# Syntheses of Pyrrolo- and Indoloisoquinolinones by Intramolecular Cyclizations of 1-(2-Arylethyl)-5-benzotriazolylpyrrolidin-2-ones and 3-Benzotriazolyl-2-(2-arylethyl)-1-isoindolinones

Alan R. Katritzky,* Shamal Mehta, and Hai-Ying He

*Center for Heterocyclic Chemistry, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200*

*katritzky@chem.ufl.edu*

*Received August 22, 2000*

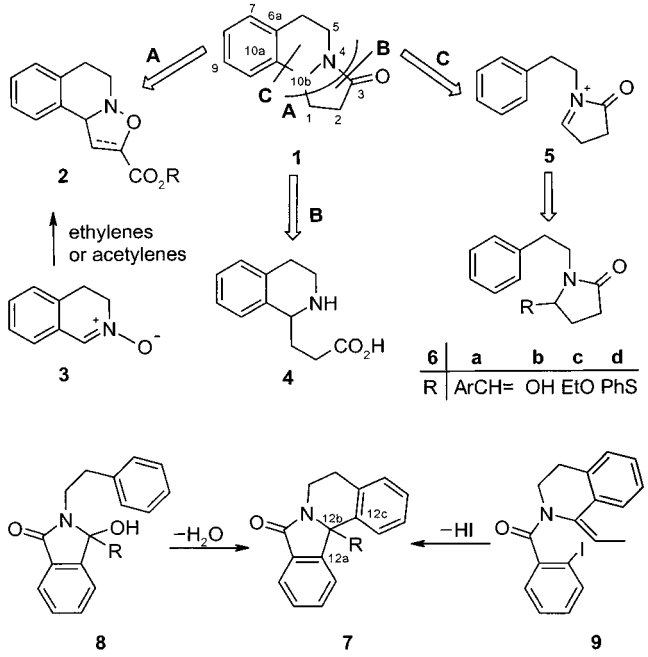
1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones **17a**,**b**, **17d**,**e**, and 5,12b-dihydroisoindolo-[1,2-*a*]isoquinolin-8(6*H*)-ones **22a**−**e** were prepared by intramolecular cyclizations of 1-(2-arylethyl)-5-benzotriazolyl-pyrrolidin-2-ones **15a**,**b**, **15d**,**e**, and 3-benzotriazolyl-2-(2-arylethyl)-1-isoindolinones **20a**−**e**, respectively, in the presence of titanium chloride. Products from chiral amines were obtained with stereoselectivities of ≥94%.

## Introduction

Our ongoing work with 5-(benzotriazolyl)pyrrolidin-2-ones[1] has now led to novel routes to the polycyclic ring system 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones **1** and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones **7**, both of which are of interest as components of natural products and biologically active compounds.

Three main routes have been reported for the preparation of **1** (Scheme 1): (A) C3−N4 bond formation via the reduction of the intermediates **2**, obtained by 1,3-dipolar cycloadditions of nitrones **3** with electron-deficient ethylenes[2] or acetylenes;[3] (B) C3−N4 bond formation by the intramolecular condensation of **4** with the elimination of $H_2O$;[4] and most importantly (C) C10a−C10b bond formation from the cyclization of a transient *N*-acyliminium ion, generated by protonation of the C−C double bond of an enamide **6a**[5] or by the elimination of a hydroxy group from **6b**,[6] ethoxy group from **6c**,[7] or phenylthio group from **6d**.[8] In a recent paper, treatment of amido-substituted thioacetals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) afforded five-membered alkylthio-substituted lactams **6** (R = $CH_3S$, EtS, or PhS) as transient intermediates, which subsequently cyclized with the tethered aromatic ring to produce an azapolycyclic ring system *via N*-acyliminium ion **5**.[9] Ring system **7** has been produced by the acid-catalyzed cyclodehydration of α-hydroxy lactams **8**[6e,10] or by the catalytic cyclization of enamides **9**.[11]

**Scheme 1**

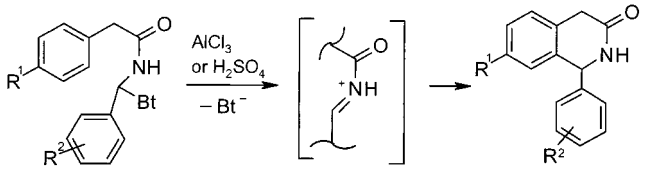



Most of the reported methods need at least three steps to reach the fused ring systems **1** or **7**. Our research

(1) Katritzky, A. R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* **2000**, *65*, 4364.
(2) Burdisso, M.; Gamba, A.; Gandolfi, R. *Tetrahedron* **1988**, *44*, 3735.
(3) (a) Huisgen, R.; Seidl, H. *Tetrahedron Lett.* **1963**, *29*, 2019. (b) Seidl, H.; Huisgen, R. *Tetrahedron Lett.* **1963**, *29*, 2023.
(4) (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S. *Bull. Chem. Soc. Jpn.* **1974**, *11*, 1023. (b) Orito, K.; Matsuzaki, T.; Suginome, H. *Heterocycles* **1988**, *27*, 2403.
(5) Burnett, D. A.; Hart, D. J. *J. Org. Chem.* **1987**, *52*, 5662.
(6) (a) Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, *40*, 3797. (b) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park. H. *J. Org. Chem.* **1995**, *60*, 7149. (c) Collado, M. I.; Lete, E.; Sotomayor, N.; Villa, M. J. *Tetrahedron* **1995**, *51*, 4701. (d) Fontaine, H.; Baussanne, I.; Royer, J. *Synth. Commun.* **1997**, *27*, 2817. (e) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080. (f) Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 7841.
(7) (a) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. L.; Olofson, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 2487. (b) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S. *J. Org. Chem.* **1986**, *51*, 1341. (c) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *Synth. Commun.* **1995**, *25*, 1947. (d) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.
(8) Padwa, A.; Waterson, A. G. *Tetrahedron Lett.* **1998**, *39*, 8585.
(9) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235.
(10) (a) Hitchings, G. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1757. (b) Winn, M.; Zaugg, H. E. *J. Org. Chem.* **1968**, *33*, 3779. (c) Alonso, R.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1985**, *26*, 2925.
(11) Grigg, R.; Sridharan, V.; Stevenson, P. *Tetrahedron* **1990**, *46*, 4003.

10.1021/jo001273f CCC: $20.00 
Published on Web 12/07/2000

**Scheme 2**



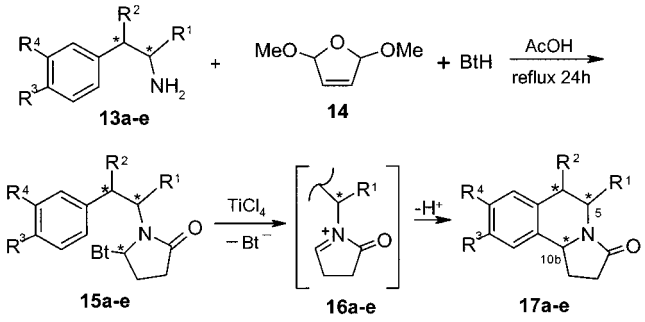

group previously reported intramolecular cyclizations of *N*-(α-benzotriazolylalkyl)arylacetamides **10** (readily obtained from benzotriazole, an amide and an aldehyde[12]) to 1-aryl-1,4-dihydro-3-isoquinolinones **12**.[13] These reactions involve *N*-acyliminium cation **11** formed by loss of benzotriazolyl anion from **10** in the presence of $AlCl_3$ or $H_2SO_4$ (Scheme 2). We now extend benzotriazole methodology to prepare in two steps the ring systems **1** and **7**, generally in good yields.

## Results and Discussion

**Syntheses of 1-(2-Arylethyl)-5-(benzotriazolyl)-pyrrolidin-2-ones 15a,b and 15d,e.** 1-(2-Arylethyl)-5-(benzotriazolyl)pyrrolidin-2-ones **15a**,**b** and **15d**,**e** were readily prepared by intermolecular condensations of 2-arylethylamines **13**, 2,5-dimethoxy-2,5-dihydrofuran (**14**), and benzotriazole in refluxing acetic acid (Scheme 3). However, no detectable amount of **15c** was isolated; instead, reaction of **13c**, **14**, and benzotriazole directly gave the cyclized product **17c** in 92% yield, as discussed in the following paragraphs. The nucleophilic replacement of the Bt group from analogues of **15** with allylsilanes, organozinc reagents, and triethyl phosphite was found to give novel 1,5-disubstituted pyrrolidin-2-ones in good to excellent yields.[1] The $^1$H NMR and $^{13}$C NMR spectra show that **15a**,**b** and **15d**,**e** are mixtures of $Bt^1$ and $Bt^2$ isomers. As well established,[14] $Bt^1$ and $Bt^2$ are both good leaving groups in the presence of Lewis acids, e.g., $ZnBr_2$, $AlCl_3$, $TiCl_4$, and $BF_3$ etc., and the removal of benzotriazolyl groups from $Bt^1$ and $Bt^2$ isomers results in the same iminium cation **16**, which can be attacked by nucleophiles to give the same products. Therefore, the crude intermediates **15a**,**b** and **15d**,**e** were used directly as mixtures of $Bt^1$ and $Bt^2$ isomers for the subsequent cyclizations.

**Syntheses of 1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]-isoquinolin-3(2*H*)-ones 17 via the Cyclizations of 15.** Treatment of 1-(2-arylethyl)-5-(benzotriazolyl)pyrrolidin-2-ones **15a**,**b** or **15d**,**e** with 1.5 equiv of $TiCl_4$ in refluxing toluene for 24 h furnished 1,5,6,10b-tetrahydropyrrolo-[2,1-*a*]isoquinolin-3(2*H*)-ones **17a**,**b** or **17d**,**e** in good to excellent yields. In addition, **17c** was obtained by an one-pot reaction of **13c**, **14**, and benzotriazole (Scheme 3). The structures of **17a**−**e** were confirmed by $^1$H and $^{13}$C NMR spectra and HRMS analyses. The correct number of aromatic tertiary carbon peaks in $^{13}$C NMR spectra clearly shows that the cyclized products **17a**−**e** are formed.

**Scheme 3**




| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | **15**[a] | **17**[b] |
|---|---|---|---|---|---|---|
| **a** | H | H | H | H | 94 | 75 |
| **b** | H | H | OMe | H | 96 | 80 |
| **c** | H | H | OMe | OMe | [c] | 92[d] |
| **d** | (*S*)-$CO_2$Me | H | H | H | 78 | 83 |
| **e** | (*R*)-Me | (*S*)-OH | H | H | 95 | 40 |

[a] Yield for total $Bt^1$ and $Bt^2$ isomers based on the corresponding amine **13**. [b] Isolated yield based on the intermediate **15**. [c] No detectable amount of **15c** was isolated. Instead, an one-pot reaction of **13c**, **14** and BtH produced **17c** in 92% yield. [d] An isolated yield of 52% was obtained from a one-pot reaction of **13c** and **14** in the absence of BtH.

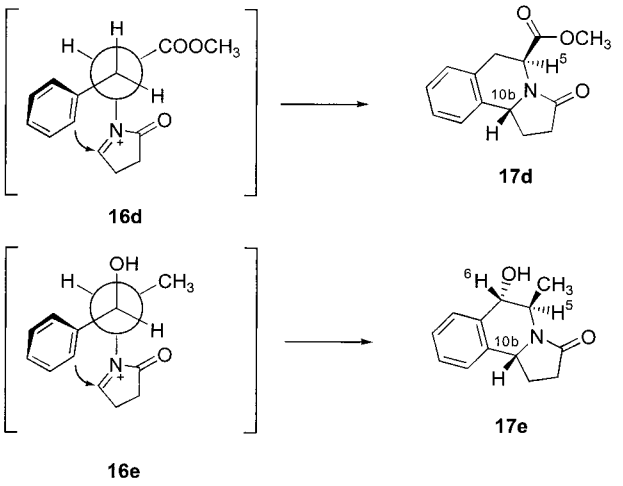
The yields of **17a**, **17b,** and **17c** (with none, one, and two methoxy groups, respectively, on the benzene ring) are 75%, 80%, and 92%, respectively: as expected, methoxy groups raise the electron densities of the benzene rings and facilitate their intramolecular nucleophilic attack on the iminium cations **16**. Although 8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (**17c**) was produced in one step with 52% yield in the absence of benzotriazole,[6d] its yield is increased to 92% (also in one step based on amine **13c**) using benzotriazole methodology. We believe that in the presence of benzotriazole, **15c** is also a transient intermediate, which readily eliminates the benzotriazole anion under the influence of acetic acid (similar role to a Lewis acid) to form the iminium cation **16c**.

When chiral amines **13d** and **13e** were used, the 5-position of pyrrolidin-2-one ring in **15d** and **15e** becomes a new chiral center. However, since the subsequent elimination of benzotriazolyl group from **15d** and **15e** in the presence of titanium chloride leads to identical iminium cations **16** despite possible different stereochemistry at the 5-position, it is not so important to determine the absolute configuration at the 5-position for **15d** and **15e**.

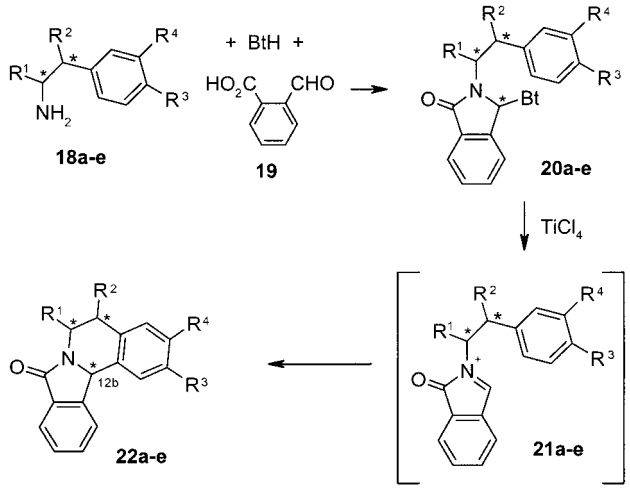
The 10b position of the cyclized product **17d**,**e** is also a new chiral center. After separation on column chromatography (silica gel), the $^1$H and $^{13}$C NMR spectra show that **17d** and **17e** were each obtained essentially as a single diastereomer; d.e. values of ca. 95% and 94%, respectively (determined by $^1$H NMR spectra). The absolute configuration at the 10b position for **17d** and **17e** was further determined by NOE experiments. When the hydrogen peak at 10b position of **17d** was irradiated, no significant NOE effect was observed for H(5). This

(12) Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339.
(13) Katritzky, A. R.; Lan, X.; Zhang, Z. *J. Heterocycl. Chem.* **1993**, *30*, 381.
(14) (a) Katritzky, A. R.; Qiu, G.; Yang, B. *J. Org. Chem.* **1997**, *62*, 8210. (b) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409. (c) Katritzky, A. R.; Qiu, G.; Yang, B.; He, H.-Y. *J. Org. Chem.* **1999**, *64*, 7618. (d) Katritzky, A. R.; Qiu, G.; He, H.-Y.; Yang, B. *J. Org. Chem.* **2000**, *65*, 3683.

**Scheme 4**




**Scheme 5**




| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | **20**[a] | **22**[b] |
|---|---|---|---|---|---|---|
| **a** | H | H | H | H | 94 | 50 |
| **b** | H | H | OMe | H | 96 | 65 |
| **c** | H | H | OMe | OMe | 94 | 75 |
| **d** | H | (*S*)-$CH_2OH$ | H | H | 92 | 60 |
| **e** | (*R*)-$CH_3$ | (*S*)-OH | H | H | 92 | 65 |

[a] Yield based on the corresponding amines **18**. [b] Isolated yield based on the intermediate **20**.

suggests that H(10b) and H(5) are located in a trans-orientation. For **17e**, H(6) appears as doublet at 5.06 ppm; H(5) as multiplet at 4.57 ppm. When H(5) at 4.57 ppm was irradiated, no NOE effect was observed between H(5) and H(10b) (multiplet at 5.66 ppm). However, irradiation of $CH_3$(5) (doublet at 0.76 ppm) caused a strong NOE effect for H(10b). These results prove the trans-orientation of H(5) and H(10b). Therefore, **17d** and **17e** were obtained as diastereomers with high de values, and this fact is rationalized in Scheme 4. Treatment of Bt intermediates **15d** and **15e** with titanium chloride leads to the transition states **16d** and **16e**. Because of the repulsion between the ester and the phenyl groups in **16d**, the ester group prefers to be located at the anti-position to the phenyl group and thus induces the phenyl group to attack the iminium cation in **16d** favorably from the anti-direction to the ester group and give the major diastereomer **17d**. Similarly, the methyl group induces the phenyl group to attack the iminium cation in **16e** from anti-direction to the methyl group. Thus, steric effects drive these reactions.

**Syntheses of 3-Benzotriazolyl-2-(2-arylethyl)-1-isoindolinones 20a−e.** The intermolecular condensations of 2-arylethylamines **18**, benzotriazole, and 2-carboxybenzaldehyde (**19**) in refluxing toluene using a Dean−Stark apparatus for 24 h generated 3-benzotriazolyl-2-(2-arylethyl)-1-isoindolinones **20a−e**. The $^1$H NMR and $^{13}$C NMR spectra also show that **20a−e** were obtained as mixtures of $Bt^1$ and $Bt^2$ isomers. On the basis of our previous work, crude intermediates **20a−e** could be used directly as mixtures of $Bt^1$ and $Bt^2$ isomers for the subsequent cyclizations.

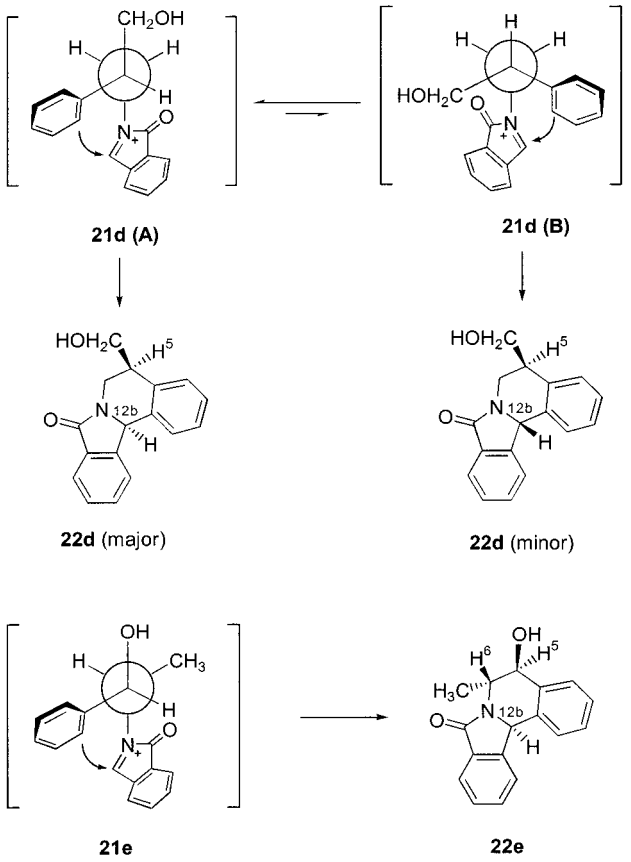
**Syntheses of 5,12b-Dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones 22a−e via the Cyclization of 20a−e.** Treatment of **20a−e** with 1.5 equiv of $TiCl_4$ in refluxing toluene produced 5,12b-dihydroisoindolo[1,2-*a*]-isoquinolin-8(6*H*)-ones **22a−e** in good yields (Scheme 5). The singlet peak for H(12b) (from 5.54 to 6.62 ppm) in $^1$H NMR spectra and the correct number for tertiary aromatic carbon peaks in $^{13}$C NMR spectra confirm the formation of the cyclized **22a−e**. As expected, the introduction of methoxy groups improves the yield from 50% (for **22a**) to 65% (for **22b**) and to 75% (for **22c**) due to their strong electron-releasing role.

When chiral amines **18d** and **18e** were used as starting materials, the final products **22d** and **22e** were isolated by column chromatography each essentially as a single diastereomer; d.e. values of ca. 98% and 99%, respectively (determined by $^1$H NMR spectra). For **22d**, although no strong NOE effect was observed between H(5) and H(12b), this does not reliably indicate their relative trans-configuration because of the long distance. As **22d** is an oil, its stereochemistry cannot be determined by X-ray analysis. However, according to Cram's rule, the conformation **A** in the transition state **21d** should be more stable than the conformation **B**, since strong repulsion between hydroxymethyl group and iminium cation ring exists in the conformation **B**. Cyclization of **21d** in the more stable conformation **A** would lead to the major product **22d** with H(5) and H(12b) cis (Scheme 6).

The absolute configuration of the new chiral center at the 12b-position for **22e** was determined by NOE experiments. When H(12b) (singlet at 6.22 ppm) was irradiated, no significant NOE effect was detected for H(6) (multiplet at 4.67 ppm), but a strong NOE effect was observed between H(12b) and the annular methyl group $CH_3$(6) (doublet at 0.94 ppm). These results demonstrate the trans-orientation of H(12b) and H(6) as shown in Scheme 6. This can also be explained by the attack of the iminium cation in **21e** by the phenyl group being favored from the anti-direction to the methyl group.

In summary, we have developed a simple and efficient route to the fused ring systems 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones **17a**,**b** and **17d**,**e** and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones **22a−e** by titanium chloride induced intramolecular cyclizations of 1-(2-arylethyl)-5-benzotriazolyl-pyrrolidin-2-ones **15a**,**b**, **15d**,**e,** and 3-benzotriazolyl-2-(2-arylethyl)-1-isoindolinones **20a−e** respectively, which are readily available in one step from 2-arylethylamines, benzotriazole and 2,5-dimethoxy-2,5-dihydrofuran (**14**) or 2-carboxybenzaldehyde (**19**).

**Scheme 6**




## Experimental Section

$^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in $CDCl_3$ (with TMS for $^1$H and $CDCl_3$ for $^{13}$C as the internal reference).

**General Procedure for the Preparation of 1-(2-Arylethyl)-5-(benzotriazolyl)pyrrolidin-2-ones 15a,b and 15d,e.** 2,5-Dimethoxy-2,5-dihydrofuran (**14**, 2.89 g, 22 mmol), an appropriate amine **13a**−**e** (22 mmol), and benzotriazole (5.81 g, 48 mmol) were dissolved in acetic acid (20 mL) and refluxed under $N_2$ for 24 h. After the mixture was cooled, 2 M NaOH (20 mL) was added and the mixture was extracted with $CH_2Cl_2$. The organic phase was dried over anhyd $Na_2SO_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (from 5:1 to 3:1) as an eluent to give **15a**,**b** and **15d**,**e** as mixtures of Bt$^1$ and Bt$^2$ isomers, which were further used for the subsequent cyclizations. However, the reaction of **13c**, **14** and benzotriazole did not afford **15c**, but directly produced **17c** in 92% yield.

**General Procedure for the Preparation of 1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones 17 via Cyclization of 15.** To a stirred solution of **15a**,**b** or **15d**,**e** (2 mmol, a mixture of Bt$^1$ and Bt$^2$ isomers) in toluene (20 mL) under $N_2$ was added $TiCl_4$ (3 mmol), and the reaction mixture was refluxed for 24 h. The cooled dark solution was quenched with 2 M NaOH (20 mL) and extracted with $CH_2Cl_2$. The combined organic layers were dried over anhyd $Na_2SO_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (7:3) as an eluent to give **17a**,**b** or **17d**,**e**.

In a separate reaction for **17c** without use of benzotriazole, 2,5-dimethoxy-2,5-dihydrofuran (**14**, 0.33 g, 2.5 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (**13c**, 0.45 g, 2.5 mmol) were added to acetic acid (10 mL) and refluxed under $N_2$ for 24 h. After cooling, $CH_2Cl_2$ was added and the organic phase was washed with 2 M NaOH and dried over anhyd $Na_2SO_4$. After removal of solvent in vacuo, the residue was separated by flash chromatography on silica gel using hexanes/EtOAc (7:3) as an eluent to give 8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (**17c**) in 52% yield. However, when the reaction was carried out in the presence of benzotriazole, the yield of **17c** was increased to 92% based on **13c** in one step.

**1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (17a):**[6b] yellow oil; $^1$H NMR $\delta$ 1.71−2.00 (m, 1H), 2.40−3.18 (m, 6H), 4.20−4.38 (m, 1H), 4.79 (t, $J$ = 7.6 Hz, 1H), 7.05−7.35 (m, 4H); $^{13}$C NMR 27.5, 28.5, 31.8, 37.0, 56.7, 124.8, 126.8, 126.9, 129.1, 133.5, 137.5, 173.2 (C=O).

**9-Methoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (17b):** yellow oil; $^1$H NMR $\delta$ 1.80−2.00 (m, 1H), 2.42−2.80 (m, 4H), 2.80−2.98 (m, 1H), 2.98−3.15 (m, 1H), 3.80 (s, 3H), 4.20−4.35 (m, 1H), 4.75 (t, $J$ = 7.7 Hz, 1H), 6.63 (s, 1H), 6.77 (dd, $J$ = 8.2, 2.5 Hz, 1H), 7.07 (d, $J$ = 8.5 Hz, 1H); $^{13}$C NMR 27.3, 27.6, 31.6, 37.1, 55.2, 56.8, 109.9, 112.5, 125.4, 129.9, 138.4, 158.3, 173.1 (C=O); HRMS calcd for $C_{13}H_{16}NO_2$ 218.1181 (M + 1), found 218.1158.

**8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (17c):** colorless needles (from $CHCl_3$/$Et_2O$); mp 104−105 °C (lit.[6d] mp 104 °C); $^1$H NMR $\delta$ 1.75−1.92 (m, 1H), 2.40−2.75 (m, 4H), 2.83−3.11 (m, 2H), 3.86 (s, 6H), 4.25−4.37 (m, 1H), 4.70−4.80 (m, 1H), 6.58 (s, 1H), 6.63 (s, 1H); $^{13}$C NMR $\delta$ 27.6, 27.9, 31.6, 36.9, 55.8, 55.9, 56.4, 107.5, 111.5, 125.4, 129.2, 147.8, 148.0, 173.0 (C=O); HRMS calcd for $C_{14}H_{18}NO_3$ 248.1287 (M + 1), found 248.1287.

**Methyl (5*S*,10b*R*)-3-Oxo-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-5-carboxylate (17d):** yellow oil; $[\alpha]^{25}_D$ = +0.1 (*c* 1.20, $CHCl_3$); $^1$H NMR $\delta$ 1.80−2.05 (m, 1H), 2.45−2.62 (m, 1H), 2.62−2.82 (m, 2H), 3.20−3.35 (m, 2H), 3.69 (s, 3H), 5.00−5.20 (m, 2H), 7.05−7.35 (m, 4H); $^{13}$C NMR $\delta$ 27.6, 30.5, 31.4, 49.2, 52.4, 54.7, 124.7, 127.1, 127.2, 129, 130.8, 136.6, 170.9, 173.7; HRMS calcd for $C_{14}H_{16}NO_3$ 246.1130 (M + 1), found 246.1129.

**(5*R*,6*S*,10b*R*)-6-Hydroxy-5-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (17e):** yellow oil; $[\alpha]^{25}_D$ = +4.3 (*c* 2.01, $CHCl_3$); $^1$H NMR $\delta$ 0.76 (d, $J$ = 7.2 Hz, 3H), 2.04−2.11 (m, 1H), 2.40−2.79 (m, 4H), 4.50−4.60 (m, 1H), 5.06 (d, $J$ = 5.7 Hz, 1H), 5.64−5.68 (m, 1H), 7.25−7.38 (m, 4H); $^{13}$C NMR $\delta$ 14.3, 27.6, 31.9, 54.3, 81.9, 90.7, 126.0, 126.2, 127.7, 128.3, 128.6, 137.2, 178.2 (C=O); HRMS calcd for $C_{13}H_{16}NO_2$ 218.1181 (M + 1), found 218.1183.

**General Procedure for the Preparation of 3-Benzotriazolyl-2-(2-arylethyl)-1-isoindolinones 20a−e.** 2-Carboxybenzaldehyde (**19**, 1.50 g, 10 mmol), an appropriate amine **18a**−**e** (10 mmol), and benzotriazole (1.79 g, 15 mmol) were dissolved in toluene and refluxed under $N_2$ for 24 h with a Dean−Stark apparatus. After cooling, the toluene was removed in vacuo. Then, 2 M NaOH (20 mL) was added, and the mixture was extracted with $CH_2Cl_2$. The combined organic layers were dried over anhyd $Na_2SO_4$. After removal of solvent in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (from 5:1 to 3:1) as an eluent to give **20a**−**e** as mixtures of Bt$^1$ and Bt$^2$ isomers, which were further used for the subsequent cyclizations.

**General Procedure for the Preparation of 5,12b-Dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones 22a−e via Cyclization of 20a−e.** To a stirred solution of **20a**−**e** (2 mmol, a mixture of Bt$^1$ and Bt$^2$ isomers) in toluene (20 mL) under $N_2$ was added $TiCl_4$ (3 mmol), and the reaction mixture was refluxed for 24 h. The cooled dark solution was quenched with 2 M NaOH (20 mL) and extracted with $CH_2Cl_2$. The combined organic layers were dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was separated by column chromatography (silica gel) with hexanes/EtOAc (7:3) as an eluent to give **22a**−**e**.

**5,12b-Dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (22a):** colorless needles; mp 114−116 °C (lit.[10b] mp 114−116 °C); $^1$H NMR $\delta$ 2.87−2.94 (m, 1H), 3.04−3.15 (m, 1H), 3.50−3.59 (m, 1H), 4.36−4.44 (m, 1H), 5.69 [s, 1H, H(12b)], 7.10−7.16 (m, 2H), 7.19−7.22 (m, 1H), 7.50 (dd, $J$ = 7.2, 7.2 Hz, 1H), 7.58−7.64 (m, 2H), 7.89 (dd, $J$ = 7.2, 7.2 Hz, 2H); $^{13}$C NMR $\delta$ 29.4, 38.3, 59.2, 123.5, 123.9, 125.1, 126.7, 127.5, 128.6, 129.2, 131.6, 132.7, 134.2, 134.7, 144.1, 168.2 (C=O).

**2-Methoxy-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (22b):** yellow oil; $^1$H NMR $\delta$ 2.83 (dt, $J$ = 15.6, 4.5 Hz, 1H), 2.95−3.05 (m, 1H), 3.44−3.82 (m, 1H), 3.82 (s, 3H), 4.36−4.44 (m, 1H), 5.64 [s, 1H, H(12b)], 6.79 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.10−7.16 (m, 2H), 7.50 (dd, $J$ = 7.2, 7.2 Hz, 1H), 7.61 (dd, $J$ = 7.2, 7.2 Hz, 1H), 7.85 (dd, $J$ = 7.5, 2.4 Hz, 2H); $^{13}$C NMR 28.5, 38.4, 55.4, 59.2, 111.4, 112.5, 123.4, 123.9, 126.8, 128.5, 130.1, 131.5, 132.8, 135.3, 144.0, 158.3, 167.9 (C=O); HRMS calcd for $C_{17}H_{16}NO_2$ 266.1181 (M + 1), found 266.1137.

**2,3-Dimethoxy-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (22c):** colorless needles (from diethyl ether); mp 172−173 °C (lit.[10c] mp 173 °C); $^1$H NMR $\delta$ 2.72−2.77 (m, 1H), 2.93−3.03 (m, 1H), 3.35−3.44 (m, 1H), 3.84 (s, 3H), 3.93 (s, 3H), 4.45−4.49 (m, 1H), 5.59 [s, 1H, H(12b)], 6.66 (s, 1H), 7.12 (s, 1H), 7.47 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.59 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.84 (dd, $J$ = 6.9, 6.9 Hz, 2H); $^{13}$C NMR $\delta$ 28.8, 38.0, 55.7, 56.0, 58.8, 108.5, 111.8, 122.9, 123.7, 125.8, 126.7, 128.2, 131.4, 132.5, 144.4, 147.6, 148.1, 167.7 (C=O).

**(5*S*,12b*S*)-5-(Hydroxymethyl)-5,12b-dihydroisoindolo-[1,2-*a*]isoquinolin-8(6*H*)-one (22d):** brown oil; $[\alpha]^{25}_D$ = −27.1 (*c* 1.32, $CHCl_3$); $^1$H NMR $\delta$ 2.95−3.14 (m, 2H), 3.86−3.92 (m, 1H), 4.03−4.14 (m, 1H), 4.20−4.28 (m, 1H), 4.72 (br s, 1H), 5.54 [s, 1H, H(12b)], 7.15−7.40 (m, 4H), 7.49 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.64 (dd, $J$ = 8.1, 8.1 Hz, 1H), 7.76 (d, $J$ = 7.5 Hz, 1H), 7.82 (d, $J$ = 7.5 Hz, 1H); $^{13}$C NMR $\delta$ 30.9, 53.1, 58.7, 65.7, 123.5, 124.0, 124.2, 126.6, 128.0, 128.2, 128.5, 131.3, 132.5, 133.9, 135.2, 142.5, 169.5 (C=O); HRMS calcd for $C_{17}H_{16}NO_2$ 266.1181 (M + 1), found 266.1173.

**(5*S*,6*R*,12b*S*)-5-Hydroxy-6-methyl-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (22e):** yellow oil; $[\alpha]^{25}_D$ = −8.0 (*c* 1.60, $CHCl_3$); $^1$H NMR $\delta$ 0.94 (d, $J$ = 7.2 Hz, 3H), 4.67 (dq, $J$ = 5.7, 5.7 Hz, 1H), 5.00 (d, $J$ = 5.7 Hz, 1H), 6.22 [s, 1H, H(12b)], 7.20−7.35 (m, 5H), 7.48 (dd, $J$ = 7.2, 7.2 Hz, 1H), 7.55 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.63 (d, $J$ = 7.2 Hz, 1H), 7.80 (d, $J$ = 7.2 Hz, 1H); $^{13}$C NMR $\delta$ 14.4, 55.1, 83.3, 89.4, 123.7, 123.9, 125.7, 127.4, 127.9, 130.0, 132.3, 132.8, 136.5, 143.9, 173.1 (C=O); HRMS calcd for $C_{17}H_{16}NO_2$ 266.1181 (M + 1), found 266.1194.

JO001273F