Facile synthesis of γ-alkylidenebutenolides†

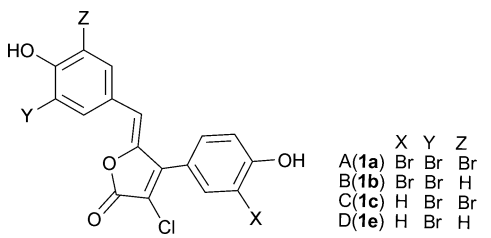
Hai-Wei Xu, Jun-Feng Wang, Gai-Zhi Liu, Guang-Feng Hong and Hong-Min Liu*

Received 25th January 2007, Accepted 8th February 2007
First published as an Advance Article on the web 16th March 2007
DOI: 10.1039/b701051f

In this paper, a novel route to γ-alkylidenebutenolides (γ-AIBs) by way of stereoselective vinylogous aldol reaction of the unactivated butenolide in simple and general conditions is reported.

Introduction

γ-Alkylidenebutenolides (γ-AIBs) are an important class of organic compounds, *e.g.*, rubrolides **1** (Fig. 1), existing in natural products.[1-3] Most of them exhibit various interesting biological activities, such as antibacterial, anticancer, antibiotic, phospholipase A2 inhibition activity and so on.[2,4] Over the past few decades, great attention has been attracted to the development of efficient synthetic strategies towards the γ-AIBs, which were reviewed comprehensively by Rao,[3] Negishi and Kotora,[5] and Bruckner.[5] The structural arrangement is available *via* three major routes: (1) alkylidenation of five-membered heterocycles, such as 2-oxyfuran,[6,7] γ-lactones[6,8] and maleic anhydrides[9] (Fig. 2); (2) cyclization of γ-hydroxy and γ-oxoacids or their equivalents,[10] such as γ-oxoacylpalladium complexes;[11] (3) lactonization reactions of alk-4-ynoic and alk-4-enoic acids.[12] The efficiency of the first two strategies depends on the accessibility of suitable precursors (especially when more complex substitution on the desired butenolide is required), and a number of the methods are non-stereoselective, affording a mixture of *E*/*Z* isomers of the target γ-AIBs.[10,13] Selective control has been achieved,[10,14] for example, through the preparation of diastereopure γ-(1-heteroalkyl)-substituted butenolide, and subsequent stereospecific *anti*-elimination of a leaving group located at C-1 of the alkyl moiety. The third strategy has become increasingly popular in recent years.[15] However, this approach does not allow a single-step construction of γ-AIBs. Besides, the reaction conditions are comparatively harsh and not suitable for application to the synthesis of andrographolide derivatives and digoxin derivatives containing the γ-AIB moiety.



	X	Y	Z
A(**1a**)	Br	Br	Br
B(**1b**)	Br	Br	H
C(**1c**)	H	Br	Br
D(**1e**)	H	Br	H

Fig. 1 Rubrolides **1**.

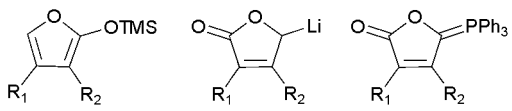


Fig. 2 Alkylidenation of five-membered heterocycles can give γ-AIBs.

Andrographis paniculata is extensively used as traditional Chinese medicine. The extracts and the isolated constituents are reported to possess a wide spectrum of biological activities.[16] **2**, **4** and **3f** are natural diterpene constituents isolated from *A. paniculata*, all of which contain an α-substituted-γ-butenolide. Our group implemented a program aimed at the preparation of γ-AIBs, analogues of **3f**, from andrographolide derivative **2**. Most of them have selective α-glucosidase inhibition activity. Among them, **3c** is a good α-glucosidase inhibitor (IC_{50},16 μM).[17]

Digoxin is one of the constituents of digitalis, which has been utilized medicinally in the treatment of cardiac diseases for centuries.[18] The synthesis of its analogues and the pharmacological action have attracted some researchers' attention.[19] The structure of digoxin contains a β-substituted-γ-butenolide. Digoxin substituted at the butenolide moiety probably regulates the intercellular Na^+ concentration.[20]

Results and discussion

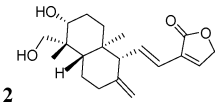
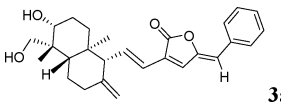
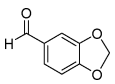
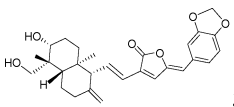
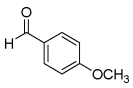
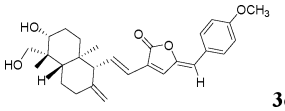
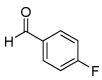
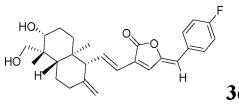
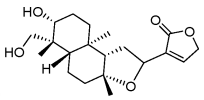
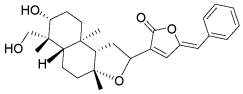
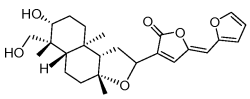
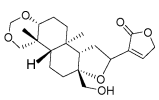
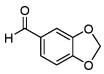
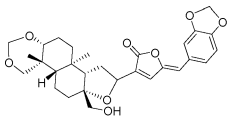
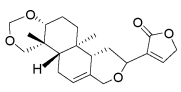
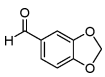
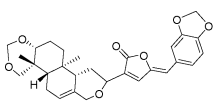
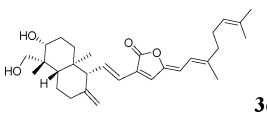
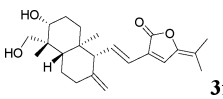
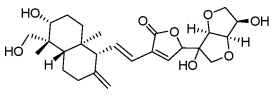
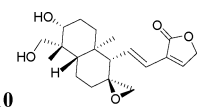
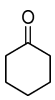
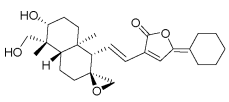
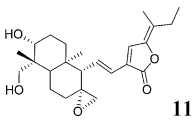
As a research of the direct vinylogous aldol condensation, and in order to develop new drugs, our group developed an efficient method for the construction of γ-AIBs. Andrographolide derivatives and digoxin derivatives containing γ-AIB were stereoselectively synthesized which revealed that the conditions were simple and general.

Our strategy involves the investigation of the effects of bases and solvents in the aldol condensation of **2** with acetone and benzaldehyde, respectively, at room temperature monitored by TLC. At first, bases such as pyridine, 1,2-diaminoethane, DMAP, $NaHCO_3$, K_2CO_3 and Na_2CO_3 were used. Na_2CO_3 proved to be more effective in promoting the aldol condensation. The catalyst 1,2-diaminoethane could also promote the reaction of andrographolide derivatives with ketones. Solvents such as $CHCl_3$, CH_3CN, THF and methanol were also investigated, which, excepting methanol, proved to be ineffective in promoting the aldol reaction. Interestingly, the desired (*Z*)-γ-AIBs (**3**, **5**, **7**, **9**) (Scheme 1, Table 1) were obtained as single isomers based on the analysis of the NMR and NOE spectra. The stereoproperties of **3e**, **3g** and **11b**, which were obtained as mixtures of isomers in 3 : 1, 3 : 1, and 2 : 1 ratio respectively, were not confirmed. After

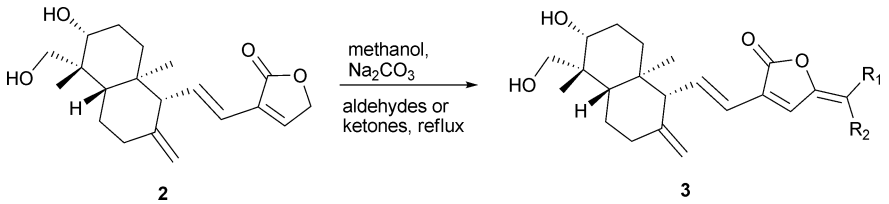
New Drug Research & Development Center, Zhengzhou University, 75 Daxue Road, Zhengzhou City, 450052, Henna Province, P.R. China. E-mail: liuhm@zzu.edu.cn; Fax: +86-371-67767200; Tel: +86-371-67767200

† Electronic supplementary information (ESI) available: ^1H NMR, ^{13}C NMR and selected HRMS. See DOI: 10.1039/b701051f

Table 1 Reactions of andrographolide derivatives with aldehydes and ketones

Entry	Butenolides	Carbonyl comps.	Time/h	γ-AIBs	Yield (%)
1	 **2**		6	 **3a**	90
	2		6	 **3b**	82
2	**2**		6	 **3c**	93
3	**2**		5	 **3d**	87
4	 **4**		7	 **5a**	95
5	**4**		5	 **5b**	90
6	 **6**		5	 **7**	80
7	 **8**		5	 **9**	77
8	**2**		16	 **3e**	60(**mix**. 3 : 1)
9	**2**		10	 **3f**	85
10	**2**		10	 **3g**	77(**mix**. 3 : 1)
11	 **10**		8[a]	 **11a**	95
12	**10**		8[a]	 **11b**	85(**mix**. 2 : 1)

Reagents and conditions: methanol, Na_2CO_3, butenolide : aldehyde or ketone: 1 : 1.5–3, reflux. [a] Methanol, $NH_2CH_2CH_2NH_2$, butenolide : ketone: 1 : 1.5–3, reflux.



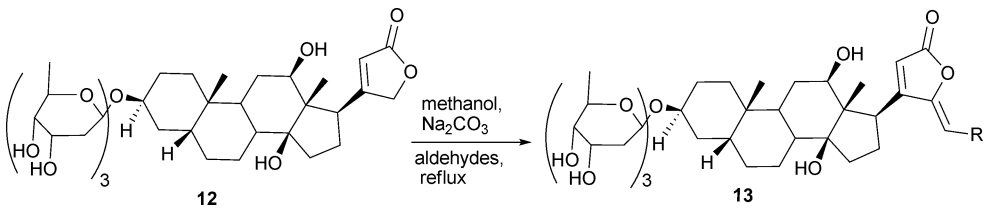
Scheme 1 Synthesis of 15-idene andrographolide.

extensive study, we found that the α-substituted butenolides (**2**, **4**, **6**, **8**, **10**) could react easily with most of the aldehydes and ketones concerned. Following the aldol reaction, most of the products could precipitate from the reaction solution.

In order to fully reveal the performance of the vinylogous aldol reaction under these conditions, the aldol condensation of digoxin to aldehydes or ketones concerned was investigated. Fortunately, the aldol condensations of digoxin to aldehydes were smoothly carried out in the conditions optimized above. After chromatography, **13a–e** were obtained as single isomers based on the analysis of NMR in excellent yield (Scheme 2, Table 2). Based on the andrographolide derivatives and the steric interaction of the β-substituted group in the butenolide moiety, **13a–e** were assumed to be (*Z*)-γ-AIBs. However, the desired products of the digoxin to ketone condensations were not obtained under these conditions; this could be caused by the high steric hindrance of the β-substituted group in the butenolide moiety and low reactivity of the ketone.

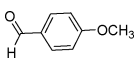
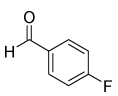
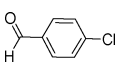
Conclusions

The andrographolide derivatives and digoxin derivatives containing α- or β-substituted-γ-AIBs were successfully synthesized in a simple and general manner, providing a valuable way for the synthesis of α- or β-substituted-γ-AIBs.



Scheme 2 Synthesis of 21-idene digoxin.

Table 2 Reaction of digoxin with aldehydes

Entry	Butenolide	Carbonyl comps.	Time/h	γ-AIBs	Yield (%)
1	**12**		7	**13a**	88
2	**12**		7	**13b**	80
3	**12**		10	**13c**	65
4	**12**		5	**13d**	90
5	**12**		5	**13e**	75

Reagents and conditions: methanol, Na_2CO_3, butenolide : aldehyde: 1 : 1.5–3, reflux.

Notes and references

1 T.-J. Hsieh, F.-R. Chang, Y.-C. Chia, C.-Y. Chen, H.-C. Lin, H.-F. Chiu and Y.-C. Wu, *J. Nat. Prod.*, 2001, **64**, 1157.

2 D. Kuhnt, T. Anke, H. Besl, M. Bross, R. Herrmann, U. Mocek, B. Steffan and W. Steglich, *J. Antibiot.*, 1990, **43**, 1413.

3 Y. S. Rao, *Chem. Rev.*, 1964, **64**, 353; Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625.

4 T. K. M. Shing, V. W. F. Tai and H. C. Tsui, *J. Chem. Soc., Chem. Commun.*, 1994, 1293; T. K. M. Shing, H. C. Tsui and Z. H. Zhou, *J. Org. Chem.*, 1995, **60**, 3121; S. Ma, Z. Shi and Z. Yu, *Tetrahedron*, 1999, **55**, 12137.

5 E. Negishi and M. Kotora, *Tetrahedron*, 1997, **53**(20), 6707; R. Bruckner, *Curr. Org. Chem.*, 2001, **5**, 679.

6 F. Bellina, C. Anselmi and R. Rossi, *Tetrahedron Lett.*, 2002, **43**, 2023.

7 M. Szlosek and B. Figadere, *Angew. Chem., Int. Ed.*, 2000, **39**(10), 1799; F. Velazquez and H. F. Olivo, *Org. Lett.*, 2002, **4**(19), 3175; C. Piper and N. Risch, *ARKIVOC*, 2003, 86; S. C. Bang, Y. Kim, M. Y. Yun and B. Z. Ahn, *Arch. Pharmacal Res.*, 2004, **27**, 485.

8 D. C. Harrowven, J. D. Wilden, M. J. Tyte, M. B. Hursthouse and S. J. Coles, *Tetrahedron Lett.*, 2001, **42**(6), 1193; M. Bella, G. Piancatelli, A. Squarcia and G. Trolli, *Tetrahedron Lett.*, 2000, **41**, 3669; M. Bella, G. Piancatelli and A. Squarcia, *Tetrahedron*, 2001, **57**, 4429; F. Bellina, C. Anselmi, F. Martina and R. Rossi, *Eur. J. Org. Chem.*, 2003, 2290.

9 M. Ito, T. Iwata and K. Tsukida, *Chem. Pharm. Bull.*, 1984, **32**, 1709; X. C. Li, D. Ferreira, M. R. Jacob, Q. Zhang, S. I. Khan, H. N. ElSohly, D. G. Nagle, T. J. Smillie, I. A. Khan, L. A. Walker and A. M. Clark, *J. Am. Chem. Soc.*, 2004, **126**, 6872.

10 A. Sorg, K. Siegel and R. Bruckner, *Synlett*, 2004, 321; A. Sorg and R. Bruckner, *Angew. Chem., Int. Ed.*, 2004, **43**, 4523.

11 C. Coperet, T. Sugihara, G. Wu, I. Shimoyama and E. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 3422.

12 S. Rousset, J. Thibonnet, M. Abarbri, A. Duchene and J. L. Parrain, *Synlett*, 2000, 260; L. Anastasia, C. Xu and E. Negishi, *Tetrahedron Lett.*, 2002, **43**, 5673; S. Rousset, M. Abarbri, J. Thibonnet, J. L. Parrain and A. Duchene, *Tetrahedron Lett.*, 2003, **44**, 7633.

13 H. Fakova, M. Pour, J. Kunes and P. Senel, *Tetrahedron Lett.*, 2005, **46**, 8137.

14 C. Mukai, S. Hirai, I. J. Kim, M. Kido and M. Hanaoka, *Tetrahedron*, 1996, **52**, 6547; R. Bruckner, *Chem. Commun.*, 2001, 141.

15 F. Liu and E. Negishi, *J. Org. Chem.*, 1997, **62**, 8591; S. Rousset, M. Abarbri, J. Thibonnet, A. Duchene and J. L Parrain, *Org. Lett.*, 1999, **1**, 701; E. Negishi, A. Alimardanov and C. Xu, *Org. Lett.*, 2000, **2**, 65; B. Vaz, R. Alvarez, R. Bruckner and A. R. de Lera, *Org. Lett.*, 2005, **7**(4), 545.

16 Y. C. Shen, C. F. Chen and W. F. Chiou, *Br. J. Pharmacol.*, 2002, **135**, 399; S. Madav, H. C. Tripathi and S. K. Tandan, *Indian J. Pharm. Sci.*, 1998, **60**, 176; E. Amroyan, E. Gabrielian, A. Panossian, G. Wikman and H. Wagner, *Phytomedicine*, 1999, **6**, 27.

17 G. F. Dai, H. W. Xu, J. F. Wang, F. W. Liu and H. M. Liu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2710.

18 J. A. Stone and S. J. Soldin, *Clin. Chem.*, 1989, **35**, 1326; I. Rubin, *Pharmacy Times*, 1987, **53**, 32; M. Adamczyk, J. Grote and P. G. Mattingly, *Steroids*, 1995, **60**, 753.

19 A. Cerri, N. Almirante, P. Barassi, A. Benicchio, S. De Munari, G. Marazzi, I. Molinari, F. Serra and P. Melloni, *J. Med. Chem.*, 2002, **45**, 189; S. De Munari, A. Cerri, M. Gobbini, N. Almirante, L. Banfi, G. Carzana, P. Ferrari, G. Marazzi, R. Micheletti, A. Schiavone, S. Sputore, M. Torri, M. P. Zappavigna and P. Melloni, *J. Med. Chem.*, 2003, **46**, 3644.

20 T. Staroske, L. Hennig, P. Welzel, H. J. Hofmann, D. Muller, T. Hausler, W. S. Sheldrick, S. Zillikens, B. Gretzer, H. Pusch and H. G. Glitsch, *Tetrahedron*, 1996, **52**(39), 12723.