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Asymmetric Synthesis of the Highly Methylated Tryptophan Portion of the Hemiasterlin Tripeptides

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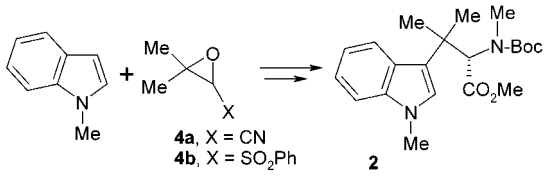
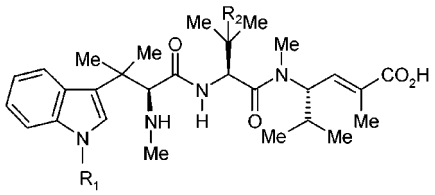
ABSTRACT



The asymmetric synthesis of the methylated tryptophan portion of hemiasterlin peptides is described. The key reactions are a $SnCl_4$-mediated ring opening of epoxynitriles or epoxysulfones by *N*-methylindole followed by an asymmetric Strecker reaction. A second approach involving opening of glycidic esters by indoles is also described.

A number of hemiasterlins **1** (Figure 1) have been isolated from several species of marine sponges.[1] These novel tripeptides show in vitro cytotoxicities toward human breast, lung, and colon cancer cell lines that are comparable to taxol and vinblastine.[2] Anderson and co-workers have shown that the mode of action of these compounds involves tubulin binding, thereby inhibiting microtubulin activity and causing mitotic arrest.[2]



1a Hemiasterlin; $R_1 = R_2 = Me$
1b Hemiasterlin A; $R_1 = H$, $R_2 = Me$
1c Hemiasterlin B; $R_1 = R_2 = H$

Figure 1.

The total synthesis of (−) hemiasterlin has been reported.[3] The route involved preperation of the three individual α-amino acid building blocks followed by coupling. The reported synthesis of the tryptophan moiety **2** commenced with the methyl ester of 3-indoylacetic acid and was linear and 16 steps long. We felt that a successful convergent approach would make **2** and analogues more readily available. This would open the possibility of generating not only significant quantities of hemiasterlin itself but also analogues for screening and further biological assays.

We report herein two successful approaches to **2**. Both require only a few steps starting from *N*-methylindole, **3**, and both routes can yield enantiomerically highly enriched material. Each method can be adapted to yield analogues of **2** and hence potential hemiasterlin analogues.

After completion of this work we became aware of a second hemiasterlin synthesis by the Vedejs group.[4] These

(1) (a) Talphir, R.; Benayahu, Y.; Emrich, R.; Keifer, P. A. *Tetrahedron Lett.* **1994**, *35*, 4453. (b) Coleman, J. E.; Dilip de Silva, E.; Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51*, 10653.

(2) Andersen, H. J.; Coleman, J. E.; Andersen, R. J.; Roberge, M. *Cancer Chemother. Pharmacol.* **1997**, *39*, 223.

(3) Andersen, R. J.; Coleman, J. E.; Piers, E.; Wallace, D. J. *Tetrahedron Lett.* **1997**, *38*, 317.

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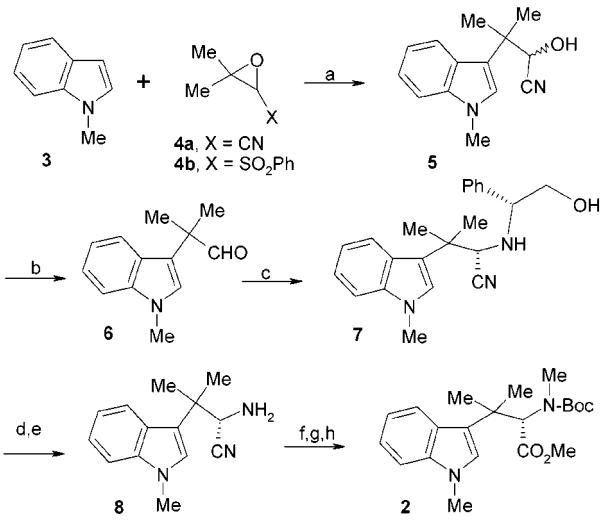
authers used an asymmetric Strecker amino acid approach for the preparation of the key tryptophan **2** starting with the aldehyde **6**. One of our two routes to **2** involves the aldehyde **6**. Our synthesis of **6** is one step from *N*-methylindole, and our version of an asymmetric Strecker synthesis complements that of Vedejs group.

The sequence for the first route is shown in Scheme 1. Tin tetrachloride mediated ring opening of the cyanoepoxide

Scheme 1[a]

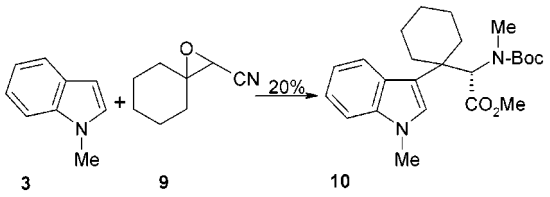


[a] Reagents and conditions: (a) $SnCl_4$, CH_2Cl_2, −78 °C, 70%; (b) NaOH, EtOH 95%; (c) (*R*)-phenylglycinol, CH_2Cl_2, TMSCN; (d) $Pb(OAc)_4$, $MeOH/CH_2Cl_2$; (e) 3 N HCl, Et_2O, 55% over two steps; (f) concentrated HCl reflux; (g) $(Boc)_2O$, Na_2CO_3, THF/H_2O; (h) NaH, MeI, DMF, 65% over three steps.

4a[5] in CH_2Cl_2 at −78 °C in the presence of *N*-methylindole, **3**, gave the 3-indoyl-substituted cyanohydrin **5** in 72% yield. Exposure of **5** to NaOH provided aldehyde **6** in quantitative yield. The same aldehyde could be obtained directly in 52% yield via the $SnCl_4$-catalyzed ring opening of the epoxysulfone **4b**[6] in the presence of **3**. The stage was now set to transform **6** into the highly methylated, enantiomerically enriched tryptophan derivative **2**. There have been a number of reports outlining asymmetric versions of the classic Strecker α-amino acid synthesis.[7] We chose to use (*R*)-phenylglycinol[7a] as chiral auxiliary to accomplish this goal. Aldehyde **6** was reacted with (*R*)-phenylglycinol to give the expected imine which was captured with TMSCN. This sequence led to the formation of an 85:15 diastereomeric mixture of α-cyano amines; chromatographic separation gave the desired isomer **7** in 70% yield. The auxiliary was removed via $Pb(OAc)_4$ in $MeOH:CH_2Cl_2$, and the resultant chiral α-aminonitrile **8** was hydrolyzed in refluxing concentrated hydrochloric acid. The amino acid thus obtained was capped as the Boc derivative and methylated with NaH/CH_3I to afford **2**. The overall yield of **2** from *N*-methylindole was 16%. The HPLC purity of the corresponding deprotected amino acid was 96%. The absolute stereochemistry was assigned on the basis of analogy with the synthesis of *tert*-butylglycine from pivalaldehyde via this route.[7a]

To illustrate the potential for analogue synthesis, the spiro epoxynitrile **9** and *N*-methylindole were converted to the tryptophan derivative **10** in 20% overall yield using the same synthetic sequence (Scheme 2). Coupling of **4a** or **9** to

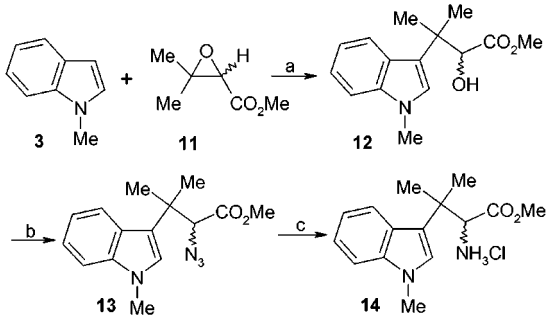
Scheme 2



indoles substituted in the benzenoid ring should readily lead to additional analogues of **2** and **10**.

In an alternative approach, racemic *N*-methyl-β,β-dimethyltryptophan methyl ester hydrochloride **14** was prepared as shown in Scheme 3. Acid-catalyzed ring opening

Scheme 3. Synthesis of *rac*-*N*-Methyl-ss,ss-dimethyltryptophan Methyl Ester·HCl (**14**)[a]

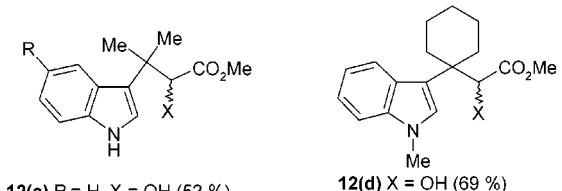


[a] Reagents and conditions: (a) $SnCl_4$, CH_2Cl_2, −78 °C, 70%; (b) DEAD/Ph_3P, DPPA, pyridine, CH_2Cl_2, 0 °C, 85%; (c) Ph_3P, H_2O, THF, 65%.

of the glycidic ester **11** with $SnCl_4$ in CH_2Cl_2 at −78 °C in the presence of *N*-methylindole afforded the tryptol **12** in 70% yield. We were pleased with the 70% yield obtained in the reaction of **11** with *N*-methylindole, as earlier reports using 3-methylglycidates with various indoles and $SnCl_4$ typically displayed yields under 40%.[6]

Mitsunobu azidation of **12** gave the azide **13** which was reduced with triphenylphosphine in wet THF to afford the

(4) Vedejs, E.; Kongkittingam, C. *J. Org. Chem.* **2001**, *22*, 7355.
(5) Ayi, A. I., Guedz. R. M. R. *Tetrahedron Lett.* **1981**, *22*, 1505.
(6) (a) Vogt, P. F.; Travers, D. F. *Can. J. Chem.* **1969**, *47*, 2875. (b) Durst, T.; Tin, K.-C. *Tetrahedron Lett.* **1970**, 2369.
(7) (a) Chakraborty, T. K.; Azhar Hussain.; Venkat Reddy, G. *Tetrahedron*. **1995**, *51*, 9179. (b) Weinges, K.; Gries, K.; Stemmle, B.; Schrank, W. *Chem. Ber*. **1977**, *110*, 2098. (c) Davis, F. A.; Reddy, R. E.; Portonovo, P.S. *Tetrahedron Lett*. **1994**, *35*, 9351. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 762. (e) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 5315. (f) Inaba, T.; Kozono, I.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 2359. (g) Kunz, H.; Sager, W. *Angew Chem*, **1987**, *99*, 595. *Angew Chem., Int. Ed. Engl*. **1987**, *26*, 557.



12(a) R = H, X = OH (52 %)
13(a) R = H, X = N_3 (85 %)
12(b) R = Br, X = OH (52 %)
12(c) R = OCH_3, X = OH (43 %)

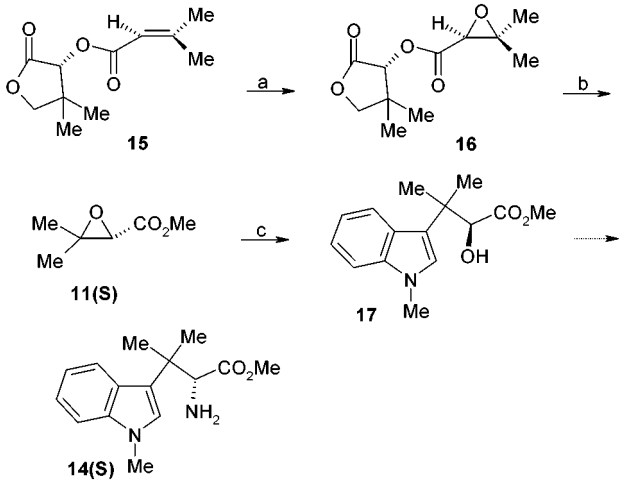
12(d) X = OH (69 %)
13(d) X = N_3 (90 %)

Figure 2.

amino ester **14**, which was isolated as the hydrochloride. The yield of **14** from **3** and **11** was nearly 40%.

This methodology was extended to the synthesis of several analogues of tryptols **12** and azides **13** shown in Figure 2.

Scheme 4[a]

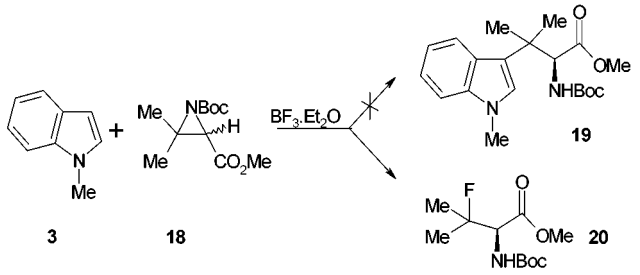


[a] Reagents and conditions: (a) *m*-CPBA, BHT, $CHCl_3$, reflux; fractional crystallization from ether at −30 °C; (b) K_2CO_3, MeOH; (c) *N*-methylindole, $SnCl_4$, CH_2Cl_2, −78 °C.

Reaction of the optically active **11**(S) [89% ee], prepared by *m*-CPBA epoxidation of acrylic ester **15**, with **3** in the presence of $SnCl_4$ afforded **17** with the same enantiomeric purity as **11**(S)[8] (Scheme 4). Further manipulation following Scheme 3 can be expected to yield enantiomerically enriched **14**.

Despite the report by Hashimoto[9] indicating that suitably substituted aziridines could be opened with $BF_3{\cdot}Et_2O$ and trapped at the C-3 position of indoles, we were unable to observe such a reaction when applied to the *N*-Boc aziridine ester **18**. Instead of the desired reaction, we observed formation of the fluorinated valine **20**. The use of other Lewis acids such as $SnCl_4$ also did not produce **19** (Scheme 5).

Scheme 5



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Supporting Information Available: Spectroscopic data and experimental details for compounds **2**, **5**−**8**, **10**−**13**, and **15**−**17**. This material is avaialble free of charge via the Internet at http://pubs.acs.org.

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(8) Chiracel OD column, eluting with 95:5 hexane/2-propanol.

(9) Shima, I.; Shimazaki, N.; Imai, K.; Hemmi, K.; Hashimoto, M. *Chem. Pharm. Bull.* **1990**, *38*, 564.