ORGANIC LETTERS

2005
Vol. 7, No. 13
2795−2797

Asymmetric Construction of Quaternary Carbon Stereocenters: High Stereoselection in Mukaiyama Aldol Reactions of 2-Siloxyindoles with Chiral Aldehydes

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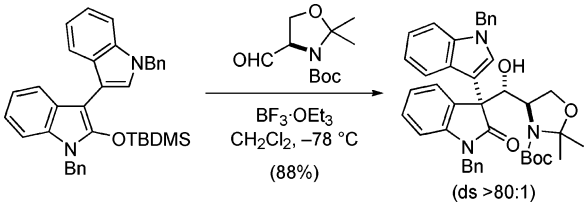
Received May 18, 2005

ABSTRACT



A new synthesis of enantiopure 3,3-disubstituted oxindoles by stereoselective Mukaiyama aldol reaction of 3-substituted 2-siloxyindoles and chiral, enantiopure aldehydes having nitrogen or oxygen substituents at the α carbon is described. When the C3 substituent of the prochiral nucleophile is aryl or heteroaryl, stereoselectivity is high (10–80:1).

The asymmetric construction of quaternary carbon stereocenters presents a substantial challenge because of severe steric congestion about such carbons and the requirement that a C−C bond-forming reaction be employed.[1] In the context of ongoing total synthesis programs in our laboratories directed at complex antitumor pyrrolidinoindoline alkaloids such as leptosins D (**1**)[2] and K (**2**) (Figure 1),[3] we became interested in the possibility of simultaneously constructing the all-carbon quaternary and adjacent secondary alcohol stereocenters of these alkaloids by Mukaiyama aldol condensation of prochiral 2-siloxyindoles **3** and chiral, enantiopure α-aminoaldehydes **4** (eq 1). Despite their ready

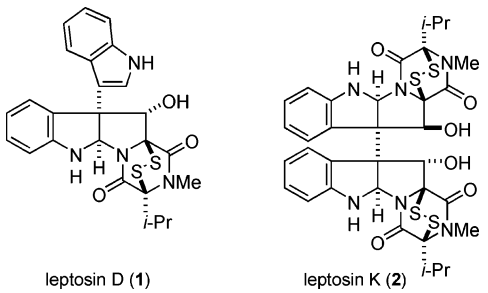


Figure 1. Representative leptosins.

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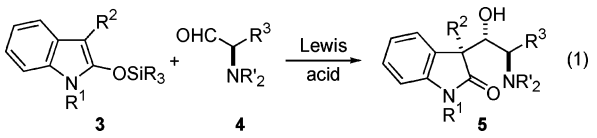
(1) For recent reviews of enantioselective generation of quaternary stereocenters, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688−1690. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(2) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859−1864.

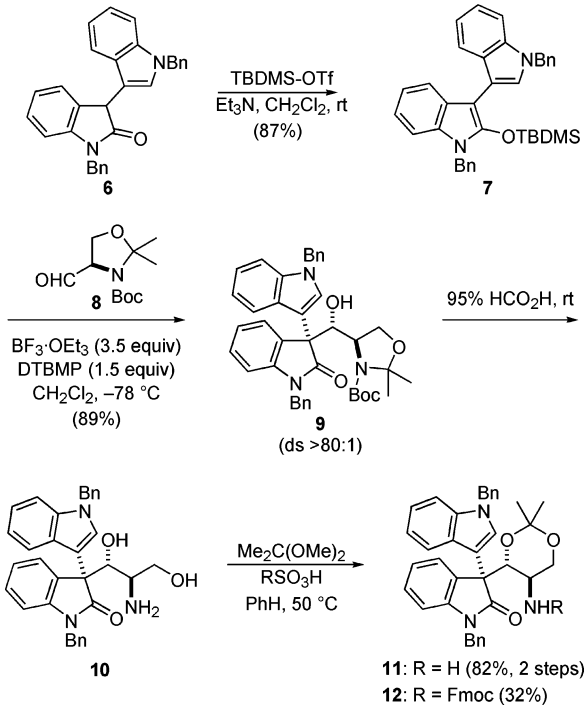
10.1021/ol051172+ CCC: $30.25
Published on Web 05/27/2005



generation from oxindoles,[4] few 2-siloxyindoles are documented in the literature, and to the best of our knowledge only two reactions of these species have been described.[5] Moreover, Mukaiyama aldol reactions of prochiral enoxysilanes or silyl ketene acetals have been employed rarely for stereoselective construction of quaternary carbon stereocenters,[6] perhaps a result of the low selectivities described in the inaugural disclosure of this chemistry.[7] In this communication, we report that a variety of enantiopure 3,3-disubstituted oxindoles can be prepared in high yield and high diastereoselectivity by Mukaiyama aldol reactions of 2-siloxyindoles and chiral, enantiopure aldehydes having nitrogen or oxygen substituents at the α carbon.[8]

Our investigations began by examining the reaction of siloxyindole **7** and *tert*-butyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (**8**, Garner's aldehyde),[9] with the *R* enantiomer being chosen on the expectation that Felkin stereoselection would predominate and lead to the secondary alcohol configuration found in leptosin D (Scheme 1). Oxindole **6**, which is available in high yield in three steps from isatin,[10] was converted to siloxyindole **7** by reaction at room temperature with *tert*-butyldimethylsilyl triflate (TBDMS-OTf) and Et_3N. Several Lewis acids commonly used in Mukaiyama aldol reactions [$LiClO_4$, $Sc(OTf)_3$, and ZnI_2][6] did not promote the reaction of **7** and aldehyde **8**.[11] However, aldol condensation did take place in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$ at temperatures between −78 and −50 °C. This reaction was slow in the presence of 1 equiv of this Lewis acid; however, it proceeded in high yield at a useful rate in the presence of excess $BF_3{\cdot}Et_2O$ as long as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was added to prevent desilylation of the siloxy nucleophile. Under optimum conditions (3.5 equiv of $BF_3{\cdot}Et_2O$, 1.5 equiv DTBMP, −78 °C), crystalline aldol adduct **9** was formed in 89% yield.[12,13] HPLC−MS analysis of the crude reaction product showed that diastereoselectivity was at least 80:1.[14] Acidic cleavage of the Boc and oxazolidine units of adduct **9** gave amino diol **10**, which after conversion to 1,3-dioxane derivative **11** and Fmoc protection provided crystalline **12** suitable for X-ray analysis.[15]

Scheme 1



The scope of the Mukaiyama aldol reaction of Garner's aldehyde with siloxyindoles having various carbon substituents at C3 is illustrated by the data summarized in Table 1. The relative and absolute configuration of *ent*-**9**[15] and **14e** was secured by single-crystal X-ray analysis, whereas the absolute configuration of **14b**−**d** at C3 was determined by CD analysis. As expected, the major products have the *anti* relationship of the hydroxy and *N*-acyloxyamino substituents.

(3) Takahashi, C.; Minoura, K.; Yamada, T.; Numata, A.; Kushida, K.; Shingu, T.; Hagishita, S.; Nakai, H.; Sato, T.; Harada, H. *Tetrahedron* **1995**, *51*, 3483−3498.

(4) Klebe, J. F.; Finkbeiner, H.; White, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 3390−3395.

(5) Rh(II)-catalyzed reaction with a diazoketone: (a) Sawada, T.; Fuerst, D. E.; Wood, J. L. *Tetrahedron Lett.* **2003**, *44*, 4919−4921. Mukaiyama aldol reaction with formaldehyde: (b) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897−12906.

(6) For a recent authoritative review, see: Carreira, E. Mukaiyama Aldol Reaction. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E., Pfaltz, E., Yamamoto, Y., Eds.; Springer: Berlin, 1999; Vol. 3, pp 997−1065.

(7) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509.

(8) The closest analogy, of which we are aware, to the chemistry reported herein is the high selectivity reported for the reaction of silylketene acetals derived from methyl 2-methoxypropionate and (*S*)-2-(phenylmethoxy)-propanal in the Heathcock group's asymmetric synthesis of L-cladinose: Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Carbohydr. Res.* **1990**, *202*, 13−32.

(9) Garner, P.; Park, J. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 300−305.

(10) Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *J. Chem. Soc., Chem. Commun.* **2002**, 824−825.

(11) Attempted aldol reaction of the lithium enolate of **6** (LDA, THF, −78 °C, 1 h) and **8** (in the presence or absence of HMPA or DMPU) at temperatures from −78 °C to room temperature resulted only in the recovery of starting materials.

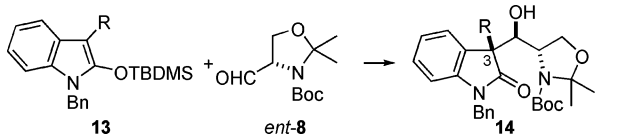
(12) (a) The alcohol, not the silyl ether, is produced directly, as the TBDMS derivative of **9** was stable to the reaction and workup conditions.[13] (b) A similar reaction was seen with congeners of **7** in which the siloxyindole nitrogen was protected with a *p*-methoxybenzyl or SEM group; however, the reaction failed if this substituent was Boc or TBDMS.

(13) Carriera, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326.

(14) (a) Adduct **9** and related Mukaiyama aldol products having aryl substituents at C3 undergo rapid retro-aldolization in the presence of base and fragment slowly even under neutral conditions. This lability complicates purification of these products. (b) No isomers were seen by HPLC analysis. Stereoselectivity is estimated to be at least 80:1 as isomer ratios of 90:1 could be measured in this way. (c) Oxindole **9** and other similar products derived from Garner's aldehyde exhibit broad signals in their ^1H NMR spectra and multiple signals in their ^{13}C NMR spectra because of carbamate rotamers. Confirmation by NMR of high isomeric purity of **9** (at least >15:1) is possible at the stage of **11**, a derivative showing sharp NMR signals.

(15) X-ray analysis carried out with *ent*-**12** prepared from the reaction of **7** and *ent*-**8**.

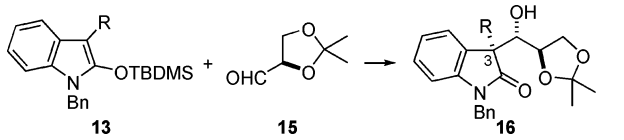
Table 1. Mukaiyama Aldol Reaction of Siloxyindoles **13** and Enantiopure Aldehyde *ent*-**8**[a]



entry	compd	R	yield, %[b]	diastereosel[c]
1	*ent*-**9**	3-(1-benzylindolyl)	92	>80:1
2	**14b**	4-methoxyphenyl	73	64:1
3	**14c**	3,4-dimethoxyphenyl	64	80:1
4	**14d**	3,4-(methylenedioxy)phenyl	93	55:1
5	**14e**	Bn	86	3:1[d]
6	**14f**	1-isopropenyl	92	9:1[e]

[a] Conditions: *ent*-**8** (2 equiv), $BF_3{\cdot}Et_2O$ (7 equiv), DTBMP (8 equiv), CH_2Cl_2, −78 to −50 °C. [b] Of the mixture of isomers after purification by flash chromatography. [c] Major isomer:∑other isomers; determined by HPLC analysis of duplicate experiments. [d] One minor isomer that was epimeric at the quaternary stereocenter was formed. [e] Configuration unassigned.

Table 2. Mukaiyama Aldol Reaction of Siloxyindoles **13** and (*R*)-glyceraldehyde Acetonide (**15**)[a]



entry	compd	R	yield, %[b]	diastereosel[c]
1	**16a**	3-(1-benzylindolyl)	82	36:1
2	**16b**	4-methoxyphenyl	83	11:1
3	**16c**	3,4-dimethoxyphenyl	61	11:1
4	**16d**	3,4-(methylenedioxy)phenyl	91	13:1
5	**16e**	Bn	57	1:1[d]
6	**16f**	*i*-Pr	70	14:1[e]

[a] Conditions: **15** (2 equiv), $BF_3{\cdot}Et_2O$ (5 equiv), DTBMP (6 equiv), CH_2Cl_2, −78 to −50 °C. [b] Of the mixture of isomers after purification by flash chromatography. [c] Major isomer:∑other isomers; determined by HPLC analysis of duplicate experiments. [d] Three isomers were formed in a 7:6:1 ratio; these isomers have, respectively. the *S*, *R*, and *R* configurations at C3. [e] By ^1H NMR analysis.

Stereoinduction at the new quaternary stereocenter (C3) was >50:1 when R was an electron-rich aryl substituent (entries 1−4), 9:1 for 1-isopropenyl (entry 6), and low when this substituent was an alkyl group (entry 5).

As summarized in Table 2, high stereoselection was seen also in the reaction of siloxyindoles **13** with (*R*)-glyceraldehyde acetonide (**15**). In this series, the relative and absolute configuration of four products (**16b**−**d** and **16f**) was secured by single-crystal X-ray analysis, whereas the absolute configuration of **16a** at C3 was determined by CD measurements. As in similar condensations with Garner's aldehyde, the C3 and hydroxyl substituents are *syn*[16] and the oxygen substituents are *anti* in the major product.[17] In this series, stereoselection was high only when the siloxyindole C3 substituent was 3-(1-benzylindolyl) and was moderate (~10:1) when this substituent was an aryl group or isopropyl; no stereoselection was seen when this group was benzyl.

(16) A preference for forming the *syn* stereoisomer is observed also in condensations of **13** with achiral aldehydes such as 4-phenylbutanal. Stereoselection is substantial (15−40:1) when R = 3-(1-benzylindolyl) [relative configuration by X-ray analysis] and modest (3−4:1) when R = 3,4-dimethoxyphenyl.

(17) A diversity of models involving both open, extended and closed, cyclic transition structures have been considered for Mukaiyama aldol reactions.[6] Further studies will be needed before a model for the stereoselective reactions reported herein can be advanced.

In conclusion, enantiopure 3,3-disubstituted oxindoles can be prepared in convenient fashion by Mukaiyama aldol reactions of 3-substituted 2-siloxyindoles and chiral, enantiopure aldehydes having nitrogen or oxygen substituents at the α carbon. When the C3 substituent of the prochiral nucleophile is aryl or heteroaryl, stereoselectivity is excellent (10−80:1). These results suggest that a reexamination of the potential utility of the versatile Mukaiyama aldol reaction for the asymmetric construction of quaternary carbon stereocenters is warranted.

Acknowledgment. We thank the National Institutes of General Medical Sciences of NIH (GM-30859) and Amgen for financial support. Postdoctoral fellowship support to M.H from the Austrian Science Fund and to S.A. from Ibis Therapeutics is gratefully acknowledged.

Supporting Information Available: Experimental procedures; copies of HPLC traces used to determine diastereoselectivity; copies of ^1H and ^{13}C NMR spectra of **9**, **11**, **12**, **14b**−**f**, and **16a**−**f**; and CD spectra for **9**, *ent*-**9**, **14b**−**f**, and **16a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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