Diastereoselective Alkylation of Tricyclic Lactim Ethers[‡]

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Dedicated to Professor Ekkehard Winterfeldt, on the occasion of his 70th birthday

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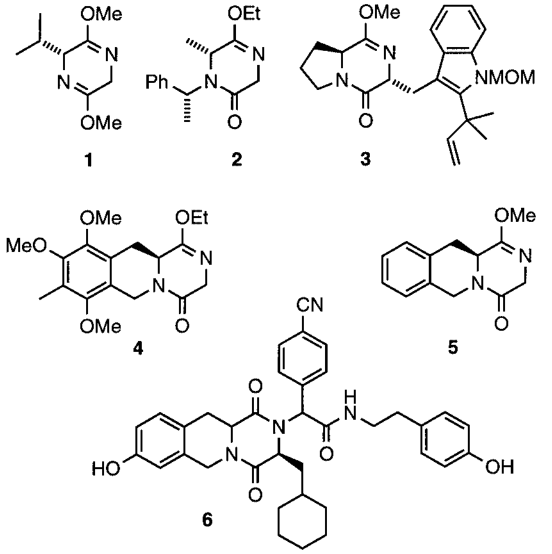
Alkylations of tricyclic 1-methoxy-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (**5**) were studied under various conditions. The highest conversions were obtained when LDA or LHMDS were used for the deprotonation step. The diastereoselectivity turned out to be highly dependent on the electrophile. While methyl iodide, isobutyl bromide, 4-methylpent-3-enyl bromide, and isopropyl bromide yielded mixtures of *trans* and *cis* diastereomers **10** and **11**, respectively, allyl bromide, 3-methylbut-2-enyl bromide, and benzyl bromide yielded the *trans*-product **10** with high diastereoselectivity. X-ray crystal structures of **5** and its synthetic precursor **9** were determined. The alkylated lactim ethers **10a**,**c**,**g** and **11a**–**c** were converted into the corresponding dioxopiperazines **12a**,**c**,**g** and **13a**–**c** in high yields.

Introduction

Since its introduction in 1981 the Schöllkopf bis(lactim ether) **1** has proved to be a powerful chiral auxiliary for the synthesis of α-amino acids (Scheme 1).[1,2] Deprotonation of the bis(lactim ether) and subsequent reaction with various electrophiles afforded the corresponding 5-substituted 2,5-dihydro-3,6-dimethoxypyrazines with high diastereoselectivities.[3] In contrast, the reactions of carbanions derived from mono(lactim ethers) have received much less attention. Sammes, for example, reported the conjugate addition of allylic sulfones to *N*-benzyllactim ethers in studies towards the synthesis of the antibiotic dioxopiperazine bicyclomycin.[4] However, no details concerning the diastereoselectivity were given. Sandri studied mono- and dialkylations, and also aldol reactions, of carbanions derived from lactim ethers **2**.[5] Although Williams utilized the *epi*-deoxybrevianamide E derivative **3** in the biomimetic total synthesis of the alkaloid UM 55599, the starting material **3** was prepared by cyclocondensation from tryptophan precursors rather than by diastereoselective alkylation of a cyclic lactim ether.[6−8] Fukuyama observed the formation of a single *trans* diastereomer upon alkylation of tricyclic lactim ether **4**.[9] This lack of information about bi- or tricyclic lactim ethers prompted us to study their alkylation more systematically. In particular, these lactim ethers can be easily converted into the corresponding 2,5-dioxopiperazines and thus serve as building blocks for natural products such as spirotryprostatins A and B,[10] tryprostatins A and B,[3b] fumitremorgins,[3b] ditryptophenaline,[11] and asperazine.[12] We were particularly interested in a concise approach to the ABC ring system of quinocarcin. Thus, tricyclic lactim ether **5** was used as a model system for the study of such alkylations, the results of which are described below.[13] In



Scheme 1

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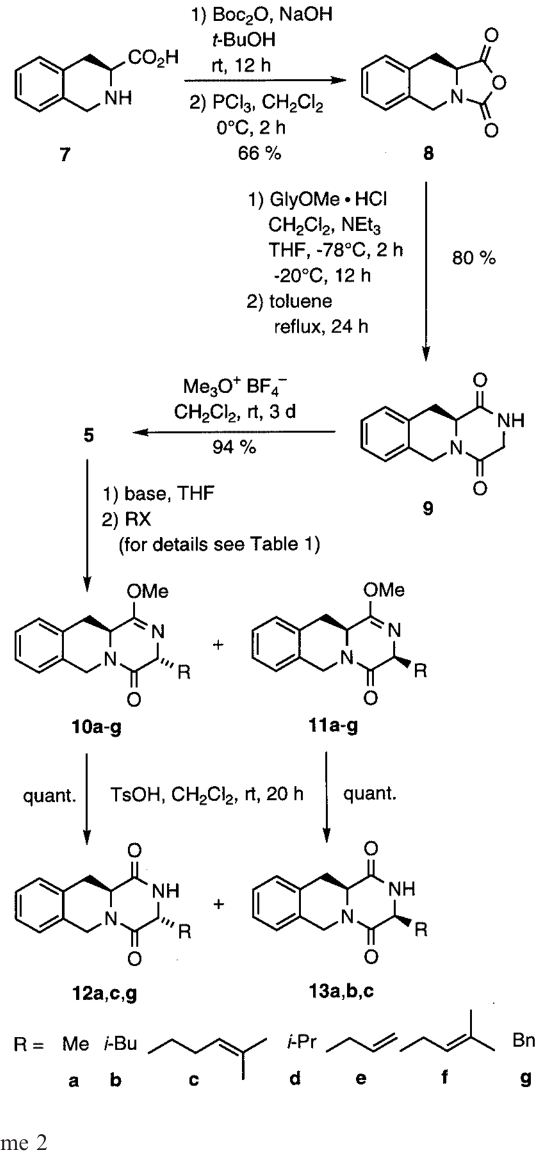
addition, the alkylation of **7** should provide convenient access to analogues of **6**, which has recently been identified as a potent inhibitor of fructose-1,6-biphosphatase.[14]

Results and Discussion

As shown in Scheme 2, enantiomerically pure L-tetrahydroisoquinolinecarboxylic acid **7**, obtained from L-phenylalanine by Pictet−Spengler cyclization,[15] was converted into the known *N*-Boc-protected derivative.[16] Further treatment with phosphorus trichloride[17] provided the anhydride **8** in 66% overall yield. Reaction of compound **8** with glycine methyl ester hydrochloride in the presence of triethylamine, followed by heating in toluene,[3b] afforded the tricyclic dioxopiperazine **9** in 80% yield. Upon treatment of **9** with Meerwein's salt, the desired mono(lactim ether) **5** was obtained in 94% yield.

An X-ray crystal structure determination of dioxopiperazine **9** revealed the presence in the solid state of hydrogen-bonded dimers (Figure 1).[18] The O···O bond lengths of the hydrogen bonds are 2.817 and 2.912 Å and the O−H···O angles are 174 and 173°. An X-ray crystal structure of **5** was also obtained (Figure 2).[18] From inspection of the latter structure it was not obvious whether the slight twisting of the tetrahydroisoquinoline moiety with respect to the lactim ether ring would provide sufficient steric control during the alkylation step.



Scheme 2

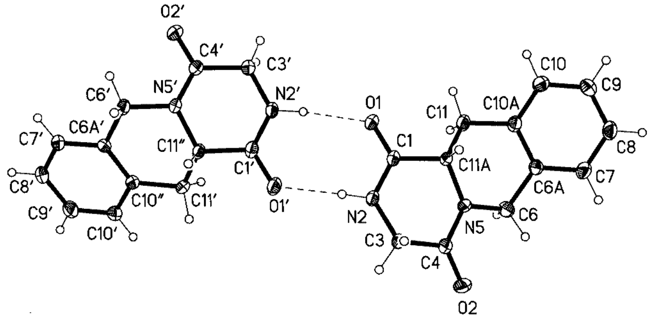


Figure 1. X-ray crystal structure of dioxopiperazine **9**; two independent molecules drawn with 50% ellipsoids; the absolute configuration at C-11a was assumed (based on **7**); selected bond lengths [Å] and angles [°] of the intermolecular hydrogen bonds: N(2)−H(02) 0.89(3), H(02)−O(1′) 1.93(3), N(2′)−H(02′) 0.90(3), H(02′)−O(1) 2.02(3); N(2)−H(02)−O(1′) 174(2), N(2′)−H(02′)−O(1) 173(2)

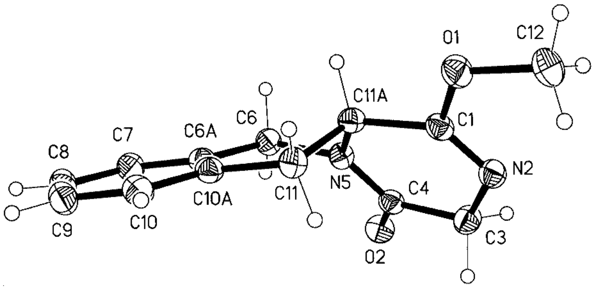


Figure 2. X-ray crystal structure of lactim ether **5**; ellipsoids are drawn at the 50% level; the absolute configuration at C-11a was assumed (based on **7**)

In order to investigate the diastereoselectivity of the alkylation reaction, lactim ether **5** was deprotonated with various bases in THF at −78 °C. Various electrophiles were then added, and the reactions monitored by ^{1}H NMR spectroscopy and capillary GC. The results are summarized in Table 1. Irrespective of the base, primary alkyl halides such as methyl iodide and isobutyl bromide displayed almost no selectivity (Entries 1−6). The same was true for 4-methylpent-3-enyl bromide (Entries 7, 8). A slight increase of the selectivity was observed for isopropyl bromide, depending on the base. While KO*t*Bu led to a slight preference for the *trans* diastereomer **10d** (**10d**/**11d** = 58:42), LDA and LHMDS resulted in the preferred formation of the *cis* diastereomer **11d** (**10d**/**11d** = 42:58) (Entries 9, 10). It was anticipated that the use of different leaving groups might improve the selectivity. However, in contrast to a recent report by Cook,[3a] the use of alkyl tosylates or alkyl diphenylphosphates instead of the corresponding alkyl halides gave

Table 1. Alkylation of lactim ether **5** under various conditions

Entry	R	Base	Products[a]	Conversion [%][b]	Yield [%][c] **10/11**	Ratio[b] **10/11**
1	Me	LDA	**10a**, **11a**	45	32:13	42:58
2	Me	LHMDS	**10a**, **11a**	87	−:−	43:57
3	*i*Bu	*n*BuLi	**10b**, **11b**	38	−:−	50:50
4	*i*Bu	LDA	**10b**, **11b**	66	33:32	50:50
5	*i*Bu	LHMDS	**10b**, **11b**	80	−:−	53:47
6	*i*Bu	KO*t*Bu	**10b**, **11b**	12	−:−	54:46
7	$CH_2CH_2CH=CMe_2$	LDA	**10c**, **11c**	−	−:−	50:50
8	$CH_2CH_2CH=CMe_2$	LHMDS	**10c**, **11c**	95	40:40	50:50
9	*i*Pr	LDA[d]	**10d**, **11d**	95	40:55	42:58
10	*i*Pr	LHMDS[d]	**10d**, **11d**	98	−:−	42:58
11	*i*Pr	KO*t*Bu[d]	**10d**, **11d**	49	−:−	58:42
12	$CH_2CH=CH_2$	LDA	**10e**, **11e**	87	−:−	80:20
13	$CH_2CH=CH_2$	LHMDS	**10e**, **11e**	99	−:−	78:22
14	$CH_2CH=CH_2$	*n*BuLi	**10e**, **11e**	68	51:17	75:25
15	$CH_2CH=CMe_2$	*n*BuLi	**10f**, **11f**	81	−:−	72:28
16	$CH_2CH=CMe_2$	LDA	**10f**, **11f**	87	−:−	84:16
17	$CH_2CH=CMe_2$	LDA[e]	**10f**, **11f**	−	−:−	80:20
18	$CH_2CH=CMe_2$	LHMDS	**10f**, **11f**	96	−:−	92:8
19	$CH_2CH=CMe_2$	NaHMDS	**10f**, **11f**	89	78:11	87:13
20	$CH_2CH=CMe_2$	KHMDS	**10f**, **11f**	89	−:−	77:23
21	Bn	*n*BuLi	**10g**, **11g**	−	−:−	95:5
22	Bn	LDA	**10g**, **11g**	> 90	−:−	97:3
23	Bn	LHMDS	**10g**, **11g**	98	91:7	93:7
24	Bn	KO*t*Bu	**10g**, **11g**	−	−:−	37:63

[a] Reaction conditions: 1) 1.1 equiv. of base, THF, −78 °C, 4 h; 2) 1.1 equiv. of RX (R = Me, X = I; all other R, X = Br), −78 °C, 12 h. [b] Conversions and diastereomeric ratios were determined by capillary GC of the crude products. [c] Yields refer to isolated yields. Diastereomeric ratios were determined by capillary GC (Entries 3−19) and ^1H NMR (Entries 1, 2 and 20−24) of the crude products. [d] Deprotonation was carried out in the presence of 6 equiv. of DMPU. [e]The reaction mixture was stirred for an additional 3 d at room temp.

very poor conversions and low selectivities, and thus this approach was not pursued further. Fortunately, the reaction of **5** with allylic and benzylic halides turned out to be much more selective (Entries 12−24). For allyl bromide, LDA was found to give the best diastereoselectivity (**10e**/**11e** = 80:20) (Entry 12). The amount of *trans* isomer slightly decreased when *n*BuLi or LHMDS were used instead (Entries 13, 14). For 3-methylbut-2-enyl bromide a variety of bases were screened (Entries 15−20). The highest degree of diastereoselectivity (**10f**/**11f** = 92:8) was observed for LHMDS (Entry 18). All other bases gave worse *cis*/*trans* ratios. When LDA was used in combination with DMPU, the selectivity was even lower than for LDA alone (Entries 16, 17). In case of benzyl bromide, LDA was the base of choice, giving the products **10g**, **11g** with exceptional diastereoselectivity (**10g**/**11g** = 97:3) (Entry 22). The relative configuration of diastereomers **10**, **11** was assigned by diagnostic NOEs between 3-H and 11a-H in *cis*-configured derivatives **11b**,**d**,**g** as compared to the *trans* isomers **10b**,**d**,**g**.

We were worried that the presence of base might compromise the diastereoselectivity and/or the enantiomeric purity of lactim ethers **5**, **10**, **11** by deprotonation and equilibration. Thus, lactim ether **5** was treated with 1 equiv. of LHMDS and quenched with satd. $NaHCO_3$. Inspection of the optical rotation revealed less than 5% of racemization at C-11a. In addition, both **5** and diastereomeric alkylation products **10f**, **11f** were subjected to chiral HPLC analysis, which indicated optical purities of greater than 95%.[19]

Next, the conversion of the lactim ethers **10**, **11** into the corresponding dioxopiperazines **12**, **13** was attempted. While treatment of unsubstituted lactim ether **5** with dilute HCl did not give any conversion, the use of TsOH resulted in clean conversion into the starting dioxopiperazine **9** within 1 d. Thus, diastereomeric alkylation products **10a**,**c**,**g** and **11a**−**c** were treated with 1 equiv. of TsOH in CH_2Cl_2 at room temp. overnight and the corresponding dioxopiperazines **12a**,**c**,**g** and **13a**−**c** were isolated in quantitative yield. We also checked whether hydrolysis could be achieved without prior chromatographic separation of the diastereomers **10**, **11**. However, the diastereomeric dioxopiperazines **12**, **13** are much more difficult to separate by chromatography than the corresponding lactim ethers **10**, **11**; therefore, it was found advantageous to carry out the alkylation/chromatographic separation/hydrolysis sequence in that order.

From the above results, the following conclusions can be drawn. In alkylations of tricyclic lactim ether **5**, steric constraints are not sufficient to achieve useful discrimination between the diastereotopic faces of the carbanion. However, alkylations using allylic and benzylic halides capable of π-stacking interactions with the tetrahydroisoquinoline moiety result in improved diastereoselectivities. The results obtained with different disilazide bases LHMDS, NaHMDS, KHMDS (Table 1, Entries 18−20) clearly show that the counterion has a prominent effect on the selectivity. For an estimation of the thermodynamic stability of the diastereomeric alkylation products **10**, **11**, semiempirical (PM3)[20] and density functional [B3LYP-6/31G(d)][21] calculations of *trans*-3-methyllactim ether **10a**, *cis*-3-methyllactim ether **11a**, *trans*-3-benzyllactim ether **10g** and *cis*-3-benzyllactim ether **11g** were performed. The calculations revealed similar thermodynamic stabilities for the *trans* and *cis* isomers regardless of the substituent in the 3-position, with the *cis* isomers being slightly more stable (0.3 kcal/mol) than the corresponding *trans* isomers. Despite the varying diastereoselectivities, our method provides rapid access to non-natural dioxopiperazines, which otherwise require the stereoselective synthesis and selective condensation of non-natural amino acid precursors.[2a]

Experimental Section

General: All reactions were carried out under nitrogen using standard Schlenk techniques. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated Macherey−Nagel SIL G/UV$_{254}$ plates (0.25 mm thickness) and the products were visualized by UV detection or phosphomolybdic acid (5 wt% in EtOH). Flash chromatography[22] was carried out with Merck silica gel 60 (230−400 mesh). NMR spectra: Bruker AM 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), Bruker AC 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz). Multiplets in ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Optical rotations (1-dm cells, 1 mL capacity, room temp.): Perkin−Elmer Model 241 polarimeter. Melting points (uncorrected): Gallenkamp melting point apparatus. IR: Nicolet 320 FT-IR spectrometer. MS: Finnigan Model MAT 8430 (EI). GC-MS: Carlo Erba HRGC 5160 coupled with a Finnigan MAT 4515 (EI, 40 eV). HPLC: Merck−Hitachi L-7100 pump and Merck−Hitachi L-7450 diode array detector, Daicel Chiralcel OD column, solvent: *n*-hexane/*i*PrOH,[19] flow 0.75 mL min^{-1}. (3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**7**) was prepared according to ref.[15]

(10a*S*)-10,10a-Dihydro[1,3]oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (8): Boc$_2$O (65.5 g, 0.30 mol) was added dropwise to a solution of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**7**) (51.5 g, 0.29 mol) in 1 N NaOH (580 mL, 0.58 mol) and *t*BuOH (180 mL), while maintaining pH = 8.5 by further addition of 1 N NaOH. The resulting mixture was stirred overnight at room temperature. Then the mixture was extracted with hexanes (2 × 30 mL) and the combined organic layers were extracted with satd. NaHCO$_3$ solution (2 × 20 mL) and adjusted to pH = 1 by careful addition of a KHSO$_4$ solution (75.7 g in 500 mL H$_2$O) under ice-cooling. The resulting mixture was extracted with Et$_2$O (2 × 200 mL) and ethyl acetate (2 × 200 mL). The combined organic layers were washed with H$_2$O (20 mL), brine (20 mL) and dried with Na$_2$SO$_4$. After removal of the solvent in vacuo and addition of *n*-hexane, 66.0 g (82%) of a colorless solid was obtained. PCl$_3$ (32.7 g, 238 mmol) was added dropwise to a solution of (3*S*)-*N*-(*tert*-butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (55.0 g, 199 mmol) in CH$_2$Cl$_2$ (400 mL) at 0 °C and the resulting mixture was stirred for 2 h at 0 °C. The solvent was removed in vacuo and the residue was washed with *n*-hexane and recrystallized from Et$_2$O to yield 39.1 g (81%) of a colorless solid; m.p. 150 °C. $[\alpha]_{20}^{D} = -187$ (*c* = 2.10, CHCl$_3$). IR (KBr): $\tilde{\nu}$ = 1699, 1654 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.05 (dd, *J* = 15.6, 11.8 Hz, 1 H, 10-H$_a$), 3.30 (dd, *J* = 15.6, 4.8 Hz, 1 H, 10-H$_b$), 4.36 (dd, *J* = 11.8, 4.8 Hz, 1 H, 10a-H), 4.51 (d, *J* = 16.8 Hz, 1 H, 5-H$_a$), 5.00 (d, *J* = 16.8 Hz, 1 H, 5-H$_b$), 7.19−7.33 (m, 4 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 30.5 (C-10), 42.4 (C-5), 54.5 (C-10a), 126.6, 127.6, 127.8 (C-7, C-8, C-9), 129.6 (C-6), 129.73 (C-5a), 129.75 (C-9a), 150.7 (C-1), 168.3 (C-3) ppm. MS (EI): *m*/*z* (%) = 203 (19) [M$^+$], 175 (100), 130 (42), 104 (96), 77 (21). HRMS (EI): calcd. for C$_{11}$H$_9$NO$_3$ 203.0582, found 203.0580.

11,11a-Dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (9): Solid **10** (15.6 g, 76.6 mmol) was added to a cooled solution of glycine methyl ester hydrochloride (10.6 g, 84.3 mmol) and NEt$_3$ (23.5 mL, 169 mmol) in CH$_2$Cl$_2$ (150 mL) at −78 °C. Stirring was continued for 2 h at −78 °C. The mixture was kept overnight at −20 °C. The precipitate was removed by filtration through Celite and the solvent was evaporated. The residual oil was dissolved in toluene (100 mL), refluxed for 24 h and the precipitate was collected, redissolved in H$_2$O (150 mL), treated with charcoal and refluxed for 1 h. After filtration through Celite, the solvent was removed by azeotropic distillation with EtOH. Purification by recrystallization from H$_2$O yielded 13.3 g (80%) of a colorless solid; m.p. 362 °C. $[\alpha]_{20}^{D} = -163$ (*c* = 1.00, THF). IR (KBr): $\tilde{\nu}$ = 3279, 3276, 1687, 1632 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.04 (dd, *J* = 16.1, 11.8 Hz, 1 H, 11-H$_a$), 3.19 (dd, *J* = 16.1, 4.0 Hz, 1 H, 11-H$_b$), 3.88 (d, *J* = 17.4 Hz, 1 H, 3-H$_a$), 3.93 (d, *J* = 17.4 Hz, 1 H, 3-H$_b$), 4.22 (dd, *J* = 11.8, 4.0 Hz, 1 H, 11a-H), 4.30 (d, *J* = 16.7 Hz, 1 H, 6-H$_a$), 5.09 (d, *J* = 16.7 Hz, 1 H, 6-H$_b$), 7.21−7.26 (m, 4 H), 8.24 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 32.0 (C-11), 43.2 (C-6), 44.1 (C-3), 54.6 (C-11a), 126.2, 126.5, 126.6 (C-8, C-9, C-10), 128.7 (C-7), 132.3, 133.1 (C-6a, C-10a), 163.2 (C-1), 166.5 (C-4) ppm. MS (EI): *m*/*z* (%) = 216 (100) [M$^+$], 199 (10), 145 (30), 130 (38), 104 (89), 77 (19). HRMS (EI): calcd. for C$_{12}$H$_{12}$N$_2$O$_2$ 216.0899, found 216.0898. C$_{12}$H$_{12}$N$_2$O$_2$ (216.24): calcd. C 66.65, H 5.59, N 12.96; found C 66.61, H 5.62, N 12.96.

X-ray Structure Analysis of 9: C$_{12}$H$_{12}$N$_2$O$_2$, M_r = 216.24, crystal size 0.45 × 0.18 × 0.13 mm, triclinic, space group *P*1, *a* = 4.7147(4), *b* = 10.2583(8), *c* = 11.3732(11) Å, α = 107.195(3), β = 95.037(3), γ = 100.330(3)°, *V* = 511.12(8) Å^3, $\rho_{\text{calcd.}}$ = 1.405 Mg·m^{-3}, *T* = 133(2) K, *Z* = 2, λ = 0.71073 Å. Bruker SMART 1000 CCD diffractometer, 7884 reflections collected, 1.90° ≤ θ ≤ 30.03°, 2970 independent reflections, 297 refined parameters, *R*1 = 0.0326, *wR*2 = 0.0914. Program used: SHELXL-97. See ref.[18]

1-Methoxy-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (5): A mixture of **9** (9.95 g, 46.0 mmol) and trimethyloxonium tetrafluoroborate (7.48 g, 51.0 mmol) were ground together in a mortar, dissolved in CH$_2$Cl$_2$ (150 mL) and refluxed for 12 h. Trimethyloxonium tetrafluoroborate (3.74 g, 25.5 mmol) was then added, and refluxing was continued for 12 h. The mixture was slowly poured into an ice-cooled satd. NaHCO$_3$ solution (pH > 7.5) under vigorous stirring, the layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 80 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated to yield 10.1 g (94%) of a colorless solid; m.p. 144 °C. $[\alpha]_{20}^{D} = -255.8$ (*c* = 1.00, THF). IR (KBr): $\tilde{\nu}$ = 1699, 1654, 1238 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 2.37 (dd, *J* = 15.7, 12.5 Hz, 1 H, 11-H$_a$), 2.80 (dd, *J* = 15.7, 3.5 Hz, 11-H$_b$), 3.44−3.50 (m, 1 H, 11a-H), 3.47 (s, 3 H, OMe), 3.70 (d, *J* = 17.3 Hz, 1 H, 6-H$_a$), 4.15 (dd, *J* = 21.0, 2.5 Hz, 1 H, 3-H$_a$), 4.24 (dd, *J* = 21.0, 2.7 Hz, 1 H, 3-H$_b$), 5.52 (d, *J* = 17.3 Hz, 1 H, 6-H$_b$), 6.70−6.74 (m, 2 H), 6.90−6.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 33.7 (C-11), 43.1

(C-6), 50.1 (C-3), 52.6 (OMe), 126.6, 126.7, 126.9 (C-8, C-9, C-10), 128.9 (C-7), 132.4, 132.4 (C-6a, C-10a), 158.7 (C-1), 164.2 (C-4) ppm. MS (EI): *m/z* (%) = 230 (100) [M$^+$], 130 (18), 104 (34). HRMS (EI): calcd. for $C_{13}H_{14}N_2O_2$ 230.1055, found 230.1058. $C_{13}H_{14}N_2O_2$ (239.27): calcd. C 67.81, H 6.13, N 12.17; found C 67.92, H 6.15, N 11.69.

X-ray Structure Analysis of 5: $C_{13}H_{14}N_2O_2$, M_r = 230.26, crystal size 0.5 × 0.12 × 0.10 mm, orthorhombic, space group $P2_12_12_1$, a = 6.8455(6), b = 11.1697(11), c = 14.5467(12) Å, V = 1112.27(17) Å^3, $\rho_{calcd.}$ = 1.375 Mg·m^{-3}, T = 133(2) K, Z = 4, λ = 0.71073 Å. Bruker SMART 1000 CCD diffractometer, 13260 reflections collected, 2.30° ≤ θ ≤ 30.51°, 1947 independent reflections, 155 refined parameters, $R1$ = 0.0343, $wR2$ = 0.0923. Program used: SHELXL-97. See ref.[18]

General Procedure for the Alkylation of Lactim Ether 5: A solution of lactim ether **5** (115 mg, 0.50 mmol) in THF (1 mL) was added dropwise to a cooled solution of the base (0.53 mmol) in THF (4 mL) at −78 °C. After stirring for 4 h at −78 °C, freshly distilled electrophile (0.55 mmol) was added and stirring was continued overnight. The reaction mixture was warmed to room temperature and hydrolyzed by addition of satd. $NaHCO_3$ solution (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, concentrated and purified by flash chromatography on SiO_2.

1-Methoxy-3-methyl-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10a, 11a): Base: LDA (0.53 mL, 0.53 mmol, 1 M solution in THF, freshly prepared from *n*BuLi and HN*i*Pr$_2$). Flash chromatography (Et$_2$O/NEt$_3$, 95:5) yielded 39 mg (32%) of a pale yellow solid as the first fraction and 16 mg (13%) of a yellow oil as the second fraction. **(3*R*,11a*S*) Isomer 10a:** $[\alpha]^{D}_{20}$ = −80.7 (*c* = 4.30, THF). IR (KBr): ṽ = 1680, 1654 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.70 (d, *J* = 7.3 Hz, 3 H, CMe), 2.40 (dd, *J* = 15.8, 12.2 Hz, 1 H, 11-H$_a$), 2.82 (dd, *J* = 15.8, 3.6 Hz, 1 H, 11-H$_b$), 3.50 (s, 3 H, OMe), 3.59 (ddd, *J* = 12.2, 3.6, 2.3 Hz, 1 H, 11a-H), 3.78 (d, *J* = 17.3 Hz, 1 H, 6-H$_a$), 4.20 (dq, *J* = 7.3, 2.3 Hz, 1 H, 3-H), 5.51 (d, *J* = 17.3 Hz, 1 H, 6-H$_b$), 6.69−6.80 (m, 2 H), 6.90−6.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 21.6 (C*Me*), 33.7 (C-11), 43.5 (C-6), 52.7 (OMe), 53.0 (C-11a), 54.7 (C-3), 132.6 (C-6a), 132.6 (C-10a), 126.6, 126.7, 127.0 (C-8, C-9, C-10), 128.8 (C-7), 157.9 (C-1), 167.8 (C-4) ppm. MS (EI): *m/z* (%) = 244 (100) [M$^+$], 229 (17), 201 (33), 130 (17), 117 (10), 104 (16), 84 (48). HRMS (EI): calcd. for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1212. **(3*S*,11a*S*) Isomer 11a:** $[\alpha]^{D}_{20}$ = −155.7 (*c* = 1.00, THF). IR (KBr): ṽ = 1702, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.53 (d, *J* = 7.2 Hz, 3 H, CMe), 2.51 (dd, *J* = 15.6, 12.2 Hz, 1 H, 11-H$_a$), 2.88 (dd, *J* = 15.6, 3.5 Hz, 1 H, 11-H$_b$), 3.49 (s, 3 H, OMe), 3.48−3.52 (m, 1 H, 11a-H), 3.73 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.27 (dq, *J* = 7.2, 2.2 Hz, 1 H, 3-H), 5.49 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.70−6.71 (m, 2 H), 6.72−6.73 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 22.5 (CMe), 34.6 (C-11), 43.4 (C-6), 52.6 (OMe), 53.0 (C-11a), 55.4 (C-3), 126.6, 126.8, 127.0 (C-8, C-9, C-10), 128.9 (C-7), 132.4, 132.7 (C-6a, C-10a), 158.1 (C-1), 167.8 (C-4) ppm. MS (EI): *m/z* (%) = 244 (100) [M$^+$], 229 (36), 201 (54), 130 (30), 117 (16), 104 (22), 91 (4), 77 (8). HRMS (EI): calcd. for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1219.

1-Methoxy-3-(2-methylpropyl)-3,6,11,11a-tetrahydro-4*H*-pyrazino-[1,2-*b*]isoquinolin-4-one (10b, 11b): Base: LHMDS (0.53 mL, 0.53 mmol, 1.0 M solution, freshly prepared from *n*BuLi and HMDS in THF). Flash chromatography (hexanes/Et$_2$O/NEt$_3$, 47:47:6) yielded 47 mg (33%) of a pale yellow amorphous solid as the first fraction and 47 mg (33%) of a yellow amorphous solid as the second fraction. **(3*R*,11a*S*) Isomer 10b:** $[\alpha]^{D}_{20}$ = −120.7 (*c* = 2.02, THF). IR (KBr): ṽ = 1704, 1650 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.04 (d, 3 H, *J* = 6.6 Hz, 3′-H), 1.06 (d, *J* = 6.3 Hz, 3 H, 4′-H), 1.70−1.77 (m, 1 H, 1′-H$_a$), 2.16−2.27 (m, 2 H, 1′-H$_b$, 2′-H), 2.44 (dd, *J* = 15.8, 12.0 Hz, 1 H, 11-H$_a$), 2.88 (dd, *J* = 15.8, 3.4 Hz, 1 H, 11-H$_b$), 3.50 (s, 3 H, OMe), 3.63 (ddd, *J* = 12.0, 3.4, 2.3 Hz, 1 H, 11a-H), 3.86 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.23 (ddd, *J* = 9.4, 3.7, 2.3 Hz, 1 H, 3-H), 5.48 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.71−6.80 (m, 2 H), 6.92 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 22.0, 23.6 (C-3′, C-4′), 25.1 (C-2′), 33.8 (C-11), 43.6 (C-6), 44.1 (C-1′), 52.5 (OMe), 52.6 (C-11a), 57.1 (C-3), 126.6, 126.7, 127.0 (C-8, C-9, C-10), 128.7 (C-7), 132.6 (C-6a), 132.6 (C-10a), 157.8 (C-1), 167.9 (C-4) ppm. MS (EI): *m/z* (%) = 286 (16) [M$^+$], 230 (100), 201 (14), 160 (32), 146 (48), 129 (30), 104 (29), 91 (10). HRMS (EI): calcd. for $C_{17}H_{22}N_2O_2$ 286.1681, found 286.1677. **(3*S*,11a*S*) Isomer 11b:** $[\alpha]^{D}_{20}$ = −149.8 (*c* = 2.30, THF). IR (KBr): ṽ = 1702, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.97 (d, *J* = 6.6 Hz, 3 H, 3′-H), 1.03 (d, *J* = 6.3 Hz, 3 H, 4′-H), 1.53 (ddd, *J* = 14.1, 9.6, 5.1 Hz, 1 H, 1′-H$_a$), 2.06 (ddd, *J* = 14.1, 8.8, 4.5 Hz, 1 H, 1′-H$_b$), 2.13−2.19 (m, 1 H, 2′-H), 2.57 (dd, *J* = 15.7, 12.3 Hz, 1 H, 11-H$_a$), 2.90 (dd, *J* = 15.7, 3.6 Hz, 1 H, 11-H$_b$), 3.50 (s, 3 H, OMe), 3.54 (ddd, *J* = 12.3, 3.6, 2.5 Hz, 1 H, 11a-H), 3.73 (d, *J* = 17.3 Hz, 1 H, 6-H$_a$), 4.30 (ddd, *J* = 9.6, 4.5, 2.5 Hz, 1 H, 3-H), 5.53 (d, *J* = 17.3 Hz, 1 H, 6-H$_b$), 6.71−6.78 (m, 2 H), 6.90−6.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 21.9, 23.6 (C-3′, C-4′), 25.1 (C-2′), 34.6 (C-11), 43.4 (C-6), 46.0 (C-1′), 52.5 (OMe), 52.9 (C-11a), 57.7 (C-3), 126.6, 126.8, 127.0 (C-8, C-9, C-10), 128.9 (C-7), 132.3, 132.7 (C-6a, C-10a), 157.8 (C-1), 167.6 (C-4) ppm. MS (EI): *m/z* (%) = 286 (7) [M$^+$], 230 (100), 201 (9), 186 (17), 154 (100), 129 (45), 104 (28), 91 (8), 77 (12). HRMS (EI): calcd. for $C_{17}H_{22}N_2O_2$ 286.1681, found 286.1676.

1-Methoxy-3-(4-methyl-3-pentenyl)-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10c, 11c): Base: LHMDS (0.53 mL, 0.53 mmol, 1.0 M solution, freshly prepared from *n*BuLi and HMDS in THF). Flash chromatography (Et$_2$O/NEt$_3$, 95:5) yielded 63 mg (40%) of a pale yellow amorphous solid as the first fraction and 62 mg (40%) of a yellow oil as the second fraction. **(3*R*,11a*S*) Isomer 10c:** $[\alpha]^{D}_{20}$ = −41.4 (*c* = 4.20, THF). IR (neat): ṽ = 1702, 1659 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.63 (s, 3 H, 5′-H), 1.66 (s, 3 H, 6′-H), 2.10−2.16 (m, 1 H, 1′-H$_a$), 2.30−2.38 (m, 3 H, 1′-H$_b$, 2′-H$_{a,b}$), 2.44 (dd, *J* = 15.7, 12.3 Hz, 1 H, 11-H$_a$), 2.87 (dd, *J* = 15.7, 3.5 Hz, 1 H, 11-H$_b$), 3.54 (s, 3 H, OMe), 3.65 (ddd, *J* = 12.3, 3.5, 2.5 Hz, 1 H, 11a-H), 3.84 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.19−4.22 (m, 1 H, 3-H), 5.30−5.34 (m, 1 H, 3′-H), 5.50 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.74−6.79 (m, 2 H), 6.92−6.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 17.7 (C-5′), 24.4 (C-2′), 25.9 (C-6′), 33.8 (C-11), 34.9 (C-1′), 43.5 (C-6), 52.6 (OMe), 52.7 (C-11a), 57.9 (C-3), 124.7 (C-3′), 126.6, 126.7, 127.0 (C-8, C-9, C-10), 128.8 (C-7), 131.9 (C-4′), 132.5, 132.6 (C-6a, C-10a), 158.1 (C-1), 167.5 (C-4) ppm. MS (EI): *m/z* (%) = 312 (22) [M$^+$], 230 (100), 199 (10), 129 (14), 104 (39), 71 (62). HRMS (EI): calcd. for $C_{19}H_{24}N_2O_2$ 312.1838, found 312.1836. **(3*S*,11a*S*) Isomer 11c:** $[\alpha]^{D}_{20}$ = −172 (*c* = 4.2, THF). IR (neat): ṽ = 1704, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.57 (s, 3 H, C-5′), 1.61 (s, 3 H, C-6′), 1.84−1.91 (m, 1 H, 1′-H$_a$), 2.19−2.35 (m, 3 H, 1′-H$_b$, 2′-H$_{a,b}$), 2.59 (dd, *J* = 15.7, 12.4 Hz, 1 H, 11-H$_a$), 2.92 (dd, *J* = 15.7, 3.5 Hz, 1 H, 11-H$_b$), 3.51−3.57 (m, 1 H, 11a-H), 3.53 (s, 3 H, OMe), 3.76 (d, *J* = 17.6 Hz, 1 H, 6-H$_a$), 4.25−4.29 (m, 1 H, 3-H), 5.24−5.28 (m, 1 H, 3′-H), 5.51 (d, *J* = 17.6 Hz, 1 H, 6-H$_b$), 6.74−6.79 (m, 2 H), 6.91−6.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 17.7 (C-5′), 24.6 (C-2′), 25.8 (C-6′), 34.6 (C-11), 36.2 (C-1′), 43.4 (C-6), 52.6 (OMe), 52.8 (C-11a), 58.6 (C-3), 124.4 (C-3′), 126.6, 126.8, 127.0 (C-8, C-9, C-10), 128.9 (C-7), 132.1 (C-4′), 132.3, 132.5 (C-6a, C-10a), 158.0 (C-1), 167.4 (C-4) ppm. MS (EI): *m*/*z* (%) = 312 (5) [M$^+$], 243 (6), 231 (14), 230 (100), 199 (15), 149 (63), 130 (29), 104 (75), 77 (21). HRMS (EI): calcd. for $C_{19}H_{24}N_2O_2$ 312.1838, found 312.1836.

1-Methoxy-3-(1-methylethyl)-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10d, 11d): Base: LDA (0.53 mL, 0.53 mmol, 1.0 M solution in THF, freshly prepared from *n*BuLi and HN*i*Pr$_2$). Flash chromatography (hexanes/Et$_2$O/NEt$_3$ 47:47:6) yielded 54 mg (40%) of a pale yellow amorphous solid as the first fraction and 75 mg (55%) of a yellow oil as the second fraction. **(3*R*,11a*S*) Isomer 10d:** $[\alpha]^{D}_{20}$ = −135.0 (*c* = 2.01, THF). IR (KBr): $\tilde{\nu}$ = 1703, 1649 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H, CMe$_2$), 1.21 (d, *J* = 6.8 Hz, 3 H, CMe$_2$), 2.42 (dd, *J* = 15.5, 12.4 Hz, 1 H, 11-H$_a$), 2.88 (dd, *J* = 15.5, 3.3 Hz, 1 H, 11-H$_b$), 2.93 (ddd, *J* = 13.6, 6.8, 3.3 Hz, 1 H, 1′-H), 3.49 (s, 3 H, OMe), 3.62 (ddd, *J* = 12.4, 3.3, 2.4 Hz, 1 H, 11a-H), 3.84 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.09 (dd, *J* = 5.3, 2.4 Hz, 1 H, 3-H), 5.53 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.71−6.78 (m, 2 H), 6.92−6.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 16.8, 19.9 (C-2′, C-3′), 32.5 (C-1′), 33.9 (C-11), 43.5 (C-6), 52.5 (OMe), 52.5 (C-11a), 63.4 (C-3), 126.5, 126.7, 126.9 (C-8, C-9, C-10), 128.8 (C-7), 132.4, 132.6 (C-6a, C-10a), 158.5 (C-1), 167.2 (C-4) ppm. MS (EI): *m*/*z* (%) = 272 (76) [M$^+$], 229 (100), 201 (21), 132 (14), 130 (20), 115 (8), 104 (32). HRMS (EI): calcd. for $C_{16}H_{20}N_2O_2$ 272.1525, found 272.1523. **(3*S*,11a*S*) Isomer 11d:** $[\alpha]^{D}_{20}$ = −174.0 (*c* = 1.01, THF). IR (KBr): $\tilde{\nu}$ = 1709, 1655 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 0.78 (d, *J* = 6.8 Hz, 3 H, CMe$_2$), 1.17 (d, *J* = 7.0 Hz, 3 H, CMe$_2$), 2.66 (dd, *J* = 15.9, 12.1 Hz, 1 H, 11-H$_a$), 2.71−2.80 (m, 1 H, 1′-H), 2.98 (dd, *J* = 15.9, 3.5 Hz, 1 H, 11-H$_b$), 3.50 (s, 3 H, OMe), 3.53 (ddd, *J* = 12.1, 3.5, 3.5 Hz, 1 H, 11a-H), 3.75 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.16 (dd, *J* = 3.5, 3.3 Hz, 1 H, 3-H), 5.56 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.71−6.80 (m, 2 H), 6.90−6.93 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 17.2, 20.0 (C-2′, C-3′), 32.3 (C-1′), 34.81 (C-11), 43.4 (C-6), 52.4 (OMe), 52.64 (C-11a), 64.0 (C-3), 126.6, 126.8, 127.0 (C-8, C-9, C-10), 128.9 (C-7), 132.2, 132.5 (C-6a, C-10a), 158.0 (C-1), 166.6 (C-4) ppm. MS (EI): *m*/*z* (%) = 272 (87) [M$^+$], 229 (100), 201 (19), 174 (12), 132 (17), 130 (19), 104 (36). HRMS (EI): calcd. for $C_{16}H_{20}N_2O_2$ 272.1525, found 272.1516.

3-Allyl-1-methoxy-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10e, 11e): Base: *n*BuLi (0.33 mL, 0.53 mmol, 1.6 M solution in hexane). Flash chromatography (hexanes/Et$_2$O/NEt$_3$, 47:47:6) yielded 69 mg (51%) of a pale yellow solid as the first fraction and 23 mg (17%) of a yellow oil as the second fraction. **(3*R*,11a*S*) Isomer 10e:** $[\alpha]^{D}_{20}$ = −78.1 (*c* = 0.82, THF). IR (neat): $\tilde{\nu}$ = 1703, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 2.41 (dd, *J* = 15.7, 12.3 Hz, 1 H, 11-H$_a$), 2.86 (dd, *J* = 15.7, 3.3 Hz, 1 H, 11-H$_b$), 2.87−2.95 (m, 2 H, 1′-H$_a$, 1′-H$_b$), 3.51 (s, 3 H, OMe), 3.63 (ddd, *J* = 12.3, 3.3, 2.5 Hz, 1 H, 11a-H), 3.82 (d, *J* = 17.6 Hz, 1 H, 6-H$_a$), 4.26 (ddd, *J* = 6.6, 4.3, 2.5 Hz, 1 H, 3-H), 5.09 (dd, *J* = 10.3, 1.2 Hz, 1 H, 3′-H$_a$), 5.22 (dd, *J* = 17.1, 1.4 Hz, 1 H, 3′-H$_b$), 5.48 (d, *J* = 17.6 Hz, 1 H, 6-H$_b$), 5.93−6.04 (m, 1 H, 2′-H), 6.70−6.77 (m, 2 H), 6.91−6.95 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 33.8 (C-11), 39.2 (C-1′), 43.5 (C-6), 52.7 (OMe), 52.7 (C-11a), 58.7 (C-3), 117.9 (C-3′), 126.6, 126.7, 126.9 (C-8, C-9, C-10), 128.8 (C-7), 132.3, 132.4 (C-6a, C-10a), 134.9 (C-2′), 158.4 (C-1), 166.8 (C-4) ppm. MS (EI): *m*/*z* (%) = 270 (48) [M$^+$], 229 (96), 201 (32), 146 (100), 130 (29), 115 (10), 104 (19), 91 (8), 77 (12). HRMS (EI): calcd. for $C_{14}H_{18}N_2O_2$ 270.1368, found 270.1362. **(3*S*,11a*S*) Isomer 11e:**[23] IR (neat): $\tilde{\nu}$ = 1683, 1660 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 2.65 (dd, *J* = 15.6, 12.3 Hz, 1 H, 11-H$_a$), 2.74−2.84 (m, 2 H, 1′-H$_a$, 1′-H$_b$), 2.93 (dd, *J* = 15.6, 3.3 Hz, 1 H, 11-H$_b$), 3.50 (s, 3 H, OMe), 3.51 (dd, *J* = 12.3, 3.3 Hz, 1 H, 11a-H), 3.72 (d, *J* = 17.3 Hz, 1 H, 6-H$_a$), 4.33 (ddd, *J* = 6.7, 4.0, 2.7 Hz, 1 H, 3-H), 4.94 (dd, *J* = 13.7, 2.1 Hz, 1 H, 3′-H$_a$), 5.08 (dd, *J* = 13.7, 2.0 Hz, 1 H, 3′-H$_b$), 5.53 (d, *J* = 17.3 Hz, 1 H, 6-H$_b$), 5.77−5.86 (m, 1 H, 2′-H), 6.71−6.81 (m, 2 H), 6.90−6.93 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 34.9 (C-11), 39.6 (C-1′), 43.3 (C-6), 52.6 (OMe), 52.8 (C-11a), 59.2 (C-3), 118.1 (C-3′), 126.6, 126.7, 127.0 (C-8, C-9, C-10), 128.9 (C-7), 132.3, 132.4 (C-6a, C-10a), 134.6 (C-2′), 158.2 (C-1), 166.3 (C-4) ppm. MS (EI): *m*/*z* (%) = 270 (54) [M$^+$], 229 (100), 201 (42), 146 (26), 132 (74), 130 (76), 115 (16), 104 (24), 91 (7) [$C_7H_7^+$], 77 (19). HRMS (EI): calcd. for $C_{14}H_{18}N_2O_2$ 270.1368, found 270.1370.

1-Methoxy-3-(3-methyl-2-butenyl)-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10f, 11f): Base: NaHMDS (0.53 mL, 0.53 mmol, 1.0 M solution in THF). Flash chromatography (hexanes/Et$_2$O/NEt$_3$, 47:47:6) yielded 116 mg (78%) of a yellow oil as the first fraction and 17 mg (11%) of a yellow oil as the second fraction. **(3*R*,11a*S*) Isomer 10f:** $[\alpha]^{D}_{20}$ = −116.9 (*c* = 1.99, THF). IR (KBr): $\tilde{\nu}$ = 1704, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 1.64 (s, 3 H, 5′-H), 1.67 (s, 3 H, 4′-H), 2.44 (dd, *J* = 15.4, 12.1 Hz, 1 H, 11-H$_a$), 2.89 (dd, *J* = 15.4, 3.6 Hz, 1 H, 11-H$_b$), 2.89−2.99 (m, 2 H, 1′-H$_{a,b}$), 3.53 (s, 3 H, OMe), 3.69 (ddd, *J* = 12.1, 3.6, 2.2 Hz, 1 H, 11a-H), 3.86 (d, *J* = 17.5 Hz, 1 H, 6-H$_a$), 4.31 (ddd, *J* = 6.6, 4.6, 2.2 Hz, 1 H, 3-H), 5.41−5.46 (m, 1 H, 2′-H), 5.49 (d, *J* = 17.5 Hz, 1 H, 6-H$_b$), 6.70−6.78 (m, 2 H), 6.90−6.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 18.3 (C-4′), 26.1 (C-5′), 33.7 (C-1′), 33.9 (C-11), 43.6 (C-6), 52.6 (OMe), 52.7 (C-11a), 59.2 (C-3), 120.5 (C-2′), 126.6, 126.7, 126.9 (C-8, C-9, C-10), 128.8 (C-7), 132.40 (C-3′), 132.5 (C-6a), 134.4 (C-10a), 158.3 (C-1), 167.2 (C-4) ppm. MS (EI): *m*/*z* (%) = 298 (29) [M$^+$], 230 (100), 201 (16), 146 (20), 130 (20), 104 (58), 91 (7), 77 (9). HRMS (EI): calcd. for $C_{12}H_{22}N_2O_2$ 298.1681, found 298.1680. **(3*S*,11a*S*) Isomer 11f:** $[\alpha]^{D}_{20}$ = −117.7 (*c* = 1.62, THF). IR (KBr): $\tilde{\nu}$ = 1703, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 1.46 (s, 3 H, 5′-H), 1.50 (s, 3 H, 4′-H), 2.68−2.78 (m, *J* = 15.9 Hz, 2 H, 11-H$_a$, 1′-H), 2.82−2.88 (m, 1 H, 1′-H$_b$), 2.96 (dd, *J* = 15.9, 3.8 Hz, 1 H, 11-H$_b$), 3.53 (s, 3 H, OMe), 3.57 (ddd, *J* = 12.1, 3.8, 2.5 Hz, 1 H, 11a-H), 3.70 (d, *J* = 17.4 Hz, 1 H, 6-H$_a$), 4.40 (ddd, *J* = 7.3, 5.0, 2.5 Hz, 1 H, 3-H), 5.20−5.24 (m, 1 H, 2′-H), 5.57 (d, *J* = 17.4 Hz, 1 H, 6-H$_b$), 6.73−6.83 (m, 2 H), 6.90−6.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 18.1 (C-4′), 25.8 (C-5′), 33.5 (C-1′), 34.6 (C-11), 43.2 (C-6), 52.6 (OMe), 52.9 (C-11a), 59.8 (C-3), 120.3 (C-2′), 126.6, 126.8, 126.9 (C-8, C-9, C-10), 128.8 (C-7), 132.3 (C-3′), 132.5 (C-6a), 135.1 (C-10a), 158.2 (C-1), 166.7 (C-4) ppm. MS (EI): *m*/*z* (%) = 298 (25) [M$^+$], 230 (100), 201 (13), 149 (11), 129 (32), 104 (48), 78 (32). HRMS (EI): calcd. for $C_{12}H_{22}N_2O_2$ 298.1681, found 298.1673.

3-Benzyl-1-methoxy-3,6,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinolin-4-one (10g, 11g): Base: LHMDS (0.53 mL, 0.53 mmol, 1.0 M solution, freshly prepared from *n*BuLi and HMDS in THF). Flash chromatography (hexanes/Et$_2$O/NEt$_3$, 47:47:6) yielded 146 mg (91%) of a pale yellow oil as the first fraction and 11 mg (7%) of a pale yellow amorphous solid as the second fraction. **(3*R*,11a*S*) Isomer 10g:** $[\alpha]^{D}_{20}$ = −68.6 (*c* = 2.01, THF). IR (KBr): $\tilde{\nu}$ = 1702, 1656 cm^{-1}. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 2.32 (dd, *J* = 15.9, 12.1 Hz, 1 H, 1′-H$_a$), 2.73 (dd, *J* = 15.9, 3.3 Hz, 1 H, 1′-H$_b$), 2.93 (ddd, *J* = 12.1, 3.3, 2.2 Hz, 1 H, 11a-H), 3.17 (dd, *J* = 12.8, 4.0 Hz, 1 H, 11-H$_a$), 3.51 (s, 3 H, OMe), 3.52 (dd, *J* = 12.8, 5.3 Hz, 1 H, 11-H$_b$), 3.74 (d, *J* = 17.6 Hz, 1 H, 6-H$_a$), 4.51−4.54 (m, 1 H, 3-H), 5.39 (d, *J* = 17.6 Hz, 1 H, 6-H$_b$), 6.65−6.71 (m, 2 H), 6.84−6.89 (m, 2 H), 6.94−6.98 (m, 1 H), 7.04−7.08 (m, 2 H), 7.22−7.27 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 33.6 (C-1′), 40.8 (C-11), 43.6 (C-6), 52.0 (C-3), 52.7 (OMe), 60.0 (C-11a), 126.5, 126.7, 126.9, 127.9, 128.7, 130.6 (CH), 131.9, 132.3 (C-6a, C-10a), 138.0 (C-2′), 158.7 (C-1), 166.9 (C-4) ppm. MS (EI): *m/z* (%) = 320 (49) [M$^+$], 229 (100), 201 (27), 149 (14), 130 (18). HRMS (EI): calcd. for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1517. **(3*S*,11a*S*) Isomer 11g:**[23] IR (neat): $\tilde{\nu}$ = 1659, 1650 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.98 (dd, *J* = 15.8, 12.1 Hz, 1 H, 11-H$_a$), 2.45 (dd, *J* = 15.8, 3.8 Hz, 1 H, 11-H$_b$), 3.07 (dd, *J* = 12.9, 4.5 Hz, 1 H, 1′-H$_a$), 3.32 (ddd, *J* = 12.1, 3.8, 2.5 Hz, 1 H, 11a-H), 3.52 (s, 3 H, OMe), 3.56−3.63 (m, 2 H, 6-H$_a$, 1′-H$_b$), 4.56−4.59 (m, 1 H, 3-H), 5.59 (d, *J* = 17.1 Hz, 1 H, 6-H$_b$), 6.58−6.60 (m, 1 H), 6.70−6.72 (m, 1 H), 6.84−6.94 (m, 5 H), 7.09−7.13 (m, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 33.3 (C-11), 40.4 (C-1′), 43.0 (C-6), 52.6 (OMe), 52.6 (C-11a), 60.1 (C-3), 126.4, 126.5, 126.6, 126.6, 127.9, 128.1, 128.3 (C-8, C-9, C-10, C-3′, C-4′, C-6′, C-7′), 128.6 (C-7), 130.7 (C-5′), 131.9, 132.5 (C-6a, C-10a), 137.6 (C-2′), 158.5 (C-1), 166.0 (C-4) ppm. MS (EI): *m/z* (%) = 320 (8) [M$^+$], 229 (16), 201 (8), 129 (36), 71 (100). HRMS (EI): calcd. for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1522.

General Procedure for the Hydrolysis of Lactim Ethers 10, 11: A solution of lactim ether **10** or **11** (0.20 mmol) in CH_2Cl_2 (2 mL) was treated with *p*TsOH·H_2O (38 mg, 0.20 mmol) and the mixture was stirred for 20 h at room temp. Then satd. $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried with $MgSO_4$, concentrated and purified by flash chromatography on SiO_2 ($CHCl_3$/MeOH, 80:1 → 10:1) to give the dioxopiperazines **12** or **13**.

3-Methyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (12a, 13a). (3*R*,11a*S*) Isomer 12a: 45 mg (quant.) of a colorless solid; m.p. 196 °C. $[\alpha]_{20}^{D}$ = −264.9 (*c* = 0.50, MeOH). IR (KBr): $\tilde{\nu}$ = 3458, 1692, 1656, 1626 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 6.8 Hz, 3 H, 1′-H), 3.04 (dd, *J* = 15.8, 12.3 Hz, 1 H, 11-H$_a$), 3.42 (dd, *J* = 15.8, 3.3 Hz, 1 H, 11-H$_b$), 4.17−4.23 (m, 2 H, 11a-H, 3-H), 4.38 (d, *J* = 17.2 Hz, 1 H, 6-H$_a$), 5.27 (d, *J* = 17.2 Hz, 1 H, 6-H$_b$), 6.67 (br. s, 1 H, NH), 7.17−7.22 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (C-1′), 33.4 (C-11), 44.7 (C-6), 51.1 (C-3), 57.9 (C-11a), 126.6 (C-7), 127.2, 127.3 (C-8, C-9), 128.8 (C-10), 131.7 (C-6a), 132.5 (C-10a), 164.1 (C-4), 165.8 (C-1) ppm. MS (EI): *m/z* (%) = 230 (100) [M$^+$], 215 (21), 201 (8), 187 (4), 159 (15), 144 (8), 132 (15), 130 (42), 115 (8), 104 (42), 77 (14). HRMS (EI): calcd. for $C_{13}H_{14}N_2O_2$ 230.1055; found 230.1071. **(3*S*,11a*S*) Isomer 13a:** 46 mg (quant.) of a colorless solid; m.p. 179−181 °C. $[\alpha]_{20}^{D}$ = −335.3 (*c* = 0.50, MeOH). IR (KBr): $\tilde{\nu}$ = 3440, 1686, 1665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 7.0 Hz, 3 H, 1′-H), 3.06 (dd, *J* = 15.9, 12.2 Hz, 1 H, 11-H$_a$), 3.43 (dd, *J* = 15.9, 3.6 Hz, 1 H, 11-H$_b$), 4.16−4.22 (m, 2 H, 11a-H, 3-H), 4.39 (d, *J* = 16.9 Hz, 1 H, 6-H$_a$), 5.23 (d, *J* = 16.9 Hz, 1 H, 6-H$_b$), 7.17−7.20 (m, 4 H), 7.35 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (C-1′), 33.5 (C-11), 44.5 (C-6), 51.0 (C-3), 55.8 (C-11a), 126.5 (C-7), 127.3, 127.3 (C-8, C-9), 128.8 (C-10), 131.9 (C-6a), 132.5 (C-10a), 166.0 (C-4), 167.8 (C-1) ppm. MS (EI): *m/z* (%) = 230 (100) [M$^+$], 215 (17), 201 (3), 187 (3), 175 (2), 159 (18), 149 (11), 130 (32), 104 (40), 97 (14), 91 (7), 77 (17). HRMS (EI): calcd. for $C_{13}H_{14}N_2O_2$ 230.1055; found 230.1045.

(3*S*,11a*S*)-1-Methoxy-3-(2-methylpropyl)-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (13b): 55 mg (quant.) of a colorless amorphous solid. $[\alpha]_{20}^{D}$ = −120.2 (*c* = 0.62, MeOH). IR (KBr): $\tilde{\nu}$ = 3440, 1686, 1665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 4.8 Hz, 3 H, CCH_3), 0.98 (d, *J* = 4.8 Hz, 3 H, CCH_3), 1.60−1.68 (m, 1 H, 1′-H$_a$), 1.75−1.92 (m, 2 H, 2′-H, 1′-H$_b$), 3.04 (dd, *J* = 15.8, 12.4 Hz, 1 H, 11-H$_a$), 3.42 (dd, *J* = 15.8, 3.6 Hz, 1 H, 11-H$_b$), 4.09 (d, *J* = 8.1 Hz, 1 H, 3-H), 4.22 (dd, *J* = 12.1, 3.6 Hz, 1 H, 11a-H), 4.32 (d, *J* = 17.2 Hz, 1 H, 6-H$_a$), 5.32 (d, *J* = 17.2 Hz, 1 H, 6-H$_b$), 6.54 (br. s, 1 H, NH), 7.16−7.27 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CCH_3), 23.4 (CCH_3), 24.4 (C-2′), 33.7 (C-11), 44.3 (C-1′), 44.5 (C-6), 53.7 (C-3), 55.8 (C-11a), 126.6 (C-7), 127.2, 127.3 (C-8, C-9), 129.0 (C-10), 131.8 (C-6a), 132.8 (C-10a), 165.4 (C-4), 167.4 (C-1) ppm. MS (EI): *m/z* (%) = 272 (48) [M$^+$], 255 (3), 230 (26), 216 (100), 201 (4), 187 (9), 158 (9), 149 (4), 130 (40), 115 (7), 104 (63), 77 (10). HRMS (EI): calcd. for $C_{16}H_{20}N_2O_2$ 272.1525; found 272.1531.

3-(4-Methyl-3-pentenyl)-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (12c, 13c). (3*R*,11a*S*) Isomer 12c: 59 mg (quant.) of a colorless solid; m.p. 185−186 °C. $[\alpha]_{20}^{D}$ = −106.8 (*c* = 0.50, MeOH). IR (KBr): $\tilde{\nu}$ = 3424, 1682, 1671, 1646 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (s, 3 H, CCH_3), 1.69 (s, 3 H, CCH_3), 1.92−1.98 (m, 2 H, 1′-H$_a$, 1′-H$_b$), 2.11−2.17 (m, 2 H, 2′-H$_a$, 2′-H$_b$), 3.02 (dd, *J* = 15.9, 12.1 Hz, 1 H, 11-H$_a$), 3.44 (dd, *J* = 15.9, 3.5 Hz, 1 H, 11-H$_b$), 4.09−4.16 (m, 2 H, 3-H, 11a-H), 4.42 (d, *J* = 17.2 Hz, 1 H, 6-H$_a$), 5.07−5.12 (m, 1 H, 3′-H), 5.19 (d, *J* = 17.2 Hz, 1 H, 6-H$_b$), 6.50 (br. s, 1 H, NH), 7.17−7.26 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (CCH_3), 23.5 (C-2′), 25.9 (CCH_3), 33.5 (C-11), 34.2 (C-1′), 44.8 (C-6), 55.1 (C-3), 55.3 (C-11a), 122.3 (C-3′), 126.5 (C-7), 127.3, 127.3 (C-8, C-9), 128.7 (C-10), 131.6 (C-6a), 132.7 (C-10a), 133.8 (C-4′), 165.6 (C-4), 167.4 (C-1) ppm. MS (EI): *m/z* (%) = 298 (7) [M$^+$], 216 (51), 190 (39), 149 (58), 129 (56), 104 (28), 91 (16), 84 (100), 77 (18). HRMS (EI): calcd. for $C_{18}H_{22}N_2O_2$ 298.1681; found 298.1680. **(3*S*,11a*S*) Isomer 13c:** 60 mg (quant.) of a colorless amorphous solid. $[\alpha]_{20}^{D}$ = −81.6 (*c* = 3.71, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3 H, CCH_3), 1.65 (s, 3 H, CCH_3), 1.80−1.90 (m, 1 H, 1′-H$_a$), 1.95−2.03 (m, 1 H, 1′-H$_b$), 2.11−2.16 (m, 2 H, 2′-H$_a$, 2′-H$_b$), 3.02 (dd, *J* = 15.9, 12.4 Hz, 1 H, 11-H$_a$), 3.42 (dd, *J* = 15.9, 3.7 Hz, 1 H, 11-H$_b$), 4.10 (m, 1 H, 3-H), 4.19 (dd, *J* = 12.4, 3.7 Hz, 1 H, 11a-H), 4.30 (d, *J* = 17.2 Hz, 1 H, 6-H$_a$), 5.07−5.11 (m, 1 H, 3′-H), 5.33 (d, *J* = 17.2 Hz, 1 H, 6-H$_b$), 7.14−7.20 (m, 5 H, Aryl-CH, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9 (CCH_3), 23.6 (C-2′), 25.8 (CCH_3), 33.9 (C-11), 35.0 (C-1′), 44.4 (C-6), 55.0 (C-3), 55.7 (C-11a), 122.3 (C-3′), 126.5 (C-7), 127.1, 127.2 (C-8, C-9), 128.9 (C-10), 131.7 (C-6a), 132.3 (C-10a), 133.7 (C-4′), 165.1 (C-4), 167.6 (C-1) ppm. MS (EI): *m/z* (%) = 298 (5) [M$^+$], 216 (21), 190 (6), 149 (7), 130 (19), 104 (39), 77 (7). HRMS (EI): calcd. for $C_{18}H_{22}N_2O_2$ 298.1681; found 298.1680.

(3*R*,11a*S*)-3-Benzyl-11,11a-dihydro-2*H*-pyrazino[1,2-*b*]isoquinoline-1,4(3*H*,6*H*)-dione (12g): 61 mg (quant.) of a colorless solid; m.p. 66 °C. $[\alpha]_{20}^{D}$ = −51.9 (*c* = 0.50, MeOH). IR (KBr): $\tilde{\nu}$ = 3458, 1682, 1671, 1646 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 2.53 (dd, *J* = 15.8, 12.1 Hz, 1 H, 11-H$_a$), 2.81 (dd, *J* = 11.9, 3.5 Hz, 1 H, 11a-H), 2.96 (dd, *J* = 13.4, 4.3 Hz, 1 H, 1′-H$_a$), 3.10 (dd, *J* = 15.8, 3.5 Hz, 1 H, 11-H$_b$), 3.29 (dd, *J* = 13.4, 4.3 Hz, 1 H, 1′-H$_b$), 3.90 (d, *J* = 17.7 Hz, 1 H, 6-H$_a$), 4.18−4.23 (m, 1 H, 3-H), 5.06 (d, *J* = 17.7 Hz, 1 H, 6-H$_b$), 6.67−6.70 (m, 2 H), 6.76−6.88 (m, 3 H), 6.99−7.06 (m, 2 H), 7.23−7.25 (m, 2 H), 8.26 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 33.7 (C-11), 41.0 (C-1′), 44.7 (C-6), 54.4 (C-11a), 56.7 (C-3), 126.4 (C-7), 126.9, 127.0, 127.6, 127.9, 128.7, (CH$_{Ar}$), 128.7 (C-10) 130.7, 130.7 (CH$_{Ar}$), 131.6 (C-6a), 132.9 (C-10a), 136.0 (C-2′), 165.3 (C-4), 168.4 (C-1) ppm. MS (EI): *m/z* (%) = 306 (3) [M$^+$], 215 (7), 187 (1), 130 (4), 115 (2), 91 (5), 84 (80), 71 (16), 56 (30), 42 (100). HRMS (EI): calcd. for $C_{19}H_{18}N_2O_2$ 306.1368; found 306.1370.

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[1] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem.* **1981**, *93*, 793−795; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798−800.

[2] Reviews: [2a] C. J. Dinsmore, D. C. Beshore, *Tetrahedron* **2002**, *58*, 3297−3312. [2b] R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, **1989**. [2c]U. Schöllkopf, *Pure Appl. Chem.* **1983**, *55*, 1799−1806. [2d] U. Schöllkopf, *Top. Curr. Chem.* **1983**, *109*, 65−84.

[3] Recent examples: [3a] C. Ma, X. Liu, X. Li, J. Flippen-Anderssen, S. Yu, J. M. Cook, *J. Org. Chem.* **2001**, *66*, 4525−4542. [3b] S. D. Bull, S. G. Davies, W. O. Moss, *Tetrahedron: Asymmetry* **1998**, *9*, 321−327. [3c] V. Ojea, C. Fernandez, M. Ruiz, J. M. Quintela, *Tetrahedron Lett.* **1996**, *32*, 5801−5804. [3d] A. J. Pearson, H. Shin, *J. Org. Chem.* **1994**, *59*, 2314−2323. [3e] R. Mueller, L. Revesz, *Tetrahedron Lett.* **1994**, *35*, 4091−4092. [3f] M. Ohba, T. Mukaihira, T. Fujii, *Chem. Pharm. Bull.* **1994**, *42*, 1784. [3g] J. Paladino, C. Guyard, C. Thurieau, J. Fanchere, *Helv. Chim. Acta* **1993**, *76*, 2465−2472. [3h] J. E. Baldwin, R. M. Adlington, M. B. Mitchell, *J. Chem. Soc., Chem. Commun.* **1993**, 1332−1335.

[4] [4a] I. M. Dawson, J. A. Gregory, R. B. Herbert, P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2585−2593. [4b] I. M. Dawson, J. A. Gregory, R. B. Herbert, P. G. Sammes, *J. Chem. Soc., Chem. Commun.* **1986**, 620−621.

[5] [5a] P. Di Felice, G. Porzi, S. Sandri, *Tetrahedron: Asymmetry* **1999**, *10*, 2191−2201. [5b] G. Porzi, S. Sandri, P. Verocchio, *Tetrahedron: Asymmetry* **1998**, *9*, 119−132. [5c] V. Favero, G. Porzi, S. Sandri, *Tetrahedron: Asymmetry* **1997**, *8*, 599−612.

[6] [6a] E. M. Stocking, J. F. Sanz-Cervera, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 1675−1683. [6b] R. M. Williams, J. F. Sanz-Cervera, F. Sancenon, J. A. Marco, K. Halligan, *J. Am. Chem. Soc.* **1998**, *120*, 1090−1091.

[7] T. Kametani, N. Kanaya, M. Ikara, *J. Chem. Soc., Perkin Trans. 1* **1981**, 959−963.

[8] 5-Acyloxy-2(1*H*)-pyrazinones, which are structurally related to **3** were used as key intermediates for brevianamide A: S. Jin, P. Wessig, J. Liebscher, *J. Org. Chem.* **2001**, *66*, 3984−3997.

[9] T. Fukuyama, R. K. Frank, A. A. Laird, *Tetrahedron Lett.* **1985**, *26*, 2955−2958.

[10] L. E. Overman, M. D. Rosen, *Angew. Chem.* **2000**, *112*, 4768−4771; *Angew. Chem. Int. Ed.* **2000**, *39*, 4596−4599.

[11] L. E. Overman, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 9465−9467.

[12] S. P. Govek, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 9468−9469.

[13] For a related approach to the ABC ring system see: C. W. Ong, H. C. Lee, *Aust. J. Chem.* **1990**, *43*, 773−775.

[14] A. M. M. Mjalli, J. C. Mason, K. L. Arienti, K. M. Short, R. D. A. Kimmich, T. K. Jones, Ontogen Corporation, WO 9947549; *Chem. Abstr.* **1999**, *121*, 243287.

[15] A. Monsees, S. Laschat, S. Kotila, T. Fox, E.-U. Würthwein, *Liebigs Ann./Recueil* **1997**, 533−540.

[16] [16a] M. C. Mc Mills, D. L. Wright, J. D. Zubkowsky, E. J. Valente, *Tetrahedron Lett.* **1996**, *37*, 7205−7208. [16b] S. E. Gibson, N. Guillo, B. S. Kalindjian, J. M. Tozer, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1289−1292. [16c] J. R. Harrison, P. O′Brien, D. W. Porter, N. M. Smith, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623−3631.

[17] M. Akssirai, M. Boumzebra, H. Kasmi, A. Dakdouh, M.-L. Roumestant, P. Viallefont, *Tetrahedron* **1994**, *50*, 9051−9060.

[18] Crystallographic data (excluding structure factors) for the structures included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-181521. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[19] Chiral HPLC was performed with a Daicel CHIRALCEL OD column, *n*-hexane/*i*PrOH, 70:30 (for **5**) or *n*-hexane/*i*PrOH 55:45 (for **10f**, **11f**), flow 0.75 mL·min^{-1}, using a diode array detector.

[20] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209−220.

[21] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648−5652.

[22] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43* 2923−2925.

[23] Due to limited amounts of compounds **11e**,**g**, no optical rotations could be obtained.

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