Bioorganic & Medicinal Chemistry Letters 19 (2009) 3909–3911

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

An enantioselective synthesis of (+)-(*S*)-[*n*]-gingerols via the L-proline-catalyzed aldol reaction

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ARTICLE INFO

Article history:
Received 13 February 2009
Revised 18 March 2009
Accepted 20 March 2009
Available online 24 March 2009

Keywords:
Cross aldol
Gingerols
Organocatalysis
Proline

ABSTRACT

An enantioselective approach to (+)-(*S*)-[*n*]-gingerols (**1a–c**) has been developed. The requisite stereogenic centers of target molecules are facilely constructed by the proline-catalyzed cross-aldol reaction from readily available achiral starting materials.

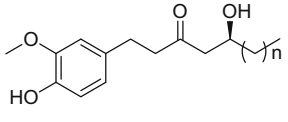
The seminal work by List et al. using L-proline catalyzed direct intermolecular aldol reactions has facilitated the formation of new field of organocatalysis.[1] A number of research groups have developed proline and its analogues for the aldol processes to improve reactivity, broadening substrate scope, and enhancing stereoselectivity.[2,3] Despite the fact that a number of highly enantioselective organocatalytic aldol processes have been developed, their synthetic values in the application of preparation of biologically important natural products and synthetic molecules remain elusive.[4] Toward this end, recently our group has initiated a program aimed at exploring the asymmetric aldol approaches to synthetically valuable targets.[5,6] Herein, we wish to disclose the results of a recent investigation, which have led to an unprecedented organocatalytic enantioselective aldol as a key step for efficient preparation of (+)-(*S*)-[*n*]-gingerols **1a–c** (Fig. 1).

Ginger is widely used as a dietary condiment throughout the world, and also used as an important medicine in China and Japan. Its major pungent ingredient, (+)-(*S*)-[6]-gingerol (**1a**) (Fig. 1), has been found to exhibit diverse pharmacological activities such as antioxidant,[7] anti-inflammatory,[8] anti-tumor-promoting,[9] BuChE inhibitory,[10] anti-platelet aggregation,[11] and anti-bacterial effects.[12] In spite of the fact of their broad and interesting bioactivities and structural simplicity, surprisingly only a handful of examples for their synthesis can be identified.[13,14] Only a single catalytic asymmetric version was disclosed so far.[15]

With the realization of the significant biological activities of this class of compounds and the lack of general and catalytic enantioselective strategies for their preparation, we have developed a new convergent route to compound **1a** and its homologues, **1b** and **1c**, in good enantiomeric excess. Notably, the stereogenic centers are efficiently created by L-proline-catalyzed cross-aldol reaction.

A concise total synthesis of (+)-(*S*)-[*n*]-gingerol (**1a–c**) is shown in Scheme 1. We envisioned that two possible synthetic approaches could lead to their preparation. In both cases, the creation of the stereogenic centers relied on the use of L-proline promoted enantioselective cross-aldol reaction.

Clearly, the route 1, starting from zingiberone (**2**) and an aldehyde (**3**) for an aldol reaction, is more concise than the route 2. Unfortunately, in various tries with survey of different reaction



n=4, (+)-(*S*)-[6]-Gingerol (**1a**)
n=6, (+)-(*S*)-[8]-Gingerol (**1b**)
n=8, (+)-(*S*)-[10]-Gingerol (**1c**)

Figure 1. (+)-(*S*)-[*n*]-gingerol (**1**).

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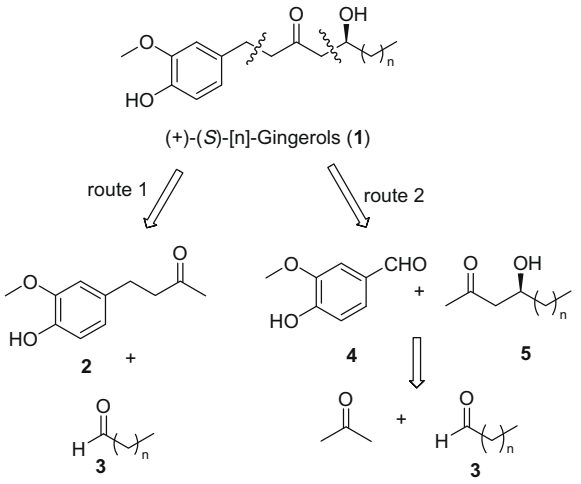
doi:10.1016/j.bmcl.2009.03.081



Scheme 1. Synthetic plan of (+)-(*S*)-[*n*]-gingerols (**1**).

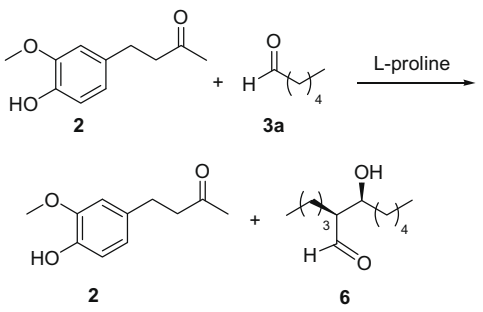
media, the reaction gave aldehyde self-aldolization product (**6**) instead of the desired cross aldols (Scheme 2).

We thus turned our attention to the route 2. The key intermediates β-hydroxy ketones **5a–c** were synthesized based on known procedures using acetone as reagent and reaction medium in moderate yields (35–46%).[16] Protection of hydroxyl group of **5a–c** with TBSCl and imidazole furnished compounds **7a–c**, which was transformed into silyl enol ethers **8a–c** by treating with TMSOTf and *i*-Pr_2NEt in CH_2Cl_2.[17] The Mukaiyama reaction between compounds **8a–c** and vanillin, with simultaneous removal of the TBS, was carried out to afford olefins **9a–c** in good yields (44%, 48%, and 43%, respectively) for three-step transformation.[18] Finally, the target (+)-(*S*)-[*n*]-gingerols **1a–c** were obtained in 70–73% yield by hydrogenation of compounds **9a–c** with H_2/Pd/C. To our delight, when the reaction was carried out in the presence of a small amount of Et_3N (5% v/v), the yield could be improved up to 86–90% (Scheme 3). The ee values of final compounds **1a–c** were determined by HPLC analysis (chiral AS column: 74% ee, 72% ee, and 70% ee, respectively).[19]

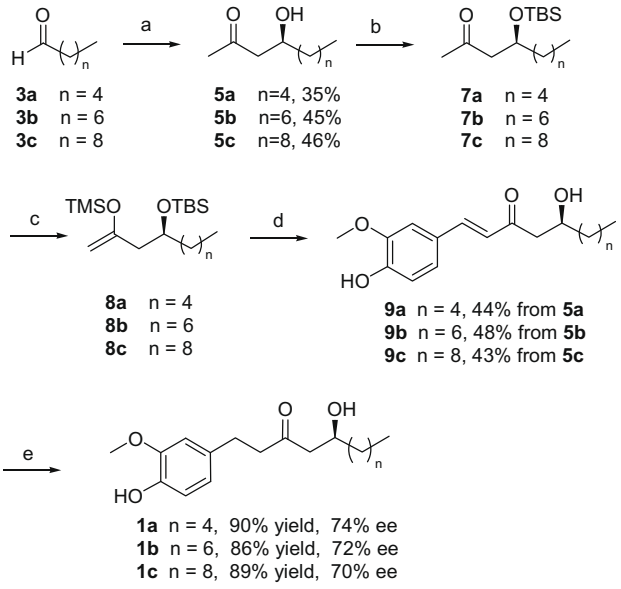
In conclusion, we have developed a concise, enantioselective approach to (+)-(*S*)-[*n*]-gingerol **1a–c** in five steps in respected overall yields (14–19%). The key step in the synthesis employs L-proline-promoted Hajos–Parrish–Eder–Sauer–Weichert–List–Barbas aldol reaction to conveniently establish the requisite chiral center under mild reaction conditions.

Acknowledgments

We are grateful for the financial support from School of Pharmacy, East China University of Science and the National Science Foundation of China (Nos. 03772648 and 30721005), and the Chinese National Programs for High Technology Research and Development (Nos. 2006AA020602 and 2007AA02Z147).



Scheme 2. L-Proline catalyzed cross-aldol reaction between **2** and **3a**.



Scheme 3. Synthesis of (+)-(*S*)-[*n*]-gingerols using L-proline catalyzed cross-aldol reaction as key step. Reagents and conditions: (a) acetone, L-proline, 30 °C, 3 d; (b) TBSCl, imidazole, CH_2Cl_2, rt, overnight; (c) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 3 h; (d) vanillin, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 3 h; (e) H_2 (1 atm), 10% Pd/C, Et_3N/EtOAc (v/v) = 1/20, rt, 4 h.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.081.

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