP-ase activity



Discodermide

antifungal and antitumor agent

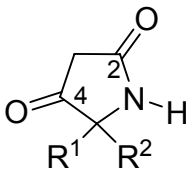


Dolastatin 15

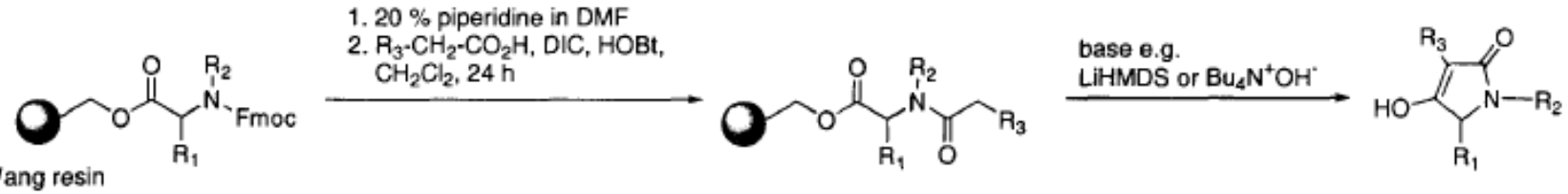
potent cytostatic agent against P388 leukemia cells

Reviews: "Naturally occurring tetramic acids: structure, isolation and synthesis" Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981.

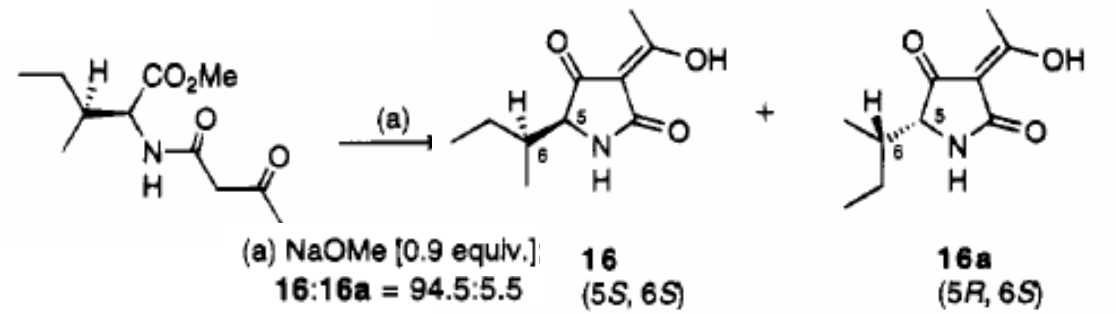
Synthesis of Pyrrolidine-2,4-diones



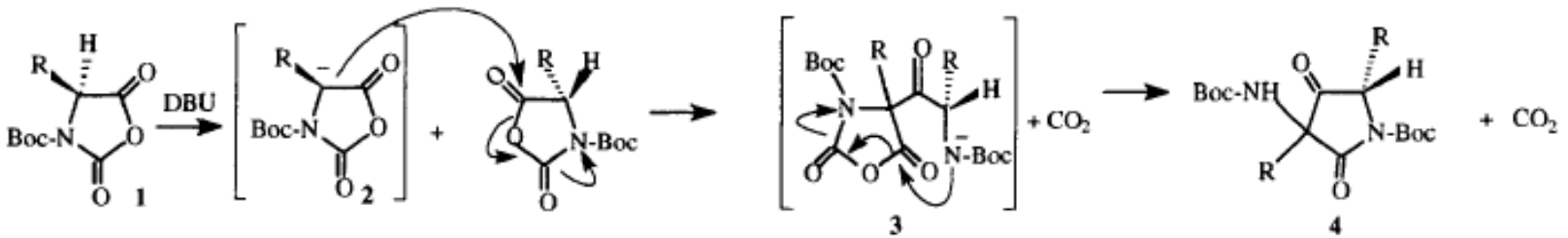
Solid-phase synthesis of tetramic acids via Claisen-type condensation:



Enantioselective Lacey-Dieckmann Cyclizations:



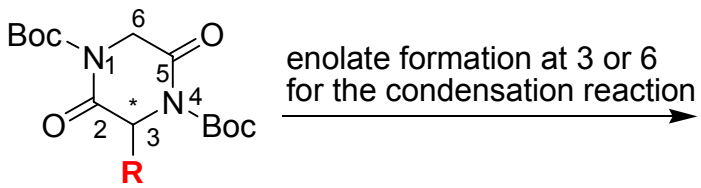
Via urethane N-carboxyanhydrides (UNCAs or Leuchs' anhydrides):



(1) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 4369. (2) Poncet, J.; Jouin, P.; Castro, B.; Nicolas, L.; Boutar, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 611. (3) Pothion, C.; Fehrenta, J.-A.; Aumelas, A.; Loffet, A.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 1027.

Title Paper

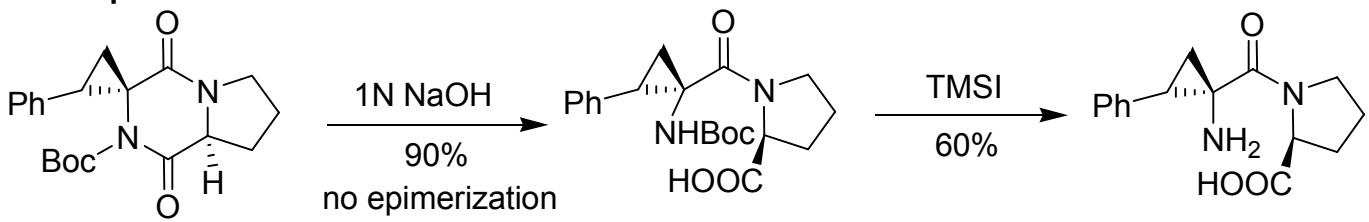
Original Plan:



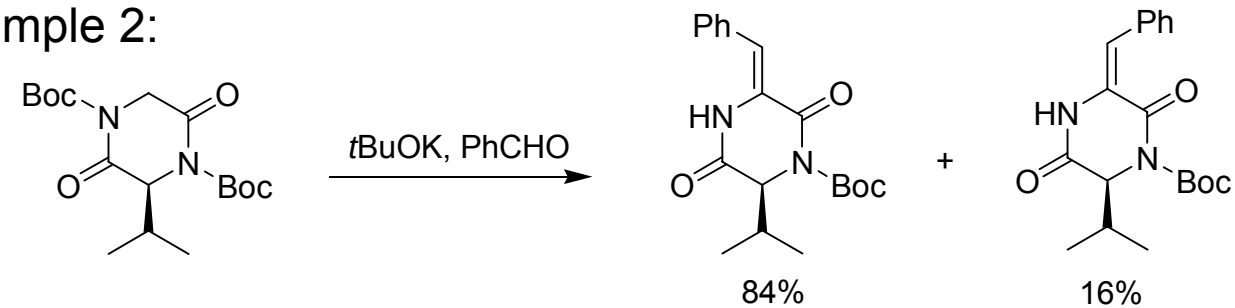
Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem. Int. Ed.* **2007**, early view

Reactions of Boc-DKPs under basic condition:

Example 1:

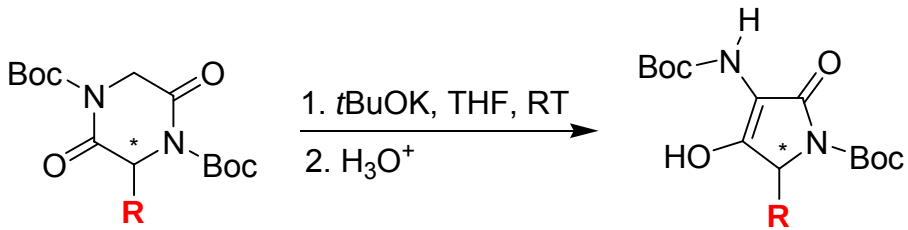


Example 2:



(1) Alcaraz, C.; Herrero, A.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1992**, *33*, 5605. (2) Oba, M.; Terauchi, T.; Owari, Y.; Imai, Y.; motoyama, I.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1275.

Stereoselective Ring Contraction of Unsymmetrical DKPs into 3-Aminotetramates

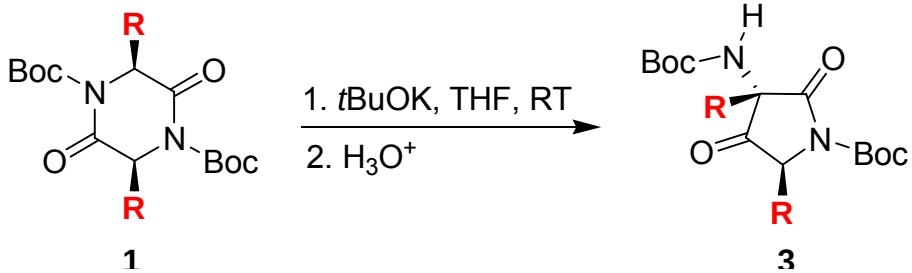


1 **2**

Entry	1	R	Product (ee)	Yield[c] [%]
1	**1a**	H	**2a**	72
2	**1b**	Me (*S*)	**2b** (>99%)[a]	60
3	**1c**	Me (*R*)	**2c** (>99%)[a]	64
4	**1d**	*i*Pr (*S*)	**2d** (>99%)[a]	82
5	**1e**	*i*Pr (*R*)	**2e** (>99%)[a]	84
6	**1f**	*s*Bu (*S*)	**2f** (>95%)[b]	71
7	**1g**	Bn (*S*)	**2g**	16[d]

[a] The diastereoisomeric excess was determined by chiral HPLC.
[b] The ^{13}C NMR spectrum gave only one set of peaks.
[c] Yield of isolated product after purification by flash chromatography.
[d] The product from thermodynamic enolate was obtained in 46% yield.

Stereoselective Ring Contraction of Symmetrical DKPs into Pyrrolidine-2,4-diones

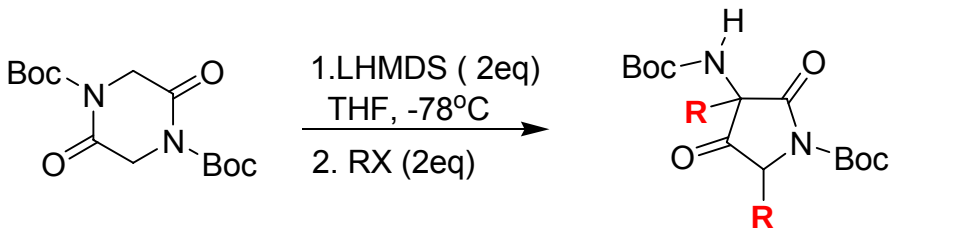


1 3

Entry	1	R	Product (de)	Yield[e] [%]
1	**1g**	Me (*S*)	**3h** (67%)[a,b]	66
2	**1h**	*i*Pr (*S*)	**3i**[c] (>95%)[b,d]	68
3	**1i**	$MeO_2C(CH_2)_2$ (*S*)	**3j** (>95%)[d]	29[f]

[a] The diastereoisomeric excess was determined by HPLC of crude.
[b] The relative configuration was determined by nOe analysis (concerning **3h**: this determination occurred after separation of the two diastereoisomers)
[c] **1i** was not isolated because **3i** was obtained during the activation of *cyclo*-[L-Val-L-Val] in conventional conditions (Boc_2O, DMAP, DMF, r.t.).[#]
[d] The ^{13}C NMR spectrum gave only one set of peaks.
[e] Yield of isolated product after purification by flash chromatography.
[f] The product from retro-Michael reaction was obtained in 42% yield.

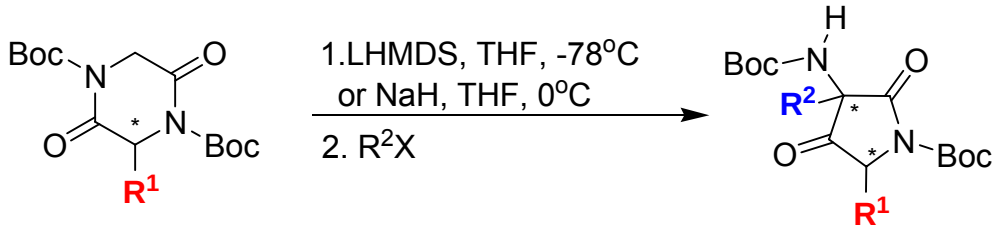
Tandem Rearrangement-alkylation of Symmetrical DKPs



1a

4a (R = allyl, 62%, de>95%)
4b (R = Bn, 57%, de>95%)

Tandem Rearrangement-alkylation of Unsymmetrical DKPs

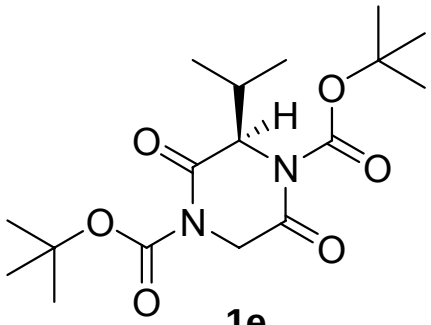


1 **5**

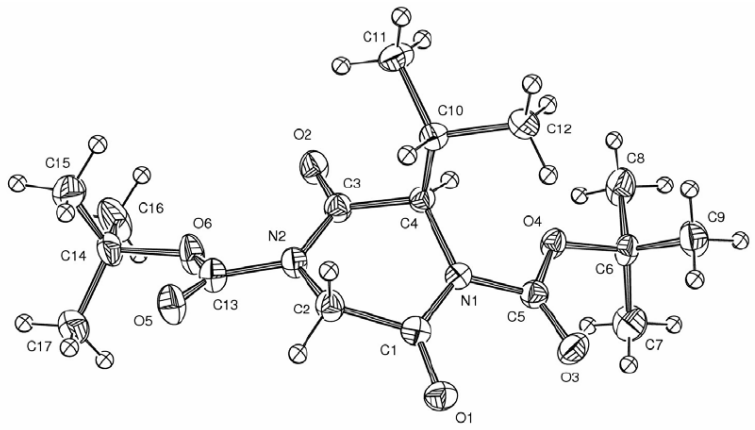
Entry	**1**	R^1	R^2X	Product	Base	Yield[b] [%] (de)
1	**1e**	*i*Pr (*R*)	MeI	**5a**[a]	LiHMDS	60 (>95%)[c]
					NaH	63 (>95%)[c]
					*t*BuOK	0
2	**1e**	*i*Pr (*R*)	BnBr	**5b**[a]	LiHMDS	72 (>95%)[c]
					NaH	62 (>95%)[c]
3	**1e**	*i*Pr (*R*)	EtO_2CCH_2I	**5c**	LiHMDS	69 (>95%)[c]
					NaH	0
4	**1e**	*i*Pr (*R*)	CH_2=$CHCH_2Br$	**5d**	LiHMDS	76 (>99%)[d]
					NaH	75 (>99%)[d]
5	**1e**	*i*Pr (*R*)	$(CH_3)_2C$=$CHCH_2Br$	**5e**	LiHMDS	84 (>95%)[c]
6	**1f**	*s*Bu (*S*)	CH_2=$CHCH_2Br$	**5f**	LiHMDS	68 (>95%)[c]

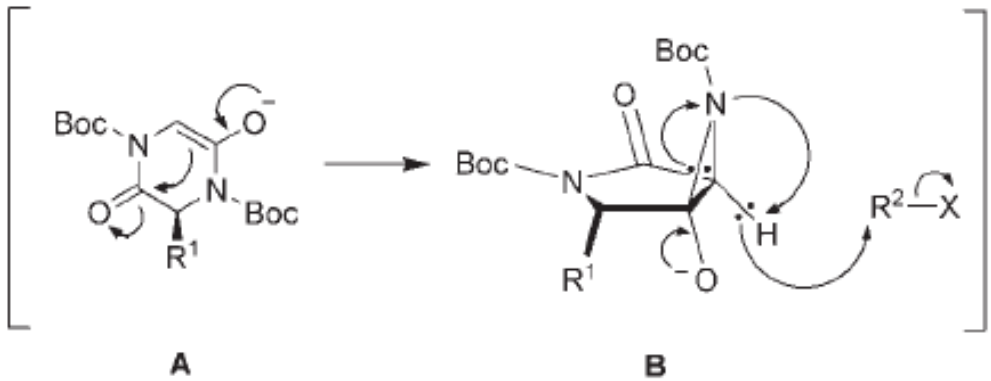
[a] The relative configuration was determined by nOe analysis.
[b] Yield of isolated product after purification by flash chromatography.
[c] The ^{13}C NMR spectrum gave only one set of peaks.
[d] The diastereoisomeric excess was determined by comparison of HPLC crude analysis between **5d** and **7**.

Plausible Mechanism to Explain the Stereochemistry



1e

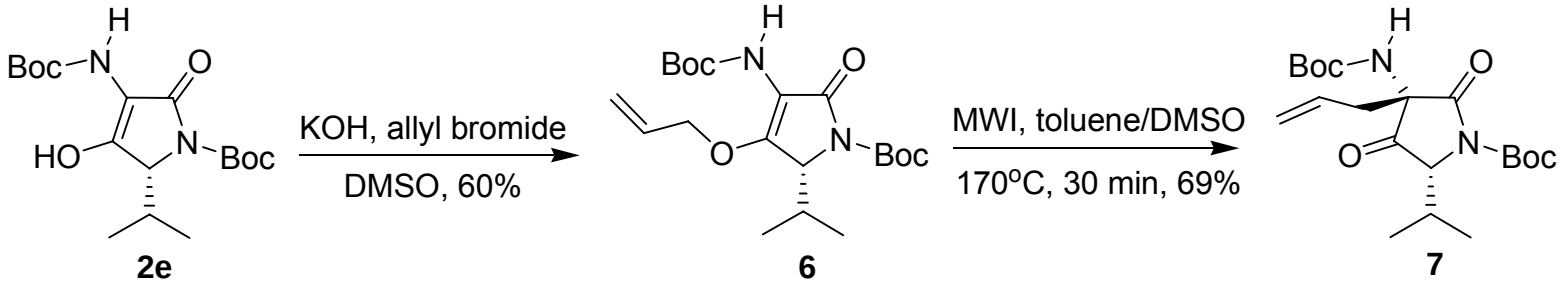




A **B**

Related reactions: Dieckmann and Gabriel-Colman reaction; Dakin-West reaction

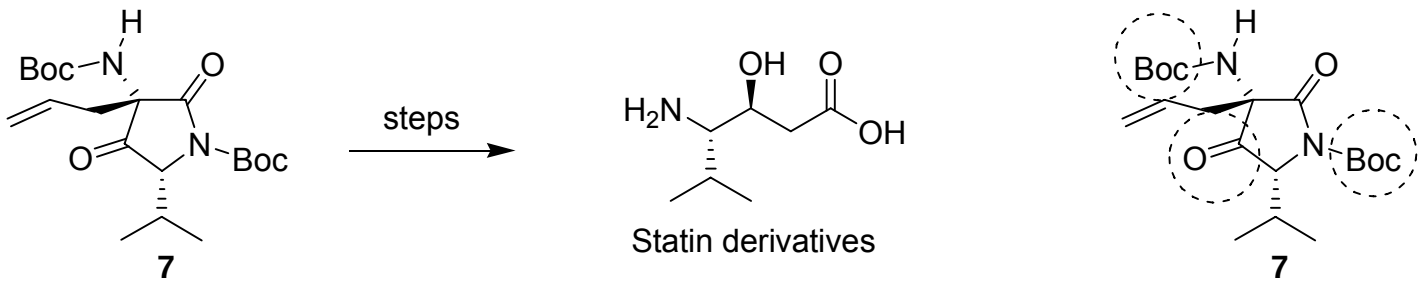
Scope Expansion: TRAL-Claisen Rearrangement



2e **6** **7**

Stereochemistry controlled via chair-like TS

What can you do with compound **7**?



7 **7**

Statin: constitutent of the naturally occuring peptide antibiotic Pepstatin, which functions as an unselective inhibitor of acid proteases such as renin, pepsin and cathepsin D.

Summary and Future Directions

- Pyrrolidine-2,4-diones was synthesized in a single step via ring contraction from DKPs;
- Reaction conditions are mild and the reaction is highly stereoselective;
- This methodology will be extended to make statine derivatives;
- Diversity can be introduced to these heterocyclic building blocks for library synthesis;
- Pyrrolidine-2,4-diones may have potential use as chiral auxillary;
- These new amino-acid derivatives can be used for the synthesis of pseudo-peptides or peptoids.

Comments from the Audience

(1) A similar acyclic version of this kind of rearrangement has been published from the Wipf group (*Org. Lett.* **2001**, *3*, 1261.) The mechanism of this rearrangement is not totally clear. (Radical may be involved?)

(2) The stereochemistry of compounds 5(a-f) was not shown in Table 3, although in the supporting information they have this information.