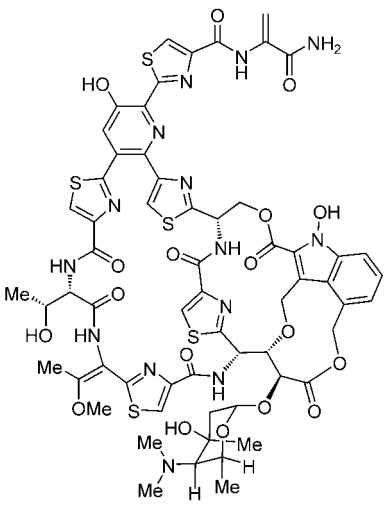


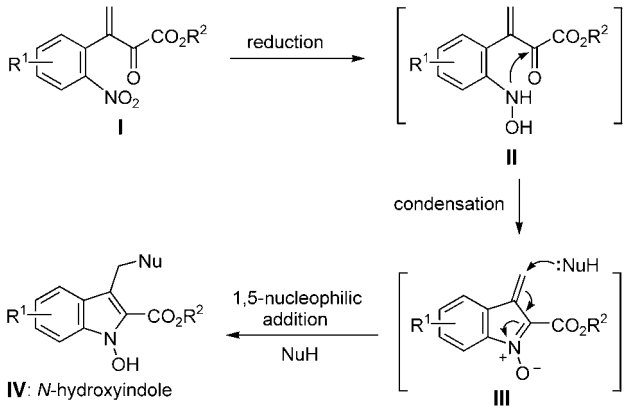
Indole Synthesis

Construction of Substituted *N*-Hydroxyindoles: Synthesis of a Nocathiacin I Model System**

K. C. Nicolaou, Sang Hyup Lee, Anthony A. Estrada, and Mark Zak*

Rare as they appear to be in nature, *N*-hydroxyindoles are intriguing chemical entities as they may play important biological roles and serve as useful synthetic building blocks.[1,2] One of the most impressive naturally-occurring molecules that features this unit is the recently discovered nocathiacin I (**1**), an antibiotic isolated from *Nocardia sp.* (ATCC-202099)[3] and the fungus *Amicolaptosis sp.*[4] Compound **1** exhibits strikingly potent activity in vitro and in vivo against Gram-positive bacteria.[3a,4] Given the complex structure of this antibiotic and the prominent position of a highly substituted *N*-hydroxyindole motif within its structure, as well as the lack of general methods for the construction of such systems, we deemed the development of suitable synthetic methodologies in this area as an important goal. Herein we report a new synthetic technology for the construction of substituted *N*-hydroxyindoles **2** from simple aromatic precursors and its application to the synthesis of a nocathiacin I model system **3**, which contains this unusual molecular framework.

Scheme 1 depicts the general concept for the construction of *N*-hydroxyindoles formulated on the basis of relevant precedents.[2] Thus, selective reduction of nitro ketoester **I**



Scheme 1. General scheme for the construction of substituted *N*-hydroxyindoles **IV**.

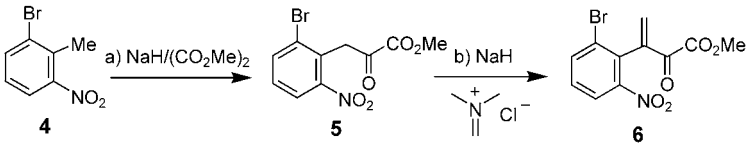
under appropriate conditions to hydroxylamine **II** was expected to initiate an intramolecular condensation with the carbonyl group, leading to the α,β-unsaturated nitrone system **III**, whose capture with nucleophiles would deliver the desired substituted *N*-hydroxyindoles **IV**.

The required starting material for these studies, nitro ketoester **6**, was readily prepared by standard chemistry[2c,5,6] in two steps from aromatic compound **4** via intermediate **5** (Scheme 2). Schemes 3 and 4 summarize the initial results of this study and demonstrate the feasibility of this plan under two different sets of experimental conditions. Thus, addition

[*] Prof. Dr. K. C. Nicolaou, Dr. S. H. Lee, A. A. Estrada, M. Zak
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

[**] We thank Dr. D. H. Huang, Dr. G. Siuzdak, and Dr. R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by grants from the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology, and fellowships from the National Institutes of Health (USA) (to A.A.E.), The Skaggs Institute for Research (to M.Z.), and Eli Lilly & Company (to M.Z.).

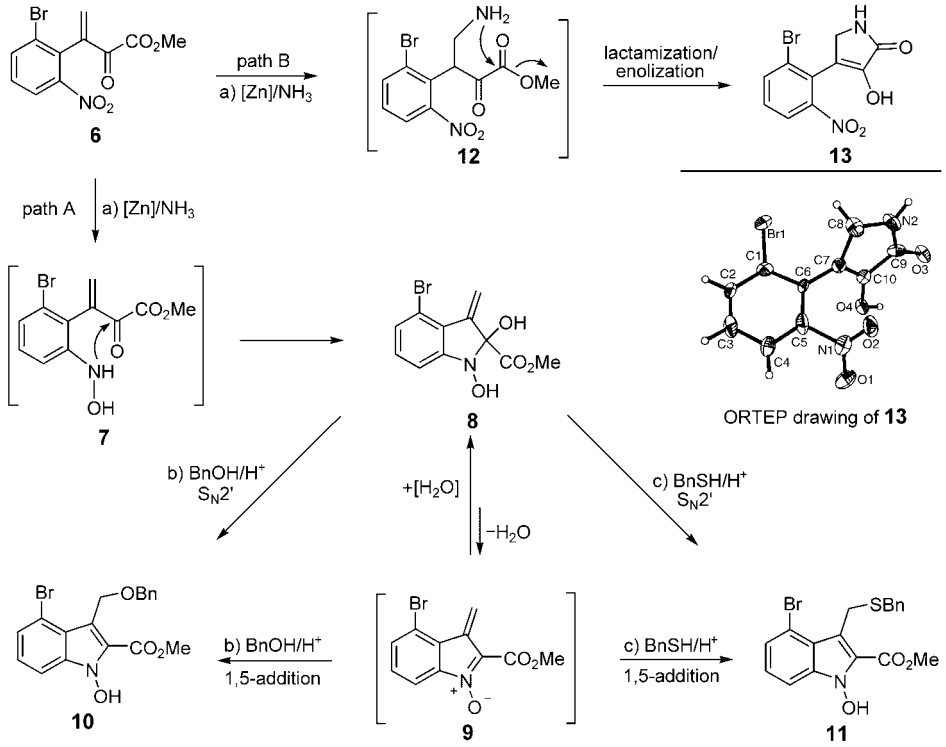
 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim DOI: 10.1002/anie.200500724



Scheme 2. Synthesis of nitro ketoester **6**. Reagents and conditions: a) NaH (4.0 equiv), $(CO_2Me)_2$ (5.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 18 h, 60%; b) NaH (1.1 equiv), $CH_2{=}N^+Me_2Cl^-$ (3.0 equiv), THF, 0 °C, 1 h; then 25 °C, 12 h, 80%. DMF = *N*,*N*-dimethylformamide.

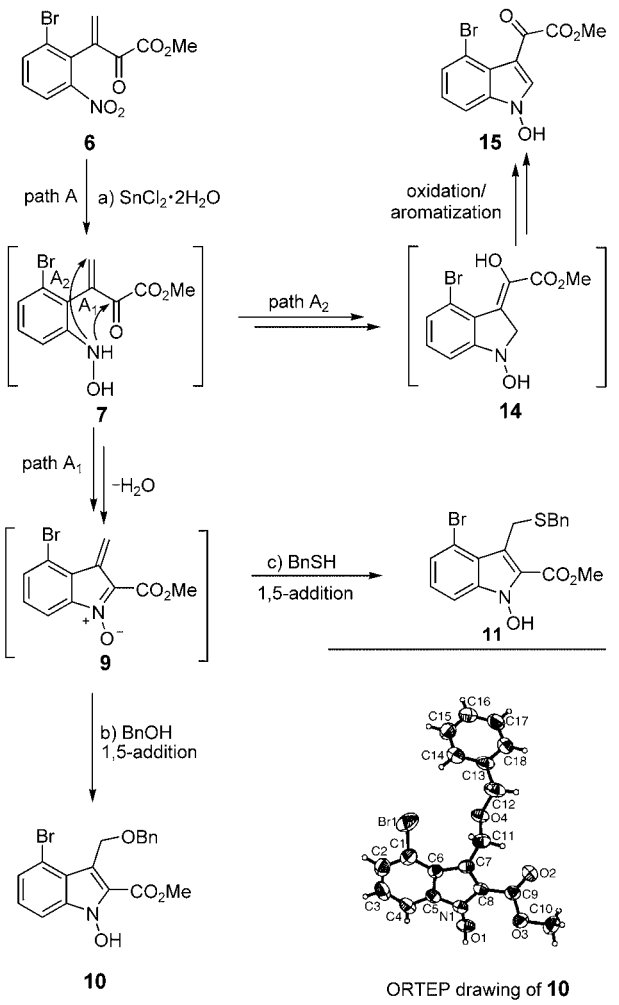
of activated zinc [Zn][2b] (prepared from zinc dust, 1,2-dibromoethane, and TMSCl) in THF to a solution of **6** and NH_4Cl in THF at 25 °C (Scheme 3) resulted in the formation of *N*-hydroxyindoline derivative **8** (56%; Table 2) along with small amounts of hydroxylactam **13** (10%) whose structure was proven beyond doubt through X-ray crystallographic analysis[7] (see ORTEP drawing, Scheme 3). These observations can be explained by invoking ring closure of the initially formed hydroxylamine **7**, leading to *N*-hydroxy tertiary alcohol **8** (path A; Scheme 3), and 1,4-addition of NH_3 to unreduced starting material **6** followed by lactamization and enolization of the initially formed amino ester **12** to form **13** (path B; Scheme 3). The *N*-hydroxy tertiary alcohol **8** was found to be rather labile, losing a molecule of water to generate nitrone **9** whose isolation remains elusive, although its presence can be surmised by TLC and NMR spectroscopy as well as through trapping by a variety of nucleophiles. Indeed, **8** reacted with benzyl alcohol or phenylmethanethiol in DME at 40 °C in the presence of *p*TsOH to afford *N*-hydroxyindoles **10** (55%; Table 2) and **11** (90%), respectively. These *N*-hydroxyindole-forming reactions are assumed to proceed either directly from *N*-hydroxy tertiary alcohol **8** by S_N2'-type displacement or by 1,5-addition to the initially formed nitrone **9**, or through both mechanistic pathways. These results are in contrast to those of Myers and Herzon[2b] in which the products obtained by 1,5-addition to a sterically congested α,β-unsaturated nitrone proved unstable to isolation, readily reverting back to the starting material.

In an effort to find a more direct access to the desired *N*-hydroxyindoles, a second protocol involving $SnCl_2$ as a reducing agent[2c,e] was explored. According to this method, **6** was treated with $SnCl_2{\cdot}2H_2O$ (2.2 equiv) and benzyl alcohol or phenylmethanethiol (benzyl mercaptan, 5.0 equiv) in DME in the presence of 4-Å molecular sieves at 40 °C for 1–1.5 h, circumstances that led, through path A_1, directly to the formation of adducts **10** (60%, see ORTEP drawing[7]) or **11** (55%), respectively (Scheme 4). These conditions were arrived at after a systematic investigation in which benzyl alcohol was used as the nucleophile, whereby the effects of solvent, temperature, time, amount of water, and stoichiometry were examined. The absence of the *N*-hydroxy tertiary alcohol **8** from the reaction mixture under these conditions is presumably due to its fleeting nature under the reaction



Scheme 3. Zn/NH_4Cl-induced generation and trapping of α,β-unsaturated nitrone **9** to form *N*-hydroxyindoles. Reagents and conditions: a) Zn dust (4.9 equiv), $BrCH_2CH_2Br$ (0.33 equiv), THF, reflux, 1 h; then cool to 25 °C; then TMSCl (0.2 equiv); and then a mixture of aqueous NH_4Cl (1.0 N; 2.2 equiv) and **6** (1.0 equiv), 25 °C, 15 min, **8** (56%), **13** (10%); b) **8** (1.0 equiv), *p*TsOH (3.0 equiv), molecular sieves (4 Å; 20 wt%), BnOH (5.0 equiv), DME, 40 °C, 3 h, **10** (55%); c) **8** (1.0 equiv), *p*TsOH (3.0 equiv), molecular sieves (4 Å; 20 wt%), BnSH (5.0 equiv), DME, 40 °C, 1 h, **11** (90%). TMS = trimethylsilyl; *p*TsOH = *p*-toluenesulfonic acid; Bn = benzyl; DME = 1,2-dimethoxyethane. ORTEP drawing of **13** drawn at the 50% probability level.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

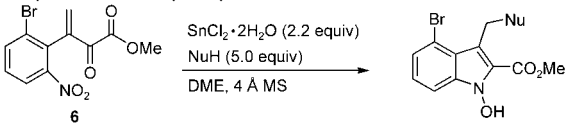


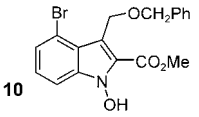
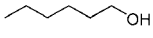
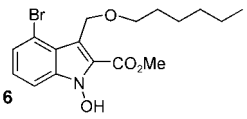
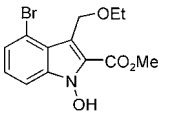
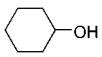
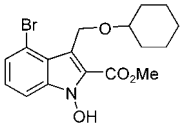
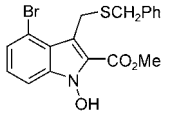
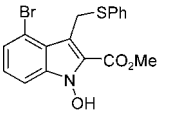
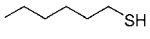
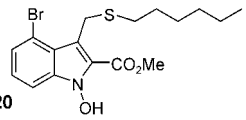
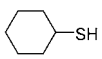
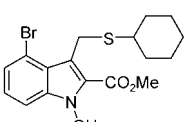
Scheme 4. $SnCl_2 \cdot 2H_2O$-induced generation and trapping of α,β-unsaturated nitrone **9** to form *N*-hydroxyindoles. Reagents and conditions: a, b) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), molecular sieves (4 Å; 20 wt%), BnOH (5.0 equiv), **6** (1.0 equiv), DME, 40°C, 1.5 h, **10** (60%), **15** (17%); a, c) $SnCl_2 \cdot 2H_2O$ (2.2 equiv), molecular sieves (4 Å; 20 wt%), BnSH (5.0 equiv), **6** (1.0 equiv), DME, 40°C, 1 h, **11** (55%), **15** (15%). ORTEP drawing of **10** drawn at the 50% probability level.

conditions (acidic), which promote its conversion into nitrone **9** and/or its trapping by the nucleophile. The $SnCl_2$-promoted reaction, however, also yields ketoester *N*-hydroxyindole **15** in small amounts (15–17%). This byproduct presumably arises from the initially generated hydroxylamine **7** through path A_2, which involves intramolecular 1,4-addition followed by oxidation/aromatization of the resulting enolic species **14** (Scheme 4). An alternative mechanism for the generation of **15** may involve the nitroso intermediate (formed by partial reduction of **6**) or its hydrated counterpart, which could undergo, through its nitrogen atom, intramolecular addition to the neighboring Michael acceptor; this event may then be followed by rearrangement (or elimination of H_2O) to the observed compound **15**.

To explore the generality and scope of the developed reaction, a number of nucleophiles were employed to capture the labile nitrone (**9** or its hydrated form **8**) under the direct $SnCl_2 \cdot 2H_2O$ conditions. The results are shown in Table 1. Thus, both primary and secondary alcohols enter the reaction smoothly, affording good yields of the expected substituted *N*-hydroxyindoles (compounds **10** and **16–18**; Table 1, entries 1–4). The somewhat modest yields in these and the other reactions listed in Table 1 are presumably a consequence of a competing pathway through which the *N*-hydroxy group of one molecule of **8** or **7** reacts as a nucleophile to trap another of these species, thus leading to oligomeric materials. In fact, a dimer of **8** was detected by mass spectrometry. Besides hydroxy-bearing nucleophiles, thiols (Table 1, entries 5–8) and amines (Table 1, entries 9 and

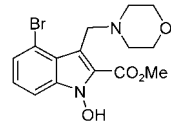
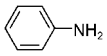
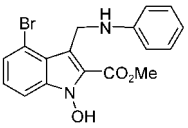
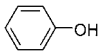
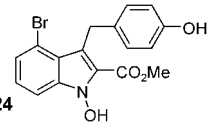
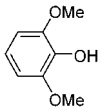
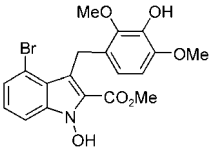
Table 1: Preparation of *N*-hydroxyindoles from nitro ketoester **6**.[a]



Entry	NuH	*T* [°C]	*t* [h]	Product	Yield [%][b]
1	$PhCH_2OH$	40	1.5	 **10**	60
2		40	2.0	 **16**	54
3	EtOH	40	1.3	 **17**	47
4[c]		40	3.0	 **18**	41
5	$PhCH_2SH$	40	1.0	 **11**	55
6	PhSH	40	0.7	 **19**	68
7		40	2.0	 **20**	75
8		40	2.5	 **21**	73

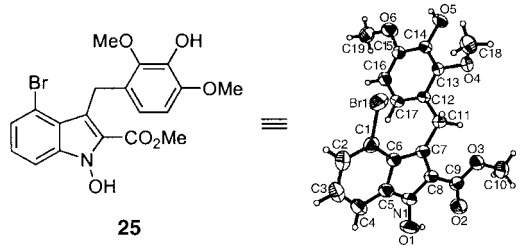
 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1: (Continued)

Entry	NuH	T [°C]	t [h]	Product	Yield [%][b]
9		40	6.0	 **22**	27
10		40	3.0	 **23**	18
11		40	22	 **24**	40
12		50	3.0	 **25**	31

[a] Reactions were carried out on a 0.06–0.10-mmol scale in anhydrous DME (concentration: 0.12–0.16 M) and the products were purified by PTLC (silica gel). [b] Yields of isolated products. [c] $SnCl_2 \cdot 2H_2O$ (3 equiv).

10) also participated in this reaction to furnish *S*-substituted *N*-hydroxyindoles **11** and **19–21** and *N*′-substituted *N*-hydroxyindoles **22** and **23**, respectively. Interestingly, phenols react as carbon nucleophiles in this process and form carbon–carbon rather than carbon–oxygen bonds to give compounds **24** and **25** (Table 1, entries 11 and 12). Compound **25** (Table 2) was recrystallized from acetonitrile and its structure was confirmed by X-ray crystallographic analysis[7] (Figure 1).

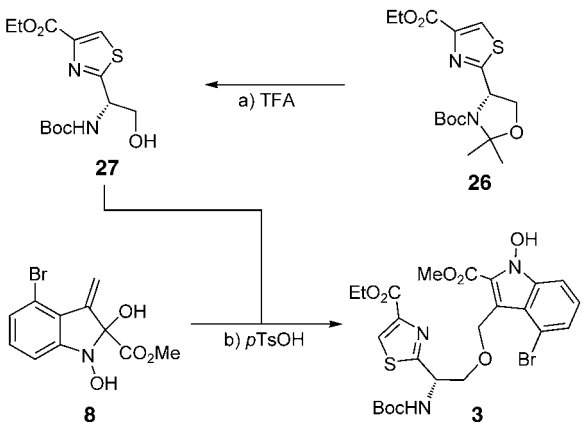


25

Figure 1. ORTEP drawing of compound **25** drawn at the 50% probability level.

Despite the presently unknown origins of this rather special and exclusive reactivity of phenolic nucleophiles towards these reactive species (i.e. **8** and/or **9**), its potential in delivering novel molecular diversity remains considerable and warrants further exploration.

Having developed this technology, we then proceeded to apply it to the synthesis of the nocathiacin I model system **3**, which contains the *N*-hydroxyindole structural motif and one of the thiazole rings of the natural product. Scheme 5 outlines the successful execution of this explorative study. Thus, the



Scheme 5. Construction of *N*-hydroxyindole nocathiacin I model system **3**. Reagents and conditions: a) TFA/MeOH/CH_2Cl_2 (3:1:2), 25 °C, 30 min, 68%; b) *p*TsOH (3.0 equiv), molecular sieves (4 Å; 20 wt%), **27** (4.0 equiv), **8** (1.0 equiv), DME, 25 °C, 10 min; then 40 °C, 2 h, 44%. Boc = *tert*-butoxycarbonyl; TFA = trifluoroacetic acid.

Table 2: Selected physical properties for compounds **3**, **8**, **10**, and **25**.

3: $R_f = 0.43$ (silica gel, EtOAc/hexanes 7:3); $[\alpha]_D^{32} = -3.0$ ($c = 0.5$, $CHCl_3$); IR (film) $\tilde{\nu}_{max} = 3354, 2978, 2919, 1707, 1490, 1460, 1437, 1390, 1360, 1255, 1231, 1161, 1119, 1090, 1025, 879, 773, 743\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 66 °C): $\delta = 9.22$ (s, 1H), 8.06 (s, 1H), 7.50 (d, $J = 7.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.22 (t, $J = 7.7$ Hz, 1H), 5.81 (br s, 1H), 5.17 ($^1/_2$ABq, $J = 11.4$ Hz, 1H), 5.14 ($^1/_2$ABq, $J = 11.4$ Hz, 1H), 5.04 (dt, $J = 7.4$, 4.8 Hz, 1H), 4.33 (q, $J = 7.0$ Hz, 2H), 3.97 (s, 3H), 3.96 (dd, $J = 10.0$, 4.8 Hz, 1H), 3.93 (dd, $J = 10.0$, 4.8 Hz, 1H), 1.39 (s, 9H), 1.35 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 174.0$, 162.2, 162.0, 156.2, 147.7, 137.2, 128.9, 127.2, 127.0, 126.9, 120.9, 115.9, 115.2, 110.2, 80.4, 71.2, 62.1, 61.9, 54.2, 53.1, 28.4, 14.5 ppm; HRMS (ESI) (%): calcd for $C_{24}H_{28}BrN_3O_8SNa$ [M+Na^+]: 620.0673; found: 620.0674

8: $R_f = 0.53$ (silica gel, EtOAc/hexanes 6:4); IR (film) $\tilde{\nu}_{max} = 3389, 2954, 2849, 1737, 1596, 1566, 1460, 1431, 1290, 1255, 1231, 1184, 1155, 1096, 1026, 885, 802, 749\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.64$ (s, 1H), 7.14 (t, $J = 7.9$ Hz, 1H), 7.11 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.85 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.32 (s, 1H), 5.40 (s, 1H), 5.08 (br s, 1H), 3.61 ppm (s, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 170.3$, 154.8, 144.3, 132.1, 127.3, 123.4, 117.9, 111.8, 111.7, 98.9, 53.6 ppm; HRMS (ESI) (%): calcd for $C_{11}H_{10}BrNO_4Na$ [M+Na^+]: 321.9685; found: 321.9684.

10: $R_f = 0.58$ (silica gel, EtOAc/hexanes 6:4); IR (film) $\tilde{\nu}_{max} = 3194, 2952, 2848, 1710, 1525, 1433, 1353, 1312, 1255, 1226, 1185, 1122, 1047, 1024, 909, 874, 771, 730, 690\ cm^{-1}$; ^1H NMR (400 MHz, CD_3CN): $\delta = 9.49$ (br s, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.39–7.23 (m, 6H), 7.18 (t, $J = 8.1$ Hz, 1H), 5.10 (s, 2H), 4.61 (s, 2H), 3.88 ppm (s, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 162.2$, 139.9, 137.2, 129.2, 128.9, 128.3, 127.1, 126.9, 126.8, 121.0, 116.0, 115.9, 110.2, 72.7, 61.8, 52.9 ppm; HRMS (ESI) (%): calcd for $C_{18}H_{16}BrNO_4Na$ [M+Na^+]: 412.0155; found: 412.0155

25: $R_f = 0.42$ (silica gel, EtOAc/hexanes 6:4); IR (film) $\tilde{\nu}_{max} = 3414, 2934, 2835, 1708, 1675, 1615, 1489, 1440, 1396, 1347, 1287, 1249, 1085, 1030, 894, 746\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 9.21$ (s, 1H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 7.9$ Hz, 1H), 7.21 (t, $J = 7.9$ Hz, 1H), 6.46 (d, $J = 8.6$ Hz, 1H), 6.38 (s, 1H), 5.92 (d, $J = 8.6$ Hz, 1H), 4.62 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 ppm (s, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 162.5$, 147.5, 146.0, 139.7, 138.0, 128.6, 127.3, 126.5, 126.4, 121.2, 119.2, 118.6, 116.3, 110.4, 107.5, 60.4, 56.7, 52.6, 24.7 ppm; HRMS (ESI) (%): calcd for $C_{19}H_{18}BrNO_6Na$ [M+Na^+]: 458.0210; found: 458.0200

© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

previously synthesized thiazole derivative **26**[8] was partially deprotected by controlled exposure to TFA in $MeOH/CH_2Cl_2$ at 25 °C to afford hydroxy Boc-protected amine **27** in 68 % yield. Coupling of the latter compound with **8** in the presence of *p*TsOH in DME at 40 °C then resulted in the formation of *N*-hydroxyindole model system **3** (Table 2) in 44 % yield (unoptimized).[9]

Besides possibly facilitating the total synthesis of nocathiacin I (**1**), the described new synthetic technology may find numerous applications in synthetic endeavors directed towards polyfunctional *N*-hydroxyindoles and other biologically interesting molecules.

Received: February 25, 2005
Published online: May 13, 2005

Keywords: indoles · natural products · nitrones · nucleophilic addition · synthetic methods

[1] For selected reviews on *N*-hydroxyindoles and their derivatives, see: a) M. Somei, *Adv. Heterocycl. Chem.* **2002**, *82*, 101 – 155; b) M. Somei, *Heterocycles* **1999**, *50*, 1157 – 1211; c) R. M. Acheson, *Adv. Heterocycl. Chem.* **1990**, *51*, 105 – 175.

[2] a) A. Wong, J. T. Kuethe, I. W. Davies, *J. Org. Chem.* **2003**, *68*, 9865 – 9866; b) A. G. Myers, S. B. Herzon, *J. Am. Chem. Soc.* **2003**, *125*, 12080 – 12081; c) S. Katayama, N. Ae, R. Nagata, *J. Org. Chem.* **2001**, *66*, 3474 – 3483; d) Z. Wróbel, M. Makosza, *Tetrahedron* **1997**, *53*, 5501 – 5514; e) A. Reissert, H. Heller, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 4364 – 4379.

[3] a) W. Li, J. E. Leet, H. A. Ax, D. R. Gustavson, D. M. Brown, L. Turner, K. Brown, J. Clark, H. Yang, J. Fung-Tomc, K. S. Lam, *J. Antibiot.* **2003**, *56*, 226 – 231; b) J. E. Leet, W. Li, H. A. Ax, J. A. Matson, S. Huang, R. Huang, J. L. Cantone, D. Drexler, R. A. Dalterio, K. S. Lam, *J. Antibiot.* **2003**, *56*, 232 – 242; c) K. L. Constantine, L. Mueller, S. Huang, S. Abid, K. S. Lam, W. Li, J. E. Leet, *J. Am. Chem. Soc.* **2002**, *124*, 7284 – 7285; d) nocathiacin antibiotics: J. E. Leet, H. A. Ax, D. R. Gustavson, D. M. Brown, L. Turner, K. Brown, W. Li, K. S. Lam, WO 2000003722 A1, **2000** [*Chem. Abstr.* **2000**, 132, 121531].

[4] T. Sasaki, T. Otani, H. Matsumoto, N. Unemi, M. Hamada, T. Takeuchi, M. Hori, *J. Antibiot.* **1998**, *8*, 715 – 721.

[5] For an example of this type of α-methylenation, see: J. Ezquerra, C. Pedregal, *Tetrahedron: Asymmetry* **1994**, *5*, 921 – 926.

[6] For α-functionalization of a substituted toluene, see: C.-g. Shin, Y. Yamada, K. Hayashi, Y. Yonezawa, K. Umemura, T. Tanji, J. Yoshimura, *Heterocycles* **1996**, *43*, 891 – 898.

[7] CCDC-264685 (**13**), -264686 (**10**), and -264687 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] a) C.-g. Shin, A. Okabe, A. Ito, A. Ito, Y. Yonezawa, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583 – 1596; b) For the thio derivative, see: K. C. Nicolaou, M. Nevalainen, B. S. Safina, M. Zak, S. Bulat, *Angew. Chem.* **2002**, *114*, 2021 – 2025; *Angew. Chem. Int. Ed.* **2002**, *41*, 1941 – 1945.

[9] We have also recently synthesized a more advanced model system containing the 15-membered lactone–ether ring of nocathiacin I through both intermolecular and intramolecular versions of this *N*-hydroxyindole method. More details will be published in due course.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim