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Highly diastereoselective synthesis of new, carbostyril-based type of conformationally-constrained β-phenylserines

Hisanori Ueki, Trevor K. Ellis, Masood A. Khan and Vadim A. Soloshonok*

Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Room 208, Norman, OK 73019, USA

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Abstract—We have demonstrated that the readily available amido–keto compounds **5**, with prearranged carbonyl and glycine moieties, under strongly basic conditions easily undergo complete and highly diastereoselective cyclization, affording a generalized and practical access to the conformationally constrained phenylserine derivatives **4**. High chemical yields, virtually complete diastereoselectivity combined with the operational convenience of the experimental procedures render this method useful for preparation of these diastereomerically pure derivatives.

1. Introduction

The availability of synthetic methods allowing the design and synthesis of tailor-made amino acids[1] and related compounds is a critical component of any current effort to understand the proteome and its relation to life, health and disease.[2] For example, application of specially designed sterically/conformationally constrained amino acids[3] for the rational modification of native peptide secondary structures has resulted in remarkable progress in understanding of peptide three-dimensional (3D) structure and its relationship to biological activity.[4] In particular, considerable effort has been focused on developing conformationally constrained analogs of aromatic amino acids because of their importance in protein folding and recognition.[5] In the case of phenylalanine (Phe) and structurally related amino acids, such as tyrosine and DOPA, the design considerations may include restriction of the torsional angles ϕ (phi), ψ (psi) and ω (omega), determining the 3D structure of peptide backbone,[6] as well as the χ (chi) torsional angles, which define the position of side-chain functional groups[5] (Fig. 1).

Of the various conformationally constrained derivatives of Phe reported in the literature,[5] cyclic models **1**[7,8] and **2**[9–11] were found to be extremely useful conformationally constrained scaffolds in the de novo peptide design. For instance, the tetraline-based constrained Phe-model Atc-**1**, allowing the restriction of both χ^1 and χ^2, has been successfully used in the design of various opioid peptides (dynorphin A,[8a] deltorphin,[8b] enkephalins[8c,d]), peptidic α-adrenergic agonists[8e] and enzyme inhibitors,[8f] as well as in the study of protein folding.[8e] Application of the tetrahydroisoquinoline-based model Tic-**2**, as a Phe analog with restricted χ^1, χ^2 as well as ϕ torsional angles, has been found to be even more successful. Thus, a systematic study of Tic-**2** for peptide design lead to the development of potent, yet highly selective angiotensin-converting enzyme inhibitor 'Quinapril',[10] a tripeptide currently under clinical trials, as well as dipeptide Dmt-Tic,[11] a potent pharmacophore, representing a conformationally constrained Tyr–Phe moiety. The most conformationally constrained in this series, the 3,4-dihydro-1*H*-quinolin-2-one (carbostyril)-based model **3**[12] with four restricted torsional angles, χ^1, χ^2, ψ and ω, has also been found useful as an analog of Phe in the design of di-tripeptides. In particular, very promising results have been reported on the application of model **3** in the design of HIV-1 reverse transcriptase inhibitors,[13a] dopamine D2/D4 receptor antagonists,[13b] metalloproteinase inhibitors[13c–e] as well as other biologically active peptides and peptidomimetics.[13f–h] Besides Phe, scaffolds **1**–**3** have been used for preparing structurally similar aromatic amino acid derivatives such as tyrosine and DOPA.[8,9,11] On the other hand the application of models **1**–**3** as conformationally constrained analogs of other amino acids with substituents on the aliphatic moiety of **1**–**3** is not straightforward and might require the development of new approaches methodologically different to those applicable for preparing Phe and its derivatives. Thus, to the best of our knowledge, no carbostyril-based models of α-hydroxyphenylalanine (phenylserine) **4** have been reported to date. Herein we report the first and highly diastereoselective (>99/1) synthesis of a new type of conformationally constrained phenylserine derivatives **4a**–**e**, starting from

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* Corresponding author. Tel.: +1-4053258279; fax: +1-4053256111; e-mail: vadim@ou.edu

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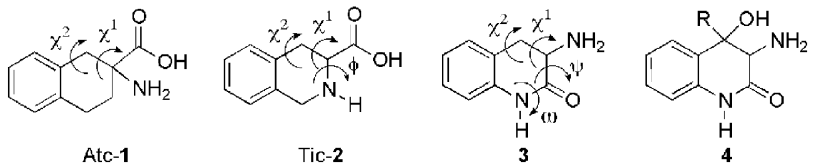


Figure 1. Tetraline- (Atc-**1**), tetrahydroisoquinoline- (Tic-**2**) and carbostyril-based (**3**, **4**) models of conformationally phenylalanine and its derivatives.

the readily available amides **5a**–**e** (Scheme 1) containing a glycine moiety and keto group, thus prearranged for the intramolecular aldol addition reaction.

2. Results and discussion

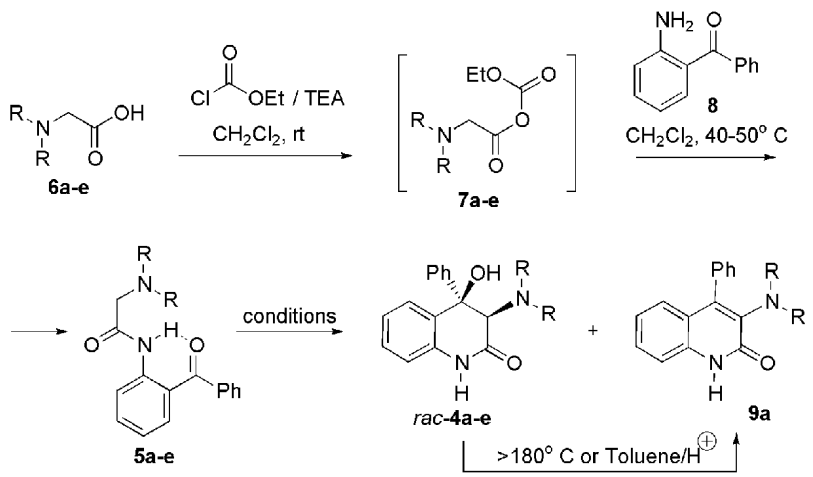
Starting compounds **5a**–**e** were prepared according to Scheme 1. Commercially available amino acids **6a**–**e** were first treated with ethyl chloroformate to form the intermediate activated mixed anhydrates **7a**–**e** which were further condensed with *o*-aminobenzophenone (**8**) to afford amides **5a**–**e** in high (>80%) isolated yields.

The cyclization step was studied first using compound **5a** due its high crystallinity and solubility in various organic solvents. Taking into account the presence of the amide hydrogen in **5a**–**e** we assumed that the cyclization might require formation of the corresponding di-anion. Therefore, we decided to use at least 2 equiv. of relatively strong base to effect the cyclization.

The first attempt, using NaOMe as a base and THF as a solvent, was rather unsuccessful. The sluggish reaction proceeded overnight at room temperature to afford only 10% conversion giving rise to the target compound **4a** (entry 1). On the other hand the compound **4a** was obtained as a single product in diastereomerically pure form, encouraging us to search for optimal reaction conditions. Application of KOH as the base increased the conversion of starting **5a** (entry 2), but the result was still unsatisfactory. The use of the stronger bases allowed us to substantially increase the conversion without compromising the diastereoselectivity of the reaction. However, the target **4a** was obtained along with the product of its dehydration **9a** (entries 3, 4). Continuation of the reaction for up to three days resulted in the increased conversion of the starting **5a**, also leading to the enhanced amounts of the dehydration product **9a** (entry 5). Further attempts to improve the reaction outcome by varying solvents did not give satisfactory results. For instance, the reactions conducted in ether or acetonitrile, using KO-*t*-Bu as the base, furnished **4a** as the individual product with virtually complete diastereoselectivity, however, the conversion of the starting **5a** was very low. On the other hand we found that the increased reaction temperature and amount of the base used had a critical effect on the reaction outcome. Thus, the reaction conducted in THF at reflux was completed in only 2 h affording the mixture of **5a** and **9a** in a ratio of 30/70 (entry 6). Continuation of the reaction for two days resulted in the formation of **9a** as the major product isolated in 87% yield (Table 1).

Further experiments revealed that elevating the temperature generally accelerated the reaction rates of both desired aldol addition and undesired dehydration, suggesting that the room temperature reactions may be a better option. To our satisfaction we found that increasing the base/substrate ratio led to the substantial acceleration of the aldol addition reaction allowing preparation of the target **4a** as an individual reaction product in quantitative chemical yield (entries 8 and 9). Thus, application of 7 equiv. of the base for cyclization of **5a** resulted in a clean and fast reaction, giving rise to the product **4a** with virtually complete chemical and stereochemical outcome (entry 9).

It should be emphasized that in all reactions studied, using different bases, solvents, reaction time and temperature, we always observed formation of a product **4a** as a single diastereomer. This perfect and robust diastereoselectivity



R,R = -$(CH_2)_5$- (**a**); Et, Et (**b**); Bn, Bn (**c**); Bn, H (**d**); *o*-$C_6H_4(CH_2)_2$ (**e**)

Scheme 1.

Table 1. Cyclization of amido–ketones **5a–e** to **4a–e**

Entry	Compound	Base (equiv.)	Time (h)	Conver. (%)[a]	Products **4**, **9**	
					Yield[b] (%)	Ratio **4/9**[a,c]
1	**5a**	NaOMe (2)	24	10	nd	>99/1
2	**5a**	KOH (2)	24	25	nd	>99/1
3	**5a**	NaO-*t*-Bu (2)	24	54	nd	89/11
4	**5a**	KO-*t*-Bu (2)	24	67	nd	88/12
5	**5a**	KO-*t*-Bu (2)	72	77	nd	53/47
6	**5a**	KO-*t*-Bu (2)[d]	2	>99	nd	30/70
7	**5a**	KO-*t*-Bu (2)[d]	48	>99	87	8/92
8	**5a**	KO-*t*-Bu (4)	12	>99	nd	86/14
9	**5a**	KO-*t*-Bu (7)	2	>99	98	>99/1
10	**5b**	KO-*t*-Bu (7)	2	>99	97	>99/1
11	**5c**	KO-*t*-Bu (7)	2	95	89	>99/1
12	**5d**	KO-*t*-Bu (7)	2	>99	97	>99/1
13	**5e**	KO-*t*-Bu (7)	2	>99	97	>99/1

All reactions were run in commercial-grade THF in the presence of the base indicated at ambient temperature.
[a] Determined by NMR (300 MHz) analysis of the crude reaction mixtures.
[b] Isolated yield of crude product.
[c] Compound **4** was isolated as a single diastereomer.
[d] The reaction was conducted at reflux.

was really a remarkable feature of this reaction. The relative configuration of the diastereomer **4a** was found to be (3*R**,4*R**) by single crystal X-ray analysis (Fig. 2).[14] It is interesting to note that crystals of compound **4a** made of successive layers of enantiomerically pure (3*R*,4*R*) and (3*S*,4*S*) diastereomers.

To account for the diastereoselectivity observed, we proposed two transition states (TS) **A** and **B**, leading to the (3*R**,4*R**) and (3*R**,4*S**) diastereomers, respectively (Fig. 3). In both TS **A** and **B** the enolate and the carbonyl oxygens are located in close proximity to each other allowing the reaction to occur with a thermodynamically advantageous minimum charge separation.[15] On the other hand, considering the steric interactions in the TS **A** and **B**, we can assume that the latter might be less favorable relative to TS **A**. Thus, in TS **B** the substituted amino group experiences unfavorable repulsive interactions with the two phenyl rings, while in the TS **A** these steric interactions are minimized. Moreover, in the TS **A** the amino group and the enolate oxygen are in *cis* position allowing the nitrogen to be involved in the stabilizing coordination to the metal.

With these results in hand we decided to study the generality

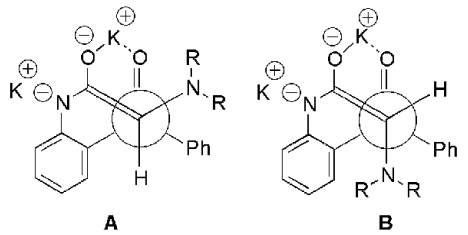


Figure 3. Transition states **A** and **B** in the intermolecular cyclization of **5a–e**.

of the stereochemical outcome of the cyclization using compounds **5b–e** bearing various substituents of the glycine moiety. All reactions were conducted under the standard conditions represented in entry 9. The diethyl derivative **5b** was converted to the cyclized product **4b**, isolated as a pure diastereomer in 97% yield (entry 10). From the point of view of potential applications of products **4** as conformationally constrained phenylserine derivatives, of particular interest were the cyclizations of compounds **5c–e**, with potentially removable substituents on the amino group. The reaction of the dibenzyl **5c** occurred at slightly lower rate allowing about 95% conversion of the starting compound to the product **4c** under the standard conditions (2 h), presumably due to the substantial steric bulk of two benzyl groups (entry 11). On the other hand, the reaction of xylyleneyl derivative **5d** occurred with a similar result to the alkyl series of perfect reaction outcomes (entry 12 vs 9, 10). Interestingly, the mono-benzyl substituted derivative **5e**, possessing an unprotected N–H group, easily underwent the cyclization to afford the diastereomerically pure product **4e** in high chemical yield, suggesting a wider than expected potential generality of this reaction.

Since in some experiments (entries 6 and 7) the compound **9a** was obtained as the major reaction product, we also decided to focus on a selective preparation of the derivatives of this type. 1*H*-Quinolin-2-one and in particular its amino derivatives have been used as pharmacophore unit in the design of various biologically active compounds, for instance with oxytocin antagonist activity, antidepressant, antiallergic activity.[16] We found that complete dehydration of **4a** to **9a** could be easily achieved by simply heating the former at temperatures above 180°C or application of classical dehydration methods such as refluxing a toluene solution of **4a** in the presence of an acidic catalyst. Using these methods compound **4a** was cleanly dehydrated to

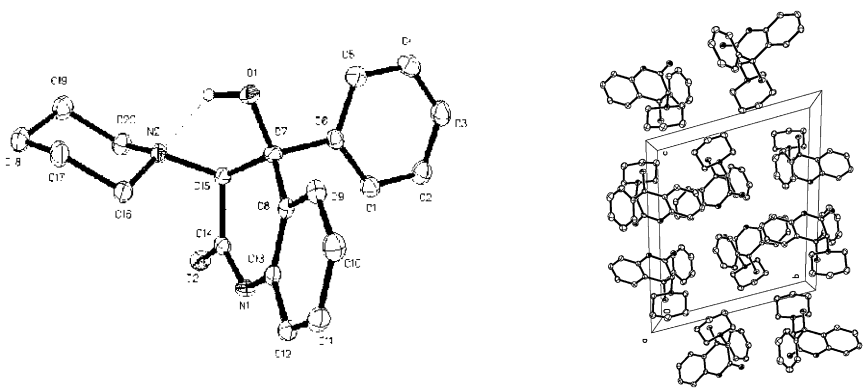


Figure 2. X-Ray structure of (3*R**,4*R**)-**4a**.

afford **9a** in high chemical yields (96–98%) rendering the cyclization reactions reported here synthetically versatile and useful for preparing biologically relevant compounds of types **4** and **9**.

3. Conclusions

In summary, we have demonstrated that the readily available amido–keto compounds **5a–e**, with prearranged carbonyl and glycine moieties, under strongly basic conditions easily undergo a complete and highly diastereoselective cyclization, affording generalized and practical access to the conformationally constrained phenylserine derivatives **4** as well as amino substituted carbostyrils **9**. High chemical yields and robust, virtually complete diastereoselectivity, combined with the operational convenience of the experimental procedures render this method worth immediate use for multi-gram scale preparation of these diastereomerically pure derivatives.

4. Experimental

4.1. General

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. Unless indicated, ^{1}H, and ^{13}C NMR spectra, were taken in $CDCl_3$ solutions at 299.95, 282.24 and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS as the internal standards.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H, ^{13}C NMR, and high resolution mass spectrometry (HRMS/ESI).

Starting amino acids **6a–d** were commercially, **6e** was prepared according to the literature procedure.[17]

4.1.1. *N*-(2-Benzoyl-phenyl)-2-piperidin-1-yl-acetamide (5a). General procedure. Triethylamine (1.69 mL, 12 mmol) was added to a flask containing **6a** (6 mmol) and 10 mL of CH_2Cl_2 and the mixture was stirred at room temperature for 20 min under N_2. Then, ethyl chloroformate (0.57 mL, 6 mmol) was added at 0°C under N_2. After stirring the mixture for 20 min at room temperature, 2-aminobenzophenone (0.99 g, 5 mmol) was added and the mixture kept stirring at 40–50°C overnight. Water was then added to quench the reaction and the organic phase was extracted with CH_2Cl_2 three times and dried over $MgSO_4$ anhydrous. After evaporation of the solvents and silica gel column chromatograph afforded the target product **5a**.

^{1}H NMR δ 1.40–1.50 (2H, m), 1.72 (4H, m), 2.50 (4H, m), 3.09 (2H, s), 7.09 (1H, dd, J=7.82, 7.32 Hz), 7.40–7.65 (5H, m), 7.70–7.80 (2H, m), 8.63 (1H, dd, J=8.31, 1.10 Hz), 11.5 (1H, bs). ^{13}C NMR δ 23.8, 25.8, 54.9, 63.1, 121.4, 121.9, 125.0, 127.9, 129.7, 132.1, 132.1, 132.9, 138.1, 138.7, 170.4, 197.1. HRMS [M+Na$^+$] found *m/s* 345.1472, calcd for $C_{20}H_{22}N_2NaO_2$ 345.1479. Mp 111.5°C.

4.1.2. *N*-(2-Benzoyl-phenyl)-2-diethylamino-acetamide (5b). ^{1}H NMR δ 1.07 (6H, t, J=7.04 Hz), 2.62 (4H, q, J=7.04 Hz), 3.17 (2H, s), 7.07 (1H, ddd, J=7.91, 7.33, 1.17 Hz), 7.40–7.60 (5H, m), 7.70–7.78 (2H, m), 8.66 (1H, dd, J=8.35, 1.17 Hz), 11.6 (1H, bs). ^{13}C NMR δ 12.1, 48.6, 58.4, 121.3, 121.9, 125.0, 128.0, 129.7, 132.2, 132.2, 133.1, 138.3, 138.8, 171.8, 197.4. HRMS [M+H$^+$] found *m/s* 311.1688, calcd for $C_{19}H_{23}N_2O_2$ 311.1681. Mp 65.5°C.

4.1.3. *N*-(2-Benzoyl-phenyl)-2-dibenzylamino-acetamide (5c). ^{1}H NMR δ 3.20 (2H, s), 3.61 (4H, s), 6.93 (1H, t, J=8.57 Hz), 7.03–7.16 (6H, m), 7.34–7.44 (4H, m), 7.44–7.54 (5H, m), 7.76–7.83 (2H, m), 8.67 (1H, d, J=8.79 Hz) 11.5 (1H, bs). ^{13}C NMR δ 58.2, 59.0, 120.9, 121.4, 124.3, 126.7, 127.7, 128.7, 129.6, 131.6, 132.1, 132.6, 136.9, 137.6, 138.5, 170.0, 197.1. HRMS [M+H$^+$] found *m/s* 435.1985, calcd for $C_{29}H_{27}N_2O_2$ 435.1994.

4.1.4. *N*-(2-Benzoyl-phenyl)-2-benzylamino-acetamide (5d). ^{1}H NMR δ 3.40 (2H, s), 3.80 (2H, s), 7.42 (1H, m), 7.15–7.26 (3H, m), 7.40–7.58 (7H, m), 7.72–7.75 (2H, m), 8.65 (1H, d, J=8.4 Hz), 11.66 (1H, bs). ^{13}C NMR δ 53.1, 54.3, 121.9, 122.5, 125.0, 127.5, 128.5, 128.6, 128.7, 130.4, 132.8, 133.0, 133.9, 138.7, 139.4, 139.4, 171.4, 198.5. HRMS [M+H$^+$] found *m/s* 345.1540, calcd for $C_{22}H_{21}N_2O_2$ 345.1532. Mp 75.4°C.

4.1.5. *N*-(2-Benzoyl-phenyl)-2-(1,3-dihydro-isoindol-2-yl)-acetamide (5e). ^{1}H NMR δ 3.56 (2H, s), 4.13 (4H, s), 7.09 (1H, ddd, J=7.82, 7.32, 1.22 Hz), 7.12–7.25 (4H, m), 7.35–7.43 (2H, m), 7.46–7.59 (3H, m), 7.62–7.68 (2H, m), 8.61 (1H, dd, J=8.43, 1.10 Hz), 11.4 (1H, bs). ^{13}C NMR δ 59.8, 60.8, 121.6, 122.0, 122.2, 125.0, 126.5, 127.9, 129.6, 132.1, 132.3, 133.1, 138.0, 138.6, 139.2, 169.9, 197.5. HRMS [M+Na$^+$] found *m/s* 379.1431, calcd for $C_{23}H_{20}N_2NaO_2$ 379.1423. Mp 152.4°C.

4.1.6. 4-Hydroxy-4-phenyl-3-piperidin-1-yl-3,4-dihydro-1*H*-quinolin-2-one (4a). General procedure. ^{1}H NMR δ 1.34–1.44 (2H, m), 1.46–1.60 (4H, m), 2.48–2.60 (2H, m), 2.66–2.78 (2H, m), 3.34 (1H, s), 6.03 (1H, s), 6.76 (1H, dd, J=7.77, 1.18 Hz), 7.10 (1H, td, J=7.62, 1.17 Hz), 7.14–7.28 (5H, m), 7.60 (1H, dd, J=7.62, 1.46 Hz), 8.43 (1H, bs). ^{13}C NMR δ 23.6, 26.5, 52.1, 72.2, 74.1 114.7, 124.3, 125.2, 127.1, 127.3, 128.3, 128.6, 129.7, 134.5, 145.4, 167.0. HRMS [M+Na$^+$] found *m/s* 345.1571, calcd for $C_{20}H_{22}N_2NaO_2$ 345.1579. Mp 188.6°C.

4.1.7. 3-Diethylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4b). ^{1}H NMR δ 1.09 (6H, t, J=7.2 Hz), 2.65 (2H, dtq, J=19.8, 13.5, 6.9 Hz) 2.73 (2H, dtq, J=19.8, 13.5, 6.9 Hz) 3.58 (1H, s), 5.94 (1H, s), 6.80 (1H, d, J=8.1 Hz), 7.11 (1H, t, J=7.5 Hz), 7.17–7.26 (5H, m), 7.60 (1H, d, J=7.8 Hz), 9.10 (1H, bs). ^{13}C NMR δ 14.0, 45.6, 69.3, 72.5, 115.0, 124.8, 125.8, 127.8, 127.8, 128.7, 129.1, 130.0, 135.0, 146.0, 168.7. HRMS [M+H$^+$] found *m/s* 311.1680, calcd for $C_{19}H_{23}N_2O_2$ 311.1688. Mp 174.6°C.

4.1.8. 3-Dibenzylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4c). ^{1}H NMR δ 3.62 (2H, d, J=12.3 Hz), 3.70 (1H, s), 3.83 (2H, d, J=12.5 Hz), 5.78 (1H, s), 6.52–6.60 (2H, m), 6.82 (1H, d, J=7.33 Hz), 7.00–7.40 (15H, m), 7.62 (1H, dd, J=7.72, 1.17 Hz), 8.46 (1H,

bs). ^{13}C NMR δ 55.3, 65.9, 72.6, 114.5, 124.5, 125.7, 127.3, 127.4, 127.5, 128.0, 128.4, 128.9, 129.5, 134.7, 137.5, 144.9, 167.1. HRMS [M+H$^+$] found *m/s* 435.1990, calcd for $C_{29}H_{27}N_2O_2$ 435.1994. Mp 241.2°C.

4.1.9. 3-Benzylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4d). ^{1}H NMR δ 1.25 (1H, m), 3.10, 3.35 (2H, AB, J=13.5 Hz), 3.84 (1H, s), 6.83 (1H, d, J=7.8 Hz), 6.91 (2H, m), 7.07 (2H, d, J=6.6 Hz), 7.17–7.27 (4H, m), 7.30–7.46 (5H, m), 9.35 (1H, s). ^{13}C NMR δ 52.7, 65.1, 75.8, 116.0, 124.0, 127.3, 127.4, 127.5, 127.7, 127.9, 128.4, 128.5, 128.6, 128.8, 129.9, 130.2, 136.2, 139.3, 143.3, 170.1. HRMS [M+H$^+$] found *m/s* 345.1383, calcd for $C_{23}H_{23}N_2O_2$ 345.1532.

4.1.10. 3-(1,3-Dihydro-isoindol-2-yl)-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one (4e). ^{1}H NMR δ 3.87 (1H, s), 4.06 (2H, d, J=11.7 Hz), 4.13 (2H, d, J=11.7 Hz), 5.37 (1H, bs), 6.83 (1H, dd, J=8.77, 1.17 Hz), 7.0–7.45 (11H, m), 7.63 (1H, dd, J=7.62, 1.17 Hz), 9.74 (1H, bs). ^{13}C NMR δ 55.8, 69.4, 73.5, 115.3, 122.1, 124.7, 125.9, 126.9, 126.9, 127.8, 128.4, 129.0, 129.4, 134.6, 138.4, 143.5, 167.9. HRMS [M+H$^+$] found *m/s* 357.1518, calcd for $C_{23}H_{21}N_2O_2$ 357.1525.

4.1.11. 4-Phenyl-3-piperidin-1-yl-1*H*-quinolin-2-one (9a). ^{1}H NMR δ 1.41 (6H, bs), 2.90 (4H, bs), 7.03 (1H, m), 7.18 (1H, ddd, J=8.21, 1.91, 0.88 Hz), 7.23–7.52 (7H, m), 11.9 (1H, bs). ^{13}C NMR δ 24.2, 26.4, 51.7, 115.2 121.5, 121.7, 125.8, 127.2, 127.7, 127.8, 129.7, 135.5, 136.6, 139.8, 141.5, 163.1. HRMS [M+Na$^+$] found *m/s* 327.1374, calcd for $C_{20}H_{20}N_2NaO$ 327.1473. Mp 233.0°C (decomp.).

Acknowledgements

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References

1. See Ref. 2 in Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V. *Tetrahedron* **1999**, *55*, 12045.
2. Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397.
3. For recent collection of papers on stereocontrolled synthesis of tailor-made amino acids, see: 'Asymmetric Synthesis of Novel Sterically Constrained Amino Acids', Tetrahedron Symposia-in-Print; # 88; Guest Editors: Hruby, V. J.; Soloshonok, V. A. *Tetrahedron* **2001**, *57*(30), 6329–6650.
4. Hruby, V. J. *Nat. Rev. Drug Discov.* **2002**, *1*, 847–858.
5. For recent review on χ-(chi)-constrained amino acids, see: Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.
6. (a) In *Molecular Conformation and Biological Interactions*; Balaram, P., Ramaseshan, S., Eds.; Indian Academy of Science: Bangalore, 1991. (b) Ramachandran, G. N.; Sasisekharan, V. *Adv. Protein Chem.* **1968**, *23*, 283. (c) Scheraga, H. A. *Chem. Rev.* **1971**, *71*, 195. (d) Bloom, S. M.; Fasman, G. D.; DeLoze, C.; Blout, E. R. *J. Am. Chem. Soc.* **1961**, *84*, 458.
7. For synthesis of 2-aminotetralin-2-carboxylic acid (Atc) (**1**), see: (a) Liu, W.; Ray, P.; Benezra, S. A. *J. Chem. Soc., Perkin Trans. 5* **1995**, 553. (b) Obrecht, D.; Spiegler, C.; Schoenholzer, P.; Mueller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta* **1992**, *75*, 1666.
8. For applications in peptide design of Atc-**1**, see: (a) Aldrich, J. V.; Zheng, Q.; Murray, T. F. *Chirality* **2001**, *13*, 125. (b) Darula, Z.; Peter, A.; Toth, G. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 817. (c) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M. D.; Lemieux, C.; Chung, N. N.; Marsden, B. J.; Wilkes, B. C. *J. Med. Chem.* **1991**, *34*, 3125. (d) Deeks, T.; Crooks, P. A.; Waigh, R. D. *J. Pharm. Sci.* **1984**, *73*, 457. (e) Cordi, A. A.; Lacoste, J.-M.; Descombes, J.-J.; Courchay, C.; Vanhoutte, P. M.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1995**, *38*, 4056. (f) Denyer, C. V.; Turner-Brown, S. J.; Knowles, R. G.; Dawson, J. *Bioorg. Med Chem. Lett.* **1992**, *2*, 1039. (g) Obrecht, D.; Altorfer, M.; Bohdal, U.; Daly, J.; Huber, W.; Labhardt, A.; Lehmann, C.; Muller, K.; Ruffieux, R.; Schonholzer, P.; Spiegler, C.; Zumbrunn, C. *Biopolymers* **1997**, *42*, 575.
9. For synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) (**2**), see: Majer, P.; Slaninova, J.; Lebl, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 62.
10. For the most recent papers on 'Quinapril' and its analogs ('Moexipril'), see: (a) Blumer, J. L.; Daniels, S. R.; Dreyer, W. J.; Batisky, D.; Walson, Ph. D.; Roman, D.; Ouellet, D. *J. Clin. Pharm.* **2003**, *43*, 128. (b) Warnica, J. W.; Van Gilst, W.; Baillot, R.; Johnstone, D.; Block, P.; Myers, M. G.; Chocron, S.; Ave, S. D.; Martineau, P.; Rouleau, J.-L. *Can. J. Cardiol.* **2002**, *18*, 1191. (c) Radauceanu, A.; Virion, J.-M.; Boivin, J.-M.; Zannad, F. *Fundam. Clin. Pharm.* **2002**, *16*, 545. (d) Resnick, L. M.; Lester, M. H. *Am. J. Hypertens.* **2002**, *15*, 1096. (e) Saran, R.; Dykstra, D. M.; Wolfe, R. A.; Gillespie, B.; Held, Ph. J.; Young, E. W. *Am. J. Kidney Dis.* **2002**, *40*, 1255. (f) Okuguchi, T.; Osanai, T.; Fujiwara, N.; Kato, T.; Metoki, N.; Konta, Y.; Okumura, K. *Am. J. Hypertens.* **2002**, *15*, 998. (g) Molinaro, G.; Cugno, M.; Perez, M.; Lepage, Y.; Gervais, N.; Agostoni, A.; Adam, A. *J. Pharm. Exp. Ther.* **2002**, *303*, 232. (h) Sakata, K.; Yoshida, H.; Obayashi, K.; Ishikawa, J.; Tamekiyo, H.; Nawada, R.; Doi, O. *J. Hypertens.* **2002**, *20*, 103. (i) Hlubocka, Z.; Umnerova, V.; Heller, S.; Peleska, J.; Jindra, A.; Jachymova, M.; Kvasnicka, J.; Horky, K.; Aschermann, M. *J. Human Hypertens.* **2002**, *16*, 557. (j) Culy, C. R.; Jarvis, B. *Drugs* **2002**, *62*, 339.
11. For examples of application of 2′,6′-dimethyl-L-tyrosine (Dmt)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) pharmacophore, see: (a) Balboni, G.; Salvadori, S.; Guerrini, R.; Negri, L.; Giannini, E.; Jinsmaa, Y.; Bryant, S. D.; Lazarus, L. H. *J. Med. Chem.* **2002**, *45*, 5556. (b) Bryant, S. D.; George, C.; Flippen-Anderson, J. L.; Deschamps, J. R.; Salvadori, S.; Balboni, G.; Guerrini, R.; Lazarus, L. H. *J. Med. Chem.* **2002**, *45*, 5506. (c) Kumar, V.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2002**, *45*, 3820.
12. For synthesis of 3-amino-3,4-dihydro-1*H*-quinolin-2-one (**3**), see: (a) Juarez-Gordiano, C.; Hernandez-Campos, A.; Castillo, R. *Synth. Commun.* **2002**, *32*, 2959. (b) Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2002**, *68*, 2960.
13. For application of model **3** in peptide design, see: (a) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943. (b) Zhao, H.; Thurkauf, A.; Braun, J.; Brodbeck, R.; Kieltyka, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*,

2119. (c) Shono, T.; Motoyama, M.; Tatsumi, K.; Ulbrich, N.; Iwamoto, Y.; Kuwano, M.; Ono, M. *Angiogenesis* **1999**, *2*, 319. (d) Iki, K.; Tsutsumi, M.; Kido, A.; Sakitani, H.; Takahama, M.; Yoshimoto, M.; Motoyama, M.; Tatsumi, K.; Tsunoda, T.; Konishi, Y. *Carcinogenesis* **1999**, *20*, 1323. (e) Kido, A.; Tsutsumi, M.; Iki, K.; Motoyama, M.; Takahama, M.; Tsujiuchi, T.; Morishita, T.; Tatsumi, K.; Tamai, S.; Konishi, Y. *Jpn. J. Cancer Res.* **1999**, *90*, 333. (f) Lewis, R. J.; Francis, C. A.; Lehr, R. E.; LeRoy Blank, C. *Tetrahedron* **2000**, *56*, 5345. (g) Masubuchi, K.; Taniguchi, M.; Umeda, I.; Hattori, K.; Suda, H.; Kohchi, Y.; Isshiki, Y.; Sakai, T.; Kohchi, M.; Shirai, M.; Okabe, H.; Sudoh, M.; Yamazaki, T.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1459. (h) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2573.

14. A colorless crystal (0.22×0.16×0.04 mm) of **4a** ($C_{20}H_{22}N_2O_2$) was used for X-ray diffraction measurement. The data were collected at 120(1) K on a Bruker APEX CCD diffractometer with Mo K_α radiation (λ=0.71073 Å). Crystal system is triclinic and space group is *P*-1 with *a*= 10.322(1), *b*=12.265(1), *c*=14.336(2) Å, α=73.487(2)°, β=70.446(2)°, γ=83.155(2)°, *V*=1639.0(3) Å^3, *Z*=4, *D*(calc)=1.307 Mg/m^3, Total reflection measured=18062 ($2\theta_{max}$=53.0°), unique reflections=6695 [*R*(int)=0.0250]. Final *R*1=0.0797 for 5795 'observed reflections' [$I>2\sigma(I)$], *wR*2=0.2282 (for 6695 unique reflections), and Goodness-of-fit on F^2=0.964. The largest diff. peak and hole=1.144 and −0.349 e Å^{-3}, respectively. The complete X-ray data were deposited with Cambridge Crystallographic Data Centre.
15. Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51.
16. (a) Beier, N.; Labitzke, E.; Medeski, W. K. R.; Radunz, H.-E. *Heterocycles* **1994**, *39*, 117. (b) Hino, K.; Kawashima, K.; Oka, M.; Nagai, Y.; Uno, H.; Matsumoto, J. *Chem. Pharm. Bull.* **1989**, *37*, 110. (c) Hino, K.; Furukawa, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1980**, *28*, 2618. (d) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1975**, *18*, 726. (e) Torisawa, Y.; Nishi, T.; Minamikawa, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 387. (f) Uray, G.; Niederreiter, K. S.; Belaj, F.; Fabian, W. M. F. *Helv. Chem. Acta* **1999**, *82*, 1408. (g) Fabian, W. M. F.; Niederreiter, K. S.; Uray, G.; Stadlbauer, W. *J. Mol. Struct.* **1999**, *477*, 209. and references there in.
17. Mancilla, T.; Carrillo, L.; Zamudio-Rivera, L. S.; Beltran, H. I.; Farfan, N. *Org. Prep. Proced. Int.* **2001**, *33*, 341.