DOI: 10.1002/adsc.200800691

Synthesis of 2,6-Dioxo-1,2,3,4,5,6-hexahydroindoles by Acid-Catalyzed Cyclization of Acetal-Protected (2,4-Dioxocyclohex-1-yl)acetamides and their Transformation into 5,8,9,10-Tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones

Benard Juma,[a] Muhammad Adeel,[a] Alexander Villinger,[a] Helmut Reinke,[a] Anke Spannenberg,[b] Christine Fischer,[b] and Peter Langer[a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax: (+49)-381-498-6412; e-mail: peter.langer@uni-rostock.de
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

Received: November 9, 2008; Published online: February 2, 2009

Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday.

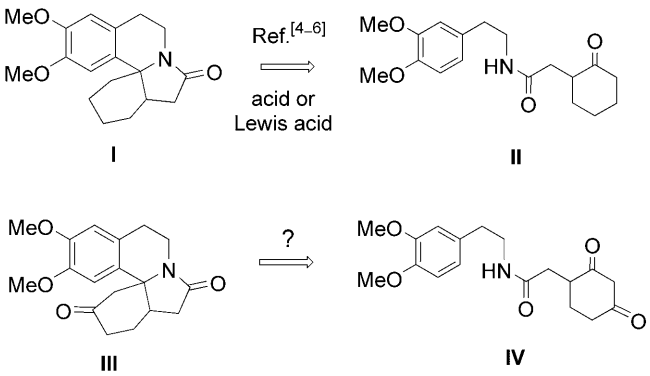
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800691.

Abstract: Acetal-protected (2,4-dioxocyclohex-1-yl)-acetic acids were prepared by allylation of dilithiated 1,3-cyclohexane-1,3-diones, protection of the carbonyl groups and oxidation of the alkene moiety. Their reaction with amines afforded the corresponding amides which were transformed, by acid-catalyzed cyclization, into various 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles. The reaction of the latter with triflic acid resulted in the formation of novel 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones.

Keywords: alkaloids; amides; C–C bond formation; cyclization; nitrogen heterocycles

Introduction

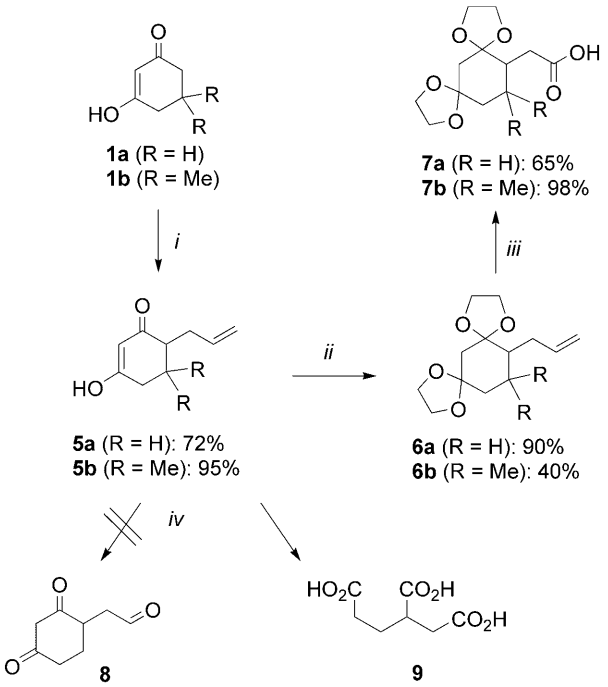
Erythrina alkaloids occur in various tropical and subtropical plants[1] and show a wide range of interesting biological properties.[2] This includes, for example, curare-like, hypotensive, sedative, anticonvulsive, and CNS-depressive activity.[3] *Erythrina* alkaloids have been prepared, for example, using photochemical [2+2]cycloadditions or Diels–Alder reactions as the key steps.[4] An important strategy for the synthesis of *Erythrina* alkaloids relies on the acid-catalyzed domino reaction of (2-oxocyclohex-1-yl)acetic amides.[4–6] This transformation proceeds by acid-catalyzed cyclization of the amide to give an *N*-(2-arylethyl)-2-oxo-1,2,3,4,5,6-hexahydroindole which is transformed *in situ* into the *Erythrina*-type spirocyclic product by a Pictet–Spengler reaction. For example, spirocycle **I** has been directly prepared from the amide **II** under various conditions (use of acids or Lewis acids) (Scheme 1). Despite its utility, the preparative scope of this reaction is very narrow and its success strongly depends on the structure of the substrate (substitution pattern of the aryl group, length of the linker between the aryl group and the nitrogen atom, etc.). This is a severe limitation because the synthesis of specific target molecules heavily relies on functional group transformations of the spiro compounds obtained by the domino process.



Scheme 1. Strategy for the synthesis of the novel *Erythrina*-type spiro-compound **III** containing an additional carbonyl group.

To address this problem, we planned to prepare the unknown *Erythrina* derivative **III**, which contains an additional carbonyl group, from the corresponding amide **IV** (Scheme 1). The carbonyl group of **III** was expected to be a useful tool for the synthesis of *Erythrina*-type natural products and their non-natural analogues. It was planned to prepare the required starting material **IV** from (2,4-dioxocyclohex-1-yl)acetic acid which, therefore, represents an important key intermediate of the present study.

Recently, we have reported[7] preliminary results related to the synthesis of (2,4-dioxocyclohex-1-yl)acetic amides, such as **IV**. Their cyclization, in the presence of catalytic amounts of *para*-toluenesulfonic acid (PTSA), resulted in the formation of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles rather than the expected *Erythrina*-type spiro compounds. Herein, we report a full account of the preparative scope of this methodology which provides, to the best of our knowledge, the as yet most general approach to 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles.[8] In addition, we report for the first time the reaction of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles with triflic acid which results in the formation of novel 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones.



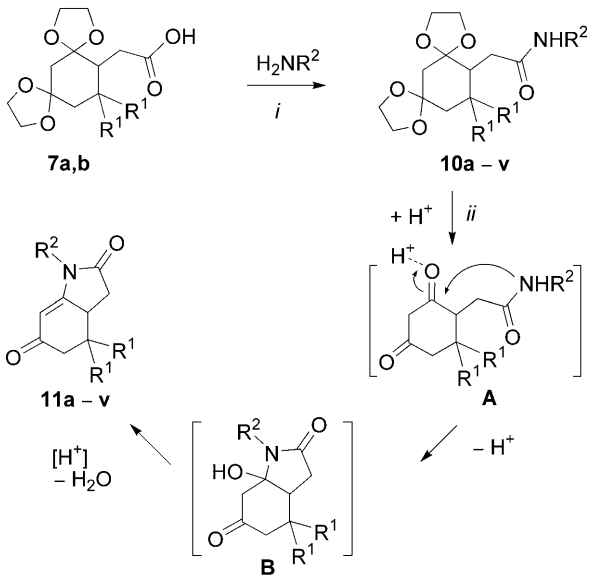
Scheme 2. Synthesis of **7a**,**b**. *Conditions: i*, 1) 2.5 equiv. LDA, HMPTA, THF, −78 °C, 1 h, 2) allyl bromide, −40 → 20 °C, 12 h. *ii*, $HO(CH_2)_2OH$, toluene, PTSA (6 mol%). *iii*, $NaIO_4$, $KMnO_4$, acetone. *iv*, 1) O_3, 2) Me_2S or other conditions (see text).

Results and Discussion

The synthesis of (2,4-dioxocyclohex-1-yl)acetic acid (**4**) has, to the best of our knowledge, not been reported to date. The synthesis of **4** proved to be very difficult in our hands, despite its structural simplicity. The reaction of the dianion[9,10] of cyclohexane-1,3-dione (**1**) with 1-bromo-2,2-diethoxyethane and epibromohydrin resulted in attack onto the carbon attached to the bromide and gave the corresonding products **2** and **3**, albeit, in low yields, respectively. The low yields can be explained by the β-oxygen effect. All attempts to prepare **4** by oxidation of **2** and **3** failed.

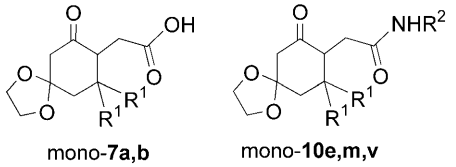
Deslongchamps and Guay reported the synthesis of 4-(3-oxopropyl)cyclopentane-1,3-dione by ozonolysis of 4-(homoallyl)cyclopentane-1,3-dione.[11] However, the ozonolysis of 4-allylcyclohexane-1,3-dione (**5a**), prepared by reaction of the dianion of **1a** with allyl bromide,[12] afforded the triacid **9** rather than the desired aldehyde **8** (Scheme 2). The triacid **9** was also isolated when the oxidation was carried out using $KMnO_4$, $KMnO_4/NaIO_4$ in acetone, or $KMnO_4/CuSO_4{\cdot}5H_2O$ in CH_2Cl_2/*t*-BuOH/H_2O. The formation of **9** can be explained by oxidative cleavage of the enolic double bond. The problem was solved by protection of the carbonyl groups of **5a** to give the bis(acetal) **6a**. The oxidation of **6a** by $KMnO_4/NaIO_4$ (in acetone) afforded the acid **7a**. Likewise, derivative **7b** was prepared in three steps from **1b**. The bis(acetal) **7a** can be deprotected to give the desired (2,4-dioxocyclohex-1-yl)acetic acid (**4**) which, however, proved to be unstable. Therefore, bis(acetals) **7a** and **b** were used directly for all further transformations.

The DCC-mediated reaction of **7a** and **b** with various amines afforded the amides **10a–v** (Scheme 3,



Scheme 3. Synthesis of **11a–v**. *Conditions: i*, 1) DCC, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 0 °C, then 12 h, 20 °C, 2) R^2NH_2, 2 h, 20 °C. *ii*, PTSA (2–7 mol%), acetone, 6 h, reflux.

Table 1. Synthesis of **11a–v**.



10, **11**	R^1	R^2	% [**10**][a]	% [**11**][a]
a	H	H	62	90
b	H	*n*-Hept	57	64
c	H	*i*-Bu	76	81
d	H	*c*-Pr	65	51
e	H	*c*-Pent	86[b]	91
f	H	*c*-Hex	46	73
g	H	Allyl	65	93
h	H	$PhCH_2$	67	86
i	H	$(4\text{-}ClC_6H_4)CH_2$	79	71
j	H	Ph(Me)CH	–	49[c]
k	H	$Ph(CH_2)_2$	64	85
l	H	$[2\text{-}(MeO)C_6H_4](CH_2)_2$	–	45[c]
m	H	$[3\text{-}(MeO)C_6H_4](CH_2)_2$	89[b]	53
n	H	$[4\text{-}(MeO)C_6H_4](CH_2)_2$	85	72
o	H	$[3,4\text{-}(MeO)_2C_6H_3](CH_2)_2$	64	65
p	H	$HO(CH_2)_2$	73	83
q	H	Ph	70	78
r	Me	$[3\text{-}(MeO)C_6H_4]CH_2$	–	43[c]
s	Me	$[3,4\text{-}(MeO)_2C_6H_3]CH_2$	–	86[c]
t	Me	$[2\text{-}(MeO)C_6H_4](CH_2)_2$	–	58[c]
u	Me	$[4\text{-}(MeO)C_6H_4](CH_2)_2$	90	84
v	Me	$[3,4\text{-}(MeO)_2C_6H_3](CH_2)_2$	74[b]	65

[a] Yields of isolated products.
[b] These products were prepared from mono-**7a**, **b** and were isolated in the form of mono-**10e**, **m**, **v** (structures see above).
[c] Overall yield based on **7a**, **b**.

Table 1). Reflux of an acetone solution of **10a–v** in the presence of catalytic amounts of *para*-toluenesulfonic acid (PTSA, 2–7 mol%) afforded the 2,6-dioxo-1,2,3,3a,4,5-tetrahydroindoles **11a–v**. The formation of an *Erythrina*-type spiro compound, such as **III** (see Scheme 1), was *not* observed. The formation of **11a–v** presumably proceeds by acid-catalyzed deacetalization and subsequent acid-catalyzed attack of the nitrogen atom onto the neighboring carbonyl group and extrusion of water. In contrast to all other products, **11e, m** and **v** were prepared from mono-**10e**, **m** and **v** containing only one (rather than two) acetal groups. The amides mono-**10e**, **m** and **v** were prepared from the corresponding acids (mono-**7a,b**). The latter are available by acetalization of **5a** and **b** using only one (rather than two) equivalents of glycol.

The structures of all products were established by spectroscopic methods. The structures of **10o**, **11o**, and **11e** were independently confirmed by X-ray crystal structure analyses (Figure 1 and Figure 2).[13]

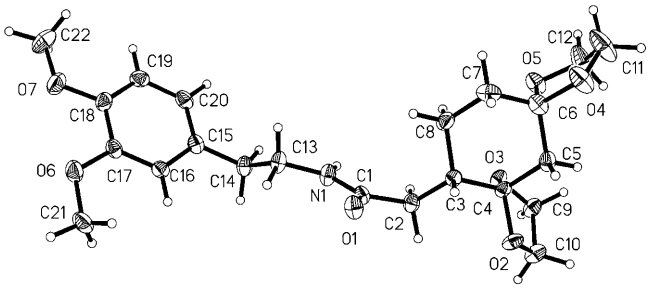


Figure 1. ORTEP plot of **10o** (50% probability level).

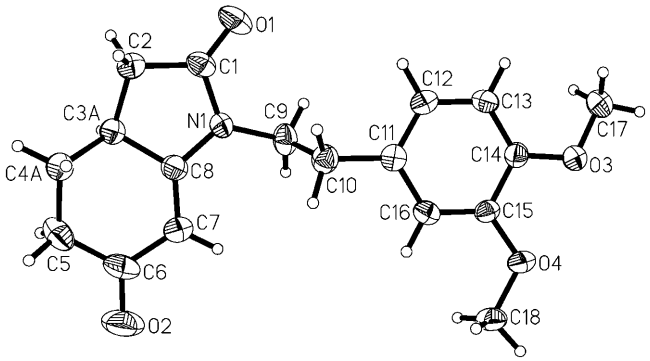
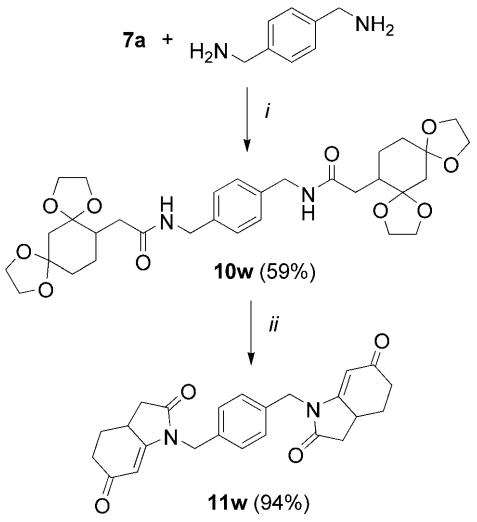


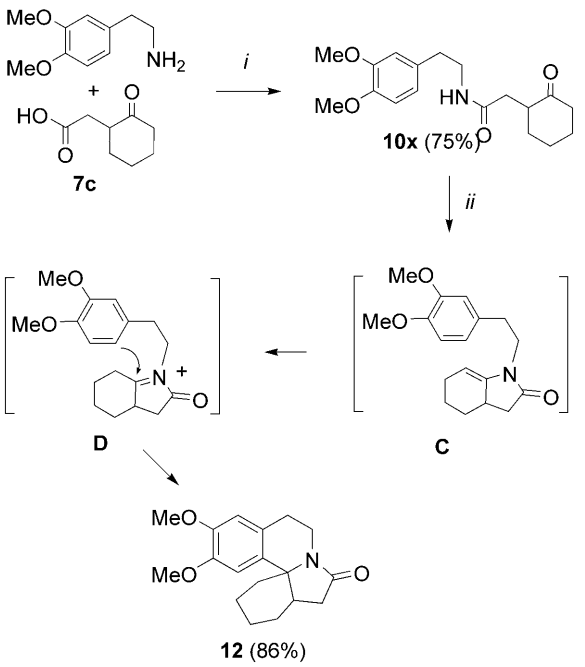
Figure 2. ORTEP plot of **11o** (50% probability level).

The reaction of **7a** with 1,4-bis(aminomethyl)benzene afforded the bis(amide) **10w** which was transformed, by two-fold acid-catalyzed cyclization, into the bis(2,6-dioxo-1,2,3,3a,4,5-tetrahydroindole) **11w** (Scheme 4).

For comparison, we studied the PTSA-catalyzed cyclization of amide **10x** which contains only one car-



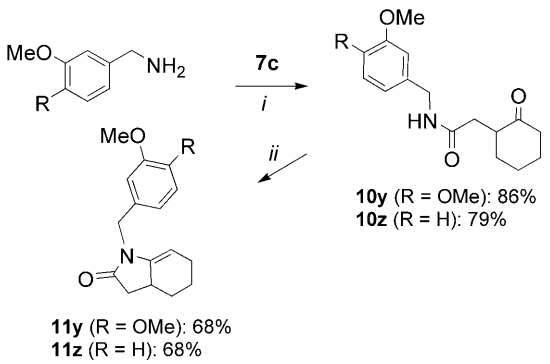
Scheme 4. Synthesis of **11w**. *Conditions: i*, 1) DCC, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 0 °C, then 12 h, 20 °C, 2) RNH_2, 2 h, 20 °C. *ii*, PTSA (10 mol%), acetone, 6 h, reflux.



Scheme 5. Synthesis of **12**. *Conditions: i*, 1) DCC, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 0 °C, then 12 h, 20 °C, 2) RNH_2, 2 h, 20 °C. *ii*, PTSA (2 mol%), acetone, 6 h, reflux.

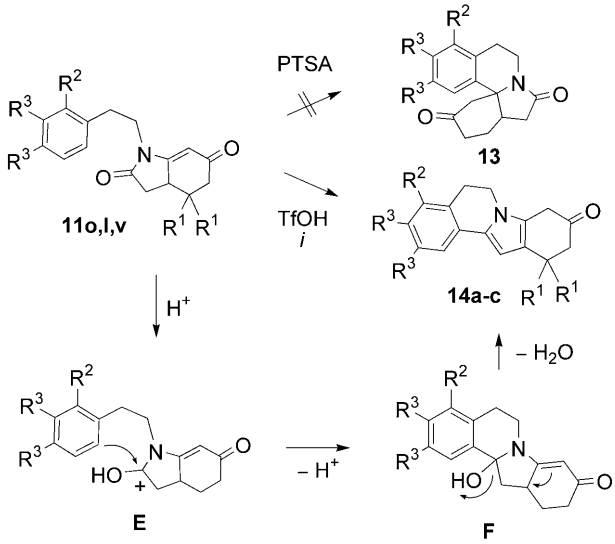
bonyl group (Scheme 5). Amide **10x** was prepared by DCC-mediated reaction of 2-(3,4-dimethoxyphenyl)-ethylamine with the known acid **7c**.[14] The reaction of **10x** with PTSA afforded the *Erythrina*-type spiro compound **12** in excellent yield. Tietze and co-workers recently reported the synthesis of **12** by $AlMe_3$/In-$(OTf)_3$-mediated reaction of 2-(3,4-dimethoxyphenyl)ethylamine with the ethyl ester of **7c**.[5] The formation of **12** can be explained, as outlined in the introduction, by acid-catalyzed reaction of the keto group with the electron-rich phenyl group to give intermediate **C**, protonation of the enamine moiety to give iminium salt **D**, and subsequent Pictet–Spengler reaction. It is important to note that this reaction is not general: The reaction of PTSA (2 mol%) with amides **10y** and **z**, which were again prepared from **7c** in good yields, afforded the 2-oxo-1,2,3,4,5,6-hexahydroindoles **11y** and **z** rather than the expected spirocyclic products (Scheme 6). This result can be explained by the higher strain of a 5,5,6- compared to a 5,6,6-spirocyclic system.

Our next plan was to study the transformation of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles **11** into *Erythrina*-type spirocycles, such as **III**, under more forcing conditions. 2,6-Dioxo-1,2,3,4,5,6-hexahydroindoles **11** represent polyfunctionalized heterocycles containing an enone, enamine, and lactam moiety. In principle, a nucleophilic attack might occur at the enone moiety (1,2- or 1,4-addition) or at the amide group. Protonation of the enamine moiety might result in the formation of an iminium ion which might be subsequently attacked by a nucleophile.



Scheme 6. Synthesis of **11y**,**z**. *Conditions: i*, 1) DCC, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 0 °C, then 12 h, 20 °C, 2) RNH_2, 2 h, 20 °C. *ii*, PTSA (2 mol%), acetone, 6 h, reflux.

Heating of 2,6-dioxo-1,2,3,4,5,6-hexahydroindole **11o** in the presence of PTSA for an extended period of time (48 h) or using stoichiometric amounts of PTSA did not result in any conversion. Therefore, we chosed triflic acid (TfOH) as a more reactive reagent. The reaction of **11o**, **l** and **v** with triflic acid (TfOH) afforded the 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones **14a–c** rather than the *Erythrina*-type spirocycles **13** (Scheme 7, Table 2). The formation of **14a–c** can be explained by protonation of the amide oxygen atom to give the cationic intermediate **E**, cyclization *via* the electron-rich aryl group (intermediate **F**), and subsequent extrusion of water and double bond migration. In contrast, the reaction of TfOH with **11k** resulted in the formation of a complex mixture. This result suggests that the cyclization is only possible for substrates containing an electron-rich



Scheme 7. Possible mechanism of the formation of **14a**. *Conditions: i*, TfOH, CH_2Cl_2, reflux, 4 h.

Table 2. Synthesis of **14a–c**.

11	14	R^1	R^2	R^3	% (**14**)[a]
o	**a**	H	H	OMe	84
l	**b**	H	OMe	H	32
v	**c**	Me	H	OMe	57

[a] Yields of isolated products.

phenyl group. This can be explained by the high reactivity of activated, electron-rich arenes in electrophilic substitution reactions. The reaction of TfOH with **11s** also gave a complex mixture. This can be explained by the higher strain of 5,5,6- compared to 5,6,6-tricyclic products.

Padwa and Wang have recently reported the TfOH-mediated transformation of a 2,6-dioxo-1,2,3,4,5,6-hexahydroindole into a 5,6-dihydroindolo-[2,1-*a*]isoquinolin-9-ol.[6,15] This reaction, which involves a cyclization, decarboxylation and an aromatization step, presumably proceeds by a mechanism similar to that suggested for the formation of 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones **14a–c**. The synthesis of 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones has, to the best of our knowledge, not been reported to date.[16]

In conclusion, we have reported the synthesis of the first (2,4-dioxocyclohex-1-yl)acetic amides. Their reaction with PTSA provides a general method for the synthesis of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles. The reaction of the latter with triflic acid afforded 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-9-ones rather than *Erythrina*-type spirocycles.

Experimental Section

General Remarks

Chemical shifts of the ^{1}H and ^{13}C NMR spectra are reported in parts per million using the solvent internal standard (chloroform, 7.26 and 77.0 ppm, respectively). Infrared spectra were recorded on an FT-IR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed using 60 A silica gel (60–200 mesh). All cyclization reactions were carried out in Schlenk tubes under an argon atmosphere. The bis(silyl enol ethers) were prepared as described in the literature. Crystallographic data were collected on a Bruker X8 Apex with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods using SHELXS-97 and refined against F^2 on all data by full-matrix least-squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically, all hydrogen atoms were refined in the model at geometrically calculated positions and refined using a riding model.

4-Allylcyclohexane-1,3-dione (5a)

To a THF solution (98 mL) of 1,3-cyclohexanedione **1a** (5.0 g, 44.6 mmol) and of anhydrous HMPA (20 mL) was added a THF solution of LDA which was prepared from *n*-BuLi (2.5 M solution in hexane, 40 mL, 98.2 mmol) and diisopropylamine at −78 °C. After stirring for 1 h, the reaction mixture was allowed to warm to −40 °C and 2-methylallyl bromide (4.1 mL, 44.6 mmol) was added rapidly. The mixture was slowly warmed to room temperature and stirred for additional 10 h at 20 °C. The reaction mixture was concentrated, diluted with hydrochloric acid (5%), and extracted with diethyl ether (3 × 100 mL). The organic layer was washed with hydrochloric acid (3%) and with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, heptanes/EtOAc = 1:1) to give **5a** as a pale yellow oil; yield: 5.90 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (m, 1H, C=CH), 5.45 (s, 1H, CH), 5.03 (m, 2H, C=CH_2), 2.67 (m, 3H, CH, CH_2), 2.43 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 1.7 (m, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (C=O), 189.5 (C=COH), 136.2 (C=CH), 117.9 (C=CH_2), 104.3 (CH), 41.9 (CH), 34.8 (CH_2), 30.2 (CH_2), 25.7 (CH_2); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3076 (m), 2934 (w), 2664 (w), 1598 (s, br), 1413 cm^{-1} (m); MS (GC, 70 eV): *m/z* (%) = 152 $[M]^+$ (13), 124 (16), 123 (27), 110 (46), 109 (24), 96 (26), 95 (52), 92 (10), 83 (42), 82 (62), 81 (33), 79 (15), 69 (22), 68 (56), 67 (100); HR-MS (EI, 70 eV): *m/z* = 152.08318, calcd. for $C_9H_{12}O_2$ $[M^+]$: 152.08367.

12-Allyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (6a)

A mixture of **5a** (6.08 g, 40.0 mmol), ethylene glycol (5.0 mL, 85.0 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 2.6 mmol, 6.5 mol%) in toluene (300 mL) was stirred under reflux for 4 h using Dean–Stark conditions. Approximately 1.6 mL of water were collected in the Dean–Stark trap. The toluene solution was washed with a saturated aqueous solution of $NaHCO_3$ (40 mL) and with brine (60 mL). The solution was dried ($MgSO_4$), filtered and the solvent of the filtrate was removed under vacuum. The residue was purified by chromatography (silica gel) to give **6a** as a colourless oil; yield: 3.65 g (18.6 mmol, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.92 (m, 1H, CH), 5.15 (m, 2H, CH_2), 4.06 (m, 8H, OCH_2), 2.58 (m, 1H, CH), 2.18–1.86 (m, 6H, CH_2), 1.69 (m, 2H, CH_2); ^{13}C NMR: ($CDCl_3$, 75.4 MHz): δ = 137.8 (C=CH), 116.1 (C=CH_2), 110.5 (C), 109.3 (C), 65.6 (OCH_2), 65.0 (OCH_2), 64.9 (OCH_2), 64.2 (OCH_2), 43.8 (CH), 43.1 (CH_2), 33.5 (CH_2), 32.7 (CH_2), 24.9 (CH_2); MS (GC, 70 eV): *m/z* (%) = 240 ($[M+1]^+$, 1), 157 (35), 154 (22), 139 (15), 138 (10), 126 (26), 125 (14), 113 (5), 99 (35), 87 (12), 86 (100), 55 (11), 42 (10); HRMS (EI, 70 eV): *m/z* = 240.13589, calcd. for $C_{13}H_{20}O_4$ $[M+1]^+$: 240.13561.

2-(1,4,8,11-Tetraoxadispiro[4.1.4.3]tetradec-12-yl)-acetic acid (7a)

To a stirred water solution (250 mL) of $NaIO_4$ (15.00 g, 196.0 mmol) and $KMnO_4$ (0.63 g, 3.9 mmol) was added an acetone solution (39 mL) of **6a** (2.30 g, 11.7 mmol). The solution was stirred at room temperature until a colour change

from violet to red was observed. The solution was then extracted with EtOAc (3×100 mL) and the combined organic layers were dried ($MgSO_4$). The solution was filtered and the filtrate was concentrated under vacuum to give **7a** as a light brown gummy substance which required no further purification; yield: 1.61 g (65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.09 (brs, 1H, COOH), 3.86 (m, 8H, OCH_2), 2.51 (dd, J=15.0, 4.5 Hz, 1H), 2.21 (m, 1H), 2.05 (dd, J=14.7, 8.1 Hz, 1H), 1.90 (dd, J=12.5, 1.8 Hz, 2H), 1.69 (m, 2H), 1.50 (brd, d, J=8.7, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 178.7 (C=O), 109.7 (C), 109.0 (C), 65.5 (OCH_2), 65.4 (OCH_2), 64.9 (OCH_2), 64.1 (OCH_2), 42.6 (CH_2), 40.9 (CH), 33.8 (CH_2), 33.5 (CH_2), 26.0 (CH_2); MS (EI, 70 eV): *m/z* (%) 258 $[M]^+$ (2), 215 (8), 172 (18), 157 (87), 152 (6), 144 (32), 128 (8), 113 (32), 100 (9), 99 (93), 87 (20), 86 (100), 85 (15), 83 (22); HR-MS (EI, 70 eV): *m/z*=258.109219, calcd. for $C_{12}H_{18}O_6$ $[M]^+$: 258.10979.

Typical Procedure for the Synthesis of Amides 10

To a CH_2Cl_2 solution (20 mL) of **7a** (200 mg, 0.8 mmol) was added *N*-hydroxysuccinimide (88 mg, 0.78 mmol) and dicyclohexylcarbodiimide (162 mg, 0.8 mmol) at 0°C and the mixture was stirred for 1 h at the same temperature. After stirring for 12 h, the mixture was filtered, 1-amino-2-phenylethane (0.01 mL, 0.85 mmol) was added to the filtrate and the mixture was stirred for 2 h. The mixture was filtered and washed for several times with water (50 mL for each washing). The organic layer was dried ($NaSO_4$), filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (silica gel, heptanes/EtOAc) to give **10k** as a colourless solid; yield: 180 mg (64%).

2-(1,4,8,11-Tetraoxadispiro[4.1.4.3]tetradec-12-yl)-acetamide (10a)

Starting with CH_2Cl_2 (40 mL), **7a** (340 mg, 1.3 mmol), *N*-hydroxysuccinimide (178.4 mg, 1.6 mmol), dicyclohexylcarbodiimide (328.8 mg, 1.6 mmol) and ammonia (25% aqueous solution, 0.12 mL, 1.6 mmol), **10a** was isolated as a white solid; yield: 210 mg (62%); mp 149–152°C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=5.81 (brs, 1H, NH), 5.69 (brs, 1H, NH), 3.89 (m, 8H, OCH_2), 2.46 (dd, J=14.5, 4.5 Hz, 1H, CH_2), 2.16 (m, 1H, CH), 1.98 (dd, J=8.5, 2.5 Hz, 1H, CH_2), 1.92 (dd, J=7.5, 5.3 Hz, 1H, CH_2), 1.77 (m, 2H, CH_2), 1.70 (br, J=13.8 Hz, 1H, CH_2), 1.53, (dd, J=11.0, 2.0 Hz, 1H, CH_2), 1.49 (dd, J=11.2, 2.7 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ_C=175.4 (NC=O), 109.7 (C), 108.6 (C), 65.0 (OCH_2), 64.7 (OCH_2), 64.6 (OCH_2), 63.9 (OCH_2), 42.3 (CH_2), 40.6 (CH), 35.0 (CH_2), 33.2 (CH_2), 25.8 (CH_2); IR (neat): $\tilde{\nu}$=3411 (w), 3175 (w), 2946 (w), 2966 (w), 2946 (w), 2880 (w), 1669 (s, br), 1625 cm^{-1} (m); MS (GC, 70 eV): *m/z* (%)=257 ($[M]^+$, 2), 214 (5), 212 (5), 199 (9), 171 (19), 157 (69), 143 (16), 127 (6), 113 (13), 99 (67), 87 (14), 86 (100); HR-MS (EI, 70 eV): *m/z*= 257.12577, calcd. for $C_{12}H_{19}O_5$ $[M]^+$: 257.125885.

General Procedure for the Synthesis of 11a–z

An acetone solution of amide **10** and of a catalytic amount (2–10 mol%) of *p*-toluenesulfonic acid (PTSA) was heated under reflux for 6 h. The solution was cooled to 20°C and concentrated under vacuum to give a solid residue which was purified by column chromatography (silica gel, heptanes/EtOAc).

3,3a,4,5-Tetrahydro-1*H*-indole-2,6-dione (11a): Starting with **10a** (70 mg, 0.27 mmol), PTSA (5 mg, 0.02 mmol) and dry acetone (40 mL), **11a** was isolated as a white solid; yield: 31 mg (90%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.05 (br, 1H, NH), 5.51 (d, J=2.0 Hz, 1H, CH), 3.14 (m, 1H, CH), 2.66 (dd, J=17.3, 8.8 Hz, 1H, CH_2), 2.49 (ddd, J= 17.3, 6.8, 2.3 Hz, 1H, CH_2), 2.38 (dd, J=13.3, 4.8 Hz, 1H, CH_2), 2.26 (dd, J=17.3, 8.8 Hz, 1H, CH_2), 2.24 (m, 1H, CH_2), 1.77 (ddd, J=27.3, 14.8, 6.3 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ=197.8 (C=O), 177.0 (NC=O), 165.3 (NC=C), 103.1 (CH), 37.4 (CH_2), 36.2 (CH), 35.4 (CH_2), 27.9 (CH_2); IR (neat): $\tilde{\nu}$=3098 (w), 2991 (w), 2950 (w), 2799 (w), 1746 (s, br), 1574 $cm^{<-M>1}$ (a, br); MS (GC, 70 eV): *m/z* (%)=151 ($[M]^+$, 51), 124 (7), 123 (100), 122 (7), 95 (35), 68 (16), 67 (21); HR-MS (EI, 70 eV): *m/z*=151.06278, calcd. for $C_8H_9O_2$ $[M]^+$: 151.063012.

2,3-Dimethoxy-5,8,10,11-tetrahydroindolo[2,1-*a*]isoquinolin-9(6*H*)-one (14a): A CH_2Cl_2 solution (16 mL) of **11o** (150 mg, 0.5 mmol) and of TfOH (0.7 mL) was heated under reflux for 4 h, cooled to room temperature, and quenched with water. The aqueous layer was extracted with $CHCl_3$ (3×80 mL) and the combined organic layers were dried ($MgSO_4$). The solution was filtered and the solvent of the filtrate was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, heptanes/EtOAc) to give **14a** as white crystals which proved to be unstable at room temperature; yield: 120 mg (84%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=6.91 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.18 (s, 1H), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.76 (dd, J=5.6, 5.3 Hz, 2H, NCH_2), 3.40 (s, 2H, CH_2), 2.90 (dd, J=5.5, 5.3 Hz, 2H, CH_2), 2.83 (dd, J=5.6, 5.5 Hz, 2H, CH_2), 2.61 (dd, J=5.4, 5.7 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ=207.6 (C=O), 147.3 (C, Ar), 146.3 (C, Ar), 129.3 (C), 122.7 (C), 121.5 (C, Ar), 121.3 (C, Ar), 116.0 (C), 110.3 (CH, Ar), 104.7 (CH, Ar), 99.3 (CH), 55.1 (OCH_3), 55.0 (OCH_3), 39.6 (CH_2), 39.1 (CH_2), 36.3 (CH_2), 27.6 (CH_2), 20.8 (CH_2); IR (neat): $\tilde{\nu}$=2961 (w), 2911 (w), 2857 (w), 2837 (w), 1711 (s, br), 1526 cm^{-1} (s); MS (EI, 70 eV): *m/z* (%)=297 ($[M]^+$, 100), 295 (15), 269 (41), 255 (11), 254 (56), 224 (7), 211 (6); HR-MS (ESI, 70 eV): *m/z*= 320.12542, calcd. for $C_{18}H_{19}NO_3$ $[M+Na]^+$: 320.12571, *m/z*=298.14340, calcd. for $[M+H]^+$: 298.14377.

1,4,5,10,11,12,13,13a-Octahydro-7,8-dimethoxy-2*H*-indolo-[7a,1-*a*]isoquinolin-2-one (12): The synthesis was carried out following the procedure as given for the synthesis of **14a**. Starting with **10x** (380 mg, 1.2 mmol), PTSA (5 mg, 0.02 mmol) and dry acetone (70 mL), **12** was isolated as a colourless viscous oil; yield: 309 mg (86%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=6.80 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.02 (ddd, J=13.3, 7.0, 3.3 Hz, 1H, NH), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.15 (ddd, J=15.8, 10.3, 5.8 Hz, 1H), 2.90 (ddd, J=16.5, 9.8, 7.3 Hz, 1H), 2.63 (m, 1H, CH), 2.50 (m, 1H, CH_2), 2.30 (brd, J=8.0 Hz, 2H, CH_2), 1.95 (m, 1H, CH_2), 1.80 (d, J=6.0 Hz, 1H, CH_2), 1.77 (d, J=5.5 Hz, 1H, CH_2), 1.69 (dd, J=10.0, 5.0 Hz, 1H, CH_2), 1.58 (m, 2H, CH_2), 1.46 (dd, J=10.3, 4.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ=174.2 (NC=O), 147.8 (C, Ar), 147.3 (C, Ar), 134.7 (C, Ar), 125.7 (C, Ar), 111.9 (CH, Ar), 108.2 (CH, Ar), 62.3 (C), 56.1 (OCH_3), 55.8 (OCH_3), 37.7 (CH),

36.5 (CH_2), 35.8 (CH_2), 34.9 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 20.6 (CH_2), 20.3 (CH_2); IR (neat): $\tilde{\nu}=2930$ (m), 2854 (w), 2250 (w), 2799 (m), 1673 (s, br), 1512 cm^{-1} (s); MS (GC, 70 eV): *m/z* (%) = 301 ($[M]^{+\cdot}$, 26), 259 (17), 258 (100), 245 (12), 244 (15), 216 (9), 67 (21); HR-MS (EI, 70 eV): *m/z* = 301.166580, calcd. for $C_{18}H_{23}NO_3$ $[M]^{+\cdot}$: 301.16725.

Acknowledgements

We are grateful for an experimental contribution by Mr. Olumide Fatunsin. Financial support from the Alexander-von-Humboldt Foundation (Georg-Forster scholarship for B. J.) is gratefully acknowledged.

References

[1] B. A. Krukoff, R. C. Barneby, *Mem. N. Y. Bot. Gard.* **1970**, *20*, 1.

[2] a) A. S. Chawla, V. K. Kapor, in: *Handbook of Plant and Fungal Toxicants*, (Ed.: J. F. D'Mello), CRC Press, New York, **1997**, p 37; b) A. J. Lehman, *J. Pharmacol.* **1937**, 69; c) M. Williams, J. L. Robinson, *J. Neurosci.* **1984**, *4*, 2906; d) M. W. Decker, D. J. Anderson, J. D. Brioni, D. L. Donnelly-Roberts, C. H. Kang, A. B. O'Neil, M. Piattoni-Kaplan, S. Swanson, J. P. Sullivan, *Eur. J. Pharmacol.* **1995**, 79.

[3] For reviews, see: a) V. Boekelheide, in: *The Alkaloids*, Vol. 7, (Ed.: R. H. F. Manske), Academic Press, New York, **1960**, p 201; b) R. K. Hill, in: *The Alkaloids*, Vol. 9, (Ed.: R. H. F. Manske), Academic Press, New York, **1967**, p 483; c) S. F. Dyke, S. N. Quessy, in: *The Alkaloids*, Vol. 18, (Ed.: R. G. A. Rodrigo), Academic Press, New York, **1981**, p 1; d) A. H. Jackson, in: *Chemistry and Biology of Isoquinoline Alkaloids*, (Eds.: J. D. Phillipson, M. F. Margaret, M. H. Zenk), Springer, Berlin, **1985**, p 62; e) A. S. Chawla, A. H. Jackson, *Nat. Prod. Rep.* **1984**, *1*, 371; for early original reports, see: f) K. Wiesner, Z. Valenta, A. J. Manson, F. W. Stonner, *J. Am. Chem. Soc.* **1955**, *77*, 675; g) V. Prelog, *Angew. Chem.* **1957**, *69*, 33; h) V. Prelog, A. Langemann, O. Rodig, M. Ternbah, *Helv. Chim. Acta* **1959**, *42*, 1301; i) A. Mondon, H. J. Nestler, *Angew. Chem.* **1964**, *76*, 651.

[4] a) P. C. Stanislawski, A. C. Willis, M. G. Banwell, *Org. Lett.* **2006**, *8*, 2143; b) A. Padwa, Q. Wang, *J. Org. Chem.* **2006**, *71*, 7391; c) A. K. Ganguly, C. H. Wang, D. Biswas, J. Misiaszek, A. Micula, *Tetrahedron Lett.* **2006**, *47*, 5539; d) S. Gao, Y. Q. Tu, X. Hu, S. Wang, R. Hua, Y. Jiang, Y. Zhao, X. Fan, S. Zhang, *Org. Lett.* **2006**, *8*, 2373; e) H. Fukumoto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Angew. Chem.* **2006**, *118*, 2797; *Angew. Chem. Int. Ed.* **2006**, *45*, 2731; f) J. H. Rigby, A. Cavezza, M. Heeg, *J. Am. Chem. Soc.* **1998**, *120*, 3664.

[5] L. F. Tietze, N. Tölle, C. Noll, *Synlett* **2008**, 525.

[6] A. Padwa, Q. Wang, *J. Org. Chem.* **2006**, *71*, 7391.

[7] B. Juma, M. Adeel, A. Villinger, P. Langer, *Tetrahedron Lett.* **2008**, *49*, 2272.

[8] For other syntheses of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles, see: a) Birch reaction: K. Ito, M. Haruna, H. Furukawa, *J. Chem. Soc. Chem. Commun.* **1975**, 681; b) aza-Claisen rearrangement of isoquinuclidines: Y. Chen, P. L. Huesmann, P. S. Mariano, *Tetrahedron Lett.* **1983**, *24*, 1021; c) Diels–Alder reaction of 2-imidofurans: A. Padwa, J. D. Ginn, *J. Org. Chem.* **2005**, *70*, 5197; d) A. Padwa, S. K. Bur, H. Zhang, *J. Org. Chem.* **2005**, *70*, 6833.

[9] a) N. M. Berry, M. C. P. Darey, L. M. Harwood, *Synthesis* **1986**, 476; see also: b) G. Vassilikogiannakis, I. Margaros, M. Tofi, *Org. Lett.* **2004**, *6*, 205.

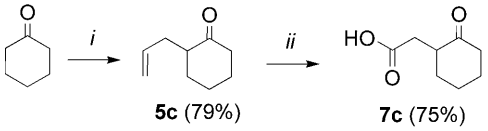
[10] For a recent review of dianions, see: P. Langer, W. Freiberg, *Chem. Rev.* **2004**, *104*, 4125, and references cited therein.

[11] B. Guay, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 6140.

[12] W. Zhang, G. Pugh, *Tetrahedron* **2003**, *59*, 4237.

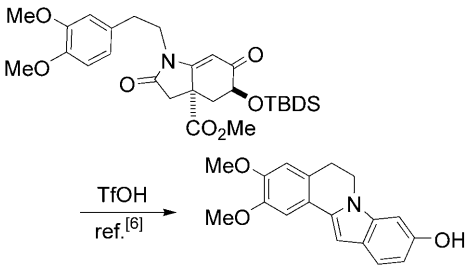
[13] CCDC 716534, CCDC 670738, and CCDC 716346 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[14] We have prepared **7c** by oxidation of 2-allylcyclohexanone (**5c**) which is readily available from cyclohexanone (see below). This approach to **7c** has, to the best of our knowledge, not yet been reported. For a different synthesis of **7c**, see for example: S. M. Allin, S. L. James, M. R. Elsegood, W. P. Martin, *J. Org. Chem.* **2002**, *67*, 9464.



Conditions: i, 1) LDA, HMPTA, THF, 78 °C, 1 h, 2) allyl bromide, –40 to 20 °C, 12 h; ii, NaIO4, KMnO4, acetone.

[15] The following reaction has been reported by Padwa and Wang (ref.[6]).



[16] For related heterocycles, such as 5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-11-ones, see: a) H. Meyer, *Liebigs Ann. Chem.* **1981**, 1534; b) Z. Vincze, P. Nemes, 'B. Balazs, G. Toth, P. Scheiber, *Synlett* **2004**, 1023; c) M. Menes-Arzate, R. Martinez, R. Cruz-Almanza, J. M. Muchowski, Y. M. Osornio, L. D. Miranda, *J. Org. Chem.* **2004**, *69*, 4001.

