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Chiral 1,3,6-trisubstituted 2,4-dioxohexahydropyrimidines: a convenient stereoselective synthesis from aspartic acid derivatives

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Abstract—Chiral 1,3,6-trisubstituted 2,4-dioxohexahydropyrimidines were easily synthesized by reaction of homoaspartic acid derivatives with isocyanates, followed by cyclization of the resulting urea, and alkylation at N1 position.

The pyrimidine ring, in its different degrees of oxidation, can often be found embedded on the structure of active compounds. In this respect, the dihydropyrimidinedione and the tetrahydropyrimidine-2-one nucleus have attracted much interest in medicinal chemistry programs due to the variety of biological activities displayed by these compounds.[1,2] However, the examples of related 2,4-dioxohexahydropyrimidines are much more scarce. A few examples of bioactive 2,4-dioxohexahydropyrimidines include ligands for somatostatin receptors,[3] α-glucosidase inhibitors,[4]antiepileptic agents,[5] and HIV-integrase inhibitors.[6] In addition, some 4-oxohexahydropyrimidine derivatives have been used as proline mimetics,[7] and as temporary chiral auxiliaries for asymmetric synthesis.[8]

Most common methods for the synthesis of 2,4-dioxohexahydropyrimidines involve the reduction and photochemical transformations of the corresponding dihydropyrimidinedione derivatives,[9] the three-component condensation of primary amines, isocyanates and β-dielectrophiles,[10] and the cyclization of β-amino-ester-derived ureas.[11] We have recently described a simple four-step procedure for the synthesis of highly functionalized 1,3,6-trisubstituted 2,4-dioxohexahydropyrimidines **I** (Chart 1), starting from dipeptide-derived

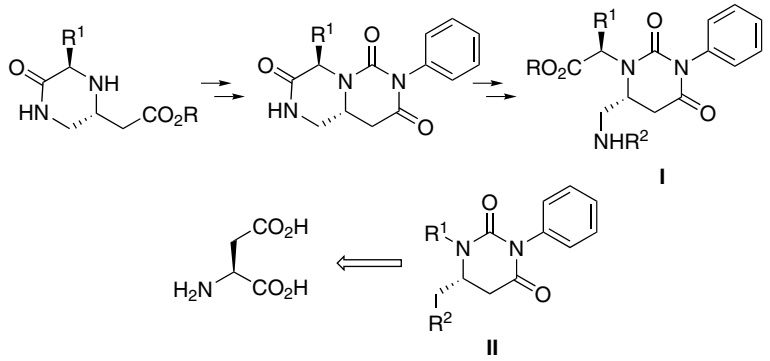

Chart 1.

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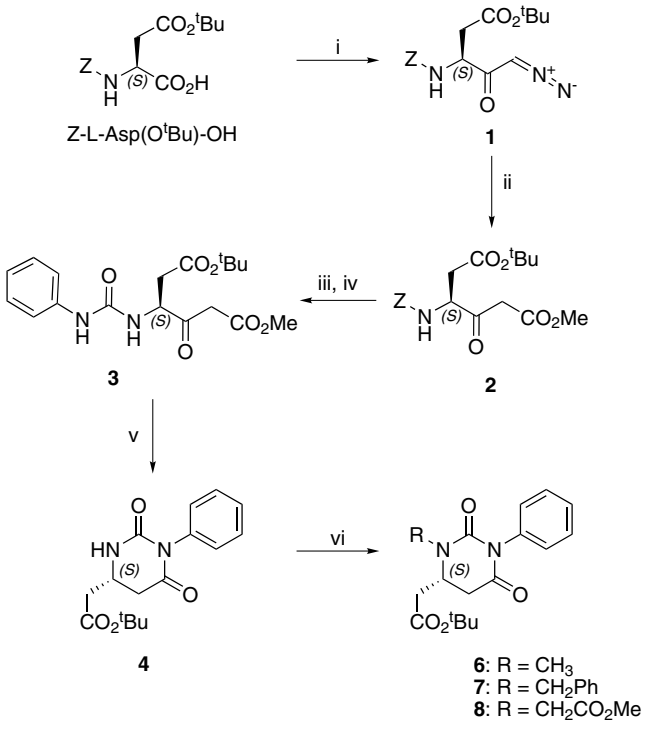
piperazin-2-ones. This procedure consists of the acylation of the piperazin-2-one with isocyanate, transformation to the corresponding perhydropyrazino[1,2-*f*]-pyrimidine-3,6,8-triones, activation with *tert*-butylcarbonate, and controlled opening of the pyrazine ring from the bicyclic skeleton.[12]

Inspired by this process and by the cyclization of β-aminoester-derived ureas,[11] we envisaged a new synthetic pathway to chiral 1,3,6-trisubstituted 2,4-dioxohexahydropyrimidines **II** from aspartic acid derivatives (Chart 1). While our first method is restricted to 1-(alkoxycarbonyl)alkyl- and 6-aminomethyl-substituted derivatives, the new procedure should permit a more flexible pattern of substituents at these two positions.

As shown in Scheme 1, diazoketone **1** was prepared from commercial *Z*-L-Asp(O^{t}Bu)-OH by activation with isobutyl chloroformate, in the presence of *N*-methylmorpholine, and reaction of the mixed anhydride intermediate with diazomethane.[13] Compound **1** undergoes the Arndt–Eistert rearrangement upon treatment with a catalytic amount of silver benzoate in the presence of MeOH to yield the orthogonally protected homoaspartic derivative **2**.[14] Catalytic hydrogenation of **2** in the presence of Pd–C as catalyst, followed by the addition of phenyl isocyanate afforded linear urea intermediate **3** in good yield. This intermediate cyclized in a regioselective manner through the methyl ester to enantioselectively provide the 3,6-disubstituted 2,4-dioxohexahydropyrimidine **4**.[15] The best result in this cyclization was found when ^{t}BuOK was used as base



Scheme 1. Reagents and conditions: (i) ^{i}BuOCOCl/NMM(THF), CH_2N_2/Et_2O; (ii) $C_6H_5CO_2Ag$/TEA/MeOH; (iii) H_2/Pd–C/MeOH. (iv) PhNCO/THF; (v) ^{t}BuOK/THF; (vi) RX/^{t}BuOK/THF.

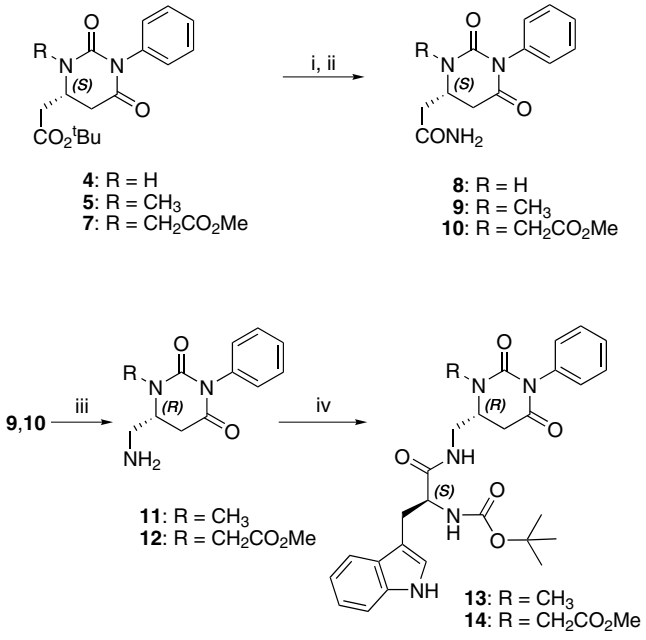
Table 1. Synthesis of 2,4-dioxohexahydropyrimidine derivatives

Starting compound	Base	RX	Final compound	Yield[a] (%)
3	KO^{t}Bu	—	**4**	70
3	NaH	—	**4**	45
3	DBU	—	**4**	38
4	KO^{t}Bu	IMe	**5**	73
4	KO^{t}Bu	$BrCH_2Ph$	**6**	93
4	KO^{t}Bu	$BrCH_2CO_2Me$	**7**	87
4	—	—	**8**	80
5	—	—	**9**	89
7	—	—	**10**	90

[a] Yield of isolated compounds.

(Table 1). To explore the incorporation of molecular diversity at position N1, compound **4** was reacted with three different alkylating agents, namely, methyl iodide, benzyl bromide, and methyl bromoacetate, in the presence of ^{t}BuOK. The expected chiral 1,3,6-trisubstituted pyrimidine-2,4-diones **5**–**7** were obtained in excellent yield (Table 1).[16]

Transformation of the substituent at position 6 was also performed. Thus, compounds **5**–**7** were easily transformed into carboxamides **8**–**10**, using a two-step procedure that involves acidic hydrolysis of the *tert*-butyl ester with TFA, followed by activation of the free carboxylic acid with isobutyl chloroformate and reaction of the mixed anhydride with NH_3/THF. An oxidative Hoffman-type rearrangement, of carboxamide derivatives **9** and **10**, promoted by PhI[OC(O)CF3]2 (PIFA),[17] afforded the corresponding 6-(amino)methyl substituted compounds **11** and **12**. Finally, these compounds were coupled to Boc-L-Trp-OH without problems, providing tryptophyl derivatives **13** and **14** as a single diastereoiso-



Scheme 2. Reagents and conditions: (i) TFA/CH_2Cl_2; (ii) 1. ^{i}BuOCOCl/NMM; 2. NH_3/THF; (iii) PIFA/MeCN/EtOAc/H_2O (2:2:1); (iv) Boc-L-Trp-OH/BOP/TEA/THF.

mer in each case. This confirms the lack of racemization during the synthesis of precursor **1**. As demonstrated with the synthesis of **13** and **14**, the 6-(amino)methyl substituent, as well as the 6-(carboxy)methyl counterpart, could serve to extend the variety of groups at the C6 substituent level. The synthesis of **14** also allowed us to unequivocally assign the C6 configuration of a pair of diastereoisomers of **14** prepared by an alternative method[12,18] (Scheme 2).

In summary, we have developed a short, simple, and highly enantioselective synthetic procedure for the preparation of 1,3,6-trisubstituted 2,4-dioxohexahydropyrimidines. The key steps of this process are the formation of urea-substituted homoaspartic acid derivatives, the base-promoted cyclization to the tetrahydropyrimidinedione ring, and the alkylation at position N1. The application of this heterocyclic scaffold in the generation of molecular diversity, by using different isocyanates (providing the substituents at N3), diverse alkylating agents (at N1), and by the incorporation of amines or acyl groups at the C6 substituents, may be anticipated.

Acknowledgment

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16. *Analytical and spectroscopic data of selected compounds*: *Compound* **7**: $[\alpha]_D$ −17.9 (*c* 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.47–7.17 (m, 5H, C_6H_5), 4.54 (d, 1H, $J = 17.7$, 1-CH_2) 4.09 (d, 1H, $J = 17.7$, 1-CH_2), 4.06 (m, 1H, H-6), 3.76 (s, 3H, OMe), 3.35 (dd, 1H, $J = 16.3$, 6.3, H-5), 2.86 (dd, 1H, $J = 16.7$, 7.3, 6-CH_2), 2.77 (dd, 1H, $J = 16.3$, 1.9, H-5), 2.59 (dd, 1H, $J = 16.7$, 6.3, 6-CH_2), 1.45 (s, 9H, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.6, 168.4, 152.8 (CO), 134.9, 129.0, 128.5, 128.4 (Ar), 82.1 (C, ^{t}Bu), 52.3 (OMe), 48.9 (C-6), 49.2 (1-CH_2), 38.9 (C-5), 37.2 (6-CH_2), 27.9 (CH_3, ^{t}Bu). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.74; H, 6.40; N, 7.47.
Compound **10**: $[\alpha]_D$ +6.20 (*c* 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.13 (m, 5H, C_6H_5), 6.38 and 5.78 (br s, 2H, $CONH_2$), 4.32 (d, 1H, $J = 17.7$, 1-CH_2) 4.11 (d, 1H, $J = 17.7$, 1-CH_2), 4.00 (m, 1H, H-6), 3.72 (s,

3H, OMe), 3.25 (dd, 1H, $J = 16.4$, 6.4, H-5), 2.74 (dd, 1H, $J = 16.4$, 1.5, H-5), 2.60 (dd, 1H, $J = 15.2$, 6.4, 6-CH_2), 2.44 (dd, 1H, $J = 16.4$, 6.5, 6-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 169.9, 168.7, 152.8 (CO), 135.1, 129.0, 128.6, 128.4 (Ar), 52.3 (OMe), 50.3 (C-6), 49.4 (1-CH_2), 38.6 (C-5), 36.7 (6-CH_2). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.52; H, 5.36; N, 13.07.

Compound **11**: $[\alpha]_D$ +2.71 (*c* 0.52, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.14 (m, 5H, C_6H_5), 5.12 (br t, 2H, NH_2), 3.73 (m, 1H, H-6), 3.53 (m, 1H, 6-CH_2), 3.36 (m, 1H, 6-CH_2), 3.17 (s, 3H, 1-CH_3), 3.11 (dd, 1H, $J = 16.8$, 7.1, H-5), 2.85 (dd, 1H, $J = 16.8$, 1.5, H-5). Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.54; H, 6.72; N, 17.88.

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18. *Compound* **14**: White foam. $[\alpha]_D$ −17.5 (*c* 0.41, $CHCl_3$), described in Ref. 12: $[\alpha]_D$ −17.3 (*c* 0.12, $CHCl_3$).