Flexible, Phase-Transfer Catalyzed Approaches to 4-Substituted Prolines

Organic LETTERS

Letter

pubs.acs.org/OrgLett

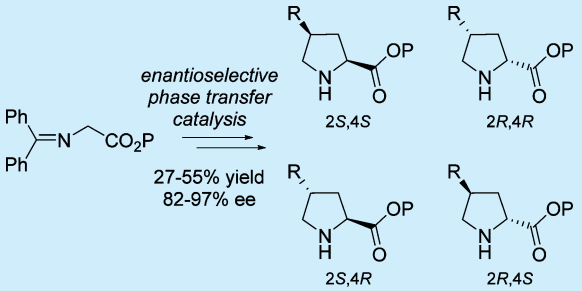
Flexible, Phase-Transfer Catalyzed Approaches to 4-Substituted Prolines

Heather J. Johnston, Fergus S. McWhinnie, Felicetta Landi, and Alison N. Hulme*

EaStCHEM School of Chemistry, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, U.K.

Supporting Information

ABSTRACT: A range of 4-substituted prolines can be rapidly synthesized from a protected glycine Schiff base in only four steps and in 27−55% overall yield. Phase transfer catalysis allows direct access to both enantiomeric series, and the relative stereochemistry at the 4-position is readily controlled (>10:1 dr) through the choice of hydrogenation conditions.



Proline is unique among the 20 proteinogenic amino acids in that it forms a conformationally restrained tertiary amide bond.[1] Proline residues thus form an important part of protein structural features such as loops, turns, and polyproline helices;[2] substituted proline derivatives[3] can enhance the inherent structural constraints which proline imparts upon a peptide, or peptide mimic. Our interest in 4-substituted prolines **1** was sparked by the incorporation of *cis* 4-methyl proline (*cis* 4-MePro) in bisebromoamide (**2**, Figure 1), a natural product isolated from marine cyanobacteria *Lyngbya* sp. that exhibits promising anticancer activity.[4] Existing routes to the synthesis of this proline analogue were lengthy, reliant on expensive starting materials, poorly stereoselective or did not allow access to either enantiomeric series.[5] Since 4-MePro is present in other classes of natural products which exhibit antibiotic, anticancer, and immunosuppressant activities,[6] and 4-substituted proline derivatives are found in several classes of ACE inhibitor, *e.g. trans* 4-ChxPro in the prodrug Fosinopril (**3**, Figure 1),[7] we set out to develop a general synthetic route which would allow ready access to both enantiomeric series of 4-substituted proline as either the *cis* or *trans* diastereomer.

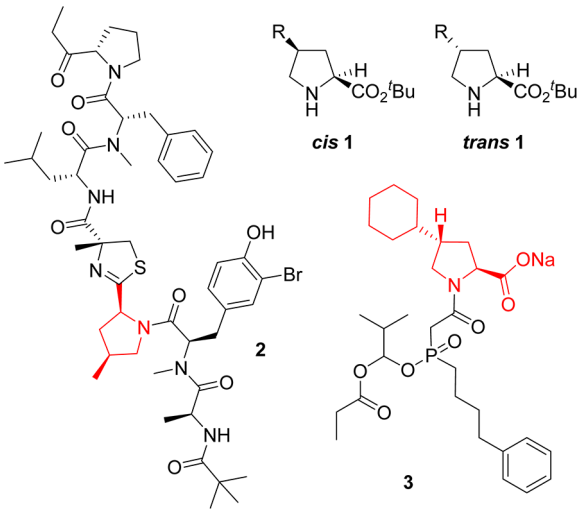


Figure 1. Marine natural product bisebromoamide **2** and ACE inhibitor prodrug Fosinopril **3**.

Retrosynthesis of the 4-substituted prolines *cis* and *trans* **1** led us to identify the corresponding 4-substituted dehydroprolines **4** as a key target (Figure 2), since literature precedent exists for their highly selective hydrogenolytic conversion to either the *cis* or *trans* 4-substituted prolines.[5a] Two approaches were investigated: (i) C−N bond disconnection with backbone formation via Michael addition to an *α,β*-unsaturated aldehyde and (ii) C=C bond disconnection preceded by *C*-allylation and *N*-functionalization. In each case it was anticipated that the

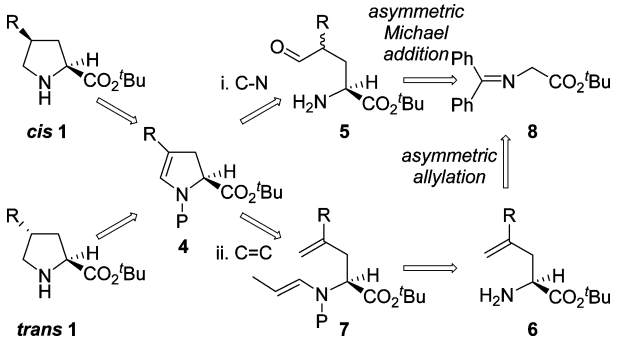


Figure 2. Retrosynthesis of 4-substituted proline derivatives; illustrated for 2*S* enantiomeric series.

Received: July 29, 2014
Published: September 5, 2014

   dx.doi.org/10.1021/ol502239g | *Org. Lett.* 2014, 16, 4778−4781

required acyclic precursor (**5** and **7**) would be readily synthesized from commercial *N*-(diphenylmethylene)glycine *tert*-butyl ester **8** and that access to either enantiomeric series might be achieved using asymmetric phase transfer catalysis (PTC).[8]

Although PTC has been widely used to mediate Michael additions of a range of nucleophiles to α,β-unsaturated ketones, esters, amides, and nitriles,[9] its use to control the addition of nucleophiles to highly reactive α,β-unsaturated aldehydes is less common.[8a] We were attracted to the pseudoenantiomeric pairing of cinchonidine **9** and cinchonine **10** based catalysts (Figure 3)

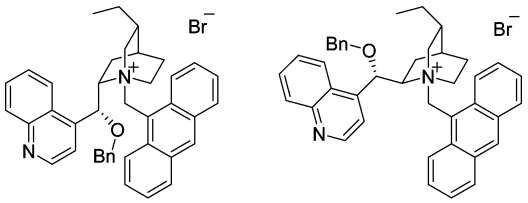
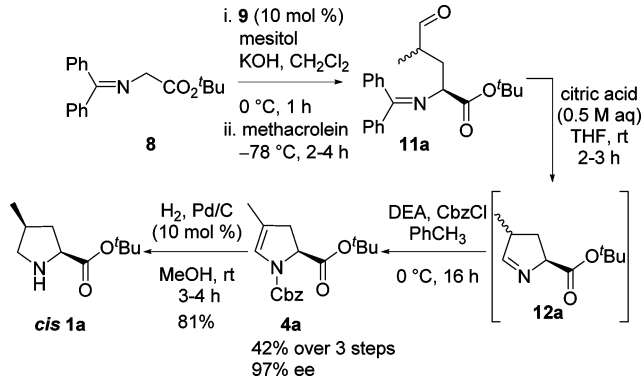


Figure 3. Cinchona alkaloid based phase transfer catalysts **9** and **10**.

reported by the Lygo group[10] and others,[11] as their use has precedent in the synthesis of unnatural amino acids.[12] Indeed, the PTC mediated synthesis of 5-substituted proline derivatives through the Michael addition of a glycine Schiff base to enones[10a] gave us confidence that this approach would allow ready access to either enantiomeric series (2*S* and 2*R*) in high ee.

Our attention focused initially on the synthesis of protected *cis* 4-MePro (***cis* 1a**) which we required for a Solid Phase Peptide Synthesis (SPPS)-based synthesis of bisebromoamide **2**. Michael addition of glycine Schiff base **8** to methacrolein in the presence of cinchonidine based PTC **9** (Scheme 1) gave access to the 2*S*

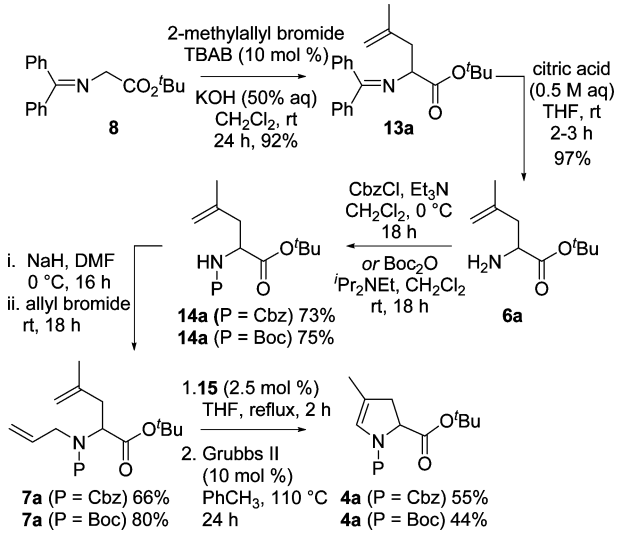
Scheme 1. Synthesis of *cis* 4-MePro (*cis* 1a) via a Michael Addition Sequence



intermediate **11a** as an ~1:1 mixture of diastereomers. The diphenylmethylene protecting group was removed using aqueous acid,[13] and the resultant free amine **5a** spontaneously cyclized to form an unstable imine **12a**. The imine was isomerized *in situ* to enamine **4a** through base-promoted Cbz protection.[14] This stable species was isolated in 42% yield over three steps; the enantiomeric excess of **4a** was confirmed as 97% ee by chiral HPLC.[15] Selective hydrogenation, using H_2 and Pd/C,[11] provided the desired *cis*-stereoisomer, ***cis* 1a**, in high yield and 19:1 selectivity. TFA-mediated deprotection of **1a** to give the free acid confirmed the absolute configuration of the major diastereomer [(2*S*,4*S*)-4-MePro $[\alpha]_D = -84$ (*c* 0.1, H_2O); lit.[16] $[\alpha]_D = -83$ (*c* 0.53, H_2O)]. To demonstrate ready access to either enantiomeric series, this sequence was repeated using cinchonine-based catalyst **10**, and the corresponding *N*-Cbz protected enamine ***ent*-4a** was synthesized in 38% overall yield and 95% ee.

The alternate retrosynthetic disconnection (ii, Figure 2) was then investigated. Ring closing metathesis (RCM) is commonly used in the formation of six-membered cyclic amino acids, but to the best of our knowledge, there is only one successful example which has utilized RCM for the synthesis of the five-membered ring of substituted prolines.[17] Thus, glycine Schiff base **8** was alkylated in the presence of TBAB with 2-methylallyl bromide to give imine **13a** which was again deprotected using aqueous acid to give the corresponding primary amine **6a** (Scheme 2). This

Scheme 2. RCM-Based Route to Enamine Intermediate 4a

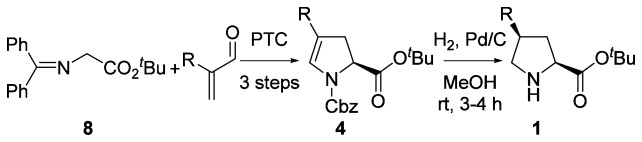


amine was protected as either its Boc or Cbz carbamate;[18] *N*-allylation of **14a** introduced the second alkene moiety which was readily isomerized in the presence of the Ru(II) catalyst, $RuClH(CO)(PPh_3)_3$ **15**, to give the RCM precursor as a rotameric mixture of *E*- and *Z*-isomers.[19] Treatment of this diene with Grubbs' second generation catalyst[20] gave the RCM product, enamine **4a**, in good yield (55% P = Cbz; 44% P = Boc, over two steps).[21] Hydrogenation (H_2, Pd/C) of **4a** (P = Cbz) gave ***cis* 1a** in only seven steps from commercial starting materials. Once again, this route lends itself to the production of either enantiomeric series through the appropriate choice of cinchonidine or cinchonine-based PTCs. To confirm that asymmetric synthesis was compatible with the RCM route, the synthesis was repeated as far as **14a** (P = Cbz) with chiral PTC **9**. Chiral HPLC of **14a** (P = Cbz) confirmed the enantioselectivity of the unoptimized PTC-catalyzed reaction as 89% ee.

Of the two approaches, the PTC-catalyzed Michael addition gives more direct access to 4-substituted proline derivatives. We thus expanded this route to encompass the synthesis of a number of *cis*-substituted targets **1b–e** (Table 1),[22] noting that high yields and % ee were maintained in the PTC reaction, and high diastereoselectivity (*cis:trans*) was observed in the Pd/C catalyzed hydrogenation.[23] In cases where the % ee dropped slightly (e.g., for the 4-cyclohexyl substituted proline, 4-ChxPro), lowering the reaction temperature from −78 to −95 °C gave rise to a significant improvement in % ee, albeit accompanied by a reduction in yield. Although the synthesis of protected 4-EtPro has been reported using two different Wittig/reduction

dx.doi.org/10.1021/ol502239g | *Org. Lett.* 2014, 16, 4778–4781

Table 1. Synthesis of 4-Substituted Proline Derivatives, *cis* 1



8 4 1

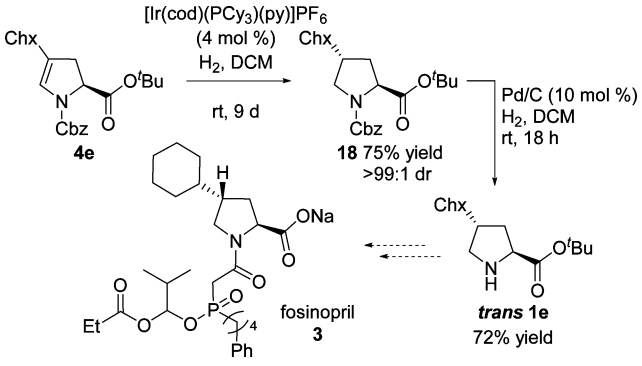
	R	yield **4** (%)[a]	ee **4** (%)	dr **1** (*cis*:*trans*)
a	Me	42	97	19:1
b	Et	35	95	14:1
c	^{i}Pr	57	93	10:1
d	Bn	31	82	10:1
e	Chx	66	80	20:1
e	Chx	54[b]	93	20:1

[a]Yield over three steps from **8**. [b]PTC reaction conducted at −95 °C.

strategies,[24] 4-^{i}PrPro has not been reported previously. However, *cis* 4-BnPro has been investigated as a constrained analogue of the $\alpha_2\delta$ ligands pregabalin and gabapentin for the treatment of neuropathic pain.[25] In each case, our PTC route allows substantially more efficient access to these interesting substituted proline derivatives.

To demonstrate the applicability of this method to the synthesis of *trans* 4-substituted prolines (***trans* 1**, Figure 2), such as the 4-ChxPro species found in Fosinopril, Chx substituted enamine **4e** was treated with H_2 in the presence of Crabtree's Ir(I) catalyst,[5a] generating **18** in 75% yield as a single diastereomer (Scheme 3). Cbz deprotection (H_2, Pd/C) gave ***trans* 1e** also in high yield (72%),[26,27] allowing direct comparison with the previously synthesized diastereomer ***cis* 1e**.[28]

Scheme 3. Synthesis of Fosinopril Intermediate *trans* 1e



The proline scaffold is a privileged motif that is found in Nature and has been exploited in many catalytic processes. By judicious choice of either the Michael- or RCM-based routes presented herein, a range of 4-substitutions (4-XPro) may be accessed from readily available, or easily prepared, achiral starting materials. This should allow the application of this interesting modification of the proline scaffold to be explored in more depth in future studies. The two routes intercept a common enamine intermediate **4** which can be obtained in high % ee using cinchona alkaloid-based PTCs, and from this either the *cis* or *trans* diastereomer of **1** is readily accessed through the appropriate choice of hydrogenation conditions. Other transformations which exploit the reactivity of the enamine intermediate (beyond hydrogenation) are yet to be explored.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the preparation of α,β-unsaturated aldehydes, **4a−e**, **1a−e**, and **18**. Chiral HPLC traces for **4a−e** and ***ent*-4a**. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Alison.Hulme@ed.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

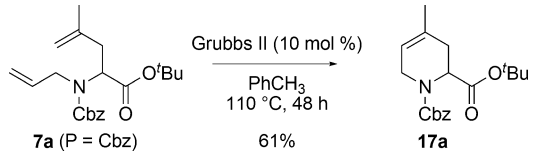
We thank Cancer Research UK (Grant ref C21383/A6950) and the EC (Contract: MEST-CT-2005-020744) for funding.

■ REFERENCES

(1) Bach, T. M. H.; Takagi, H. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 6623−6634.
(2) (a) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859−1866. (b) Mothes, C.; Caumes, C.; Guez, A.; Boullet, H.; Gendrineau, T.; Darses, S.; Delsuc, N.; Moumné, R.; Oswald, B.; Lequin, O.; Karoyan, P. *Molecules* **2013**, *18*, 2307−2327.
(3) (a) Nevalainen, M.; Kauppinen, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **2001**, *66*, 2061−2066. (b) Koivisto, J. J.; Kumpulainen, E. T. T.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2010**, *8*, 2103−2116.
(4) Teruya, T.; Sasaki, H.; Fukazawa, H.; Suenaga, K. *Org. Lett.* **2009**, *11*, 5062−5065.
(5) (a) Murphy, A. C.; Mitova, M. I.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2008**, *71*, 806−809. (b) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 3923−3931. (c) Li, W.; Yu, S.; Jin, M.; Xia, H.; Ma, D. *Tetrahedron Lett.* **2011**, *52*, 2124−2127.
(6) (a) Ukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *J. Antibiot.* **1983**, *36*, 1613−1630. (b) Fujii, K.; Sivonen, K.; Adachi, K.; Noguchi, K.; Sano, H.; Hirayama, K.; Suzuki, M.; Harada, K. *Tetrahedron Lett.* **1997**, *38*, 5525−5528. (c) Nakajima, M.; Torikata, A.; Tamaoki, H.; Haneishi, T.; Arai, M.; Kinoshita, T.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 967−975. (d) Okino, T.; Qi, S.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *J. Nat. Prod.* **1997**, *60*, 158−161. (e) Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* **2005**, *7*, 2775−2777.
(7) Deforrest, J. M.; Waldtron, T. L.; Harvey, C.; Scalese, B.; Rubin, B.; Powell, J. R.; Petrillo, E. W.; Cushman, D. W. *J. Cardiovasc. Pharmacol.* **1989**, *14*, 730−736.
(8) (a) Yeboah, E. M.O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725−1762. (b) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090−7103. (c) Marouka, K. *Org. Process Res. Dev.* **2008**, *12*, 679−697.
(9) (a) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2011**, *17*, 2266−2271. (b) Kang, J. Y.; Carter, R. G. *Org. Lett.* **2012**, *14*, 3178−3181. (c) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364−5365.
(10) (a) Lygo, B.; Beynon, C.; McLeod, M. C.; Roy, C.-E.; Wade, C. E. *Tetrahedron* **2010**, *66*, 8832−8836. (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403−2409. (c) Lygo, B.; Beynon, C.; Lumley, C.; McLeod, M.; Wade, C. E. *Tetrahedron Lett.* **2009**, *50*, 3363−3365.
(11) Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-S.; Park, H.-G.; Jeong, B.-S. *Tetrahedron* **2007**, *63*, 7906−7915.
(12) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3−15.
(13) Mild aqueous acid (citric acid, 0.5 M aq) was used, as stronger acids may promote racemization of the α stereocenter.[10a]
(14) The use of other carbamate protecting groups (Boc, Fmoc, etc.) has not been reported in the literature for this type of reaction and was not investigated at this time.

dx.doi.org/10.1021/ol502239g | *Org. Lett.* 2014, 16, 4778−4781

(15) Slow addition of a precooled solution of methacrolein to the reaction mixture was found to be critical to the reproducibility of high enantioselectivity in this reaction.
(16) Dalby, J. S.; Kenner, G. W.; Sheppard, R. C. *J. Chem. Soc.* **1962**, 4387−4396.
(17) (a) Osipov, S. N.; Dixneuf, P. *Russ. J. Org. Chem.* **2003**, *39*, 1211−1220. (b) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, *7*, 3891−3897.
(18) For practical reasons, the carbamate protecting groups investigated in this study were limited to one that would be removed by hydrogenolysis and one that would not.
(19) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270−1281.
(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(21) Attempts to introduce a vinyl group to **14a** through Pd-catalyzed vinyl transfer for a more direct RCM reaction or to conduct relay metathesis on appropriate derivatives of **14a** were both unsuccessful. When the one-pot conversion (via *in situ* isomerization and RCM) of the allyl intermediate **7a** (P = Cbz) was attempted, formation of the unsaturated piperidine **17a** was favored.



(22) Noncommercial unsaturated aldehyde precursors were synthesized in one or two steps as described in the Supporting Information.
(23) The absolute stereochemistry of **4b−e** was also defined as (2*S*) on the following grounds: the major enantiomer of each of **4a−e** was observed to elute first using the same chiral stationary phase; the mixture of enantiomers for each of **4a−e** was found to have an $[\alpha]_D$ in the range −70 to −130.
(24) (a) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3519−3530. (b) Ellsworth, B. A.; Ewing, W. R.; Jurica, E. Pyrrolidine GPR40 Modulators. U.S. Patent 2011/82165 A1, April 7, 2011.
(25) Rawson, D. J.; Brugier, D.; Harrison, A.; Hough, J.; Newman, J.; Otterburn, J.; Maw, G. N.; Price, J.; Thompson, L. R.; Turnpenny, P.; Warren, A. N. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3771−3773.
(26) It is imperative that the enamine starting material is removed before being submitted for hydrogenolysis to avoid any subsequent contamination with the *cis* diastereomer.
(27) Use of protic solvents for hydrogenolysis can result in *N*-alkylation;[29] this was avoided by carrying out the reaction in DCM.
(28) For the *cis* substituted 4-XPro derivatives **1a−c, e** the $NHCH_AH_B$ proton was observed to lie in the range 2.8−2.6 ppm and the C(α) carbon was observed to lie in the range 60.3−60.2 ppm, whereas for the *trans* substituted 4-ChxPro **1e** the $NHCH_AH_B$ proton was observed at 2.4 ppm and the C(α) carbon was at 60.7 ppm.
(29) Huang, P.; Wang, Y.; Zhuo, B.; Xiao, Z.; Xu, C. *Chem. Commun.* **2010**, *46*, 7834−7836.

dx.doi.org/10.1021/ol502239g | *Org. Lett.* 2014, 16, 4778−4781