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Efficient synthesis of 5-(hydroxymethyl)piperazin-2-ones using automatically prepared chiral bromocarboxylic acid and Garner's aldehyde as versatile building blocks

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ABSTRACT

An efficient method for the synthesis of substituted 5-(hydroxymethyl)piperazin-2-ones was established by using an automated synthesis process. Thirteen piperazinones were synthesized from chiral α-bromocarboxylic acids and Garner's aldehyde which were prepared by using our originally developed automated synthesizer, ChemKonzert®. The automated method of synthesizing chiral α-bromocarboxylic acids was efficient and safe because the rate of the dropwise addition of the reagent can be controlled using the automated synthesizer. This method is expected to contribute to the synthesis of pharmaceuticals.

Amino acids containing heterocycles such as diketopiperazine have attracted significant attention because of their biological activities.[1–4] Because these moieties can be construed as conformationally constrained amino acid analogs, they are often used as building blocks in the synthesis of peptidemimetics. However, because of the high planarity of diketopiperazine, its analogs with more sp^3 carbon atoms have been required to specifically control the interaction with target molecules. For this purpose, the synthesis of diketopiperazine analogs, in which one of the carbonyl groups is replaced by an oxetane ring, has been reported.[5] Piperazinones can be simply synthesized by lactamization[1,6–9] or alkylation[1,10–13] via nucleophilic attack by an amino group. Optically active piperazinone can be constructed by the acylation of monoprotected 1,2-diamine with chiral α-bromocarboxylic acid, followed by the deprotection of the amine and intramolecular nucleophilic substitution.[4] The conventional method for synthesizing racemic α-bromocarboxylic acid is the Hell-Volhard-Zelinsky reaction,[14–16] which involves the α-bromination of acid halides. The preparation of chiral α-halocarboxylic acid by copper(II)-mediated resolution of racemic acid has also been reported.[17] Moreover, the elegant synthesis of chiral α-halocarboxylic acid by the enantioselective protonation of ketene disilyl acetal has been investigated.[18] Synthesis using chiral substrates is also efficient. Chiral α-bromocarboxylic acid can be synthesized via the bromination of diazo intermediates that are readily prepared from α-amino acids.[19–21] This method is very important because a sufficient amount of chiral building blocks can be prepared from inexpensive amino acids. In this paper, we focused on the synthesis of 5-(hydroxymethyl)piperazin-2-ones because these compounds possess more sp^3 carbons than diketopiperazine and retain a hydroxyl group for binding to target compounds and further functional group modification.

Automated synthesis has attracted considerable attention in recent years because the automation of synthetic operations improves both the reproducibility and reliability of the synthesis.[22–26] Synthetic chemists frequently perform repetitive processes such as optimizing reaction conditions, constructing compound libraries, and preparing synthetic intermediates. In particular, the synthetic intermediates for natural products and versatile building blocks for various applications may need to be resynthesized, even after their initial synthesis on a large scale. Synthetic chemists can automatically prepare the intermediates when these compounds are needed by using an automated synthetic method and stored procedure. Thus, researchers can spend more time on addressing advanced and challenging problems. We previously reported the automated syntheses of key intermediates for natural products, including taxol,[27] *ent*-pyripyropene A,[28] spiruchostatin B,[29] and nine-membered masked enediyne[30] by utilizing our originally developed

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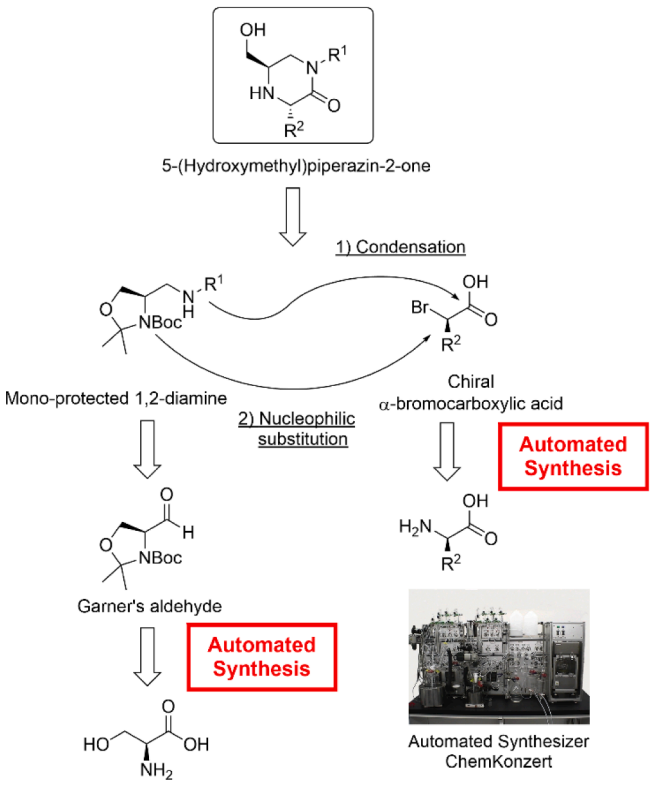


Scheme 1. Strategy for synthesizing 5-(hydroxymethyl)piperazin -2-ones.

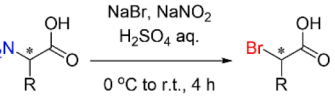
automated synthesizer, ChemKonzert.[31] We also synthesized Garner's aldehyde, a versatile building block, by using ChemKonzert.[32] Herein, we report the solution-phase automated synthesis of chiral α-bromocarboxylic acid as a versatile chiral building block and the construction of a small library of 5-(hydroxymethyl)piperazin-2-one analogs using the automatically prepared building blocks.

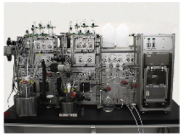
The strategy for synthesizing 5-(hydroxymethyl)piperazin-2-one analogs is shown in Scheme 1. The piperazinone structure can be constructed by condensation with mono-protected 1,2-diamine and chiral α-bromocarboxylic acid, followed by deprotection and the intramolecular *N*-alkylation. Mono-protected 1,2-diamine can be prepared by the reductive amination of Garner's aldehyde. Chiral α-bromocarboxylic acid can be obtained from the corresponding amino acid. Garner's aldehyde and chiral α-bromocarboxylic acid were provided using an automated synthesizer.

Initially, we examined the automated synthesis of chiral α-bromocarboxylic acid by the bromination of α-amino acid using sodium bromide, sodium nitrite, and sulfuric acid (Table 1). In general, the stereochemistry is retained in the bromination of amino acid because of neighboring group participation. It is important to manually verify the reaction conditions including the reaction time and the work-up method previous to the automated synthesis to confirm that the automated synthesis induces no significant decrease in the yield. Bromination had to be carried out at low temperatures as it competes with the nucleophilic substitution of water at higher temperature.[33,34] Therefore, the addition of sodium nitrite solution at a constant rate is critical for preventing an increase in the internal temperature. The crucial addition rate of the reagent was controlled using an automated synthesizer;[10] this was achieved by repeatedly opening and closing the valve attached to

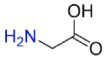
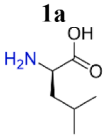
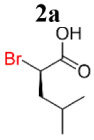
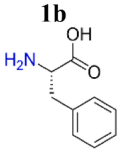
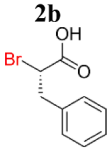
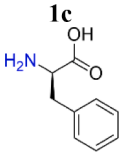
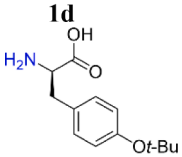
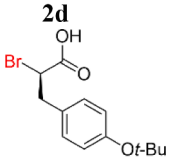
Table 1

Automated and manual bromination of α-amino acid.





Automated Synthesizer ChemKonzert

Entry[a]	Substrate	Product	Yield[b,c]
1			80% (67%)
2	**1a** 	**2a** 	99% (99%)
3	**1b** 	**2b** 	57% (68%)
4	**1c** 	**2c** 	63% (67%)
5	**1d**  **1e**	**2d**  **2e**	42% (62%)

[a] All reactions were performed on 1–10 gram scale. [b]Isolated yield. [c]Yield of manual synthesis is shown in parentheses.

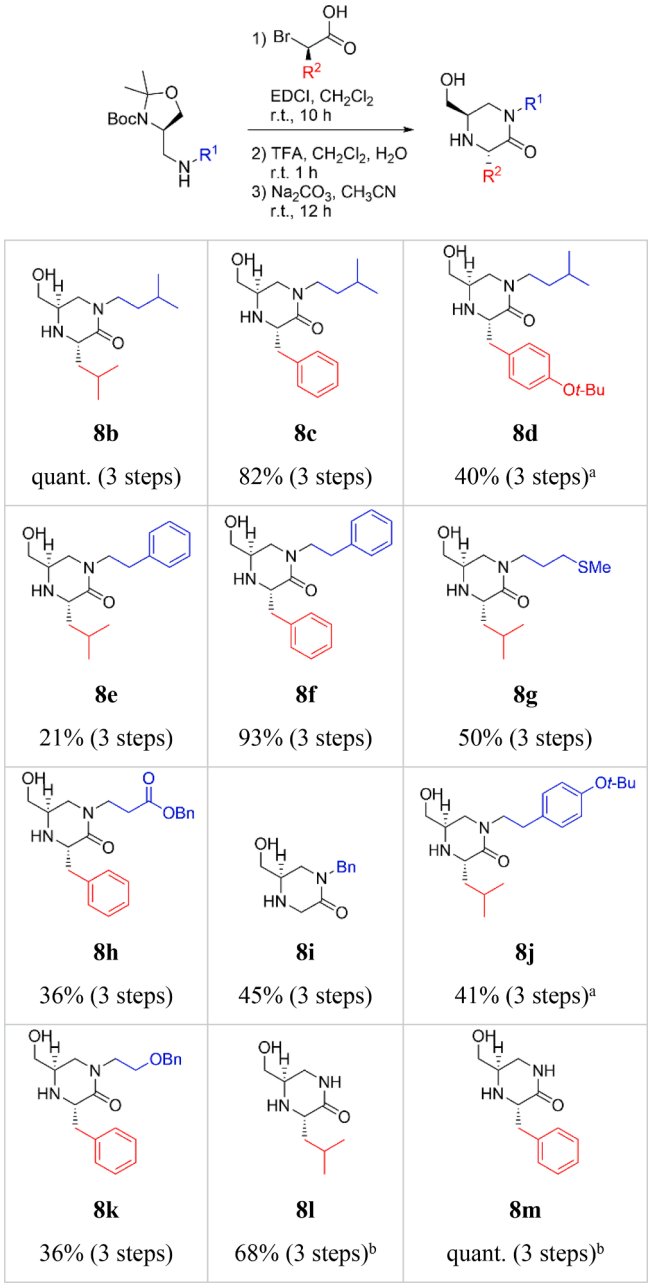
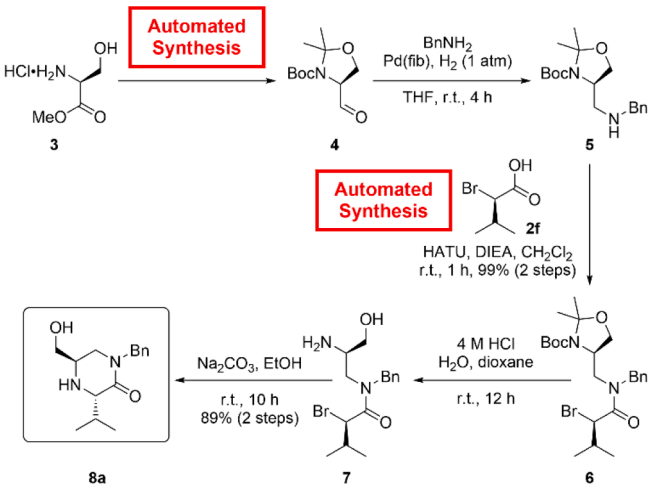


Fig. 1. Synthesis of various substituted 5-(hydroxymethyl) piperazin-2-ones.[c] [a] Trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine were used instead of TFA. [b] The cyclization was performed at 50 °C. [c] All reactions were performed in 100 mg-30 g scale.

the reagent inlet (the open and close times were 0.5 and 3 s, respectively). The yields from the automated synthesis were comparable to those of the corresponding manual syntheses (Table 1, Entries 1–4).[35] When tyrosine analog 1e was used as a substrate, the target bromide 2e was precipitated (Table 1, Entry 5). In the manual synthesis, the desired product 2e could be obtained in 62% yield by filtration; in contrast, in the automated synthesis, the precipitate had to be extracted once for the transformation in the tube, and 2e was obtained in a slightly lower yield of 42%.

Furthermore, the synthesis of functionalized 5-(hydroxymethyl) piperazin-2-one was examined using automatically prepared building blocks. Garner's aldehyde (4) was prepared from L-serine methyl ester hydrochloride (3) using an automated synthesizer according to our developed procedure.[32] Mono-protected 1,2-diamine 5 was synthesized



Scheme 2. Synthesis of highly functionalized 5-(hydroxymethyl) piperazin-2-one.

by the reductive amination of Garner's aldehyde (4) and benzyl amine using palladium fibroin[36] as a hydrogenation catalyst. The secondary amine (5) was acylated with α-bromocarboxylic acid (2f) to give the corresponding amide in 99% yield over two steps. The removal of *tert*-butoxycarbonyl (Boc) and acetonide groups under acidic conditions, followed by cyclization using sodium carbonate as a base, afforded the desired 5-(hydroxymethyl)piperazin-2-one 8a in 89% yield over two steps. No epimerization during the synthesis of piperazinone 8a was confirmed by converting the obtained piperazinone into the known cyclic carbamate[37] (see Supporting information).

The preparation of various 5-(hydroxymethyl)piperazin-2-ones was examined using the same procedure under slightly modified reaction conditions (Fig. 1). Twelve other piperazinone analogs were synthesized using the automatically prepared versatile building blocks. The secondary amine was acylated with α-bromocarboxylic acid using EDCI. The protected amino alkyl bromides were deprotected with trifluoroacetic acid (TFA). When the substrate with *tert*-butyl ether was used, the deprotection was performed using trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine.[38] Cyclization via intramolecular *N*-alkylation was performed using sodium carbonate and acetonitrile. The cyclization proceeded rapidly, except in the case of the *N*-unsubstituted substrates (8 l and 8 m), which required mild heating. All synthetic intermediates were used for the next reaction without purification. The bromine atom on the α-bromocarboxylic acids showed excellent electrophilicity because of the electron-withdrawing neighboring carbonyl group. Because α-bromocarboxylic acid has sufficient reactivity as a synthetic intermediate, our established automated synthesis is an effective tool and has various applications (See Scheme 2).

In conclusion, we established the automated synthesis of α-bromocarboxylic acid—a versatile building block—by using our originally developed automated synthesizer, ChemKonzert. Thirteen piperazinone analogs were synthesized from automatically prepared α-bromocarboxylic acid and Garner's aldehyde via the developed method. α-Bromocarboxylic acid has sufficient reactivity as a synthetic intermediate, and the established automated synthesis of α-bromocarboxylic acid is useful for the synthesis of various heterocycles. Further modifications of 5-(hydroxymethyl)piperazin-2-ones and the evaluation of their activities are currently underway.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127961.

References

1 Borthwick AD. *Chem Rev*. 2012;112:3641.
2 Daugan A, Grondin P, Ruault C, et al. *J Med Chem*. 2003;46:4525.
3 Daugan A, Grondin P, Ruault C, et al. *J Med Chem*. 2003;46:4533.
4 Golebiowski A, Klopfenstein SR, Shao X, et al. *Org Lett*. 2000;2:2615.
5 Beadle JD, Powell NH, Raubo P, Clarkson GJ, Shipman M. *Synlett*. 2016;27:169.
6 Kudoh T, Isoyama S, Kagimoto S, Kurihara K, Sakakura A. *Tetrahedron Lett*. 2016;57:4693.
7 Hong Q, Bakshi RK, Palucki BL, et al. *Bioorg Med Chem Lett*. 2011;21:2330.
8 Lukina TV, Sviridov SI, Shorshnev SV, Aleksandrov GG, Stepanov AE. *Tetrahedron Lett*. 2006;47:51.
9 Pollini GP, Baricordi N, Benetti S, De Risi C, Zanirato V. *Tetrahedron Lett*. 2005;46:3699.
10 Reginato G, Catalani MP, Pezzati B, et al. *Org Lett*. 2015;17:398.
11 Kale SS, Chavan ST, Sabharwal SG, Puranik VG, Sanjayan GJ. *Org Biomol Chem*. 2011;9:7300.
12 García-Cuadrado D, Barluenga S, Winssinger N. *Chem Commun*. 2008:4619.
13 Reginato G, Di Credico B, Andreotti D, Mingardi A, Paio A, Donati D. *Tetrahedron Asymmetry*. 2007;18:2680.
14 Zelinsky, N. Ber. Dtsch. Chem. Ges. 1887, 20, 2026.
15 Volhard J, Liebigs Justus. *Ann Chem*. 1887;242:141.
16 Hell C. *Ber Dtsch Chem Ges*. 1881;14:891.
17 Xu H-W, Wang Q-W, Zhu J, et al. *Org Biomol Chem*. 2005;3:4227.
18 Uraguchi D, Kizu T, Ohira Y, Ooi T. *Chem Commun*. 2014;50:13489.
19 Souers AJ, Schürer S, Kwack H, Virgilio AA, Ellman JA. *Synthesis*. 1999;1999:583.
20 Moumne R, Lavielle S, Karoyan P. *J Org Chem*. 2006;71:3332.
21 Tka N, Kraïem J, Hassine BB. *Synth Commun*. 2013;43:735.
22 Cork DG, Sugawara T. *Laboratory Automation in the Chemical Industries*. New York: Marcel Dekker Inc.; 2002.
23 Coley CW, Thomas III DA, Lummiss JAM, et al. *Science*. 2019:365.
24 Adamo A, Beingessner RL, Behnam M, et al. *Science*. 2016;352:61.
25 Li J, Ballmer SG, Gillis EP, et al. *Science*. 2015;347:1221.
26 Seeberger PH, Werz DB. *Nat Rev Drug Discov*. 2005;4:751.
27 Doi T, Fuse S, Miyamoto S, Nakai K, Sasuga D, Takahashi T. *Chem -Asian J*. 2006;1:370.
28 Fuse S, Ikebe A, Oosumi K, et al. *Chem -Eur J*. 2015;21:9454.
29 Fuse S, Okada K, Iijima Y, et al. *Org Biomol Chem*. 2011;9:3825.
30 Tanaka Y, Fuse S, Tanaka H, Doi T, Takahashi T. *Org Process Res Dev*. 2009;13:1111.
31 Machida K, Hirose Y, Fuse S, Sugawara T, Takahashi T. *Chem Pharm Bull*. 2010;58:87.
32 Masui H, Yosugi S, Fuse S, Takahashi T. *Beilstein J Org Chem*. 2017;13:106.
33 Akazome M, Takahashi T, Ogura K. *J Org Chem*. 1999;64:2293.
34 Kolitz M, Cohen-Arazi N, Hagag I, Katzhendler J, Domb AJ. *Macromolecules*. 2009;42:4520.
35 The bromocarboxylic acids prepared by automated synthesizer could be converted into 5-(hydroxymethyl)piperazin-2-ones as a single diastereomer.
36 Yabe Y, Sawama Y, Monguchi Y, Sajiki H. Catal. *Sci Technol*. 2014;4:260.
37 Borsini E, Broggini G, Fasana A, et al. *Adv Synth Catal*. 2011;353:985.
38 Bastiaans HMM, van der Baan JL, Ottenheijm HCJ. *J Org Chem*. 1997;62:3880.