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Facile Synthesis of 7-Alkyl-1,2,3,4-tetrahydro-[1,8]-naphthyridines as Arginine Mimetics Using a Horner–Wadsworth–Emmons Based Approach

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Abstract

Integrin inhibitors based on the tripeptide sequence Arg-Gly-Asp (RGD) are potential therapeutics for the treatment of idiopathic pulmonary fibrosis (IPF). Herein, we describe an expeditious three-step synthetic sequence of Horner–Wadsworth–Emmons olefination, diimide reduction and global deprotection to synthesise cores for these compounds in high yields (63–83% over 3 steps) with no need for chromatography. Key to this transformation is the phosphoramidate protecting group, which is stable to metalation steps.

Keywords

Arginine; Horner–Wadsworth–Emmons; Integrin; Phosphoramidate; Tetrahydronaphthyridine

Introduction

Tetrahydronaphthyridines are prominent in peptidomimetic pharmaceuticals as arginine mimetics; they are widely used in Arg-Gly-Asp (RGD) peptide mimetics such as αv integrin inhibitors [1]. Tetrahydronaphthyridines represent less basic but more permeable alternatives to arginine (pK_a ≈7 *versus* 13.8) [1], replicating the side-on salt-bridge binding interaction made between the guanidinium functionality of arginine and an aspartic acid residue in the protein. Consequently, this moiety has been used in various integrin inhibitors (Figure 1) [2-7].

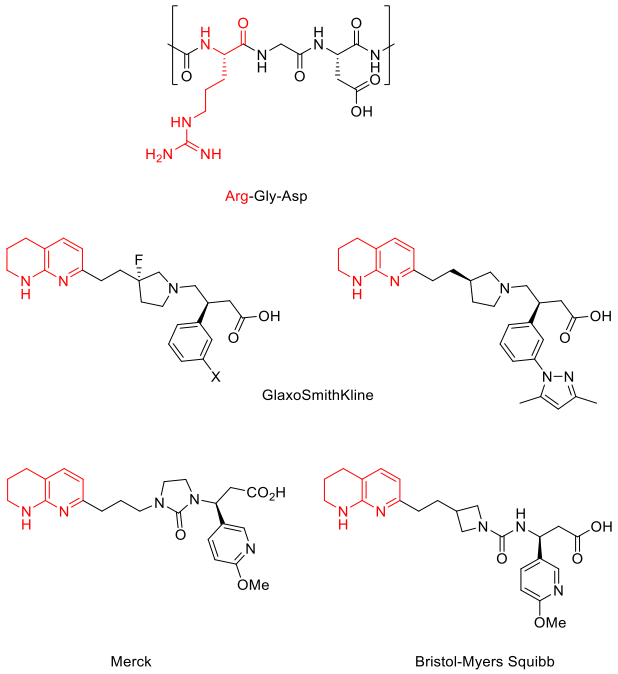
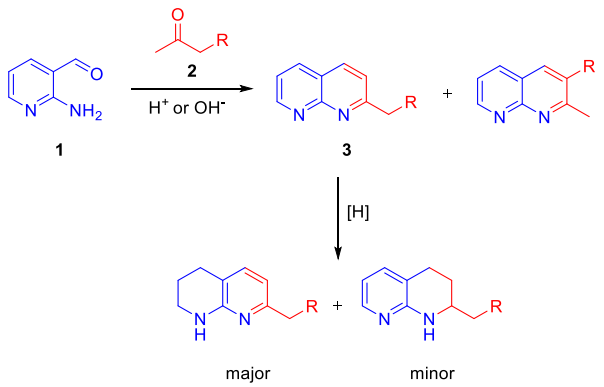


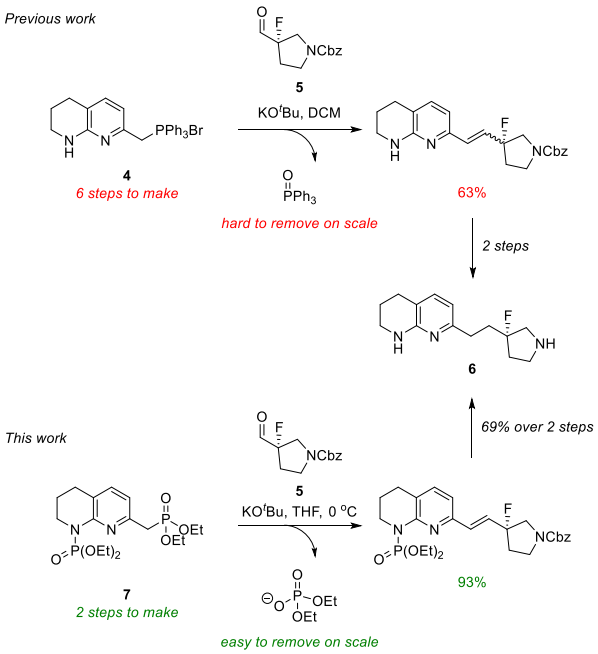
Figure 1. The Arg-Gly-Asp tripeptide sequence and examples of tetrahydro-1,8-naphthyridine-containing integrin inhibitors.

Current routes to install tetrahydronaphthyridines predominantly revolve around late-stage hydrogenation of fully unsaturated 1,8-naphthyridine derivatives **3**, usually prepared *via* an acid or base-catalysed Friedlander reaction between 2-aminonicotinaldehyde **1** and the corresponding ketone **2** (Scheme 1). Both reactions employ harsh conditions with limited functional group tolerance and lack of regiochemical control, which presents considerable purification issues during large-scale synthesis [8-10].



Scheme 1. Commonly used synthetic routes to tetrahydro-1,8-naphthyridine moieties by hydrogenation of saturated naphthyridines **3**.

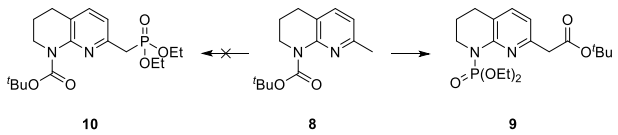
Recently, GlaxoSmithKline disclosed a route to such a fluoropyrrolidine **6** using a Wittig reaction between phosphonium salt **4** and aldehyde **5** [2]. Synthesis of phosphonium salt **4** (itself requiring 6 steps [including partial saturation of a 1,8-naphthyridine moiety)] and the formation of the triphenylphosphine oxide by-product in the Wittig step presented complications on both gram and kilogram scales. Herein, we report a novel synthetic sequence to tetrahydro-1,8-naphthyridines using a Horner-Wadsworth-Emmons reaction using diphosphorylated compound **7**, proceeding in high yields and high purities without the need for chromatographic purification (Scheme 2).



Scheme 2. Previous synthetic route to fluoropyrrolidine **6** utilising a Wittig reaction and a novel, higher yielding route using a Horner–Wadsworth–Emmons reaction.

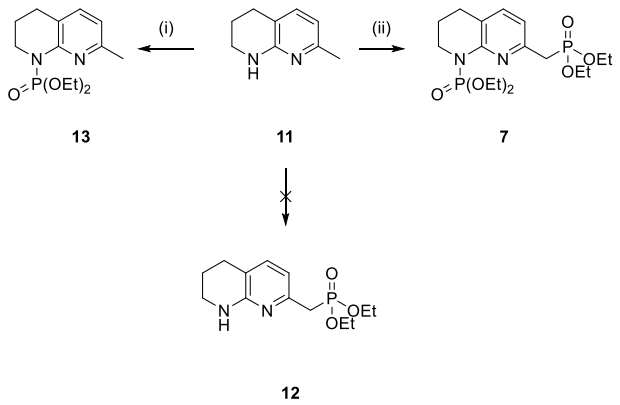
Results and Discussion

Investigation initially began using commercially available *N*-Boc protected tetrahydro-1,8-naphthyridine **8**; however, upon deprotonation and quenching with diethyl chlorophosphate, migration of the Boc group from the nitrogen atom to the exocyclic methyl group was observed, affording phosphoramidate **9** in low yield with no formation of phosphonate **10** seen (Scheme 3).



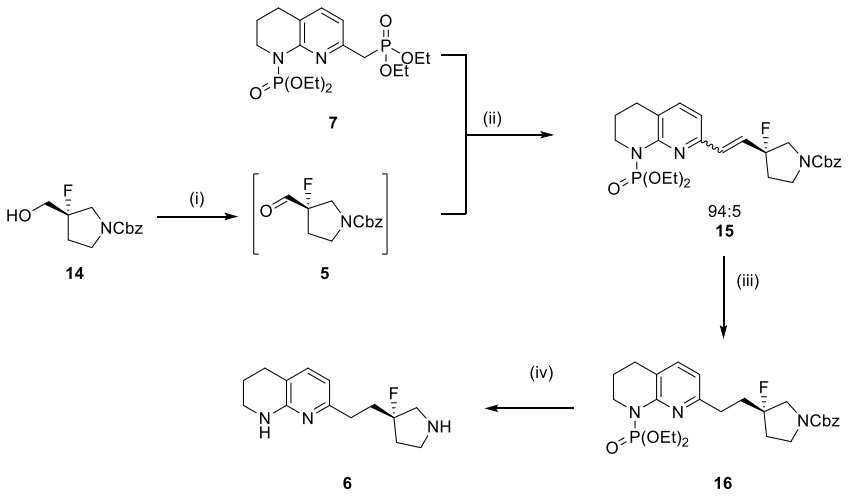
Scheme 3. Synthesis of phosphoramidate **9** from tetrahydro-1,8-naphthyridine **8**. Conditions: *sec*-BuLi (3 eq.), diethyl chlorophosphate (1.1 eq.), THF, −42 °C, 14% yield.

It was proposed that deprotonation of 7-methyl-1,2,3,4-tetrahydro-1,8-naphthyridine **11** with two equivalents of *sec*-BuLi would afford phosphonate **12** upon quenching with diethyl chlorophosphate *via* formation of the dianion. This could then be used in a subsequent Horner–Wadsworth–Emmons reaction to construct the carbon skeleton of amine **6**. Upon addition of a single equivalent of diethyl chlorophosphate, phosphoramidate **13** was obtained exclusively at both −42 and −78 °C. Addition of two equivalents of the chlorophosphate yielded diphosphorylated compound **7**, albeit in poor yield (Scheme 4).



Scheme 4. Mono- and di-phosphorylation of tetrahydro-1,8-naphthyridine **11**. Conditions: (i) sec-BuLi (2 eq.), diethyl chlorophosphate (1 eq.), THF, −78 °C, 44% yield; (ii) *sec*-BuLi (2 eq.), diethyl chlorophosphate (2 eq.), THF, −78 °C, 27% yield.

Deprotonation of phosphonate **7** and reaction with aldehyde **5** (formed *in situ* by oxidation of alcohol **14** using T3P®) [11] yielded olefin **15** in 93% yield as a 94:5 mix of stereoisomers (presumably *E*/*Z*, although this is not conclusive from the ^{1}H NMR spectrum) Reduction to compound **16** using diimide, generated *in situ*, proceeded in 80% yield and was followed by single-pot carbamate and phosphonate deprotection to afford arginine mimetic **6** in 86% yield. This represents a 64% overall yield which was increased to 68% when no column chromatography was undertaken between transformations, with no loss of purity (Scheme 5).



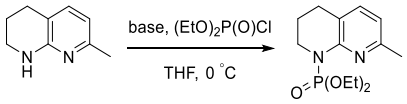
Scheme 5. Synthesis of amine **6** from phosphonate **7** and aldehyde **5**. Conditions: (i) T3P® (50% w/w in DCM) (3 eq.), DMSO (3 eq.), DIPEA (2.5 eq.), DCM, 0 °C; (ii) KO*t*Bu (6 eq.), THF, 0 °C, 93% yield (relative to phosphonate **7**); (iii) $PhSO_2NHNH_2$ (3 eq.), K_2CO_3 (4 eq.), DMF, 100 °C, 80% yield; (iv) 7.4 M HCl, 100 °C, 86% yield.

Olefin reduction and Cbz deprotection could not be performed simultaneously by palladium-catalysed hydrogenation as this results in defluorination, presumably *via* a Tsuji–Trost-like elimination of the allylic fluoride [12-13]. This sequence represents a marked improvement from the Wittig-including route, lowering the number of synthetic steps and increasing overall yield [2]. Furthermore, no problematic by-products are formed, and good purity is obtained without the use of any chromatography, which is ideal for large-scale processes.

Optimisation of the Synthesis of Phosphoramidate 13 and Phosphonate 7

Having been shown to be a feasible intermediate, attention turned to improving the synthesis of bis-phosphonate **7** *via* a two-step process, exploiting the base stability of the phosphoramidate protecting group. A variety of bases were trialed at 0 °C for the initial *N*-phosphorylation, with 10 minutes allowed for complete deprotonation to occur (Table 1).

Table 1. Bases surveyed for the formation of phosphoramidate **13**[a]



11 **13**

Entry	Base	Amount of phosphoramidate **13** / LCMS a/a%
1	KO*t*Bu (1 M in THF)	4
2	LiHMDS (1 M in THF)	58
3	LDA (2 M in hexanes/benzene)	58
4	*s*BuLi (1.4 M in cyclohexane)	65
5	*i*PrMgCl (2 M in THF)	88

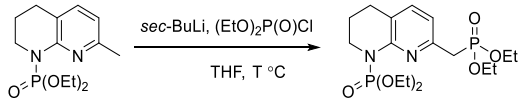
[a]Reactions performed on 0.7 mmol scale of compound **11**

Minimal phosphorylation was observed when using potassium *tert*-butoxide (Entry 1); this may be due the disparity in pK_a between the base and the tetrahydro-1,8-naphthyridine (based on 2-aminopyridine, the p*K*a of the saturated ring nitrogen is expected to be ≈28) [14]. Similarly, nitrogen-centred bases (Entries 2,3) gave moderate conversions to phosphoramidate **13** due to a close match of the p*K*a of tetrahydronaphthyridine **11** and the pK_{aH} of the base; *sec*-BuLi also gave reasonable conversion to (Entry 4) albeit with some impurities. This can likely be attributed to the temperature instability of the base and/or lithiated tetrahydronaphthyridine in THF at this temperature. Use of *i*PrMgCl, a strong but room temperature-stable base, gave the greatest conversion to phosphoramidate **13**. Further investigation into the use of *i*PrMgCl found that quantitative conversion was achieved at ambient temperature with a metalation time of <1 minute. Pleasingly, premixing of tetrahydronaphthyridine **11**

with diethyl chlorophosphate, followed by drop-wise addition of *i*PrMgCl gave clean and total conversion to phosphoramidate **13** as seen by LC-MS. When performed on a multi-gram scale, a 94% yield of compound **13** was obtained. The reaction also proceeded well (91% isolated yield) in 2-MeTHF, which offers a preferred alternative if performed on larger scale due to better partitioning with water, stability and sustainability of production [15].

Of the bases trialled, only *sec*-BuLi was efficient in promoting *C*-phosphorylation. Optimisation of the use of this base was then investigated further (Table 2).

Table 2. Optimisation of formation of phosphonate **7** using sec-BuLi as a base[a]

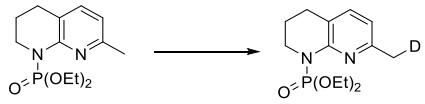


13 **7**

Entry	T / °C	Eq. *sec*-BuLi	Lithiation time / min	Amount of phosphonate **7** / LCMS a/a%
1	−78	1.5	90	53
2	−42	2.0	20	62
3	−42	2.5	20	81
4	−42	3.0	20	86
5	−42	3.5	20	67
6	−42	4.0	20	48
7	−42	3.0 (+ 3 eq. TMEDA)	20	59
8	0	2.0	10	0

[a]Reactions performed on 4.6 mmol scale (Entry 1), 0.5 mmol scale (Entries 2–6), 0.3 mmol (Entry 7) or 0.4 mmol (Entry 8).

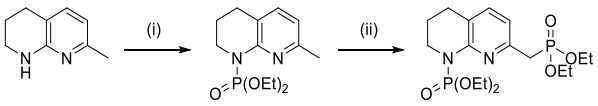
Optimal deprotonation and phosphorylation was found to occur when an excess (3 eq.) of base was used at −42 °C (Entry 4), with a lithiation time of 20 min. Addition of TMEDA was detrimental to this conversion with a large proportion of starting material **13** remaining (Entry 7). No product was formed at higher temperatures (Entry 8), likely due to instability of the *C*-lithiated species at elevated temperatures as degradation was observed. It is believed that the excess base loading is required to account for deprotonation of the more acidic phosphonate product **7** *versus* the starting material **13** and potential lithium sequestration by chelation between an oxygen atom of the phosphonate and the nitrogen atom of the unsaturated ring. Monitoring of deprotonation followed by quenching with CD_3OD by ^{1}H and ^{13}C NMR spectroscopy indicated mono-labelled **17** as the major product, demonstrating that lithiation only occurs at a single position of compound **13** (Scheme 6).



13 **17**

Scheme 6. Monodeuteration of **13** as observed by ^{1}H and ^{13}C NMR. Conditions: *sec*-BuLi (3 eq.), THF, −42 °C then CD_3OD (14 eq.).

When performed on a multi-gram scale, phosphonate **7** was synthesised in 68% yield after purification by chromatography on silica. This, combined with the formation of phosphoramidate **13** in 94% yield, represents a marked improvement to the initial simultaneous diphosphorylation (Scheme 7). When performed sequentially in a single-pot, diphosphorylated compound **7** was not observed, with phosphoramidate **13** accounting for the majority of product formed [16].

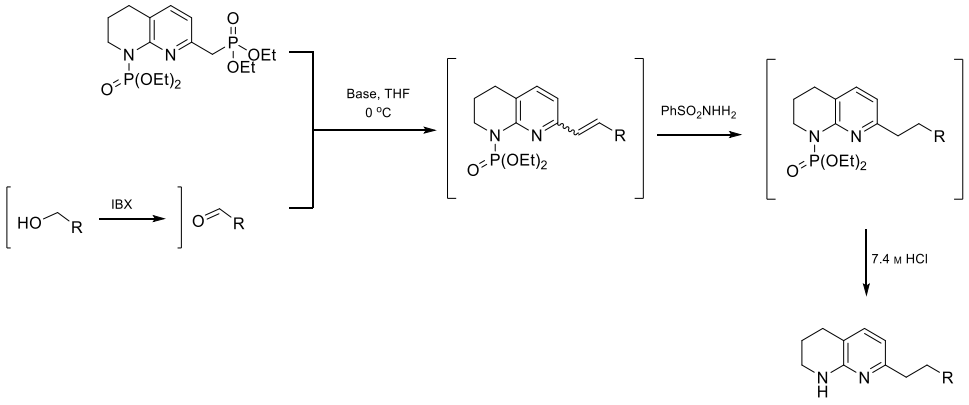


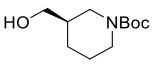
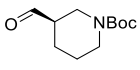
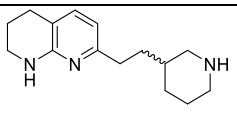
Scheme 7. Sequential diphosphorylation of tetrahydronaphthyridine **11**. Conditions: (i) *i*PrMgCl (1.5 eq.), THF, then diethyl chlorophosphate (1.2 eq.), 94% yield; (ii) *sec*-BuLi (3 eq.), THF, −42 °C then $(EtO)_2P(O)Cl$ (1.1 eq.), 68% yield

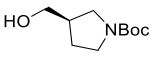
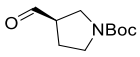
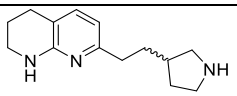
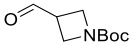
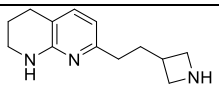
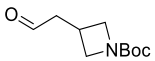
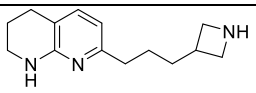
Reaction Scope

The sequence of olefination, reduction and deprotection was tested on other arginine mimetics of varying amine structure, constituting potential Arg-Gly components of Arg-Gly-Asp inhibitors (Table 3). Where the aldehyde was not commercially available, *N*-Boc-protected alcohols were oxidised using IBX in refluxing ethyl acetate and used crude. All amines were formed in high NMR and LC-MS purity without the need for purification by column chromatography.

Table 3. Cores synthesised by the sequence of olefination, reduction and deprotection and the corresponding starting alcohols and aldehydes.[a]



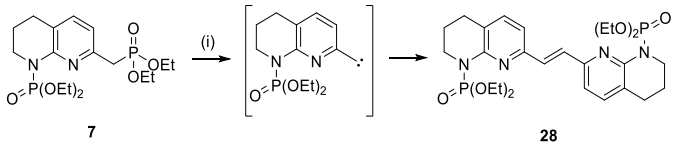
Entry	Alcohol	Aldehyde	Product	Yield
1	 **18**	 **19**	 **20**	82%[1]

2	 **21**	 **22**	 **23**	83%[1]
3	-	 **24**	 **25**	79%[2]
4	-	 **26**	 **27**	63%[3]

*Conditions: 1: IBX, EtOAc, reflux then KO*t*Bu, THF, 0 °C then K_2CO_3, $PhSO_2NHNH_2$, DMF, 100 °C then 7.4 M HCl, 100 °C; 2: KO*t*Bu, THF, 0 °C then K_2CO_3, $PhSO_2NHNH_2$, DMF, 100 °C; 7.4 M HCl, 100 °C; 3: NaH, THF, 0 °C; then K_2CO_3, $PhSO_2NHNH_2$, DMF, 100 °C then 7.4 M HCl, 100 °C

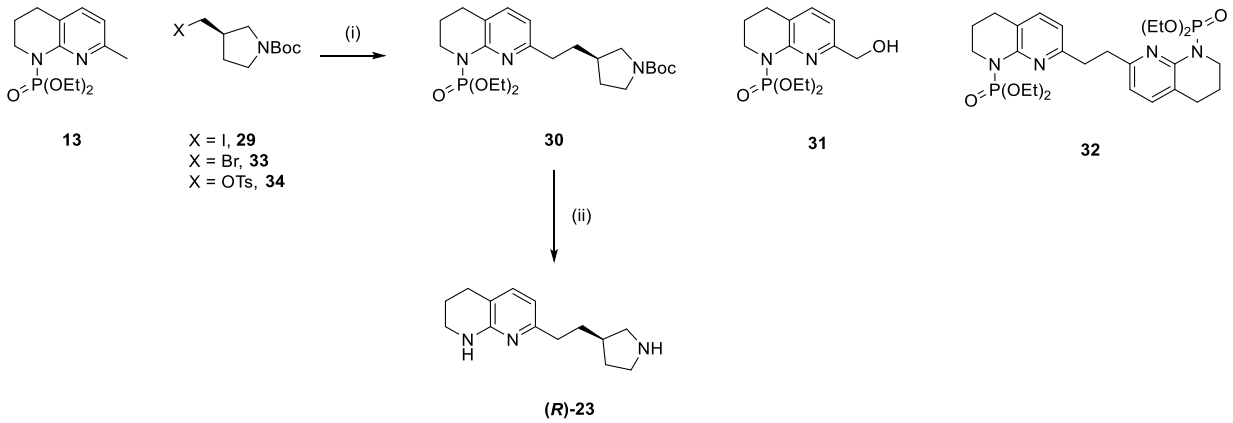
Pleasingly, the sequence proceeded in high yields (63–83%) for all substrates with no chromatography required. Despite relatively high yields, significant racemisation was seen in the synthesis of piperidine **20** and pyrrolidine cores **23**. Pyrrolidine **23** was obtained with an *e.e.* of only 24%, representing a serious loss of enantiopurity. It is believed that racemisation occurs during the olefination step, caused by base mediated keto-enol tautomerisation. As such, this sequence, as currently performed, is suitable for substrates lacking an acidic α-proton (fluoropyrrolidine core **6**) or achiral aldehydes (azetidine cores **25** and **27**).

Furthermore, key to success of the Horner–Wadsworth–Emmons olefination is premixing of the aldehyde and phosphonate **7** prior to addition of KO*t*Bu. Upon deprotonation, phosphonate **7** (in the absence of aldehyde) undergoes dimerisation to olefin **28**. While the exact mechanism is not known, it is likely to involve a reactive carbene intermediate formed by α-elimination of the phosphonate as described in previous reports (Scheme 8) [17].



Scheme 8. Possible mechanism for the formation of dimer **28** *via* a reactive carbene intermediate.

In order to circumvent racemisation of aldehyde **22** during the Horner–Wadsworth–Emmons olefination, alkylation of phosphoramidate **13** was explored using commercially available iodide **29**. Formation of compound **30** proceeded in 21% yield, with alcohol **31** and dimer **32** also formed in 20% and 5% yield respectively (Scheme 9). Indeed, when iodide **29** was replaced with bromide **33** and tosylate **34** no formation of compound **30** was observed, with alcohol **31** and dimer **32** accounting for the major products. Acidic deprotection of phosphoramidate **30** afforded amine **(*R*)-23** in 92% yield in 99% *e.e.*, offering an alternative route to the Horner–Wadsworth–Emmons-based approach.



Scheme 9. Alkylation of phosphoramidate **13** by iodide **29** to afford compound **30** and by-products alcohol **31** and dimer **32**. Use of bromide **33** or tosylate **34** afforded only compounds **31** and **32**. Conditions: (i) *sec*-BuLi (1.3 eq.), iodide **29**, THF, −78 °C; (ii) 7.4 M HCl, 100 °C, 92% yield.

The mechanism of the formation of alcohol **31** and dimer **32** was not fully explored; however, when iodide **29** was replaced by a superior oxidant in 1,2-dibromoethane, formation of dimer **32** increased (17% isolated yield). This supports previously reported proposals that oxidative coupling of the anion can take place, involving a radical pathway [18-20].

Conclusion

In conclusion, a novel method for the assembly of 7-alkyl-1,2,3,4-tetrahydro-[1,8]-naphthyridine-based arginine mimetics has been developed. Synthesis of phosphonate **7** has been optimised, with a sequential diphosphorylation process using commercially available starting materials affording the desired compound in 64% overall yield. A Horner–Wadsworth–Emmons/reduction/deprotection procedure has been used to synthesise amines in good yield requiring no chromatography. This methodology utilised the underused base-stable phosphoramidate protecting group, which was superior to the more commonly applied Boc protecting group which was unstable to the lithiation. This synthetic route replaces traditional Wittig and tandem alkylation/reduction methodologies, which suffer from complications arising from troublesome by-products and reaction selectivity; the new procedure proceeds in a higher yield than previously obtained, providing benefits in large-scale manufacture of integrin inhibitors and other arginine peptidomimetics.

Supporting Information

Supporting Information File 1

Detailed experimental procedures, and product characterisation data, along with ^{1}H and ^{13}C NMR spectra.

Acknowledgements

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References

1. Hatley, R., J. D.; Macdonald, S. J. F.; Slack, R. J.; Le, J.; Ludbrook, S. B.; Lukey, P. T.; *Angew. Chem. Int. Ed.*, **2018,** *57,* 3298–3321.

2. Anderson, N. A.; Campbell-Crawford, M. H. J.; Hancock, A. P.; Pritchard, J. M.; Redmond, J. M.; Patent WO2016046226 (31 Mar 2016).

3. Procopiou, P. A.; Barrett, T. N.; Copley, R. C. B.; Tame, C. J.; *Tetrahedron Asymmetry*, **2017**, *28*, 1384–1393.

4. Procopiou, P. A.; Anderson, N. A.; Barrett, J.; Barrett, T. N.; Crawford, M. H. J.; Fallon, B. J.; Hancock, A. P.; Le, J.; Lemma, S.; Marshall R. P.; Morrell, J.; Pritchard, J. M.; Rowedder, J. E.; Saklatvala, P.; Slack, R. J.; Sollis, S. L.; Suckling, C. J.; Thorp, L. R.; Vitulli, G.; Macdonald, S. J. F.; *J. Med. Chem.*, **2018**, *61*, 8417–8443.

5. Hutchinson, J. H.; Halczenko, W.; Brashear, K. M.; Breslin, M. J.; Coleman, P. J.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Fisher, J. E.; Hartman, G. D.; Huff, J. R.; Kimmel, D. B.; Leu, C.-T.; Meissner, R. S.; Merkle, K.; Nagy, R.; Pennypacker, B.; Perkins, J. J.; Prueksaritanont, T.; Rodan, G. A.; Varga, S. L.; Wesolowski, G. A.; Zartman, A. E.; Rodan, S. B.; Duggan, M. E.; *J. Med. Chem.*, **2003**, *46*, 4790–4798.

6. Cox, J. M.; Ma, L.; Zhou X.; Haimbach, R. E.; Coleman, P. J.; Zhou; H.; Kelley, D. E.; Stoch S. A.; Duong, L. T.; Hoek M.; Patent WO2016154369 (29 Sep 2016).

7. Devasthale, P.; Moore, F.; Zhao, G.; Pieniazek, S. N.; Selvakumar, K.; Dhanusu, S.; Panda, M.; Marcin, L. R.; Patent WO2018089355 (17 May 2016).

8. Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J.; *J. Org. Chem.*, **2004**, *69*, 1959–1966.

9. Anderson, N. A.; Campbell, I. B.; Fallon, B. J.; Lynn, S. M.; Macdonald, S. J. F.; Pritchard, J. M.; Procopiou, P. A.; Sollis, S. L.; Thorp, L. R.; *Org. Biomol. Chem.,* **2016**, *14*, 5992–6009.

10. Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P.; *J. Org. Chem.*, **2003**, *68*, 467–477.

11. Raghavendra, G. M.; Ramesha, A. B.; Revanna, C. N.; Nandeesh, K. N.; Mantelingu, K.; Rangappa, K. S.; *Tetrahedron Lett.,* **2011**, *52*, 5571–5574.

12. Hudlicky, M.; *J. Fluor. Chem.*, **1989**, *44*, 345–359.

13. Hintermann, Läng, F.; Maire, P.; Togni, A.; *Eur. J. Inorg. Chem.*, **2006**, 1397–1412.

14. Bordwell, F. G.; Algrim, D. J.; *J. Am. Chem. Soc.*, **1988**, *110*, 2964–2968.

15. Aycock, D. F.; *Org. Process Res. Dev.*, **2007**, *11*, 156–159.

16. LC-MS shows peaks consistent with phosphoramidate **13** (*m/z* = 285 $[M+H]^+$) and a triphosphorylated species (*m/z* = 557 $[M+H]^+$).

17. Subramanyam, V.; Silver, E. H.; Soloway, A. H.; *J. Org. Chem.*, **1976**, *41*, 1272–1273.

18. Lehn, J.-M.; Ziessel, R.; *Helv. Chim. Acta*, **1988**, *71*, 1511–1516.

19. Zorin, A. V.; Zaynashev, A. T.; Chanysheva, A. R.; Zorin, V. V.; *Russ. J. Gen. Chem.*, **2015**, *85*, 1382–1385.

20. Barham, J. P.; Coulthard, G.; Kane, R. G.; Delgado, N.; John, M. P.; Murphy, J. A. *Angew. Chem. Int. Ed.*, **2016**, *55*, 4492-4496.