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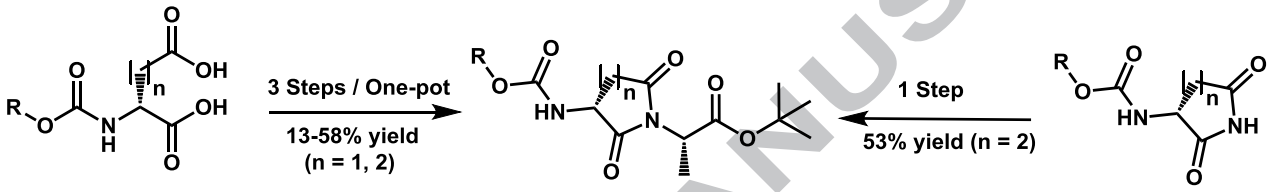

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TETRAHEDRON LETTERS

An expedient synthesis of non-racemic *N*-alkylated pyrrolidin-2,5-diones and piperidin-2,6-diones as peptidomimetics

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Abstract— In our hands, access to 2 novel peptidomimetic scaffolds, based on *N*-alkylated pyrroldin-2,5-diones and piperidin-2,6-diones, proved to be much more challenging than anticipated. In this short communication, we disclose the strategies that we explored and our final route choices to the desired scaffolds with control of both stereocenters.

During a recent project on an undisclosed target, we needed to find efficient non-racemic routes to pyrrolidin-2,5-dione and piperidin-2,6-dione central peptidomimetic scaffolds (**2**)[1] from which we could explore the two key vectors to access our target library **1**. Our retrosynthetic analysis drove us to entertain two solutions: 1) Disconnection a, taking us to readily-available D-aspartic acid and D-glutamic acid precursors **3** relying on an amide coupling reaction with a L-alanine ester precursor **4** followed by ring closing condensation;[2,3] and 2) disconnection b, an unprecedented *N*-alkylation of the imide scaffolds **5** either under *Mitsunobu*[4] or classical alkylation conditions[5] from commercially-available homochiral D-lactate derivatives **6** (Figure 1).

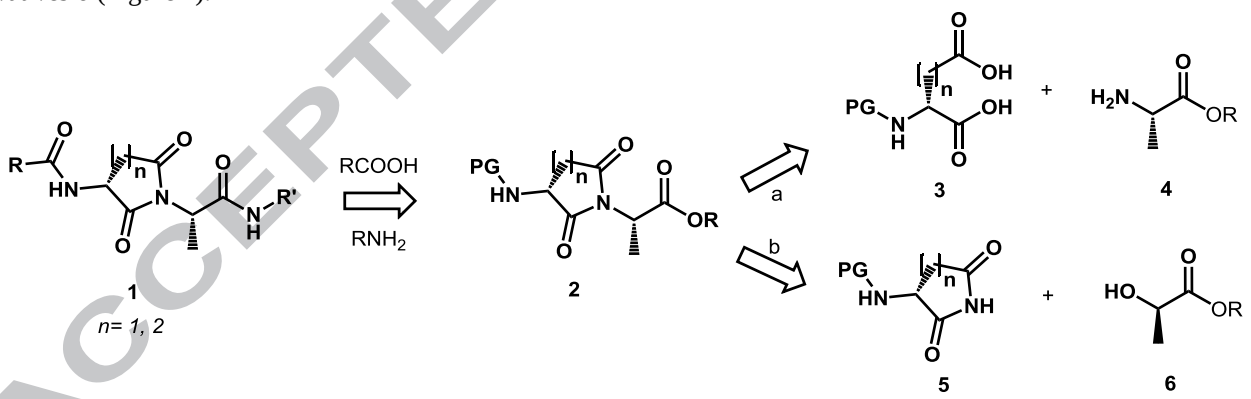

Figure 1. Retrosynthetic analysis of key scaffold **1**

We decided to focus our initial efforts on disconnection a[2,3] which represented the shortest sequence and used readily available α-amino acids as building blocks thus offering an excellent diversification point (Table 1). Our one-pot 3-step preparation of the pyrroldin-2,5-dione intermediate (**10**) started initially from either Cbz or Boc protected L-aspartic acid **7**. Cyclisation to aspartic anhydride **8** in the presence of EDCI proved to be a key step in this 3-step process whereby the reaction needed to be ran overnight to ensure complete conversion to the anhydride intermediate and limit the formation of the diamide impurity **11** (Table 1, entries 1-3 v 4-6). The anhydride **8** was subsequently ring-opened[6] *in situ* by nucleophilic attack of L-alanine *tert*-butyl ester **9** and the intermediate ring closed[7] by adding further EDCI. In the case whereby the amine group was protected by a Cbz group, only a poor isolated yield of **10** was obtained with complete *in situ* racemisation (entry 1). From the literature[8] and NMR analysis, we proved the epimerization was not occurring during the first step but during the

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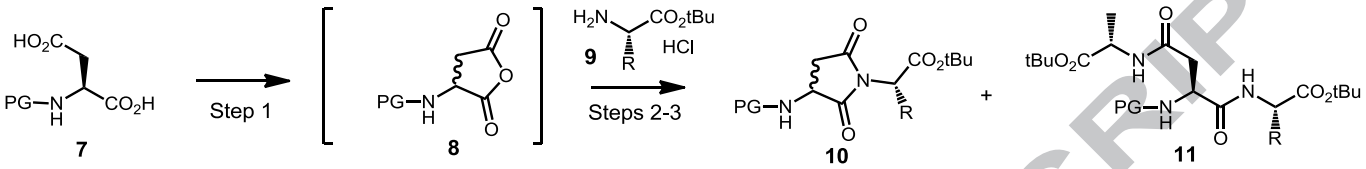
second cyclocondensation step that we propose was due to the base abstraction of the proton α to the amine protecting group. We overcame the epimerisation issue by switching to a more hindered Boc group (entries 2-6). However, extension of this methodology to the more hindered L-valine analogue afforded the desired product in just 48% yield with a disappointing *d.r.* of 82/18 (entry 6) that we believe was due to the elevated temperature necessary to complete the cyclisation step.

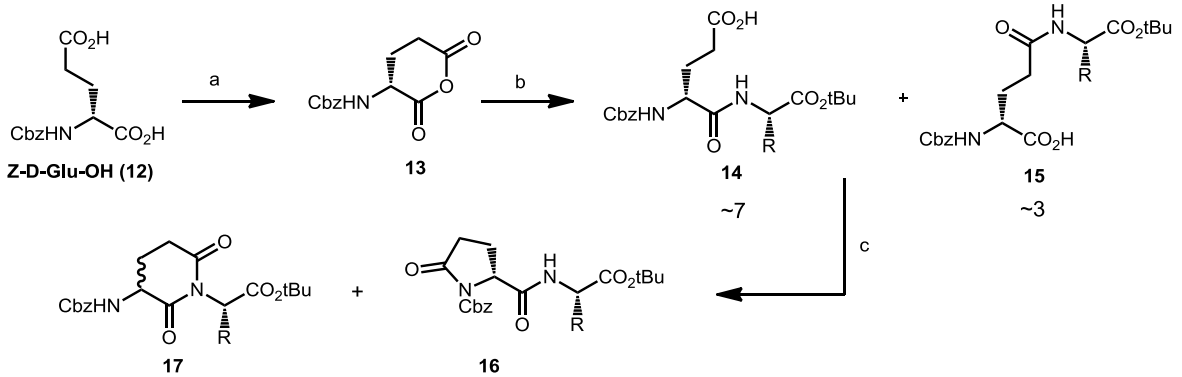
Table 1. General one-pot route developed to access the pyrrolidin-2,5-dione scaffold **10**



Entry	Protecting Group (PG)	R	Solvent	Conditions	Yield (%)	*d.r.* (NMR)
1	Cbz	Me	DCM	1) DIPEA (1.5 eq.), EDCI (1.25 eq.), 2 h, r.t. 2) H-Ala-OtBu.HCl, DIPEA (1.5 eq.), 1.5 h, r.t. 3) EDCI (1.25 eq.), HOBt (1.1 eq.), 16 h, r.t.	17	50/50
2	Boc	Me	DCM	1) H-Ala-OtBu.HCl, HOBt (2.2 eq.), EDCI (1.2 eq.), DIPEA (3.0 eq.), 30 min., r.t. 2) EDCI (1.3 eq.), 4 h, r.t.	9	> 95/5
3	Boc	Me	DCM	1) EDCI (1.25 eq.), 20 min followed by H-Ala-OtBu.HCl, DIPEA (1.0 eq.), 2 h, r.t. 2) EDCI (1.3 eq.), HOBt (1.5 eq.), 16 h, r.t.	12	> 95/5
4	Boc	Me	DCM	1) EDCI (1.1 eq.), 16 h, r.t. 2) H-Ala-OtBu.HCl, DIPEA (1.0 eq.), 4 h, r.t. 3) EDCI (1.5 eq.), HOBt (1.5 eq.), DIPEA (1.0 eq.), 16 h, r.t.	48	~90/10
5	Boc	Me	DCM	1) EDCI (1.25 eq.), 16 h, r.t. 2) H-Ala-OtBu.HCl, DIPEA (2.0 eq.), 2 h, r.t. 3) EDCI (1.3 eq.), HOBt (1.5 eq.), 16 h, r.t.	58	> 95 / 5
6	Boc	^{i}Pr	DCM	1) EDCI, THF, DCM, 16 h, r.t. 2) H-Val-OtBu.HCl, DIPEA, r.t. 3) EDCI, HOBt, r.t.-30 °C, 3 h, 48%	48	82/18

Boc = *tert*-Butyloxycarbonyl; Cbz = benzyloxycarbonyl; EDCI = *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole hydrate; DCC = *N,N*′-Dicyclohexylcarbodiimide; DIPEA = *N,N*-Diisopropylethylamine; Ala = L-alanine

In parallel, we started the synthesis of piperidin-2,6-dione analogue **17** using a similar approach as used for **10** starting from Z-D-Glu-OH (**12**).[9] Therefore, cyclisation to the intermediate anhydride **13** proceeded in quantitative yield. Nucleophilic ring-opening of anhydride **13** with the chosen *tert*-butyl amino acid ester afforded consistently a ~7/3 inseparable mixture of amide products **14** and **15**, respectively, in almost quantitative yield (Scheme 1, Table 2). The subsequent cyclocondensation step was very sensitive to steric hindrance (Table 2) α to the reacting amide bond.[9] Only acceptable yields of **17** were achieved from the glycine derivative (Table 2, entry 1) under thermal conditions. After screening numerous reaction conditions for the alanine derivative (entries 2,3), we finally identified suitable cyclisation conditions under microwave irradiation to afford the desired piperidin-2,6-dione intermediate **17** albeit in average yields with the unwanted pyrrolidin-2-one by-product **16**. Moreover, the desired piperidin-2,6-dione intermediates **17** were also obtained as an inseparable mixture of epimers at C-3 in 11 to 67% yield depending on steric hindrance α to the amide moiety (Table 2, entries 2,3 *vs* 4,5).

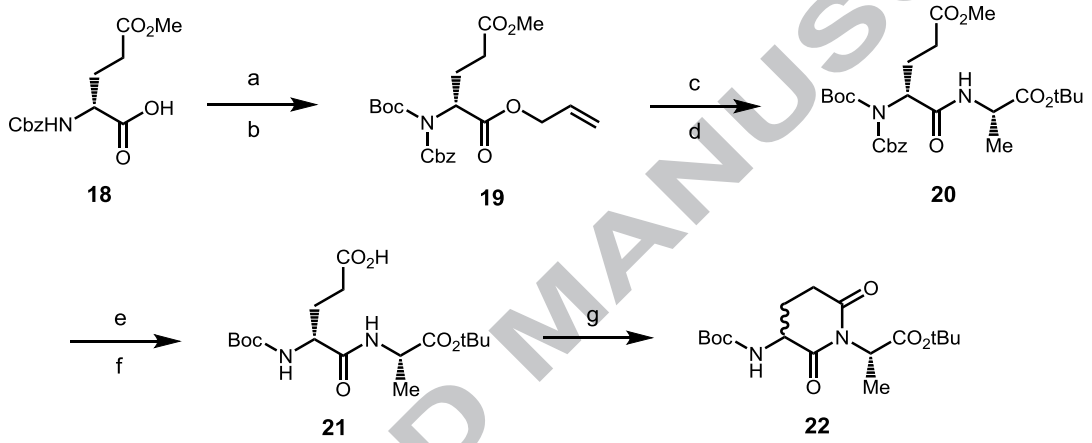


Scheme 1. First generation of conditions employed to prepare piperidin-2,6-dione analogue **17**. Conditions: a) DCC, THF, r.t., quant.; b) amino acid *t*-Bu ester. HCl (see Table 2), DIPEA, THF, r.t., 1-4 h; c) see Table 2

Table 2. Selected examples prepared using Scheme 1

Entry	R	% Yield (Step b)	Conditions (Step c)	**16** (%)	**17** (%) [*e.r.*]
1	H	90	CDI, DMF, 50 °C, 4 h	-	67 [N/A]
2	CH_3	99	CDI, DMF, 70 °C, 24 h	33	32 [76:24]
3	CH_3		CDI, DMF, 153 °C, MW, 15 min	28	52 [1:1]
4	*i*-Pr	96	CDI, DMF, 70 °C, 24 h	24	-
5	*i*-Pr		CDI, DMF, 153 °C, MW, 15 min	26	11 [1:1]

N/A = Not analysed

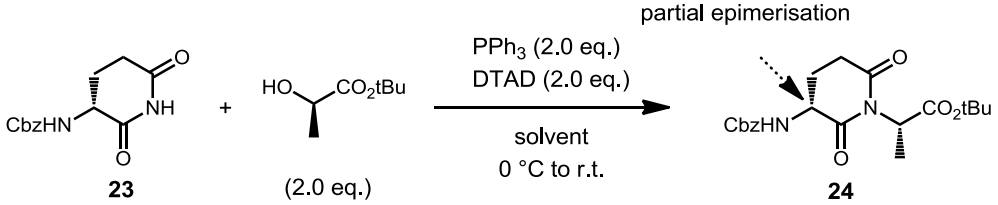


Scheme 2 Synthesis of the Boc analogue **22**. Reagents and conditions: a) Allyl bromide, K_2CO_3, DMF, r.t., 93%; b) Boc_2O, DMAP, MeCN, r.t., 99%; c) $Pd(PPh_3)_4$, *N*-Me-aniline, THF, r.t., 94%; d) *tert*-butyl L-alaninate, HATU, DIPEA, DMF, r.t., 96%; e) H_2 (1 atm), $Pd(OH)_2$/C cat., EtOH, r.t., 96%; f) LiOH, THF-H_2O, r.t., 99%; g) CDI, DMF, 153 °C, microwave irradiation, 13%

With these results in hand and based on our exploration for pyrroldin-2,5-dione series, we assumed that we could solve the problem of epimerization at C-3 during cyclisation by changing the protecting group from Cbz to a more hindered Boc group. Therefore, Z-*D*-Glu(OMe)-OH (**18**) was protected as the allyl ester by alkylation with allyl bromide and Boc protection of the Z-carbamate moiety proceeded in excellent yield to afford **19**.[11] Deprotection of the allyl ester using tetrakis(triphenylphosphine)palladium (0) followed by HATU coupling afforded the dipeptide precursor **20**. Hydrogenolysis of the Cbz group followed by saponification of the methyl ester moiety afforded the cyclisation precursor **21**. Unfortunately, application of the optimised cyclocondensation conditions successfully employed for the pyrroldin-2,5-dione series, resulted in a very poor isolated chemical yield and a 1:1 mixture of epimers at C-3 (Scheme 2)

After the disappointing results obtained for the piperidin-2,6-dione series using the cyclocondensation approach, we changed our retrosynthetic strategy to study direct *N*-alkylation of the pre-formed piperidin-2,6-dione cycle[4,5] with homochiral alkylating agents. Surprisingly, after inspection of the literature, there were few references supporting the *N*-alkylation of piperidin-2,6-dione under classical conditions[5] or under *Mitsunobu* conditions.[4] Moreover, there are no references using homochiral alkylating substrates. As most of the literature supported the use of *Mitsunobu* conditions for achiral alcohols, we initiated our exploration in this chemical reactivity space (Table 3).

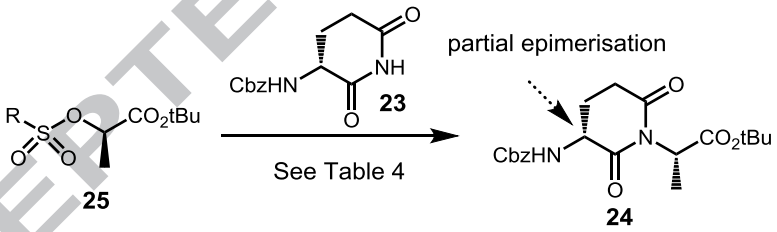
Table 3. Selected results from *Mitsunobu* screening



Entry	Solvent	[Concentration]	Time (h)	Yield (%)	*d.r.*
1	THF	0.12 M	22	67	54/46
2	DCM	0.19 M	3.5	78	56/44
3	Toluene	0.10 M	1	72	71/29

From our exploration, we were surprised how difficult it was to control the *Mitsunobu* alkylation step using commercially-available *tert*-butyl (*R*)-2-hydroxypropanoate. In DCM and THF, good yields were obtained but with an almost 1:1 ratio of epimers at the C-3 position (Table 3, entries 1,2). Changing the solvent to toluene afforded a similar chemical yield and an improved *d.r.* (entry 3) that was still not acceptable for the program. Despite much effort looking at concentration and the order of addition of *Mitsunobu* reagents, we were unable to improve on the *d.r.* and abandoned the *Mitsunobu* approach. Next, we turned our attention to screening classical alkylation conditions, using either the mesylate[11] or triflate[12] (**25**) of *tert*-butyl (*R*)-2-hydroxypropanoate. Taking into account the variable results achieved under *Mitsunobu* conditions and the absence of literature in this chemical space, we carried out a rapid solvent screen using potassium carbonate as the base. Briefly, despite screening several conditions, no product was observed using the mesylate[12] as the alkylating species at room temperature and all attempts to heat the reaction mixture led to degradation with no traces of desired product (Table 4, entries 1-3). In parallel, we prepared the triflate analogue[12] and carried out a solvent screen keeping potassium carbonate as the base. When the reaction was carried out in DMF, only 5% product was observed by LCMS and attempts to increase the yield by heating the reaction mixture only led to degradation of the starting piperidin-2,6-dione (entry 4). However, carrying out the reaction in DCM afforded the desired product in good conversion but with several unidentified close-running by-products that were difficult to remove using standard chromatographic techniques (entry 5). In MeCN, the starting piperidin-2,6-dione **23** was completely consumed affording an excellent chemical yield albeit with a *d.r.* of 86:14 (entry 6). Finally, we managed to improve the *d.r.* to 98:2 by starting the reaction at 0 °C and adding just 1.05 eq of K_2CO_3 albeit compromising the isolated yield to just 53% (entry 7). Attempts to reduce further *in situ* epimerization by using a weaker base *e.g.*, $KHCO_3$, failed whereby the starting material did not react (entry 8).

Table 4. Selected results from the conditions' screening of *N*-alkylation of **23**.



Entry	R	Conditions	Yield (%) [*d.r.*]
1	Me	K_2CO_3 (1.3 eq) DMF, r.t. to 90 °C	Deg.
2	Me	K_2CO_3(1.3 eq) MeCN, r.t. to 90 °C	Deg.
3	Me	K_2CO_3 (1.3 eq) Toluene, r.t. to 90 °C	Deg.
4	CF_3	K_2CO_3 (1.05 eq) DMF, r.t.,16 h	5 (N/I)
5	CF_3	K_2CO_3 (1.05 eq) DCM, r.t., 22 h,	69 (N/I)
6	CF_3	K_2CO_3 (1.3 eq) MeCN, r.t., 18 h	99 [86:14]
7	CF_3	K_2CO_3 (1.05 eq) MeCN, 0 °C to r.t., 24 h	53 [98:2]
8	CF_3	$KHCO_3$ (1.05 eq), MeCN, r.t., 48 h	0

*Deg. = degradation; N/I = Not isolated; Ms = methanesulfonyl; Tf = trifluoromethylsulfonyl

In conclusion, we have evaluated two separate retrosynthetic strategies to successfully prepare *N*-alkylated pyrrolidin-2,5-dione and piperidin-2,6-dione scaffolds. Obtention of the latter through a cyclisation protocol afforded poor chemical yields with a 1:1 mixture of epimers at C-3. This problem was overcome by adopting a novel strategy *via N*-alkylation of piperidin-2,6-dione scaffold using triflates derived from homochiral lactate precursors, achieving the desired product in good chemical yield with minimal *in situ* epimerisation.

Supplementary data

Full experimental procedures and supporting LCMS and ^{1}H NMR characterisation data are available for selected compounds at no extra charge via the on-line version.

References and notes

1. Avan, I.; Hall, C. D.; Katritzky, A. R. *Chem. Soc Rev.* **2014**, *43*, 3575-3594; Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292–296; Hruby, V. J.; Cai, M. *Ann. Rev. Pharm. Tox. 53*, 557-580; Cerminara, I.; Chiummiento, L.; Funicello, M.; Guarnaccio, A.; Lupattelli, P. *Pharmaceuticals* **2012**, *5*, 297-316; Guarna, A.; Trabocchi, A. *Peptidomimetics in Organic and Medicinal Chemistry* **2014**, Wiley VCH; Nielsen P. E. *Pseudo-peptides in Drug Discovery* **2004**, Wiley VCH.
2. For access to chiral pyrroldin-2,5-dione scaffolds *via* disconnection a see: a) Hamlyn, R. J.; Rigoreau, L. J. M.; Raynham, T. M.; Priestley, R. E.; Soudy, C. N. M.; Lyko, F.; Bruckner, B.; Kern, O. T. *PCT Int. Appl.* 2007007054, **2007**; b) Li, X.; Che, X.; Chen, G-H.; Zhang, J.; Yan, J-L.; Zhang, Y-F.; Zhang, L-S.; Hsu, C-P.; Gao, Y. Q.; Shi, Z-J. *Org. Lett.* **2016**, *18*, 1234-1237; c) Flaih, N.; Gadjou, C.; Lafont, O.; Galons, H. *Synlett* **2000,** *6*, 896-898; d) Thomas, A.; Bhavar, P. K.; Lingam, V. S. P. R.; Joshi, N. K. *PCT Int. Appl.* 2004022536, **2004**; d) Napolitano, R.; Pariani, G.; Fedeli, F.; Baranyai, Z.; Aswendt, M.; Aime, S.; Gianolio, E. *J. Med. Chem.* **2013**, *56*, 2466-2477; Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323-2327;
3. For access to chiral piperidin-2,6-dione scaffolds *via* disconnection a see: a) Luppi, G.; Tomasini, C. *Synlett* **2003**, *6*, 797-800; b) Reed, A. B.; Lanman, B. A.; Neira, S.; Harrington, P. E.; Sham, K. K. C.; Frohn, M.; Pickrell, A. J.; Tasker, A. S.; Gore, A.; Fiorino, M.; Itano, A.; McElvain, M.; Middleton, S.; Morrison, H.; Xu, H.; Xu, Y.; Wong, M.; Cee, V. J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1779-1783.
4. For alkylation protocol under *Mistunobu* conditions: a) Butora, G.; Pasternak, A.; Yang, L.; Zhou, C. **2004** WO 2004041279; b) Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 10629-10641;c) Santra, S.; Masalov, N.; Epstein, O. L.; Cha, J. K. *Org Lett.* **2005**, *7*, 5901-5904; d) Ent, H.; De Koning, H.; Speckamp, W. N. *Heterocycles* **1988**, *27*, 237-43; e) Baxter, A.; Cheshire, D.; Mcinally, Thomas; Mortimore, M.; Cladingboel, D. *PCT Int. Appl.,* 9929686, **1999**; f) Alcaraz, L.; Baxter, A.; Bent, J.; Bowers, K.; Braddock, M.; Cladingboel, D.; Donald, D.; Fagura, M.; Furber, M.; Laurent, C.; Lawson, M.; Mortimore, M.; McCormick, M.; Roberts, N.; Robertson, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4043-4046; g) South, M. S.; Rueppel, M. L.; Jones, D. *PCT Int. Appl.* **2001**, WO2001087852.
5. For alkylation protocol under classical conditions: a) Bongartz, J-P.; Buntinx, M.; Coesemans, E.; Hermans, B.; Van Lommen, G.; Van Wauwe, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5819-5823; b) Li, Q.; Fang, H.; Wang, X.; Hu, G.; Wang, Q.; Xu, W. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 850-853.
6. a) Huang, X.; Luo, X.; Roupioz, Y.; Keillor, J. W. *J. Org. Chem.* **1997**, *62*, 8821-8825; b) Katoh, T.; Higuchi, C.; Oura, T.; Ajioka, M.; Yamaguchi, A. *US Pat. Appl. 5302743***, 1994**; c) Yang, C. P.; Su, C. S. *J. Org. Chem.* **1986,** *51*, 5186-91; d) Rodriguez, R.; Vinets, I.; Diez, A.; Rubiralta, M. *Synth. Commun.* **1996**, *26*, 3029-3059.
7. a) Watanabe, M.; Nakatou, T.; Takehara, J.; Kanno, K.; Ichikawa, S. *Eur. Pat. Appl.* **2002,** 1188744; b) Moradei, O.; Paquin, I.; Frechette, S.; Mallais, T.; Roy, S.; Machaalani, R.; Vaisburg, A.; Besterman, J. M.; Tessier, P.; Mancuso, J.; Smil, D.; Leit, S.; Deziel, R. *PCT Int. Appl.* **2007**, 2007118137; c) Hamlyn, R. J.; Rigoreau, L. J. M.; Raynham, T. M.; Priestley, R. E.; Soudy, C. N. M.; Lyko, F.; Bruckner, B.; Kern, O. T. *PCT Int. Appl.***2007**, 2007007054; d) Barn, D. R.; Caulfield, W. L.; Cottney, J.; McGurk, K.; Morphy, J. R.; Rankovic, Z.; Roberts, B. *Bioorg. Med. Chem.* **2001**, *9*, 2609-2624.
8. a) Buron, F.; Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. *Tetrahedron: Asymmetry* **2007**, *18*, 1625-1627; b) Schön, I.; Szirtes, T.; Rill, A.; Balogh, G.; Vadàszb, Z.; Seprödi, J.; Teplàn, I.; Chino, N.; Kumogaye, K. Y.; Sakakibara, S. *J. Chem. Soc. Perkin Trans. I* **1991**, *12*, 3213-3223.
9. a) Hilker, M.; Haeberlein, C.; Trauer, U.; Buennige, M.; Vicentini, M-O; Schulz, S. *ChemBioChem*, **2010**, *11*, 1720-1726; b) Lee, J.; Choi, J.; Park, M. *Arch. Pharmacol. Res.* **1996**, *19*, 248-250; c) Mansard, G.; Estour, F.; Galons, H.; Lafont, O. *Heterocycles*, **2005**, *65*, 2957-2964; d) Chang, K-O; Kim, Y.; Groutas, W.C. *U.S. Pat. Appl.* 20150133368; e) Tam, T. F.; Leung-Toung, R.; Wang, Y.; Zhao, Y.; Xin, T.; Li, W.; Wodzinska, J. M.; Rabadia, V. S.; Shah, B.; Feeney, C. J. *U.S. Pat. Appl. Publ.* 20120157387; f) Li, Q.; Fang, H.; Wang, X.; Hu, L.; Xu, W. *Eur. J. Med. Chem.* **2009**, *44*, 4819-4825.
10. Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. *Tetrahedron: Asymmetry* **2006**, *17*, 2120-2125.
11. Rye, C. E.; Barker, D. *Eur. J. Med. Chem.* **2013**, *60*, 240-248.
12. Hoffmeister, L.; Persich, P.; Fürstner, A. *Chem. Eur. J.* **2014**, *20*, 4396-4402.

Highlights

- Efficient routes to novel peptidomimetic scaffolds while minimising *in situ* racemisation are described
- A successful route to prepare *N*-alkylated chiral pyrrolidin-2,5-dione was found with good chemical and optical yields
- A novel *N*-alkylation of the piperidin-2,6-dione scaffold from homochiral lactate precursors is revealed