ORGANIC LETTERS

2011
Vol. 13, No. 9
2418–2421

Asymmetic Organocatalytic 1,3-Dipolar Cycloaddition of Azomethine Ylide to Methyl 2-(2-Nitrophenyl)acrylate for the Synthesis of Diastereoisomers of Spirotryprostatin A

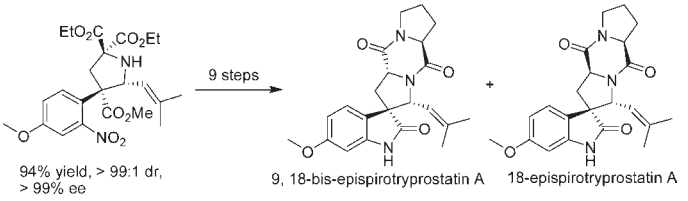
Mou-Nuo Cheng, Hao Wang, and Liu-Zhu Gong*

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China

gonglz@ustc.edu.cn

Received March 11, 2011

ABSTRACT



The total synthesis of two diastereomers of spirotryprostatin A has been established starting with an asymmetric 1,3-dipolar cycloaddition of methyl 2-(2-nitrophenyl)acrylate with azomethine ylides catalyzed by a Brønsted acid.

The spiro[pyrrolidin-3,3′-oxindole] unit constitutes a core structural element prevalent in a large family of alkaloid natural products exhibiting important bioactivity profiles and having interesting structural properties.[1,2] Spirotryprostatins A and B (Figure 1) were isolated from the fermentation broth of *Aspergillus fumigatus* and have proven to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells.[3] The unique structure of these natural compounds has attracted much attention from synthetic chemists.[4] In 2000, Williams reported the first total synthesis of spirotryprostatin B by using a chiral auxiliary-induced asymmetric synthesis of the spiro[pyrrolidin-3,3′-oxindole] core skeleton.[4c] On the other hand, the significant biological activity has intrigued intense interest in the development of biologically promising analogues with improved efficiency and selectivity.[5] Danishefsky has found that the configuration of the stereogenic center of the spirooxindole (C3) moiety

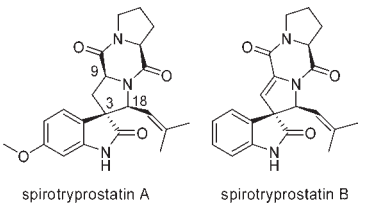


Figure 1. Structures of spirotryprostatin A and B.

(1) Bindra, J. S. In *The Alkaloids*, Vol. 14; Manske, R. H. F., Ed.; Academic Press: New York, 1973; p 84.

(2) For reviews, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

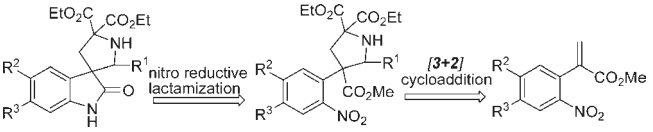
(3) (a) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651. (b) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832.

(4) (a) Edmondson, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138. (b) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (c) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (d) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311. (e) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175. (f) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 4685. (g) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596. (h) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694. (i) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357. (j) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (k) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763. (l) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135.

10.1021/ol200652j
Published on Web 04/12/2011

appears to be less important, given the spirotryprostatin analogies.[4b] It would be appealing to prepare the diastereoisomers of spirotryprostatin alkaloids to clarify the effects of the configuration on biological activities.

Scheme 1. Strategy for the Synthesis of Spiro[pyrrolidin-3, 3′-oxindole]



Recently, we established a series of chiral Brønsted acid catalyzed 1,3-dipolar cycloaddition reactions of azomethine ylides.[6] Encouraged by these achievements, we proposed to expand the protocol to use methyl 2-(2-nitrophenyl)acrylate as a substrate, resulting in the generation of pyrrolidines that are able to undergo a nitro reductive lactamization reaction[7] to afford the spiro[pyrrolidin-3,3′-oxindole] unit that appeared in the spirotryprostatin alkaloids (Scheme 1). It is noteworthy that although elegant reports describe catalytic asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides to electron-deficient olefins that yield chiral pyrrolidines,[6,8] methyl 2-(2-nitrophenyl)acrylate and its anologues were seldom successfully involved in highly enantioselective catalytic variants. Herein we report a chiral Brønsted acid catalyzed 1,3-dipolar cycloaddition reaction of methyl 2-(2-nitrophenyl)acrylate with azomethine ylides and the applications to the enantioselective synthesis of the diasteromers of spirotryprostatin A.

At the outset of the study, we examined a reaction of methyl 2-(2-nitrophenyl)acrylate (**4a**) with benzaldehyde and diethyl 2-aminomalonate in the presence of structurally diverse binol-based phosphoric acids **1a**–**d**

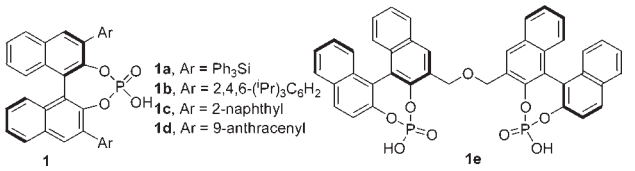
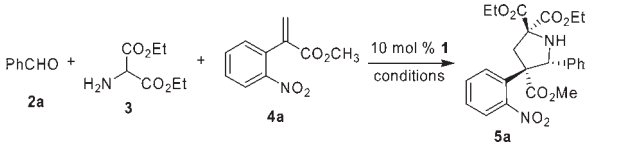


Figure 2. Brønsted acids used in this study.

(Figure 2) in dichloromethane at 0 °C (Table 1). However, none of them afforded a satisfactory cyclization reaction (entries 1–4). Encouragingly, the bisphosphoric acid **1e** enabled the reaction to give an excellent enantioselectivity of 93% ee albeit with a low yield. Elevating the reaction temperature from 0 to 30 °C rendered the reaction proceeding in 92% yield and with maintained stereoselectivity (entry 6). The solvent screening revealed that toluene was the best media in terms of enantioselectivity (entries 6–9), although the yield was slightly lower than that obtained in dichloromethane. Lowering the catalyst loading resulted in a slow reaction with a diminished enantioselectivity (entry 11).

Table 1. Screening Catalysts and Optimization of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	CH_2Cl_2	9[e]	nd	0
2	**1b**	CH_2Cl_2	12[e]	nd	−2
3	**1c**	CH_2Cl_2	trace[e]	nd	nd
4	**1d**	CH_2Cl_2	8[e]	nd	−20
5	**1e**	CH_2Cl_2	24[e]	nd	93
6	**1e**	CH_2Cl_2	92	>50:1	92
7	**1e**	$CHCl_3$	73	>50:1	93
8	**1e**	$ClCH_2CH_2Cl$	65	>50:1	92
9	**1e**	toluene	85	97:3	97
10	**1e**	toluene	87	nd	98[f]
11	**1e**	toluene	80	nd	92[g]

[a] The reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 3 Å MS (100 mg) at 30 °C for 72 h, and the ratio of **2a**/**3**/**4a** was 1.2/1/2. [b] Isolated yield based on **3**. [c] Determined by ^{1}HNMR. [d] Ee values were determined by HPLC analysis. [e] The reaction was carried at 0 °C. [f] 15 mol % of catalyst was used. [g] 5 mol % of catalyst was used.

Having the optimized conditions in hand, we next investigated the scope of aldehydes. As shown in Table 2, the protocol tolerated a wide range of aldehyde substrates. Basically, aromatic aldehydes gave higher levels of enantioselectivity than aliphatic ones. The electronic feature of the substituent on the aryl ring seemingly exerted little effect on the stereoselectivity. Thus, high levels of enantioselectivity

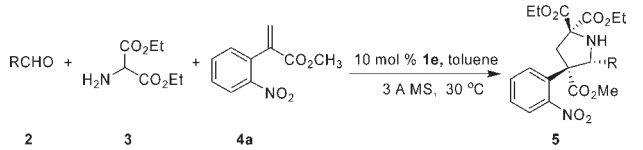
(5) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. J. *Am. Chem. Soc.* **2005**, *127*, 10130. (b) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (c) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735.

(6) (a) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (b) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357. (c) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (d) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946. (e) Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275. (f) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050.

(7) Lawrence, N. J.; Davies, C. A.; Gray, M. *Org. Lett.* **2004**, *6*, 4957.

(8) For highlights, see: (a) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. For examples, see: (b) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (c) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (d) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (e) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (f) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (g) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (h) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (i) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (j) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250. (k) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.

Table 2. Scope of Aldehydes of the Asymmetric Three-Component 1,3-Dipolar Cycloaddition Reaction[a]



2 3 4a 5

entry	5	R	yield (%)[b]	dr[c]	ee (%)[d]
1	**5b**	4-FC_6H_4	88	>99:1	98
2	**5c**	4-MeC_6H_4	86	>99:1	95
3	**5d**	4-CNC_6H_4	81	>99:1	97
4	**5e**	4-$MeOC_6H_4$	96	>99:1	95
5	**5f**	4-$CF_3C_6H_4$	73	>99:1	97
6	**5g**	4-ClC_6H_4	80	99:1	97
7	**5h**	4-BrC_6H_4	82	>99:1	98
8	**5i**	2-ClC_6H_4	97	99:1	96
9	**5j**	3-ClC_6H_4	80	99:1	97
10	**5k**	2-Cl, 3-ClC_6H_4	95	>99:1	98
11	**5l**	2-furan	73	99:1	91
12	**5m**	2-thiophene	77	99:1	96
13	**5n**	1-naphthyl	86	99:1	93
14	**5o**	2-naphthyl	88	99:1	93
15	**5p**	2-MeOPhCH=CH	75	20:1	>99
16	**5q**	c-C_6H_{11}	25	–	74

[a] The reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) at 30 °C for 72 h, and the ratio of **2/3/4a** was 1.2/1/2. [b] Isolated yield based on **3**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC.

were observed for either of the electronically rich, neutral, or poor aromatic aldehydes (entries 1−10). Heterocyclic aromatic aldehydes such as 2-furancarbaldehyde and 2-thiophenealdehyde participated in smooth cycloaddition reactions in fairly good yields and excellent enantioselectivities (entries 11−12). Either α- or β-naphthaldehyde served as a good substrate to yield **5n** or **5o** with 93% ee (entries 13−14). Significantly, an azomethine ylide generated from an α,β-unsaturated aldehyde also successfully reacted with **4a** in an excellent enantioselectivity of >99% ee (entriy 15). An attempt to use an aliphatic aldehyde as the reaction component led to a sluggish reaction with moderate enantioselectivity (entry 16). The relative and absolute configurations of **5h** were assigned by X-ray analysis (Figure 3), and the stereochemistry of the other products was assigned by analogy.

The generality for the scope with respect to the substituent on the phenyl ring of methyl 2-(2-nitrophenyl)acrylates was finally explored (Table 3). The presence of electronically withdrawing or donating substituents on the phenyl ring was nicely tolerated, giving the desired products in high yields and with excellent levels of stereoselectivity.

The synthetic potential of the 1,3-dipolar cycloaddition presented currently is demonstrated in the synthesis of spirotryprostatin alkaloid derivatives (Scheme 2). Unfortunately, the initial trial in the three-component 1,3-dipolar cycloaddition of prenyl aldehyde (**7**), diethyl 2-aminomalonate (**3**), and methyl 2-(4-methoxy-2-nitrophenyl)acrylate (**8**) catalyzed by the bisphosphoric acid (**1e**) under the

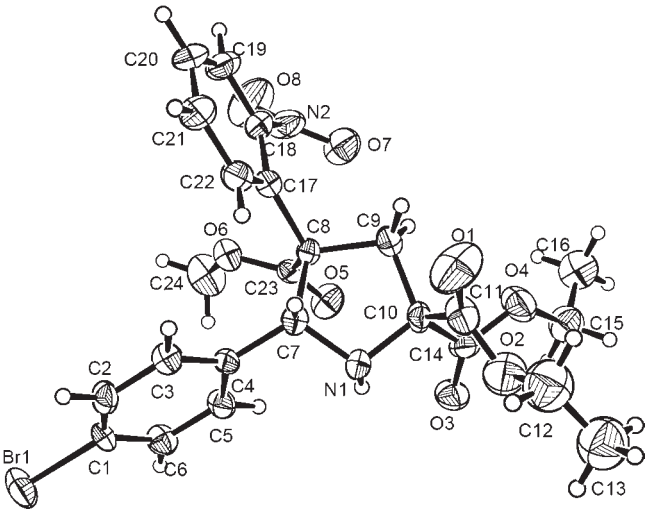
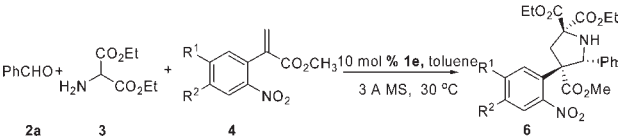


Figure 3. X-ray structure of **5h**.

Table 3. Scope of Olefins of the Asymmetric Three-Component 1,3-Dipolar Cycloaddition Reactions[a]



2a 3 4 6

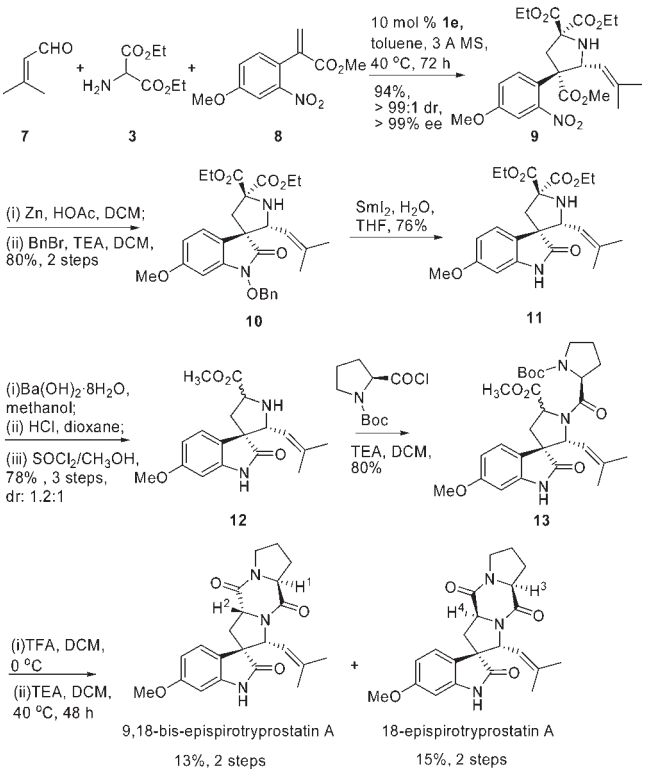
entry	6	R^1	R^2	yield (%)[b]	dr[c]	ee (%)[d]
1	**6a**	F	H	96	47:1	93
2	**6b**	H	Br	91	48:1	92
3	**6c**	H	Cl	95	99:1	93
4	**6d**	MeO	H	80	99:1	95

[a] The reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) at 30 °C for 72 h, and the ratio of **2a/3/4** was 1.2/1/2. [b] Isolated yield based on **3**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC.

optimized conditions only afforded the desired **9** in a low yield.[9] Interestingly, conducting the reaction under an argon atmosphere at 40 °C with 5 equiv of **8** gave **9** in 94% yield and with >99:1 dr and >99% ee. An attempt to perform reductive lactamization of compound **9** with Zn/HOAc failed to directly give the spiro[pyrrolidin-3,3′-oxindole] **11**. On the contrary, the major product revealed that the hydroxylamine intermediate easily underwent a cyclization reaction, but it was difficult to cleave the N−O bond under the same reduction conditions. Alternatively, a stepwise approach to the target molecule **11** ultimately proved successful. Thus, the reduction of **9** with Zn/HOAc, followed by protection of the resultant *N*-hydroxyoxindole with BnBr/TEA, and then cleavage of the N−O bond with SmI_2 in the presence of water in THF provided **11** in a good

(9) Less than 15% yield was obtained.

Scheme 2. Total Synthesis of 18-Epispirotryprostatin A and 9,18-Bis-epispirotryprostatin A



overall yield. $Ba(OH)_2 \cdot 8H_2O$ performed better than KOH or NaOH in the hydrolysis of **11**. Decarboxylation followed by esterification with $SOCl_2$ in methanol gave **12** with a dr of 1.2:1, which was treated with the acid chloride derived from *N*-Boc-L-proline to give **13**. Deprotection of the proline moiety followed by a subsequent lactamization gave 18-epispirotryprostatin A and 9,18-bis-epispirotryprostatin A, respectively. The chiral center of 18-epispirotryprostatin A was assigned the *R* configuration on the basis of the observation of a strong NOE interaction between H^3 and H^4. However, for the product 9,18-bis-epispirotryprostatin A, nearly no NOE interaction was observed, thus suggesting that the corresponding H^1 and H^2 are in *anti*-positions.

The biological investigation revealed that the diastereoisomers showed similar efficiency in inhibiting MDA MB-468 cells, but a little lower than natural product, which suggested that the configuration of C9 and C18 of the molecule was not the key element in the structure–activity relationships among spirotryprostatin A.[10]

In summary, we have disclosed a 1,3-dipolar cycloaddition reaction of azomethine ylides with methyl 2-(2-nitrophenyl)acrylate, yielding highly enantioenriched pyrrolidine derivatives, which can be readily transformed to the spiro[pyrrolidin-3,3′-oxindole] unit by easily operative reactions. The methodology holds great potenial in total synthesis as demonstrated by its applications to the synthesis of diastereoisomers of spirotryprostatin A. Moreover, the biological evaluation suggested that the configuration of the stereogenic center of spirooxindole (C9 and C18) was not the key element affecting the anticancer biological activity of spirotryprostatin alkaloids.

Acknowledgment. We are grateful for financial support from NSFC (20732006), the Ministry of Education, and the Ministry of Health (2009ZX09501-017). We also thank Min-Zhi Fan at the National Center for Drug Screening (NCDS) for the biological assay.

Supporting Information Available. Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) For biological activities, see Supporting Information.