Pergamon

Tetrahedron Letters 39 (1998) 297–300

TETRAHEDRON LETTERS

New Cleavage Approaches to Combinatorial Synthesis of Homoserine Lactones

Dong-Hyun Ko, Dong Jin Kim, Chun Seon Lyu, In Ki Min, Hong-sik Moon*

CheilJedang Corporation R & D Center, 522-1, Dokpyong-Ri, Majang-Myon, Ichon-Si, Kyonggi-Do, 467-810, Korea

Received 16 September 1997; revised 29 October 1997; accepted 31 October 1997

Abstract: The polymer-supported synthesis of a methionine-functionalized resin for new cleavage strategy and combinatorial library of homoserine lactone analogs is described. The process consists of the coupling of N-Fmoc-methionine followed by deprotection to give a free amine of methionine-functionalized resin (**3**). After the coupling with a carboxylic acid, the final cleavage step proceeds through a BrCN-mediated cyclization process to produce homoserine lactone libraries (**5**) with retention of stereochemistry. © 1997 Elsevier Science Ltd. All rights reserved.

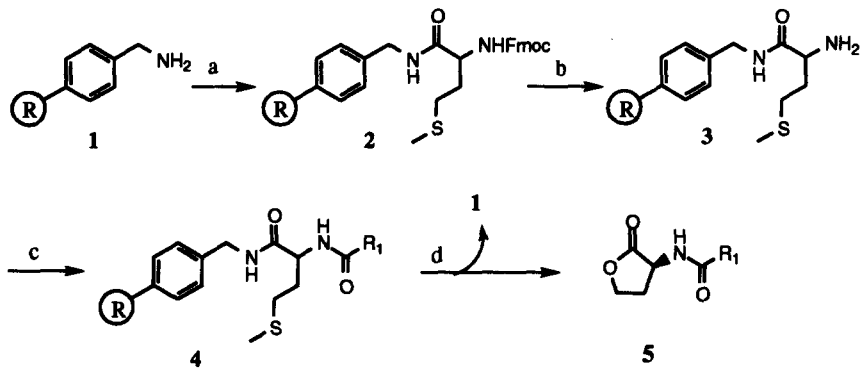
Combinatorial organic synthesis offers a growing potential for the preparation of structurally diverse chemical libraries in drug discovery[1]. Currently, a major attention of pharmaceutical companies has been focused on creating and evaluating small organic molecules by combinatorial technology and high throughput screening[2]. Over the last four years, the strategic advantages of polymer supported synthesis which include ease of work-up, ease of product isolation and ready recovery of the polymer resin by a simple filtration, have played a crucial role in accelerating processes and improving efficient in drug development. So far a considerable effort has been put into the application of cross coupling reactions[3], condensations[4], and other reaction types[5]. To make combinatorial organic synthesis a success, it is of the utmost importance to be able to choose not only the most suitable supports but also appropriate anchors such as Wang[6], Rink acid[7], BHA[8], and photolabile phenylketone[9] linkers. Even though it is possible to carry out a cleavage reaction using special linkers[10] under milder conditions, most cleavage steps require strong hydrolysis conditions. Therefore, the development of new linkers for mild cleavage is necessary for high yielding and recycling processes in solid phase synthesis. In this paper, we set out to explore a mild cleavage method for the solid phase synthesis of homoserine lactone libraries and describe herein a polymer-supported strategy for a four-step process consisting of a coupling step of an N-Fmoc-L-methionine, deprotection of N-Fmoc group, N-coupling with a carboxylic acid, and cleavage reaction through cyclization which leads to the preparation of homoserine lactones. The scaffold of homoserine lactones (**Scheme I, 5**) is common in certain biological analogs including immunosuppressant, antiallergy, asthma, and antineoplastic agents[11]. In particular, we have focused on both the synthesis of homoserine lactones and the mild cleavage for the prevention of side reactions in the polymer-supported version.

Commercially available aminomethyl polystyrene resin (2% crosslinked; 0.9 mmole/g) swelled in distilled DMF was coupled with N-Fmoc-L-methionine in the presence of HOBt, N-ethylmorpholine, and diisopropyl carbodiimide at room temperature for 48 h. Filtration of the resin and washing with DMF, methanol, acetone, and chloroform provided N-Fmoc methionine-mediated resin **2** (**Scheme I**) as evidenced by the appearance of

PII: S0040-4039(97)10546-9

an FT IR band for the amides at 1718 and 1670 cm^{-1}. Incubation of methionine resin (**2**) with 20 % piperidine/DMF at room temperature for 6 hr followed by filtration and thorough washing of the resulting resin delivered **3** (one of FT IR amide bands was disappeared at 1718 cm^{-1}). In preliminary tests, one of carboxylic acid derivative was bound to the methionine resin by a coupling reaction (**Scheme I, 4**). In the following steps, a mild cleavage was carried out by cyanogen bromide, considering the known chemical cleavage of peptides by this reagent[12].

Scheme I[a].

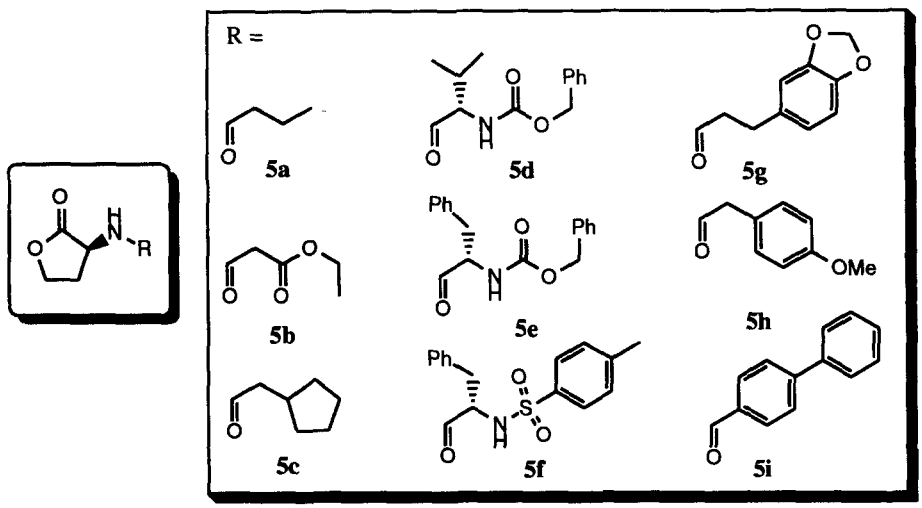


[a]Key: (a) N-Fmoc-L-methionine, HOBt, N-ethylmorpholine, DIC, DMF, 25° C; (b) 20 % piperidine/DMF, 25° C; (c) aliphatic or aromatic carboxylic acids, HOBt, N-ethylmorpholine, DIC, DMF, 25°C; (d) BrCN, TFA, $CHCl_3/H_2O$.

We decided to extend this cleavage method to a solid phase synthesis by preparing a methionine-functionalized resin for preparation of the homoserine lactone libraries. Indeed, our expectation showed that the cleavage reaction gave an excellent yield and consequently generated homoserine libraries perfectly during the cleavage step. Treatment of each amide derivative bound to the resin (**4**) with 15 equimolar amount of cyanogen bromide and two drops of 99% trifluoroacetic acid in the mixed solvent (chloroform : water = 5 mL : 2 mL, respectively) at room temperature for 1 d generated the corresponding homoserine lactone (**5**) with retention of stereochemistry. During the cleavage reaction, we were pleased to find that the cyclization of the methionine-containing resin did not affect the stereochemistry of homoserine lactone and the recovered resin could be reused for the next application. We obtained homoserine lactones [**5a** (49 %), **5b** (44 %), **5c** (45 %), **5d** (43 %), **5e** (32 %), **5f** (36 %), **5g** (47 %), **5h** (42 %), **5i** (53 %)] in 32~53 % overall yield from the aminomethylated resin **1**. Finally, we have demonstrated that the molecular diversity of **5j** (46 % yield, **Scheme II**) could efficiently provide the nine homoserine lactones in one a pot system, each lactone corresponded with the starting acid as evidenced by spectroscopic methods and GC analysis[13]. Surprisingly,

we observed not only that the cleavage reaction went to completion but also that side reactions not occurred during the lactonization.

Scheme II. Combinatorial Libraries of Homoserine lactones (5j)



In summary, we developed a polymer-supported synthesis of a methionine-functionalized resin that used a mild cleavage strategy to provide a combinatorial library of homoserine analogs through the coupling and cleavage step. Moreover, we demonstrated that chemically diverse homoserine lactones are easily obtained[14]. We are currently examining the biological activity of homoserine lactones as well as exploring mild processes for the preparation of non-peptide molecules.

Acknowledgments: The authors would like to thank Dr. Jae Heung Lee and Dr. Kwang Hyuk Lee for stimulating discussions and administrative support.

References and Notes

1. Gordon, E. M. ; Barrett, R. W. ; Dower, W. J. ; Fodor, S. P. A. ; Gallop, M. A. *J. Med. Chem.* **1994**,*37*, 1385.
2. Balkenhohl, F. ; von dem Bussche-Hunnefeld, C. ; Lansky, A. ; Zechel, C. *Angew. Chem., Int. Ed, Engl.* **1996**,*35*, 2289.
3. Young, J. K. ; Nelson, J. C. ; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 10841.

4. Kurth, M. J. ; Randall, L. A. ; Chen, C. ; Melander, C. ; Miller, R. B. ; McAllister, K. ; Reitz, G.; Kang, R. ; Nakatsu, T. ; Green, C. *J. Org. Chem.* **1994**, *59*, 5862.
5. Murphy, M. M. ; Schullek, J. R. ; Gordon, E. M. ; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029 ; Moon, H-S. ; Schore, N. E. ; Kurth, M. J. *Tetrahedron Lett.* **1994**, *35*, 8915.
6. Wang, R. B. *J. Am. Chem. Soc.* **1972**, *95*, 1328.
7. Rink, H. *Tetrahedron Lett.* **1987**, *28*, 3787.
8. Hirao, A. ; Itsuno, S. ; Hattori, I. ; Yamaguchi, K. ; Nakahama, S. ; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1983**, 25.
9. Sucholeiki, I. *Tetrahedron Lett.* **1994**, *35*, 7307.
10. Hernandez, A. S. ; Hodges, J. C. *J. Org. Chem.* **1997**, *62*, 3153.
11. Bycroft, B. W.; Sewell, H. F.; Stewart, G.; Williams, P. *WO 95/01175* , **1995**.
12. Gross, E. Witkop, B. *J. Biol. Chem.* **1962**, *237*, 1856.
13. GC/MSD: Ultra 1(crosslinked methyl silicone gum; 25m x 0.2 mm x 0.33 μm) fused silica capillary column. Mass spectra (GC/MSD) was obtained with a HP-5970B; H_2, 15 psi, 200-300° C (10° C/min) and then isothermal method, R_t(**5a**) = 2.64 min, R_t(**5b**) = 3.37 min, R_t(**5c**) = 3.96 min, R_t(**5d**) = 8.18 min, R_t(**5e**) = 7.47 min, R_t(**5f**) = 15.95 min, R_t(**5g**) = 7.05 min, R_t(**5h**) = 5.70 min, R_t(**5i**) = 9.16 min.
14. Typical prepartive procedure for **5i** [N-(N-4-biphenylcarboxyl) homoserine lactone] : The methionine-functionalized resin (0.9 mmole/g; 435 mg, 0.391 mmol) was swollen in 5 mL of dry DMF with 4-biphenyl carboxylic acid (194 mg, 0.98 mmol), HOBt (132 mg, 0.98 mmol), and N-ethylmorpholine (124 μL, 0.98 mmol). DIC (153 μL, 0.98 mmol) was added to the resin mixture and then the reaction mixture was slowly stirred at room temperature. After 2 days, the resin mixture was washed with DMF(10 mL x 2 times), acetone (10 mL x 3 times), methanol (10 mL x 2 times), chloroform (10 mL x 3 times) and then dried, providing the biphenyl acid functionalized resin (**4i**). The resin was stirred in the mixture solvent (chloroform : water = 5 mL : 2 mL) and cyanogen bromide (621 mg, 5.86 mmol) was added. Two-drop of 99 % TFA was added, and the reaction mixture was stirred at room temperature for 1 day in the fume hood. After the cleavage reaction, filtration gave a homoserine lactone of using the excess amount of chloroform. The separated organic layer was washed with water, dried with anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator under aspirator pressure to give a solid product (**5i** : 58.4 mg, 53 % from **1**) without the further purification. IR(KBr) 3058, 2917, 1657, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89 (m, 2 H), 7.69-7.61 (m, 4 H), 7.49-7.38 (m, 3 H), 6.78 (br d, J=4.7 Hz, 1 H), 4.77 (ddd, J=11.6, 8.5, 5.5 Hz, 1 H), 4.55 (ddd, J=9.0, 9.0, 1.0 Hz, 1 H), 4.38 (ddd, J=11.3, 9.3, 5.8 Hz, 1 H), 3.01 (dddd, J=12.5, 8.6, 5.8, 1.2 Hz, 1 H), 2.29 (dddd, J=11.4, 11.4, 12.5, 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 167.7, 145.2, 140, 131.8, 129.1, 128.3, 127.9, 127.4, 66.5, 50, 30.9; GC Rt = 14.941 min [25 m x 0.2 mm x 0.3 μm, 200° C (10° C/min) to 270° C and then isothermal method]. MS m/e(M+) 281.05.