

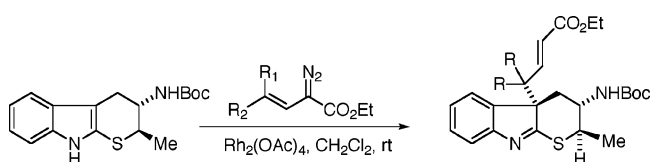
## The Diastereoselective Synthesis of Quaternary Substituted Thioindolines from Sulfur Ylide Intermediates

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The Rh(II)-catalyzed coupling of chiral 2-thiopyranylindoles with vinyl diazoacetates results in the generation of indolines having quaternary substitution at C(3) in high diastereoselectivity.

The presence of highly substituted indoles and indolines in a variety of bioactive molecular targets has inspired a number of groups, including ours, to develop new and improved routes to their synthesis.<sup>1–3</sup> Along these lines, we have found that ylide-derived Claisen rearrangements of 2-thioindoles result in the generation of indolines having quaternary substitution at C(3).<sup>4–6</sup>

(1) For recent reviews of indole-containing natural products, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2003**, *20*, 216. (c) Faulkner, D. *J. Nat. Prod. Rep.* **1999**, *16*, 155.

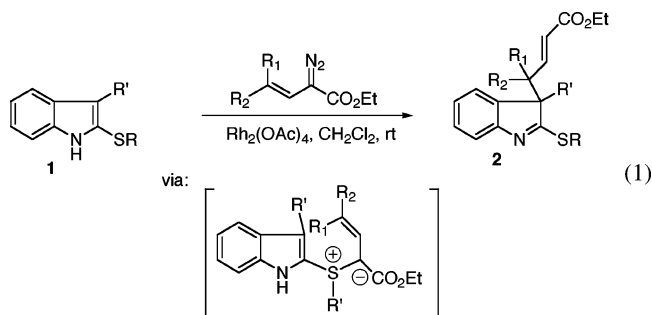
(2) For a recent review covering approaches to the synthesis of indoles and indole alkaloids see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

(3) For representative examples of the synthesis of indolines having quaternary substitution at C(3) see: (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465. (c) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (d) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (e) Nakazawa, A. R.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron: Asymmetry* **2001**, *12*, 897. (f) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675. (g) Fuji, K.; Kawabata, T.; Ohmori, T. *Heterocycles* **1998**, *47*, 951. (h) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543. (i) Booker-Milburn, K. I.; Feduoloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657. (j) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (k) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135.

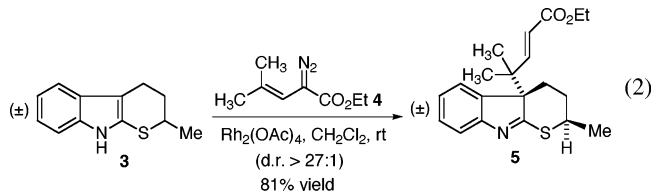
(4) (a) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407. (b) Novikov, A. N.; Kennedy, A. R.; Rainier, J. D. *J. Org. Chem.* **2003**, *68*, 993.

(5) We are aware of three other examples of ylide initiated [3,3]-sigmatropic rearrangements. See: (a) Nakano, H.; Ibata, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1393. (b) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748. (c) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371. (d) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426.

(6) For relevant reviews covering ylide-initiated cascades see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stuppel, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.



From a desire to control the relative stereochemistry of these reactions we recently reported that racemic thiopyranyl indole **3** was capable of transferring its chirality from the position adjacent to sulfur to the 3-position on the indole when vinyl diazoacetate **4** was used in the coupling reaction (eq 2).<sup>7</sup>



Described in this paper are studies that extend the scope of these initial experiments through the examination of a more extensive array of vinyl carbenoid precursors and optically active thiopyranyl indoles. Also described are related investigations that examine ring expansion reactions of thiopyranyl indoles through their coupling with malonate and  $\beta$ -ketoester carbenoid systems.

To establish the stereochemistry that we hoped would ultimately end up controlling the facial selectivity in the carbenoid coupling chemistry we turned to a one-pot DIBAL-Grignard reaction and tryptophan derivative **6**.<sup>8</sup> *N*-Boc protected D-tryptophan **6** was subjected to DIBAL and MeMgBr to give **7** in 52% yield. In addition to MeMgBr, both PhMgBr and vinyl MgBr also added to the tryptophan/DIBAL mix to give amino alcohols **8** and **9**, respectively. As expected from the work of Polt, Yamamoto, and Angle the *threo* isomer was the major or, in the case of **7**, the only diastereomer that was isolated from these reactions.

Outlined in Scheme 1 is our conversion of amino alcohol **7** into thiopyran **11**. Displacement of the tosylate from **7** with KSAc gave thiol **10** after acetate hydrolysis. Oxidative cyclization provided the desired thiopyran **11**.<sup>9</sup>


With a reasonably efficient approach to **11** in hand, we examined its conversion into thioimidates **13** and **14** through its Rh<sub>2</sub>(OAc)<sub>4</sub>-catalyzed coupling with vinyl

(7) Novikov, A. V.; Sabahi, A.; Nyong, A. M.; Rainier, J. D. *Tetrahedron: Asymmetry* **2003**, *14*, 911.

(8) (a) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fufii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (c) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947.

(9) Ishizuka, N.; Sato, T.; Makisumi, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1396.

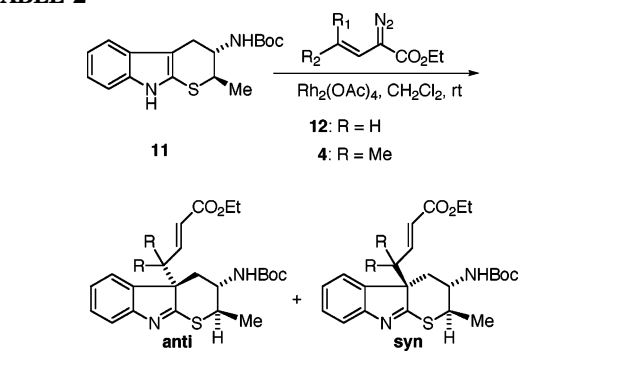
TABLE 1



| entry | R     | alcohol  | dr               | yield, % |
|-------|-------|----------|------------------|----------|
| 1     | Me    | <b>7</b> | >95:5            | 52       |
| 3     | Ph    | <b>8</b> | 7:1 <sup>a</sup> | 56       |
| 3     | vinyl | <b>9</b> | 4:1 <sup>b</sup> | 48       |

<sup>a</sup> Obtained after conversion into the corresponding cyclic carbamate. <sup>b</sup> Obtained from the integration of the vinyl signals in the <sup>1</sup>H NMR of the crude reaction mixture.

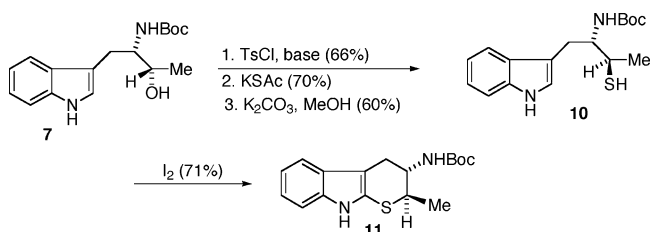
TABLE 2



| entry | R  | thioimidate | yield, % | anti:syn <sup>a</sup> |
|-------|----|-------------|----------|-----------------------|
| 1     | H  | <b>13</b>   | 64       | 3:1                   |
| 2     | Me | <b>14</b>   | 87       | >21:1                 |

<sup>a</sup> From the integration of the vinyl signals in the <sup>1</sup>H NMR of the crude reaction mixture.

SCHEME 1

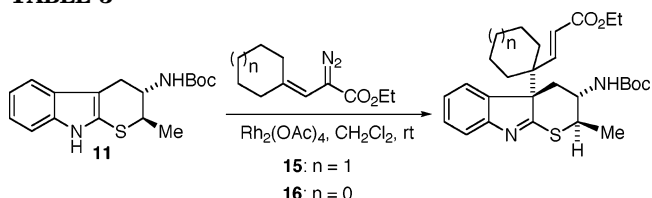


diazoacetates **12** and **4**, respectively (Table 2). Interestingly, we found that the diastereoselectivity of the reaction was dependent upon the level of substitution on the diazo moiety; *gem*-dimethyl-substituted vinyl carbenoid **4** gave indoline **14** having vicinal quaternary substitution in 87% yield with a >21:1 diastereomeric ratio while the parent vinyl diazo acetate **13** gave much lower levels of diastereoselectivity.<sup>10,11</sup> Through the use of 2D NMR experiments, we were able to show that the major diastereomer in both cases was the anticipated anti-product resulting from ylide formation on the thio-

(10) The lower levels of diastereoselectivity observed with **12** may be due to a competitive direct C(3) alkylation of the unsubstituted vinyl carbenoid.

(11) It is also possible that the lower levels of selectivity with **12** may be due to the formation of a configurationally unstable ylide. We thank a reviewer for this suggestion.

TABLE 3



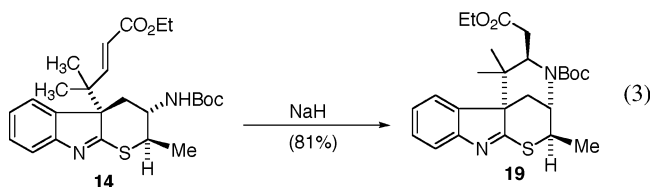
| entry | n | thioimidate | yield, % | anti:syn <sup>a</sup> |
|-------|---|-------------|----------|-----------------------|
| 1     | 1 | <b>17</b>   | 72       | >19:1                 |
| 2     | 0 | <b>18</b>   | 63       | >21:1                 |

<sup>a</sup> From the integration of the vinyl signals in the <sup>1</sup>H NMR of the crude reaction mixture.

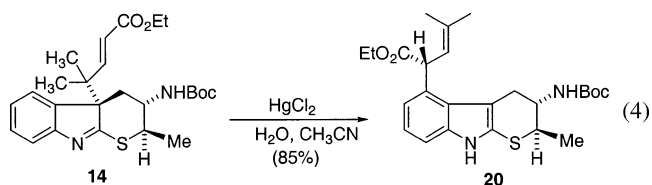
ether lone pair that sits on the face of the thiopyran opposite the methyl substituent.

Having shown that the isoprenyl diazoacetate **4** coupled with **11** with a high level of stereoselectivity, we set out to determine whether related vinyl diazoacetates would give similar results. We were pleased to find that both cyclohexenyl and cyclopentenyl diazo acetates **15** and **16** gave the corresponding thioimidates **17** and **18**, respectively, with high anti:syn diastereoselectivity.

The thioimidates from the carbenoid couplings are potentially useful precursors to other indoles and indolines. For example, by stirring **14** with NaH in THF we were able to induce an intramolecular Michael addition to give tetracyclic adduct **19** as a single diastereomer in 81% yield (eq 3). The C(3) isoprenoid group in **14** can be

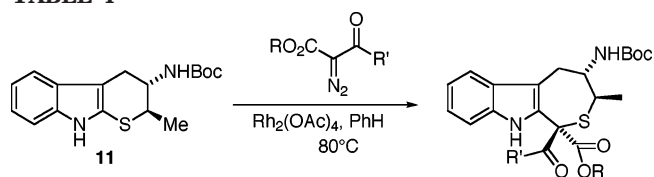


induced to undergo a stereoselective Cope rearrangement when **14** is exposed to HgCl<sub>2</sub>. This results in the generation of **20** as a single diastereomer in 85% yield (eq 4). Interestingly, the corresponding thermal rearrangement gave a 1.6:1 mixture of diastereomers in an 80% yield.



Having demonstrated the utility of thiopyranylidole **11** in the synthesis of quaternary substituted indolines, we turned our attention to the use of **11** in other ylide-initiated cascades. First on the list was the reaction of **11** with malonate and  $\beta$ -ketoester carbenoids (Table 4). Previously, we had demonstrated that acyclic 2-thioindoles undergo ylide-derived Stevens' rearrangements when exposed to malonate and  $\beta$ -ketoester carbenoids; if a similar reaction occurred with **11**, this would result in a novel one-carbon ring expansion reaction. To our delight, we found this to be the case; both malonate and  $\beta$ -ketoester rhodium carbenoids underwent successful Stevens' rearrangements to generate thiepinines **21** and

TABLE 4



| R            | R'  | thiepine  | ds  | yield, % |
|--------------|-----|-----------|-----|----------|
| Me           | OMe | <b>21</b> |     | 64       |
| <i>t</i> -Bu | Me  | <b>22</b> | 6:1 | 60       |

**22**, respectively. Impressively, **22** was isolated as a 6:1 mixture of diastereomers although the reaction was run at 80 °C.

In conclusion, we have shown that the coupling of optically active thiopyranylindoles with diazoacetates in the presence of  $\text{Rh}_2(\text{OAc})_4$  gives highly substituted indo-

lines and indoles in high yield and moderate to high levels of diastereoselectivity. We are continuing to explore these reactions including their application to the synthesis of interesting targets. These efforts will be reported in due course.

**Acknowledgment.** We are grateful to The National Institutes of Health, General Medical Sciences (GM61608) for support of this work. We would also like to thank Dr. Charles L. Mayne and Mr. Elliot M. Rachlin for help with NMR and mass spectrometry, respectively.

**Supporting Information Available:** Characterization data and copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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