Pergamon

Tetrahedron Letters 42 (2001) 7891–7892

TETRAHEDRON LETTERS

Cycloaddition–hydrogenolysis strategy for the synthesis of 2,4-disubstituted pyroglutamates†

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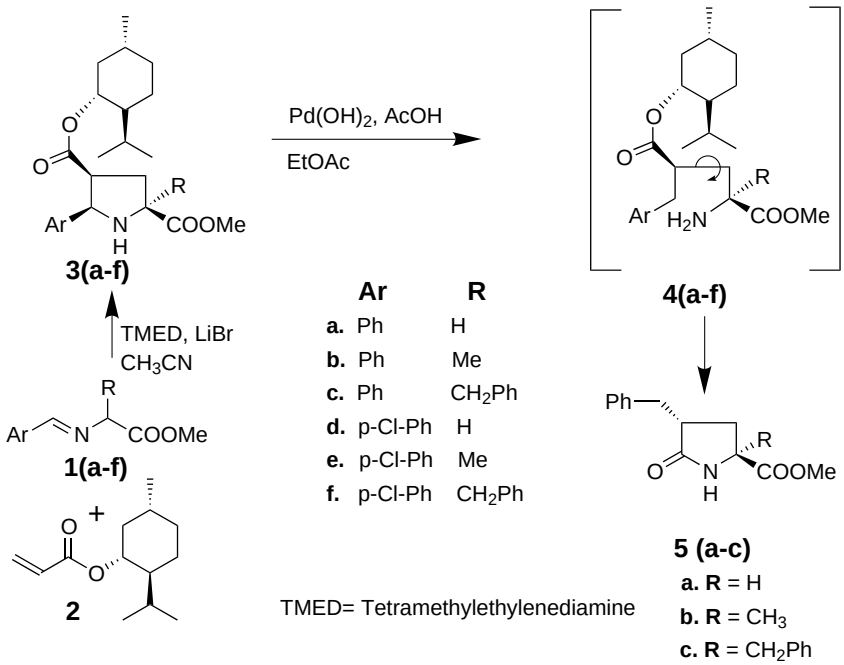
Received 29 May 2001; revised 21 August 2001; accepted 30 August 2001

Abstract—1,3-Dipolar addition of amino acid derived dipoles with menthyl acrylate followed by hydrogenolysis of the adduct gives chiral 2-α-substituted-4-α-arylmethyl-pyroglutamates.

Substituted prolines and pyroglutamates have been the favored targets of many synthetic strategies due to their importance as fragments of various bioactive substances.[1] There have been numerous reports describing strategies for stereoselective functionalisation of C-4[2,3] C-3[4,5] and C-2[6,7] of the pyroglutamate skeleton. Most of these methodologies employ low temperature enolate chemistry[3] and depend on the steric influence of the C-2 substituent.[6] This often results in a varying degree of stereoselectivity. Moreover, there are limited methodologies for functionalisation at C-2 and almost none for achieving a stereocontrolled C-2, C-4 di-substitution. 1,3-Dipolar cycloaddition of arylidene derivatives of amino acid esters with various polarized olefins is known to give a high order of stereoselection, and it is also possible to introduce an element of chirality using chiral auxiliaries.[8,9] We were intrigued by the possibility of transforming these pyrrolidine adducts to pyroglutamates having defined stereochemistry. In the present communication we report our initial results in this direction.



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† Communication No. 6183 from Central Drug Research Institute.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01629-X

Table 1.

Entry no.	Yield (%)	m.p. (°C)	$[\alpha]_D^{25}$	e.e.[12]
3a	45	100	−2.98 (*c* 0.7, $CHCl_3$)	>99
3b	50	69–70	−16.9 (*c* 0.61, $CHCl_3$)	>99
3c	53	Oil	−10.25 (*c* 2.4, $CHCl_3$)	91
3d	53	100–102	−7.3 (*c* 0.4, $CHCl_3$)	–
3e	49	80–82	−8.5 (*c* 0.95, $CHCl_3$)	–
3f	51	Oil	−10.7 (*c* 1.9, $CHCl_3$)	–
5a	61	145	+12.73 (*c* 0.11, MeOH)	88
5b	89	Oil	−15.05 (*c* 0.32, MeOH)	90
5c	52	114	−36.12 (*c* 0.08, MeOH)	70

Metallo-azomethine ylides, generated from imines **1(a–f)** by the action of an amine base in combination with LiBr or AgOAc, undergo 1,3-dipolar cycloaddition with 1*R*,2*S*,5*R*-menthyl acrylate **2** at room temperature to give homochiral pyrrolidines **3(a–f)** in excellent yields.[9,10] Our initial attempts to convert these pyrrolidines **3(a–f)** into pyroglutamates through sequential hydrogenolytic cyclization using 10% Pd/C as a catalyst in ethyl acetate, methanol and acetic acid, were unsuccessful. However, the use of 20% Pd/C (Pearlman's catalyst) in methanol-acetic acid at 60 psi resulted in smooth conversion of pyrrolidines **3(a–f)** to desired pyroglutamates **5(a–c)** via the intermediacy of **4** which was not isolated (Table 1). It was also observed that in case of (Ar=*p*-Cl–Ph) the hydrogenolytic step as expectedly resulted in the loss of halo atom to give **5(a–c)**.[11]

In these initial studies we have delineated an alternative strategy with a high degree of stereocontrol for the synthesis of C-2, C-4 di-substituted pyroglutamates. The easy oxidative conversation of aryl function to carboxylate moiety makes this strategy a method of choice for the synthesis of an intermediate in the synthesis of BIBU[13] and its analogs.

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10. Compounds **3a–f** were synthesized according to the method described in Ref. 9.
11. Synthesis of compounds **5a–c**: *Hydrogenolytic step:* compound **3a** (0.775 mmol) was dissolved in ethyl acetate (50 ml) containing CH_3COOH (1–2 ml) and hydrogenated over 100 mg $Pd(OH)_2$ catalyst at 60 psi for 10–15 h and the progress of the reaction was monitored by TLC. The mixture was filtered through Celite, washed with water, dried over Na_2SO_4, concentrated and the crude product was purified using flash chromatography over silica gel using hexane-ethyl acetate as eluant to give compound **5a** as a crystalline solid; yield, 110 mg (60.9%); IR (KBr): 3264, 2945, 1753, 1700, 1661 and 1442 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (m, 5H), 6.4 (bs, 1H), 4.01 (dd, $J=9$, 4 Hz, 1H), 3.7 (s, 3H), 3.2 (dd, $J=12$, 3 Hz, 1H), 2.74 (m, 2H) and 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 30.7, 36.6, 42.8, 52.4, 53.4, 126.5, 128.5, 129.0, 138.8, 172.4 and 178.8; FABMS (*m*/*z*): 234 ($M+1^+$). Compound **5b**: Yellow oil; yield, 170 mg (88.6%); IR (KBr): 3423, 2929, 1750, 1701 and 1386 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.23 (m, 5H), 6.32 (bs, 1H), 3.70 (s, 3H), 3.24 (dd, $J=9$, 3 Hz, 1H), 2.76 (dd, $J=9$, 3 Hz, 1H), 2.58 (m, 2H), 1.69 (m, 1H) and 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 26.2, 37.0, 39.0, 43.3, 53.1, 60.8, 126.8, 128.9, 129.3, 139.3, 174.8 and 178.7; FABMS (*m*/*z*): 248 ($M+1^+$) and 188. Compound **5c**: White powder; yield, 130 mg (52%); IR (KBr): 3419, 2927, 1755, 1703 and 1606 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.26 (m, 10H), 6.13 (bs, 1H), 3.64 (s, 3H), 3.20 (m, 2H), 2.74 (dd, $J=9$, 3 Hz, 1H), 2.58 (m, 3H) and 1.89 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 36.9, 37.3, 42.8, 45.7, 52.9, 65.1, 126.9, 127.9, 129.0, 129.1, 129.4, 130.0, 135.3, 139.2, 174.1 and 178.0; FABMS (*m*/*z*): 324 $(M+1)^+$and 264.
12. e.e. was determined by HPLC on a Merck LiCHROCART-250-4 Chiradex chiral column using methanol–water gradient (30–50% methanol in 30 min).
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