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Conformationally restricted glutamic acid derivatives: asymmetric synthesis of 4-substituted 4,5-dihydro-3(2*H*)-pyridazinones

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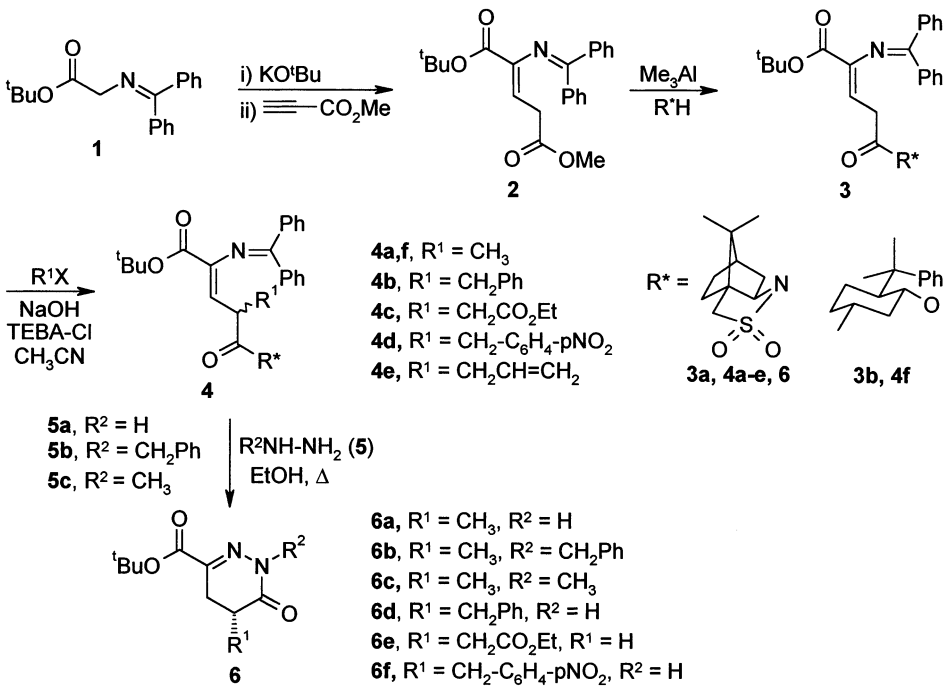
Abstract—The synthesis of optically pure 4,5-dihydro-3(2*H*)-pyridazinones substituted at C-4, which can be considered conformationally restricted cyclic Glu derivatives, has been accomplished by the asymmetric γ-alkylation of α,β-unsaturated glutamyl sultams under PTC conditions followed by reaction with hydrazines.

Conformationally constricted α-amino acids have attracted a great deal of attention in recent times in the design of peptide surrogates with improved metabolical properties over the natural peptides.[1] In particular, cyclic compounds have been much used to induce turns in peptide chains,[2] and those which include a N–N linkage in their cyclic structure are well known for their biological activities.[3] Dihydropyridazinones can be considered as rigid analogues of hydrazinolactams.[4] In view of the ability of certain cyclic glutamic acid derivatives to induce conformational restrictions to peptide chains,[5] we considered that rigid cyclic Glu-derived dihydropyridazinones which bear asymmetric carbon atoms on the heterocyclic core could be particularly attractive in this area.



Scheme 1.

Keywords: alkylation; amino acids and derivatives; cyclization; pyridazinones; sultams.

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Table 1. γ-Alkylation of substrates **3** under PTC conditions

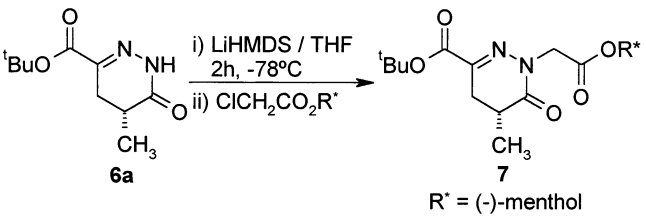
No.	**3**	R^1X	R^1	*t* (min)	**4** (2*R*:2*S*[a], %[b])	(2*R*)-**4**, %[c]
1	**3a**	MeI	Me	10	**4a** (92:08, 30)	–
2	**3a**	MeI	Me	60	**4a** (92:08, 85)	70
3	**3a**	$PhCH_2Br$	$PhCH_2$	60	**4b** (100:0, 90)	80
4	**3a**	EtO_2CCH_2Br	EtO_2CCH_2	60	**4c** (100:0, 85)	75
5	**3a**	pNO_2-C_6H_4-CH_2Br	pNO_2-C_6H_4-CH_2	60	**4d** (91:09, 85)	70
6	**3a**	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	60	**4e** (93:07, 90)	70
7	**3b**	MeI	Me	60	**4f** (70:30, 50)	–

[a] Determined by integration of the ^1H NMR (300 MHz, $CDCl_3$) spectra of the crude reaction products.
[b] Isolated yields after filtration of the reaction crude, rinsing with Et_2O, evaporation of the solvent and silica-gel chromatography (hexane:ethyl acetate, 80:20).
[c] Isolated yields after crystallization (hexane:ethyl acetate).

Table 2. Synthesis of the 4-substituted 3,4-dihydro-3(2*H*)pyridazinones **6**

Entry	**4**	R^1	**5**	R^2	**6** (%[a])
1	**4a**	CH_3	**5a**	H	**6a** (95)
2	**4a**	CH_3	**5b**	$PhCH_2$	**6b** (95)
3	**4a**	CH_3	**5c**	CH_3	**6c** (90)
4	**4b**	$PhCH_2$	**5a**	H	**6d** (90)
5	**4c**	EtO_2CCH_2	**5a**	H	**6e** (90)
6	**4d**	pNO_2-C_6H_4-CH_2Br	**5a**	H	**6f** (90)

[a] Isolated yields after extraction with Et_2O and silica-gel chromatography (hexane:ethyl acetate, 80:20).



Scheme 2.

Therefore, we report herein the asymmetric γ-alkylation of α,β-unsaturated glutamic acid derivatives under solid–liquid PTC conditions and their cyclization to optically pure 4,5-dihydro-3(2*H*)-pyridazinones as a new entry to this class of compounds.

Enolization of the *t*butyl glycinate **1** with KO*t*Bu (1.1 equiv., THF, −78°C, 30 min) followed by reaction with methyl propiolate (1.1 equiv.) afforded the α,β-didehydroglutamic acid derivative **2** via a Michael addition/1,3-prototropic shift pathway.[6] Selective Me_3Al-mediated acylation[7] of the terminal methyl ester of **2** with Oppolzer's (2*R*)-(−)-bornane-10,2-sultam[8] (1.2 equiv. Me_3Al, toluene, 50°C, 48 h) gave rise to the α,β-didehydroglutamylsultam **3a** (80% isolated yield). This was regioselectively alkylated under solid–liquid PTC conditions exclusively at the γ-position (1.1 equiv. RX, acetonitrile, 1.0 equiv. NaOH, 10% mol TEBA–Cl, 1 h, rt)[9] with very good overall yields and high diastereomeric excesses in favor of the 2*R* isomers[10] of compounds **4a–e** (Scheme 1).

The results are given in Table 1. It is worth mentioning that no racemization was observed upon increasing the reaction time under the same reaction conditions (Table 1, entries 1 and 2). Furthermore, the diastereomeric excesses observed in the asymmetric γ-alkylation of sultam **3a** under PTC conditions were higher than those previously reported for the corresponding 8-phenylmenthyl ester **3b** in homogeneous solution (LDA or KO*t*Bu, THF).[11] As a matter of fact, the γ-alkylation of **3b** under the aforementioned PTC conditions (Table 1, entry 7) took place with low diastereoselectivity and low overall yield.

An additional benefit in the use of Oppolzer's camphorsultam arises in both the ease of cleave and the recovery of the chiral auxiliary.[8] Thus, the reaction of compounds **4a–d** with hydrazines **5** (2 equiv., EtOH, Δ, 24 h) allowed for the synthesis of the 4-substituted 3(2*H*)-pyridazinones **6** in a one-pot *N*-deprotection[12]/cyclization sequence (Scheme 1), with recovery of the chiral inducer after chromatography of the reaction mixture. The results are given in Table 2.

No epimerization at C4 occurred in the cyclization process, as evidenced by the transformation of compound **6a** into **7** (LiHMDS, $ClCH_2CO_2R^*$, R*=(−)-menthyl), which gave rise to a single diastereomer as evidenced by ^1H NMR ($CDCl_3$, 300 MHz) of the reaction crude (Scheme 2).

In conclusion, the procedure described herein constitutes a novel entry to optically pure cyclic glutamic acid derivatives, which may be of use in the preparation of new conformationally restricted azapeptides. Further research in this area is in progress, and will be reported in due course.

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References

1. *Peptide Secondary Structure Mimetics*, *Tetrahedron*; Kahn, M., Ed.; Tetrahedron Symposia in Print No. 50, 1993; Vol. 49, pp. 3433–3689.
2. Cativela, C.; Diaz de Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 647–732.
3. (a) Hale, K. J.; Cai, J.; Delissir, V.; Manaviazar, S.; Peak, S. A.; Bhatia, G. S.; Collins, T. C.; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047–1068; (b) Roussi, F.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett*. **1998**, *39*, 8081–8084.
4. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
5. See for example: Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. *J. Med. Chem*. **1991**, *34*, 455 and references cited therein.
6. Alvarez-Ibarra, C.; Csákÿ, A. G.; Martín, E.; de la Morena, M. J.; Quiroga, M. L. *Tetrahedron Lett*. **1997**, *38*, 4501–4502.
7. For the Me_3Al-mediated acylation or *N*-protected glycinates, see: (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *30*, 5603–5606. (b) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2379.
8. Oppolzer, W. *Pure Appl. Chem*. **1990**, *62*, 1241–1250 and references cited therein.
9. For the enolization of glycinesultams under solid–liquid PTC conditions, see: López, A.; Pleixats, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1967–1977.
10. Configurational assignment of the major diastereomers of compounds **4** as 2*R* is based on the well-known π-face discrimination in sultamyl enolates either under PTC or homogeneous conditions. See: Refs. 8 and 9.
11. Alvarez-Ibarra, C.; Csákÿ, A. G.; Martín, E.; Quiroga, M. L. *Tetrahedron* **1999**, *55*, 7319–7330.
12. For the deprotection of imine-protected α-amino acids to the NH_2-free compounds with hydrazine, see for example: Kanemasa, S.; Tatsukawa, A.; Wada, C. *J. Org. Chem*. **1991**, *56*, 2875–2883.