Structural Features in the Seven-Membered vs. Fourteen-Membered Ring Cyclization of Hydroxyamido Ketals Derived from β-Amino Alcohols

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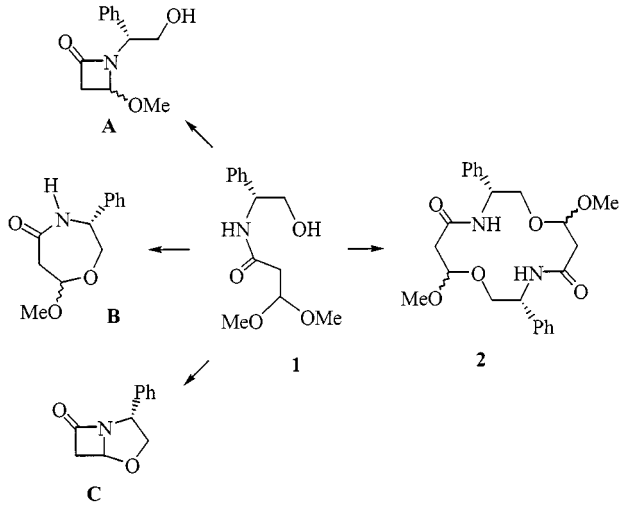
Hydroxyamido ketals **1** and **3**–**12**, prepared from β-amino alcohols, are obtained either as a single form with a *trans* (**1** and **3**–**8**) or *cis* (**9**) conformation in the R = H series or as two *cis* and *trans* rotamers in the R ≠ H series (**10**–**12**). – The cyclization of these compounds was studied under acidic conditions (PTSA) and over a well defined range of concentrations (*c* = 0.1–0.2 M). While *cis* amide **9** and mixtures of *cis* and *trans* rotamers **10**–**12** resulted practically exclusively in the formation of seven-membered ring lactams **22**–**25**, *trans* compounds **1** and **3**–**8** afforded fourteen-membered ring bislactams **2**, **13**–**18**, the formation of which involves a dimerization. Macrocycles were obtained as three diastereomers in the chiral series **2**, **13**–**16** and as two isomers in the achiral series **17** and **18**. Nineteen macrocyclic bislactams have thus been synthesized.

Introduction

Upon acidic treatment, hydroxyamido ketals such as **1**, derived from *R*-(−)-phenylglycinol, could, a priori, undergo cyclization through several modes. Formation of a four-membered (**A**) or seven-membered (**B**) ring could also compete with the formation of bicyclic derivative **C** (Scheme 1). Indeed, as we have previously reported,[1] when compound **1** was treated with PTSA, a 14-membered diketal bislactam ring **2** was formed, as a mixture of stereoisomers, in 51% yield. This dimerization−cyclization could be carried out over a well defined and unexpectedly high concentration range (*c* = 0.1−0.2 M).



Scheme 1

In order to learn more about this macrocyclization and to determine its scope and limitations, a study was undertaken, starting from several hydroxyamido ketals **3**−**12** (Scheme 2) derived from variously substituted β-amino alcohols: 1) seven of them bear a primary amine function (R = H) and are either chiral [(*S*)-(+)-alaninol, (*S*)-(+)-leucinol, (*S*)-(−)-phenylalaninol, (1*R*,2*S*)-(−)-norephedrine] or achiral compounds [amino ethanol, 2,2-dimethylamino ethanol, and amino phenol); 2) three of them possess a secondary amine function (R ≠ H) [(1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-pseudoephedrine, and (*S*)-(+)-prolinol].

In this paper we wish to describe the acid-catalyzed cyclization of the amino ketals formed from these amino alcohols and to discuss the observed cyclization modes in terms of structural analysis.

Results

Synthesis of Amido Ketals and Cyclization

The hydroxyamido ketals **3**−**12** were obtained in good yields (Scheme 2) by condensation of methyl 3,3-dimethoxypropionate with the corresponding amino alcohol in the presence of catalytic amounts of potassium cyanide.[2] The DCC−mediated condensation of 3-dimethoxypropionic acid with the amino alcohol was also found to be successful and was used for the preparation of amido ketals **9** and **11**.[3]

With these variously substituted amido ketals **3**−**12** in hand, we undertook the study of their cyclization in the presence of PTSA.[1] It can be seen from Scheme 2 that formation of either a 14-membered ring or of a 7-membered

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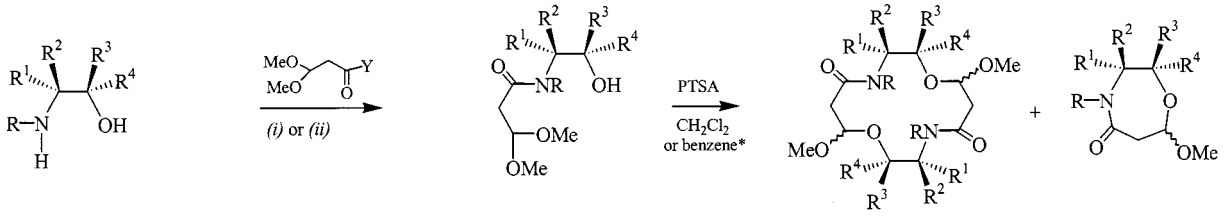


S-(+)-alaninol	R = H ; R^2 = Me ; R^1 = R^3 = R^4 = H	**3** (92%)	**13** (27%)	-
S-(+)-leucinol	R = H ; R^2 = *i*Bu ; R^1 = R^3 = R^4 = H	**4** (83%)	**14** (25%)	-
S-(-)-phenylalaninol	R = H ; R^2 = Bn ; R^1 = R^3 = R^4 = H	**5** (98%)	**15** (40%)	-
1*R*,2*S*-(-)-norephedrine	R = H ; R^2 = Me ; R^3 = Ph ; R^1 = R^4 = H	**6** (74%)	**16** (48%)	**20** (5%)
aminoethanol	R = H ; R^1 = R^2 = R^3 = R^4 = H	**7** (77%)	**17** (34%)	**21** (1%)
dimethylaminoethanol	R = H ; R^1 = R^2 = CH_3 ; R^3 = R^4 = H	**8** (64%)	**18** (12%)*	-
2-aminophenol	R = H ; R^1,R^2–R^3,R^4 = $(HC{=}CH)_4$	**9** (93%) *ii*	-	**22** (65%)
1*R*,2*S*-(-)-ephedrine	R = Me ; R^2 = Me ; R^3 = Ph ; R^1 = R^4 = H	**10** (38%)	-	**23** (38%)
1*S*,2*S*-(+)-*pseudo*-ephedrine	R = Me ; R^2 = Me ; R^4 = Ph ; R^1 = R^3 = H	**11** (60%) *ii*	-	**24** (19%)
2*S*-(+)-prolinol	R-R^2 = $(-CH_2)_3$; R^1 = R^3 = R^4 = H	**12** (83%)	**19** (2%)	**25** (55%)

(i) Y = Me : KCN, MeOH, Δ = 70 h ; *(ii)* Y = H : DCC, HOBt, THF, Δ = 5-10 h

Scheme 2

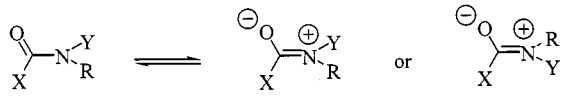
ring could be achieved in reasonable yield, depending upon the substitution pattern. The amido ketals can thus be split into two groups: one − those bearing an NH group (arising from primary amines) − being specific for the formation of 14-membered rings, the other − those incorporating an *N*-alkyl substituent −exclusively affording 7-membered rings. One exception to this assertion, however, is the formation of a 7-membered ring from the amino phenol-derived N−H amido ketal **9**. As well as this, the formation (as minor products) of oxazepines **20** (5%) and **21** (1%) in the N−H series (R = H) and of a macrocycle **19** (2%) in the *N*-alkyl series should also be noted. Variation of the solvent (CH_2Cl_2 or benzene), the number of PTSA equivalents (0.1−0.25), and the reaction time (7−24 h) permitted optimization of the yield in each case. Steric hindrance on the C-3 carbon seems to be an important obstacle in the development of the reaction (yield for compound **18** = 12%).

Distinction between seven-membered ring compounds and their symmetric fourteen-membered counterparts (vide infra), which exhibited very similar analytical data, was based on: *i)* their polarity differences in comparison with the starting hydroxyamido ketal, which was more polar than the oxazepinone and less polar than the macrocycle; *ii)* the formation of three different diastereomers in the chiral fourteen-membered rings; *iii)* the mass spectrometry data (CI or FAB^+), in which intense peaks $[M + X]^+$ (X = H, Li or Na) or $[MH - MeOH]^+$ were observed. These three criteria were used in the assignment of compounds **13−25** and without exception were found unambiguous. As the different cyclization modes allow the starting amido ketals to be split into two groups, we decided to scrutinize their structures with the hope of determining the factors that can direct towards the 7-membered ring cyclization or towards the dimerization-cyclization to form the 14-membered ring.

Isomerism − Stereochemistry

Hydroxyamido Ketals 1 and 3−12

The partial double bond character of the amide C(O)−N bond, which arises from the contribution of resonance structures **II** (Scheme 3), implies the existence of conformational isomers,[4a,5,6] the presence and identification of which have been extensively studied by NMR techniques.[4a,5]

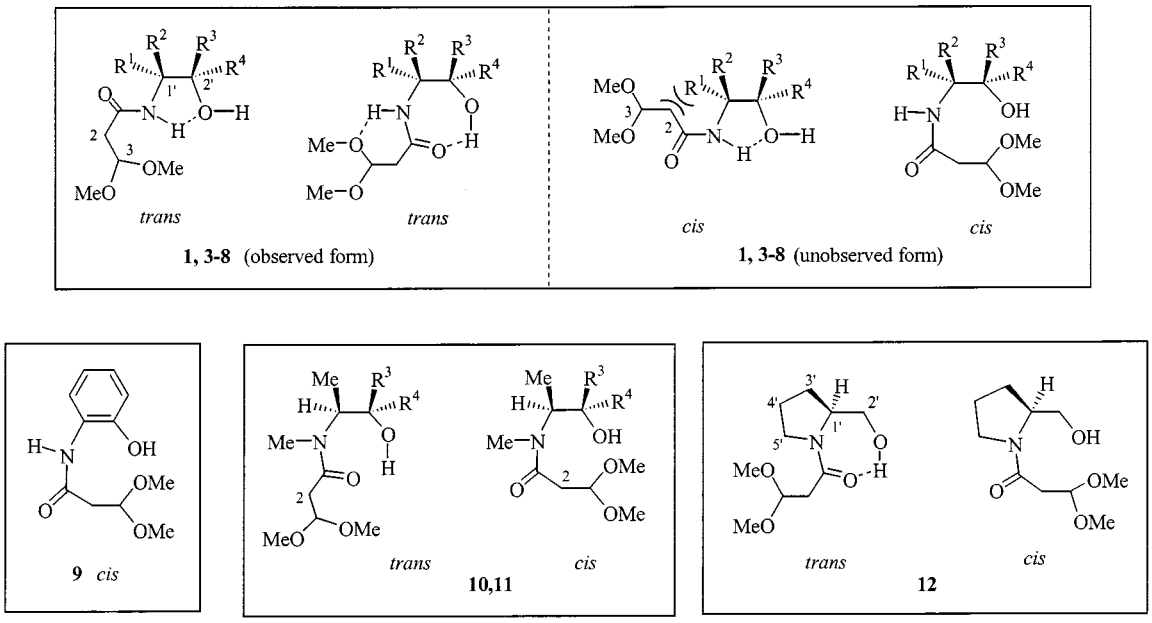


I **II**

Scheme 3

Examination of the NMR spectra ($CDCl_3$) revealed the presence of a single form for secondary amides **1** and **3−9** (R = H) and of two conformers for tertiary amides **10−12** (R ≠ H) with the following distribution: − **10**: 70:30, **11**: 60:40, **12**: 90:10.

A decrease in the temperature (−60 °C) did not change the general aspect of the ^1H NMR spectrum ($CDCl_3$) of **1**. In contrast, on increasing the temperature, the ^1H NMR spectra (DMSO) of **10** and **12** showed coalescence for all the signals of both isomers, between 95−100 °C and 90−95 °C, respectively.



Scheme 4. Different conformations of hydroxyamido ketals **1**, **3**−**12**

A thermodynamically more stable *trans* conformation (H *anti* to the carbonyl oxygen atom) was naturally assigned to the single rotamer of secondary amides **1** and **3**−**8**,[4b,5−7] since the *cis* form would display steric interactions between the N−CR^{1}R^2 substituent and the CH_2-2 group α to the carbonyl[5,6] (Scheme 4). Such interactions do not exist in the NH aromatic amide **9** (amino phenol series), in which the single form could be identified as *cis* as shown below by IR and NMR H−bonding studies.

In the case of tertiary amides **10**−**12**, the assignment of a *trans* conformation (Me or CH_2-5′ *anti* to the carbonyl oxygen atom) for the major rotamer was based on the following NMR considerations: *i)* in ^{1}H NMR, a shielding effect of C_6D_6 − relative to $CDCl_3$ − for the *N*-substituents (**10**, **11**: δ ≈ 0.60−0.90 for N−CH_3; **12**: δ ≈ 0.78−0.89 for NCH_2-5′)[5] (Table 1); *ii)* in ^{1}H NMR, a broader absorption of the NMe signal in the *cis* isomers of **10** and **11**[4c,5] (Table 2); *iii)* in ^{13}C NMR, lower field resonance of the N−CH_3 (**10**, **11**) or NCH_2-5′ group (**12**) in the *trans* derivative[8,9] (Table 3). Moreover, for amide **12** (prolinol series) additional corroboration was given by features concerning the C-3′−C-4′ bond, in the form of a lower chemical shift of the C-3′ carbon and a higher chemical shift of the C-4′ carbon in the *trans* form than in the *cis*, as reported by Bovey.[10]

Table 1. ^{1}H NMR chemical shift δ (ppm) of hydroxyamides **10**−**12** in $CDCl_3$ and C_6D_6 (ill. = illegible)

Cpd	N−R	Major isomer		Minor isomer	
		$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
10	N−Me	2.72	2.19	2.81	2.73
11	N−Me	2.87	2.22	2.93	2.79
12	NCH-5′B	3.45	2.67	ill.	ill.
	NCH-5′A	3.57	2.68	ill.	ill.

Table 2. Line width (Hz) of N−Me signal in ^{1}H NMR ($CDCl_3$)

Cpd	Major isomer	Minor isomer
10	2.0	2.3
11	2.2	2.5

Table 3. ^{13}C NMR chemical shift δ (ppm) of hydroxyamides **10**−**12** in $CDCl_3$

Cpd	N−R	Major isomer	Minor isomer
10	N−Me	32.6	28.3
11	N−Me	31.9	26.8
12	NCH_2-5′	48.3	45.6

Additionally, in the *trans* compounds, the coupling constant values observed for protons H-1′ and H-2′ (Table 4) do not correspond to the expected values for a linear chain ($J \approx 7$ Hz).

Table 4. ^{1}H-^{1}H coupling constants *J* (Hz) of hydroxyamides **1**, **3**−**7** and **10**−**12** (major isomer)

Cpd	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**11**	**12**
$J_{1'\text{-}2'B}$	6.3	4.8	5.8	4.9	3.0	5.1	5.3	9.6	7.3
$J_{1'\text{-}2'A}$	3.7	4.8	3.6	3.8		5.1			3.2

Instead, they reflect a quasi-blocked cyclic form of the molecule, probably due to one (or two) intramolecular hydrogen bonds, stabilizing the *trans* conformer (Scheme 4). The presence of such bonds involving OH and (or) NH protons could be verified by IR and NMR studies of compounds **1**, **6**, **9**, and **10**.

Thus, the IR spectra of secondary amides **1**, **6**, and **9** in CCl_4 solution are characterized by a strong absorption at 3394−3345 cm^{-1} (intramolecular associations) accompanied by two weaker vibrations at 3635−3612 cm^{-1} (free OH) and 3443−3427 cm^{-1} (free NH), intensity of which increases with dilution; in the film spectra, these absorptions are hidden by a large band at 3339−3300 cm^{-1} resulting from intermolecular associations. In tertiary amide **10** (ephedrine series), the IR spectra in solution show only two vibrations: the free OH absorption at 3620 cm^{-1} which also becomes stronger with dilution and a broad band at 3367−3402 cm^{-1} (intramolecular and intermolecular OH bonds). Moreover, the low frequencies of the carbonyl absorption (1660−1615 cm^{-1}) for *trans* hydroxyamides **1**, **3**−**8**, and **10**−**12** emphasize the participation of the CO group in intramolecular interactions. In contrast, in hydroxyamide **9** (amino phenol series), the intensity of the free OH band (3612 cm^{-1}) observed in the solution spectra does not increase with dilution; this fact implies the absence of intramolecular bonding in this compound.

Two additive studies were performed with the aid of ^1H NMR spectroscopy. Firstly, dilution of **1**, **6**, and **10** in $CDCl_3$ solution produced an upfield shift of the OH and NH resonances, demonstrating the engagement of both protons in hydrogen bonding,[11] while no such variation was observed for **9** (Table 5). Next, a study of the exchange rate of the NH hydrogen was effected by performing the spectra of hydroxyamides **1**, **6**, **8**, and **9** in $CDCl_3$ in the presence of D_2O (10 μL).[12] *N*-Ethylacetamide, which exhibits exclusively intermolecular associations, was taken as reference. The observed exchange rates (**1**: 4 h; **6**: 6 h; **8**: 8 h; **9**: 0.5 h; *N*-ethylacetamide: 2 h) reflect a high level of participation of the NH proton in intramolecular bonding, except in the case of amide **9** (amino phenol series).

Table 5. ^1H NMR chemical shift δ (ppm) of OH and NH protons in $CDCl_3$ at different concentrations

Cpd	Concentration [M]	OH	NH
	1.0	3.70	7.25
	0.5	3.40	7.14
1	0.1	2.83	6.93
	0.05	2.69	6.89
	0.01	2.57	6.85
	1.0	4.39	6.61
	0.5	4.13	6.47
6	0.1	3.71	6.27
	0.05	3.61	6.23
	0.01	3.52	6.18
	0.5	8.88	8.75
	0.1	8.82	8.57
9	0.05	8.82	8.53
	0.01	8.81	8.50
	1.0	4.31	–
	0.5	4.23	–
10	0.1	4.05	–
	0.05	4.01	–
	0.01	3.98	–

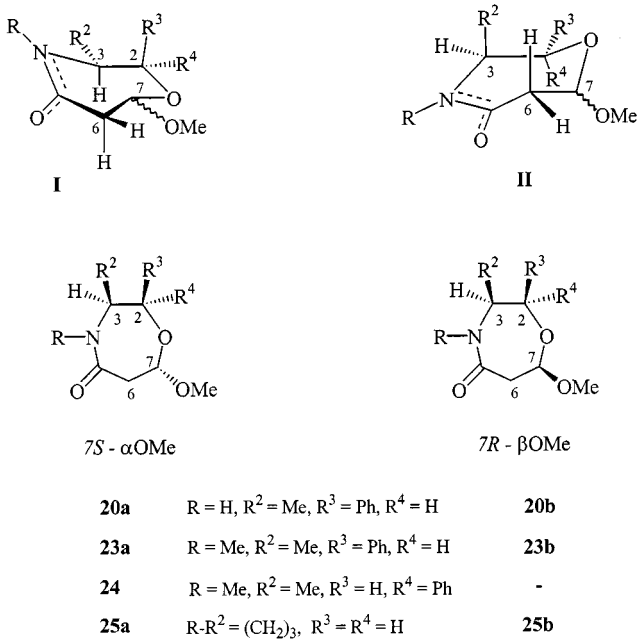
Consequently, the IR and NMR results confirm the presence of intramolecular interactions in *trans* amides. The O−H···O=C bonds formed in all compounds are probably accompanied by NH···OMe bonds in secondary amides **1** and **3**−**8**, as shown in Scheme 4. In case of hydroxyamide **9**, the absence of intramolecular association is compatible with a *cis* stereochemistry.

Seven-membered Ketal Lactams 20−25

In the chiral series, these compounds were obtained either as single isomers **24** in the pseudoephedrine series, or as mixtures of two diastereomers **a** and **b**, differing in the α or β positioning of the OMe groups, in the other series (ratios **20a**/**20b**: 60:40; **23a**/**23b**: 30:70; **25a**/**25b**: 42:58). All isomers were separated by chromatography on silica gel.

The configuration of each derivative was established on the basis of ^1H NMR spectroscopic data (coupling constants and NOESY 1D).

Of the two *pseudo*-chair conformations, **I** and **II**, that may be adopted by the seven-membered lactam ring (Scheme 5), form **I** is compatible with compounds **24** and **25** since it implies an energetically favorable equatorial position of the substituents (R^2 = Me, R^4 = Ph for **24**; R^2 = CH_2 for **25**) as confirmed by the observed J_{3-2} coupling constant values (Table 6). The coupling constants of H-7 then permit determination of the configuration at C-7: i.e., an α-equatorial positioning of the OMe group [(7*S*) configuration] in **24** and **25a** and a β-axial positioning of the OMe group [(7*R*) configuration] in **25b**.



Scheme 5

In contrast, for compounds **20** and **23,** both chair conformations afford an equatorial substituent (R^2 = Me in **I** or R^3 = Ph in **II**). In order to distinguish between the two possibilities, NOE experiments were performed on both isomers of **23**. In the less polar isomer, irradiation of the H-2 hydrogen (R^4; δ = 4.91) produced a nuclear Overhauser

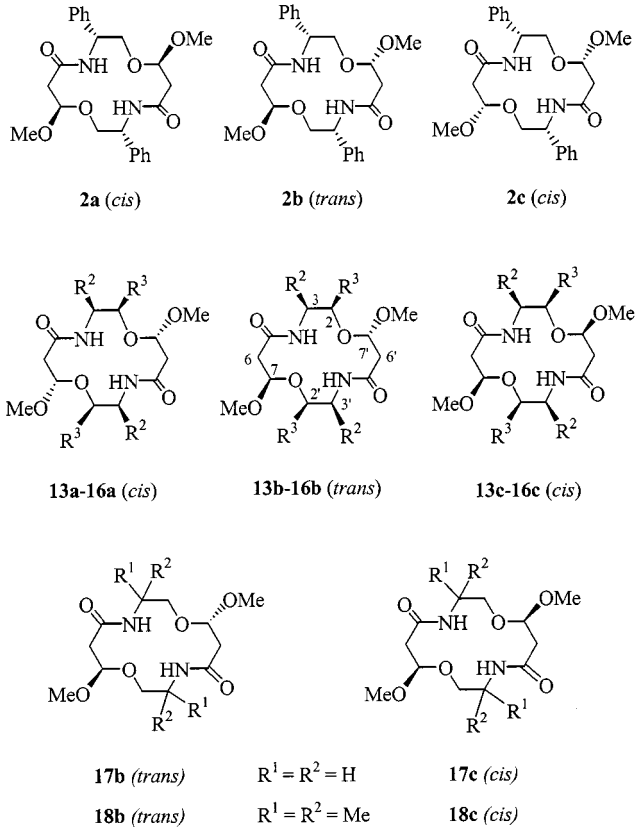
Table 6. ^{1}H-^{1}H coupling constants J (Hz) of seven-membered ring ketal lactams

Series	norephedrine		ephedrine		pseudo-ephedrine	prolinol	
Isomers	**20a**	**20b**	**23a**	**23b**	**24**	**25a**	**25b**
J_{3-2B}	2.7	2.1	1.6	1.3	9.2	8.8	1.2
J_{3-2A}						1.7	9.2
J_{7-6B}	4.4	2.0	3.2	0.9	4.2	1.0	4.4
J_{7-6A}	4.4	8.7	3.2	9.0	9.5	8.4	1.4

effect on H-7 (δ = 4.69) and vice versa, while no change was observed in the second isomer. Such effects, which may occur solely in the chair conformation **II**, with an axial H-7 proton, enable us to attribute a β-equatorial position to the OMe group: i.e., a (7*R*) configuration to the concerned isomer **23b** and consequently a (7*S*) configuration to **23a**. Identical assignments were made for compounds **20a** and **20b**.

Fourteen-membered Ring Diketal Bislactams

As previously observed for **2**,[1] the fourteen-membered rings lactams could be generated in three diastereoisomeric forms: an unsymmetrical isomer **b**,[13] in which the two OMe substituents are in a *trans* relationship, and one (for **17** and **18** where $R^1 = R^2$) or two isomers (for compounds **13**−**16**) of C_2 symmetry, in which the OMe groups are in a *cis* configuration (**a**: α-*cis*; **c**: β-*cis*) (Scheme 6).



Scheme 6

All the diastereomers could be isolated by chromatography and their analysis by NMR spectroscopy permitted the assignment of their relative configurations.

In the ^{1}H and ^{13}C NMR spectra, isomers **a** and **c** showed one signal for each pair of identical groups of the macrocycle, while isomers **b** exhibited double signals due to asymmetry of the two ring chains. COSY ^{1}H-^{1}H, HMQC ^{1}H-^{13}C, and INEPT long-range correlations[14] performed on **2b** and **13b**−**16b** allowed all hydrogens and carbons to be identified and the two chains to be distinguished. The ratios of the different isomers are reported in Table 7.

Table 7. Isomer ratio of 14 membered ring diketal bislactams

Series	R^2	R^3	Isomer ratio
(+)-alaninol	Me	H	**13a**[a] **/13b**[a]**/13c** = 8:43:49
(+)-leucinol	*i*Bu	H	**14a/14b/14c** = 8:42:50
(−)-phenylalaninol	Bn	H	**15a/15b/15c** = 6:36:58
(−)-norephedrine	Me	Ph	**16a/16b/16c** = 30:53:17

Series	$R^1 = R^2$	Isomer ratio
aminoethanol	H	**17b/17c** = 38:62
dimethylaminoethanol	Me	**18b/18c** = 55:45

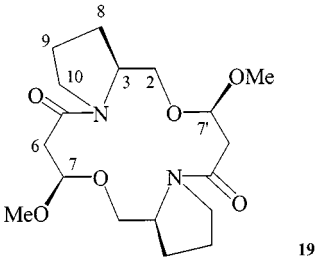
[a] Isomers **13a** and **13b** were obtained as an inseparable mixture **13a**,**b** (16:84).

*cis Isomers **a** and **c**:* In each series, the relative configuration of isomers **a** and **c** was established by comparison with their corresponding analogs in the phenylglycinol series, for which X-ray diffraction analysis was performed on **2c**.[1] A *cis* arrangement of the OMe, R^2, and R^3 groups, as exists in **2c**, could be assigned to **13c**−**16c** on the basis of the following considerations: *i)* polarity; *ii)* identical upfield or downfield chemical shifts for the NH proton in the ^{1}H NMR and for the C-6, OCH_3, C-2, and C-7 carbon atoms in the ^{13}C NMR in the **a** series relative to the **c** series (Table 8).

Table 8. Chemical shifts δ (ppm) and difference of chemical shifts Δδ (ppm) between *cis* **a** and **c** macrocycles in ^{1}H and ^{13}C NMR

δ	NH	C-6	OMe	C-2	C-7
2a	7.38	40.0	54.5	67.6	100.1
2c	7.09	41.2	53.2	70.6	101.2
2a−**2c**	+0.29	−1.2	+1.3	−3.0	−1.1
13a	6.80	39.9	54.4	66.8	99.9
13c	6.45	41.5	52.7	70.4	100.9
13a−**13c**	+0.35	−1.6	+1.7	−3.6	−1.0
14a	6.47	39.4	54.9	64.6	99.7
14c	6.35	41.6	52.8	69.6	101.2
14a−**14c**	+0.12	−2.2	+2.1	−5.0	−1.5
15a	6.68	40.3	54.4	65.4	100.3
15c	6.47	41.5	53.8	67.7	101.4
15a−**15c**	+0.21	−1.2	+0.6	−2.3	−1.1
16a	7.24	40.6	56.5	78.0	98.6
16c	7.05	40.9	54.6	80.7	100.0
16a−**16c**	+0.19	−0.3	+1.9	−2.7	−1.4

Finally, macrocycle **19** (Scheme 7), obtained from prolinol in low yield (2%), was isolated as a single isomer. According to NMR spectroscopic data, this compound displays C_2 symmetry and, consequently, a *cis* configuration. The absence of the second *cis* isomer does not permit the establishment of the OMe stereochemistry, as a function of the elements underlined in Table 8. However it should be possible to attribute a β-*cis*-OMe configuration to **19**, which would correspond to the major *cis* isomer of macrocycles **2** and **13−15**, unsubstituted at C-2.



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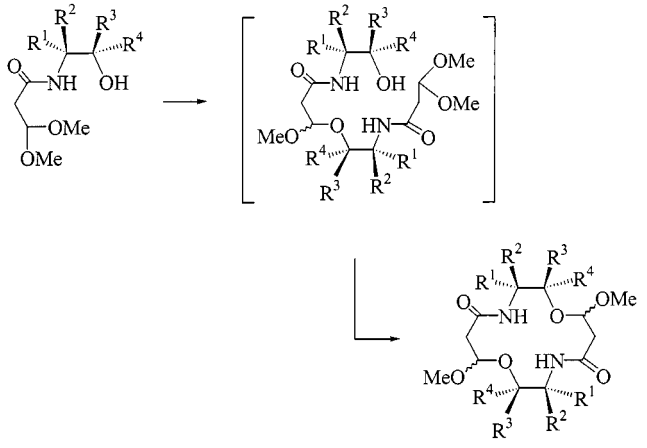
Scheme 7

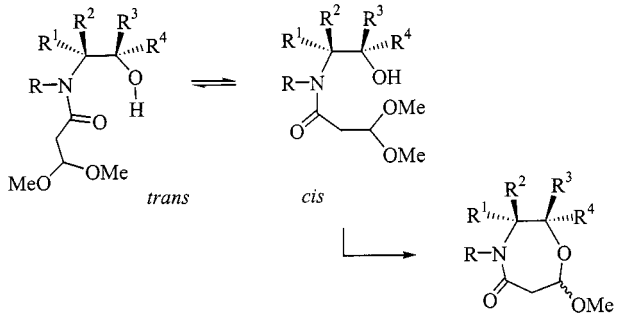
Discussion

From all the results gathered, two important features can clearly be identified. Firstly, 14-membered macrocycles are obtained practically exclusively from the secondary hydroxyamides **1** and **3−8** (R = H), which exhibit a *trans* configuration (Scheme 8). These compounds, in which the OH oxygen is too distant from the acetal carbon to allow a direct cyclization, react in a bimolecular reaction. The intermediate dimer thus formed, which possesses a *trans* + *trans* conformation, is then perfectly fitted to a ring-closure.



Scheme 8

Secondly, oxazepinones are generated by intramolecular cyclization of *cis* hydroxyamides **9** (R = H: amino phenol series) and **10−12** (R ≠ H), the conformations of which are perfectly adapted to this reaction. The rapid cyclization of the *cis* hydroxyamide probably shifts the *trans*-*cis* equilibrium of **10−12** in favor of the *cis* derivative; hence the exclusive formation of seven-membered rings (Scheme 9).



Scheme 9

Conclusion

The elaboration of macrocyclic compounds still remains an important challenge, especially in supramolecular chemistry, in which chiral receptors are of great interest.[15,16] In the course of our study, we have developed and generalized a two-step methodology for access to 14-membered diketal bislactam rings by dimerization and cyclization of hydroxyamido ketals. The reaction occurred exclusively from *trans* secondary amides, requiring the use of primary β-amino alcohols as starting material.

Macrocycles were generated: *i)* in two diastereoisomeric forms in the achiral series, *ii)* as three diastereomers, two of them displaying C_2 symmetry, in the chiral series. Nineteen macrocyclic molecules have thus been synthesized.

Various chemical transformations of these compounds can be envisaged. For example, they should be interesting intermediates for the elaboration of diketals diamines, homologues of cyclams, and also of macrobicyclic systems. These approaches will be the subject of our forthcoming investigations.

Experimental Section

Organic layers were dried with $MgSO_4$. − Thin layer chromatography was performed with Merck 60 F254 silica gel. Chromatographic purification was carried out with Merck silica gel, either 0.040−0.063 mm (flash technique) or 0.063−0.500 mm. − Melting points were measured on a Reichert hot−stage microscope and are uncorrected. − Infrared spectra were run on a Perkin−Elmer 881 spectrophotometer [$\tilde{\nu}$ in cm^{-1}]. − Mass spectra were measured on a HP 5989B (EI), AEI MS−9 (CI), or KRATOS−MS 80 (FAB^+) apparatus. − ^1H and ^{13}C NMR spectra were performed on a Bruker AC 400 spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz). Gradient COSY ^1H-^1H and HMQC ^1H-^{13}C were performed on an Avance 300 DSX Bruker spectrometer at 25 °C with 5 mm diameter tubes (^1H, 300 MHz; ^{13}C, 75 MHz). Values of δ are given in ppm and *J* values in Hz; the solvent ($CDCl_3$) was taken as an internal reference. Protons and carbons were assigned according to the numbering indicated in schemes 4, 5, 6, and 7. NOE spectra were recorded at 30 °C using the DPFGSE NOE sequence described by Stott et al.,[17] with the following parameters: mixing time, 350 ms; Gaussian 180° selective pulses (180 ms for proton H-2 and 110 ms

for H-7); 296 transients; relaxation delay, 3s. − Elemental analyses were obtained from ICSN, Gif-sur-Yvette, France.

Preparation of Hydroxyamido Ketals. − General Procedure. − Method A: A solution of amino alcohol (1.1 equiv.), methyl 3,3-dimethoxypropionate (1 equiv.), and potassium cyanide (0.1−0.15 equiv.) in dry methanol (3 mL/mmol) was refluxed for 6 days. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (2 mL/mmol). The solution was washed with water. The aqueous layer was carefully neutralized with 1 M HCl and continuously extracted with dichloromethane for 3 days in a Soxhlet apparatus. After evaporation of the solvent, the residue was washed twice with hexane to remove the excess of methyl 3,3-dimethoxypropionate. The residual oil was purified by chromatography with dichloromethane/methanol or diethyl ether/methanol.

Method B. − 3,3-Dimethoxypropionic Acid: Methyl 3,3-dimethoxypropionate (14.82 g, 100.0 mmol, 1 equiv.) was added to a solution of potassium hydroxide (8.42 g, 150.0 mmol, 1.5 equiv.) in dry methanol (200 mL). The mixture was refluxed for 5 h. The solvent was removed and the residue dissolved in dichloromethane. The solution was washed with water (3 × 40 mL). The aqueous layers were acidified with 1 M HCl (pH ≥ 3.0) and continuously extracted for 3 days with a Soxhlet apparatus. Removal of the solvent afforded 3,3-dimethoxypropanoic acid (8.60 g, 64.1 mmol, 64%) as an oil of satisfactory purity. − IR ($CHCl_3$): $\tilde{\nu}$ = 3520 cm^{-1}, 1720, 1750, 1120. − ^1H NMR ($CDCl_3$): δ = 2.76 (d, 2 H, 2 H-2, *J* = 5.8 Hz), 3.37 (s, 6 H, 2 OCH_3), 4.83 (t, 1 H, H-3, *J* = 5.8 Hz), 10.58 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 38.7 (C-2), 53.5 (O*C*H_3), 100.9 (C-3), 175.7 (*C*OOH). − MS (EI): *m*/*z* (%) = 103 (49) [$M^{+\cdot}$ − OCH_3], 75 (100), 61 (91), 47 (29), 43 (77), 29 (78).

Peptidic Condensation: A solution of 3,3-dimethoxypropanoic acid (1.05 equiv.), amino alcohol (1 equiv.), *N*,*N*-dicyclohexylcarbodiimide (1.05 equiv.), and 1-hydroxybenzotriazole (1.05 equiv.) in dry THF (20 mL/mmol) was refluxed for 5−10 h. After cooling, the mixture was filtered on Celite to remove the generated *N*,*N*-dicyclohexylurea. The solvent was evaporated and the residue purified by flash chromatography.

(1*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3,3-dimethoxypropanamide (1): This compound was prepared from (−)-phenylglycinol (6.85 g, 50.0 mmol), methyl 3,3-dimethoxypropionate (6.73 g, 45.4 mmol), and potassium cyanide (300 mg, 4.61 mmol) in dry methanol (150 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **1** as a solid (7.79 g, 30.8 mmol, yield 73%, conversion 93%). − White crystals, m.p. 61−63 °C (diethyl ether). − $[\alpha]_D^{25}$ = −50.6 (*c* = 1.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3585 cm^{-1}, 3325, 1652. − ^1H NMR ($CDCl_3$): δ = 2.60 (ABX, AB part, 2 H, H-2B, H-2A, *J* = 14.5, 5.5, 5.3 Hz, Δν = 6.8 Hz), 2.80 (br. s, 1 H, OH), 3.38 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 3.85 (A′B′X′, A′B′ part, 2 H, H-2′B, H-2′A, *J* = 11.2, 6.3, 3.7 Hz, Δν = 22.3 Hz), 4.70 (ABX, X part, 1 H, H-3, *J* = 5.5, 5.3 Hz), 5.10 (ddd, 1 H, H-1′, *J* = 6.9, 6.3, 3.7 Hz), 6.93 (d, 1 H, NH, *J* = 6.9 Hz), 7.30−7.40 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 40.9 (C-2), 54.2 (OCH_3), 54.3 (OCH_3), 55.5 (C-1′), 66.0 (C-2′), 102.3 (C-3), 126.6, 127.5, 128.6 (5 Ar-CH), 139.1 (Ar-C), 169.6 (CO). − MS (EI): *m*/*z* (%) = 222 (99) [$M^{+\cdot}$ − CH_2OH], 190 (99), 139 (34), 132 (100), 121 (89), 108 (99), 106 (81), 91 (56), 77 (75). − $C_{13}H_{19}NO_4$ (253.30): calcd. C 61.64, H 7.56, N 5.53; found C 61.85, H 7.33, N 5.52.

(1*S*)-*N*-(2-Hydroxy-1-methylethyl)-3,3-dimethoxypropanamide (3): This compound was prepared from (+)-alaninol (3.00 g, 40.0 mmol), methyl 3,3-dimethoxypropionate (5.39 g, 36.4 mmol), and potassium cyanide (236 mg, 3.62 mmol) in dry methanol (120 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **3** as a solid (6.21 g, 32.5 mmol, yield 92%, conversion 97%). − White crystals, m.p. 64 °C (diethyl ether). − $[\alpha]_D^{25}$ = −18.9 (*c* = 2.1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3630 cm^{-1}, 3440, 3380, 1660. − ^1H NMR ($CDCl_3$): δ = 1.08 (d, 3 H, CH_3, *J* = 7.0 Hz), 2.46 (d, 2 H, H-2B, H-2A, *J* = 5.4 Hz), 3.30 (s, 6 H, 2 OCH_3), 3.42 (ddd, 1 H, H-2′B, *J* = 10.3, 5.3, 4.8 Hz), 3.53 (ddd, 1 H, H-2′A, *J* = 10.3, 4.8, 4.3 Hz), 3.81 (br. s, 1 H, OH), 3.95 (qdt, 1 H, H-1′, *J* = 7.0, 7.0, 4.8 Hz), 4.64 (t, 1 H, H-3, *J* = 5.4 Hz), 6.63 (d, 1 H, NH, *J* = 7.0 Hz). − ^{13}C NMR ($CDCl_3$): δ = 18.0 (CH_3), 40.8 (C-2), 47.4 (C-1′), 54.1 (2 OCH_3), 66.1 (C-2′), 102.2 (C-3), 169.6 (CO). − MS (EI): *m*/*z* (%) = 192 (7) [MH^+], 160 (42), 128 (76), 102 (16), 86 (22), 75 (100), 70 (16), 59 (66). − $C_8H_{17}NO_4$ (191.23): calcd. C 50.25, H 8.96, N 7.33; found C 50.03, H 8.72, N 7.34.

(1*S*)-*N*-(1-*iso*-Butyl-2-hydroxyethyl)-3,3-dimethoxypropanamide (4): This compound was prepared from (+)-leucinol (2.35 g, 20.0 mmol), methyl 3,3-dimethoxypropionate (2.69 g, 18.2 mmol), and potassium cyanide (118 mg, 1.82 mmol) in dry methanol (62 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **4** as a solid (3.31 g, 14.2 mmol, yield 83%, conversion 94%). − White crystals, m.p. 47−48 °C (benzene/cyclohexane). − $[\alpha]_D^{25}$ = −35.2 (*c* = 1.8, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3635 cm^{-1}, 3440, 3380, 1660. − ^1H NMR ($CDCl_3$): δ = 0.88 (d, 3 H, CH_3, *J* = 6.5 Hz), 0.90 (d, 3 H, CH_3, *J* = 6.6 Hz), 1.29 (ddd, 1 H, H-3′B, *J* = 13.9, 8.6, 5.4 Hz), 1.36 (ddd, 1 H, H-3′A, *J* = 13.9, 9.2, 5.7 Hz), 1.61 (dqqd, 1 H, H-4′, *J* = 8.6, 6.6, 6.5, 5.7 Hz), 2.50 (d, 2 H, H-2B, H-2A, *J* = 5.4 Hz), 3.35 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.43 (br. s, 1 H, OH), 3.46 (dd, 1 H, H-2′B, *J* = 11.0, 5.8 Hz), 3.60 (dd, 1 H, H-2′A, *J* = 11.0, 3.6 Hz), 3.99 (ddddd, 1 H, H-1′, *J* = 9.2, 8.2, 5.8, 5.4, 3.6 Hz), 4.66 (t, 1 H, H-3, *J* = 5.4 Hz), 6.40 (d, 1 H, NH, *J* = 8.2 Hz). − ^{13}C NMR ($CDCl_3$): δ = 22.1 (CH_3), 23.2 (CH_3), 24.9 (C-4′), 40.1 (C-3′), 41.1 (C-2), 50.2 (C-1′), 54.3 (2 OCH_3), 66.1 (C-2′), 102.4 (C-3), 170.0 (CO). − MS (EI): *m*/*z* (%) = 234 (62) [MH^+], 216 (18), 202 (100), 170 (97), 144 (11), 128 (10), 114 (16), 86 (17), 75 (44), 59 (18), 47 (12), 43 (29), 31 (29). − $C_{11}H_{23}NO_4$ (233.31): calcd. C 56.63, H 9.94, N 6.00; found C 56.57, H 10.09, N 5.97.

(1*S*)-*N*-(1-Benzyl-2-hydroxyethyl)-3,3-dimethoxypropanamide (5): This compound was prepared from (−)-phenylalaninol (3.02 g, 20.0 mmol), methyl 3,3-dimethoxypropionate (2.69 g, 18.2 mmol), and potassium cyanide (118 mg, 1.82 mmol) in dry methanol (62 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **5** as a solid (4.01 g, 15.0 mmol, yield 98%, conversion 84%). − White crystals, m.p. 76 °C (diethyl ether). − $[\alpha]_D^{25}$ = −20.0 (*c* = 3.6, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3620 cm^{-1}, 3440, 3380, 1660. − ^1H NMR ($CDCl_3$): δ = 2.54 (ABX, AB part, 2 H, H-2B, H-2A, *J* = 15.0, 5.4, 5.4 Hz, Δν = 5.7 Hz), 2.90 (A′B′X′, A′B′ part, 2 H, H-3′B, H-3′A, *J* = 13.9, 7.5, 7.0 Hz, Δν = 23.8 Hz), 3.33 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.42 (t, 1 H, OH, *J* = 5.3 Hz), 3.59 (ddd, 1 H, H-2′B, *J* = 11.2, 5.3, 4.9 Hz), 3.69 (ddd, 1 H, H-2′A, *J* = 11.2, 5.3, 3.8 Hz), 4.22 (m, 1 H, H-1′), 4.63 (ABX, X part, 1 H, H-3, *J* = 5.4, 5.4 Hz), 6.60 (br. d, 1 H, NH, *J* = 7.5 Hz), 7.20−7.40 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 36.8 (C-2), 40.8 (Ph-*C*H_2), 52.6 (C-1′), 54.0, 54.1 (2 OCH_3), 63.6 (C-2′), 102.0 (C-3), 126.4, 128.4, 129.2 (5 Ar-CH), 137.7 (Ar-C), 169.6 (CO). − MS (EI): *m*/*z* (%) = 268 (4) [MH^+], 236 (12), 176 (18), 144 (32), 130 (16), 120 (12), 91 (59), 85 (16), 75 (100), 60 (27). − HRMS (EI): calcd. for ($C_{14}H_{21}NO_4$ + H^+) 268.1549, found 268.1557.

(1*S*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-3,3-dimethoxypropanamide (6): This compound was prepared from (−)-norephedrine (7.56 g, 50.0 mmol), methyl 3,3-dimethoxypropionate (6.73 g, 45.4 mmol), and potassium cyanide (300 mg, 4.61 mmol) in dry methanol (150 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **6** as a solid (8.21 g, 30.7 mmol, yield 74%, conversion 91%). − White crystals, m.p. 88−89 °C (diethyl ether). − $[\alpha]_D^{25} = -74.5$ (*c* = 2.6, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3605 cm^{-1}, 3381, 3430, 1655. − ^1H NMR ($CDCl_3$): δ = 1.00 (d, 3 H, CH_3, *J* = 7.0 Hz), 2.55 (d, 2 H, H-2B, H-2A, *J* = 5.3 Hz), 3.36 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.72 (d, 1 H, OH, *J* = 4.2 Hz), 4.32 (dqd, 1 H, H-1′, *J* = 7.7, 7.0, 3.0 Hz), 4.67 (t, 1 H, H-3, *J* = 5.3 Hz), 4.86 (dd, 1 H, H-2′, *J* = 4.2, 3.0 Hz), 6.26 (d, 1 H, NH, *J* = 7.7 Hz), 7.20−7.40 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 14.3 (CH_3), 40.8 (C-2), 50.9 (C-1′), 53.9 (OCH_3), 54.1 (OCH_3), 75.9 (C-2′), 102.1 (C-3), 126.3, 127.3, 128.1 (5 Ar-CH), 140.8 (Ar-C), 169.6 (CO). − MS (CI): *m*/*z* (%) = 268 (73) [MH^+], 250 (5), 236 (13), 181 (5), 57 (100). − $C_{14}H_{21}NO_4$ (267.33): calcd. C 62.90, H 7.92, N 5.24; found C 62.69, H 7.81, N 5.09.

***N*-(2-Hydroxyethyl)-3,3-dimethoxypropanamide (7):** This compound was prepared from aminoethanol (3.05 g, 50.0 mmol), methyl 3,3-dimethoxypropionate (6.73 g, 45.4 mmol), and potassium cyanide (300 mg, 4.61 mmol) in dry methanol (150 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **7** as a solid (6.04 g, 34.1 mmol, yield 77%, conversion 98%). − White crystals, m.p. 25−28 °C (diethyl ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3630 cm^{-1}, 3450, 3400, 1660. − ^1H NMR ($CDCl_3$): δ = 2.51 (d, 2 H, H-2B, H-2A, *J* = 5.4 Hz), 3.34 (s, 6 H, 2 OCH_3), 3.35 (m, 2 H, H-1′B, H-1′A), 3.63 (t, 2 H, H-2′B, H-2′A, *J* = 5.1 Hz), 3.81 (br. s, 1 H, OH), 4.67 (t, 1 H, H-3, *J* = 5.4 Hz), 6.95 (br. s, 1 H, NH). − XHCORR ^1H-^{13}C NMR ($CDCl_3$): δ = 40.6 (C-2), 42.0 (C-1′), 54.0 (2 OCH_3), 61.2 (C-2′), 102.1 (C-3), 170.1 (CO). − MS (EI): *m*/*z* (%) = 146 (9) [$M^{+\cdot} - CH_2OH$], 129 (14), 114 (30), 85 (19), 75 (100), 59 (48), 58 (36), 43 (30), 28 (27). − $C_7H_{15}NO_4$ (177.20): calcd. C 47.45, H 8.53, N 7.90; found C 47.17, H 8.42, N 7.79.

***N*-(2-Hydroxy-1,1-dimethylethyl)-3,3-dimethoxypropanamide (8):** This compound was prepared from 2-amino-2-methyl-1-propanol (4.46 g, 50.0 mmol), methyl 3,3-dimethoxypropionate (6.73 g, 45.4 mmol), and potassium cyanide (300 mg, 4.61 mmol) in dry methanol (150 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **8** as a solid (3.96 g, 19.3 mmol, yield 64%, conversion 66%). − Crystals, m.p. 68−71 °C (diethyl ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3630 cm^{-1}, 3435, 3370, 1655. − ^1H NMR ($CDCl_3$): δ = 1.27 (s, 6 H, 2 CH_3), 2.50 (d, 2 H, H-2B, H-2A, *J* = 5.3 Hz), 3.40 (s, 6 H, 2 OCH_3), 3.57 (d, 2 H, H-2′B, H-2′A, *J* = 6.4 Hz), 4.64 (t, 1 H, H-3, *J* = 5.3 Hz), 4.67 (t, 1 H, OH, *J* = 6.4 Hz), 6.25 (br. s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 24.6 (2 CH_3), 41.5 (C-2), 54.3 (2 OCH_3), 56.1 (C-1′), 70.1 (C-2′), 102.3 (C-3), 170.0 (CO). − MS (EI): *m*/*z* (%) = 174 (12) [$M^{+\cdot} - CH_2OH$], 142 (23), 84 (19), 75 (35), 58 (42), 45 (100), 44 (38). − $C_9H_{19}NO_4$ (205.26): calcd. C 52.67, H 9.33, N 6.82; found C 52.72, H 9.38, N 6.81.

***N*-(2-Hydroxyphenyl)-3,3-dimethoxypropanamide (9):** This compound was prepared from 2-amino phenol (327 mg, 3.00 mmol), 3,3-dimethoxypropionic acid (422 mg, 3.15 mmol), *N*,*N*-dicyclohexylcarbodiimide (650 mg, 3.15 mmol), and 1-hydroxybenzotriazole (426 mg, 3.15 mmol) in dry THF (60 mL), according to method B. Chromatography with cyclohexane/ethyl acetate (gradient: 100:0→50:50) afforded **9** as a solid (630 mg, 2.80 mmol, 93%). − White crystals, m.p. 119−120 °C (diethyl ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3580 cm^{-1}, 3420, 3340, 1655, 1600. − ^1H NMR ($CDCl_3$): δ = 2.79 (d, 2 H, H-2B, H-2A, *J* = 5.1 Hz), 3.45 (s, 6 H, 2 OCH_3), 4.76 (t, 1 H, H-3, *J* = 5.1 Hz), 6.85 (td, 1 H, H-4′, *J* = 8.2, 1.1 Hz), 6.99 (dd, 1 H, H-6′, *J* = 8.1, 1.1 Hz), 7.09 (td, 1 H, H-5′, *J* = 8.2, 1.3 Hz), 7.20 (dd, 1 H, H-3′, *J* = 8.2, 1.3 Hz), 8.70 (br. s, 1 H, NH), 8.87 (s, 1 H, OH). − ^{13}C NMR ($CDCl_3$): δ = 41.1 (C-2), 54.5 (OCH_3), 101.9 (C-3), 119.0 (C-3′), 120.4 (C-5′), 122.2 (C-6′), 125.7 (C-1′), 126.8 (C-4′), 148.3 (C-2′), 169.1 (CO). − MS (EI): *m*/*z* (%) = 225 (6) [M^+], 193 (24), 135 (47), 109 (29), 85 (100), 75 (57), 59 (25), 47 (24). − $C_{11}H_{15}NO_4$ (225.25): calcd. C 58.65, H 6.71, N 6.22; found C 58.86, H 6.77, N 6.43.

(1*S*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-3,3-dimethoxy-*N*-methylpropanamide (10): This compound was prepared from (−)-ephedrine (8.26 g, 50.0 mmol), methyl 3,3-dimethoxypropionate (6.73 g, 45.4 mmol), and potassium cyanide (450 mg, 6.91 mmol) in dry methanol (150 mL), according to method A. Chromatography with dichloromethane/methanol (gradient: 100:0→90:10) afforded **10** as an oil (4.50 g, 16.0 mmol, yield 38%, conversion 92%). − Two rotamers (maj./min.: 70:30). − $[\alpha]_D^{25} = -83.2$ (*c* = 2.7, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3620 cm^{-1}, 3330, 1630. − ^1H NMR ($CDCl_3$): *major isomer:* δ = 1.20 (d, 3 H, CH_3, *J* = 7.0 Hz), 2.62 (d, 2 H, H-2B, H-2A, *J* = 5.5 Hz), 2.72 (s, 3 H, NCH_3), 3.41 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 4.03 (br. s, 1 H, OH), 4.55 (qd, 1 H, H-1′, *J* = 7.0, 5.3 Hz), 4.84 (d, 1 H, H-3, *J* = 5.5 Hz), 4.85 (d, 1 H, H-2′, *J* = 5.3 Hz), 7.24−7.42 (m, 5 H, 5 Ar-H); *minor isomer:* δ = 1.35 (d, 3 H, CH_3, *J* = 6.5 Hz), 2.16 (dd, 1 H, H-2B, *J* = 14.9, 4.3 Hz), 2.51 (dd, 1 H, H-2A, *J* = 14.9, 6.6 Hz), 2.81 (s, 3 H, NCH_3), 3.29 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 4.00 (br. s, 1 H, OH), 4.09 (dq, 1 H, H-1′, *J* = 7.0, 6.5 Hz), 4.68 (d, 1 H, H-2′, *J* = 7.0 Hz), 4.69 (dd, 1 H, H-3, *J* = 6.6, 4.3 Hz), 7.24−7.42 (m, 5 H, 5 Ar-H). − XHCORR ^1H-^{13}C NMR ($CDCl_3$): *major isomer:* δ = 11.9 (CH_3), 32.6 (NCH_3), 38.3 (C-2), 54.3 (OCH_3), 54.5 (OCH_3), 56.6 (C-1′), 76.6 (C-2′), 103.0 (C-3), 126.2, 127.3, 127.9 (5 Ar-CH), 141.8 (Ar-C), 170.7 (CO); *minor isomer:* δ = 14.4 (CH_3), 28.3 (NCH_3), 37.4 (C-2), 53.6 (OCH_3), 54.8 (OCH_3), 58.4 (C-1′), 75.4 (C-2′), 103.0 (C-3), 125.9, 127.7, 128.2 (5 Ar-CH), 142.3 (Ar-C), 169.4 (CO). − MS (EI): *m*/*z* (%) = 282 (100) [MH^+], 264 (31), 250 (24), 174 (11), 107 (9), 79 (23), 77 (22), 75 (27), 58 (30), 42 (17). − HRMS (EI): calcd. for ($C_{15}H_{23}NO_4 + H^+$) 282.1705, found 282.1725.

(1*S*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-3,3-dimethoxy-*N*-methylpropanamide (11): This compound was prepared from (+)-pseudoephedrine (99 mg, 0.60 mmol), 3,3-dimethoxypropionic acid (84 mg, 0.63 mmol), *N*,*N*-dicyclohexylcarbodiimide (130 mg, 0.63 mmol), and 1-hydroxybenzotriazole (85 mg, 0.63 mmol) in dry THF (12 mL), according to method B. Chromatography with diethyl ether/methanol (gradient: 100:0→95:5) afforded **11** as an oil (100 mg, 0.36 mmol, 60%). − Two rotamers (maj./min.: 60:40). − $[\alpha]_D^{25} = +102.9$ (*c* = 3.7, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3618 cm^{-1}, 3470, 1630, 1660. − ^1H NMR ($CDCl_3$): *major isomer:* δ = 1.05 (d, 3 H, CH_3, *J* = 6.5 Hz), 2.67 (ABX, X part, 2 H, H-2B, H-2A, *J* = 14.8, 5.6, 5.2 Hz, Δν = 20.6 Hz), 2.87 (s, 3 H, NCH_3), 3.40 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.97 (br. s, 1 H, OH), 4.10 (dq, 1 H, H-1′, *J* = 9.6, 6.5 Hz), 4.56 (dd, 1 H, H-2′, *J* = 10.8, 9.6 Hz), 4.84 (ABX, X part, 1 H, H-3, *J* = 5.6, 5.2 Hz), 7.20−7.40 (m, 5 H, 5 Ar-H); *minor isomer:* δ = 0.96 (d, 3 H, CH_3, *J* = 6.7 Hz), 2.74 (ABX, X part, 2 H, H-2B, H-2A, *J* = 14.8, 5.6, 5.6 Hz, Δν = 42.8 Hz), 2.93 (s, 3 H, NCH_3), 3.43 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 4.52 (d, 1 H, H-2′, *J* = 9.0 Hz), 4.56 (br. s, 1 H, OH), 4.59 (dq, 1 H, H-1′, *J* = 9.0, 6.7 Hz), 4.87 (ABX, X part, 1 H, H-3, *J* = 5.6, 5.6 Hz), 7.20−7.40 (m, 5 H, 5 Ar-H). − XHCORR ^1H-^{13}C NMR ($CDCl_3$): *major isomer:* δ = 14.1 (CH_3), 31.9 (NCH_3), 38.4

(C-2), 54.3 (OCH_3), 54.6 (OCH_3), 58.6 (C-1′), 75.7 (C-2′), 103.1 (C-3), 126.6, 127.5, 128.1 (5 Ar-CH), 141.9 (Ar-C), 171.2 (CO); *minor isomer:* 15.3 (CH_3), 26.8 (NCH_3), 37.8 (C-2), 54.1 (OCH_3), 54.6 (OCH_3), 56.9 (C-1′), 75.1 (C-2′), 103.3 (C-3), 126.7, 127.9, 128.4 (5 Ar-CH), 141.8 (Ar-C), 170.1 (CO). − MS (EI): *m/z* (%) = 282 (100) [MH^+], 264 (16), 250 (37), 174 (39), 107 (8), 75 (44), 58 (100), 42 (21). − HRMS (EI): calcd. for ($C_{15}H_{23}NO_4$ + H^+) 282.1705, found 282.1728.

(2*S*)-1-(3,3-Dimethoxypropionyl)-2-hydroxymethylpyrrolidine (12): This compound was prepared from (+)-prolinol (4.05 g, 40.0 mmol), methyl 3,3-dimethoxypropionate (5.39 g, 36.4 mmol), and potassium cyanide (236 mg, 3.62 mmol) in 120 mL of dry methanol, according to method A. Chromatography with diethyl ether/methanol (gradient: 100:0→95:5) afforded **12** as an oil (6.47 g, 29.8 mmol, yield 83%, conversion 98%). − Two rotamers (maj./min.: 90:10). − $[\alpha]_D^{25}$ = −52.2 (*c* = 1.4; $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3690 cm^{-1}, 3610, 3350, 1615, 1500. − ^1H NMR ($CDCl_3$): *major isomer:* δ = 1.60 (dq, 1 H, H-3′B, *J* = 12.6, 6.3 Hz), 1.82 (m, 1 H, H-4′B), 1.88 (m, 1 H, H-4′A), 1.98 (dq, 1 H, H-3′A, *J* = 12.6, 7.3 Hz), 2.60 (ABX, AB part, 2 H, H-2B, H-2A, *J* = 15.0, 5.3, 5.3 Hz, Δ = 5.8 Hz), 3.36 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.45 (dt, 1 H, H-5′B, *J* = 10.2, 6.7 Hz), 3.53 (m, 1 H, H-2′B), 3.57 (m, 1 H, H-5′A), 3.60 (ddd, 1 H, H-2′A, *J* = 11.2, 7.5, 3.2 Hz), 4.15 (tdd, 1 H, H-1′, *J* = 7.3, 6.3, 3.2 Hz), 4.79 (ABX, X part, 1 H, H-3, *J* = 5.3, 5.3 Hz), 4.87 (dd, 1 H, OH, *J* = 7.5, 2.7 Hz); *minor isomer:* δ = 1.56−2.06 (m, 4 H, H-3′B, H-3′A, H-4′B, H-4′A), 2.56 (dd, 1 H, H-2B, *J* = 14.1, 4.9 Hz), 2.87 (dd, 1 H, H-2A, *J* = 14.1, 6.9 Hz), 3.33 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.38−3.68 (m, 4 H, H-5′B, H-5′A, H-2′B, H-2′A), 4.02 (m, 1 H, H-1′), 4.89 (dd, 1 H, H-3, *J* = 6.9, 4.9 Hz). − XHCORR ^1H-^{13}C NMR ($CDCl_3$): *major isomer:* δ = 24.2 (C-4′), 28.1 (C-3′), 39.6 (C-2), 48.3 (C-5′), 54.7 (OCH_3), 60.8 (C-1′), 66.4 (C-2′), 103.0 (C-3), 170.4 (CO); *minor isomer:* δ = 22.0 (C-4′), 28.4 (C-3′), 38.8 (C-2), 45.6 (C-5′), 54.3 (OCH_3), 59.5 (C-1′), 64.2 (C-2′), 103.6 (C-3), 168.6 (CO). − MS (EI): *m/z* (%) = 186 (35) [$M^{+\cdot}$ − CH_2OH], 154 (7), 128 (10), 85 (14), 75 (65), 70 (100), 58 (11), 43 (18), 31 (19). − HRMS (EI): calcd. for ($C_{10}H_{19}NO_4$ + H^+) 217.1392, found 217.1374.

Cyclization of Hydroxyamido Ketals. − General Procedure: *para*-Toluenesulfonic acid (PTSA) (0.10−0.15 equiv.) was added to a stirred solution of hydroxyamido ketal (1 equiv.) in dry dichloromethane (*c* = 0.15−0.20 M) or dry benzene (*c* = 0.15 M). The mixture was refluxed for 7−24 h under a Soxhlet extractor containing 4 Å molecular sieves. The solution was neutralized with K_2CO_3 (2 equiv.)/PTSA. After filtration, the solvent was removed. The residual oil was purified by flash chromatography.

(+)-Alaninol Series: (1*S*)-*N*-(2-Hydroxy-1-methylethyl)-3,3-dimethoxypropanamide (**3**) (382 mg, 2.0 mmol) and PTSA (38 mg, 0.20 mmol, 0.1 equiv.) in CH_2Cl_2 (10 mL, *c* = 0.20 M) were refluxed for 9 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **13** as three diastereomers **a**,**b**,**c** (85 mg, 0.27 mmol, 27%, ratio 8:43:49), two of which (**a**,**b**) showed identical R_f values.

14-Membered Ring 13a/13b (13:87): White crystals, m.p. 168−170 °C (methanol). − IR ($CHCl_3$): $\tilde{\nu}$ = 3440 cm^{-1}, 3385, 1660.

13a: ^1H NMR ($CDCl_3$): δ = 1.26 (d, 6 H, CH_3, CH_3′, *J* = 6.7 Hz), 2.55 (dd, 2 H, H-6B, H-6′B, *J* = 16.1, 2.1 Hz), 2.74 (dd, 2 H, H-6A, H-6′A, *J* = 16.1, 7.5 Hz), 3.38 (s, 6 H, 2 OCH_3), 3.43 (dd, 2 H, H-2B, H-2′B, *J* = 10.0, 4.3 Hz), 3.73 (dd, 2 H, H-2A, H-2′A, *J* = 10.0, 3.2 Hz), 4.19 (m, 2 H, H-3, H-3′), 4.77 (dd, 2 H, H-7, H-7′, *J* = 7.5, 2.1 Hz), 6.80 (d, 2 H, NH, NH′, *J* = 7.0 Hz). − ^{13}C NMR ($CDCl_3$): δ = 18.1 (2 CH_3), 39.9 (C-6, C-6′), 44.8 (C-3, C-3′), 54.4 (2 OCH_3), 66.8 (C-2, C-2′), 99.9 (C-7, C-7′), 167.9 (2 CO).

13b: COSY ^1H−^1H NMR ($CDCl_3$): δ = 1.24 (d, 6 H, CH_3, CH_3′, *J* = 6.4 Hz), 2.50 (dd, 1 H, H-6B, *J* = 16.1, 1.8 Hz), 2.54 (ABX, AB part, 2 H, H-6′B, H-6′A, *J* = 13.4, 9.3, 1.9 Hz, Δν = 11.6 Hz), 2.77 (dd, 1 H, H-6A, *J* = 16.1, 8.6 Hz), 3.32 (dd, 1 H, H-2′B, *J* = 9.7, 4.8 Hz), 3.35 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.44 (dd, 1 H, H-2B, *J* = 9.1, 2.7 Hz), 3.75 (dd, 1 H, H-2A, *J* = 9.1, 2.1 Hz), 3.77 (dd, 1 H, H-2′A, *J* = 9.7, 2.7 Hz), 4.25 (m, 1 H, H-3), 4.32 (m, 1 H, H-3′), 4.74 (dd, 1 H, H-7, *J* = 8.6, 1.8 Hz), 4.75 (ABX, X part, 1 H, H-7′, *J* = 9.3, 1.9 Hz), 6.00 (d, 1 H, NH′, *J* = 8.0 Hz), 7.04 (d, 1 H, NH, *J* = 8.6 Hz). − HMQC ^1H-^{13}C NMR ($CDCl_3$): δ = 17.7 (2 CH_3), 39.4 (C-6), 41.9 (C-6′), 44.2 (C-3), 44.6 (C-3′), 52.8, 54.2 (2 OCH_3), 65.7 (C-2′), 71.0 (C-2), 99.7 (C-7), 101.3 (C-7′), 167.8 (CO), 168.3 (CO′).

14-Membered Ring 13c: White crystals, m.p. 180−182 °C (methanol). − $[\alpha]_D^{25}$ = +14.0 (*c* = 1.3, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3440 cm^{-1}, 3390, 1660. − ^1H NMR ($CDCl_3$): δ = 1.25 (d, 6 H, CH_3, CH_3′, *J* = 7.0 Hz), 2.56 (ABX, AB part, 4 H, H-6B, H-6′B, H-6A, H-6′A, *J* = 14.5, 8.5, 2.2 Hz, Δν = 17.4 Hz), 3.33 (s, 6 H, 2 OCH_3), 3.55 (dd, 2 H, H-2B, H-2′B, *J* = 9.6, 2.9 Hz), 3.67 (dd, 2 H, H-2A, H-2′A, *J* = 9.6, 3.2 Hz), 4.20 (dqdd, 2 H, H-3, H-3′, *J* = 7.5, 7.0, 3.2, 2.9 Hz), 4.69 (ABX, X part, 2 H, H-7, H-7′, *J* = 8.5, 2.2 Hz), 6.45 (d, 2 H, NH, NH′, *J* = 7.5 Hz). − ^{13}C NMR ($CDCl_3$): δ = 17.5 (2 CH_3), 41.5 (C-6, C-6′), 44.7 (C-3, C-3′), 52.7 (2 OCH_3), 70.4 (C-2, C-2′), 100.9 (C-7, C-7′), 168.3 (2 CO). − MS (CI): *m/z* (%) = 319 (86) [MH^+], 287 (16) [MH^+ − CH_3OH], 257 (2) [MK^+], 57 (100). − $C_{14}H_{26}N_2O_6$ (318.37): calcd. C 52.81, H 8.23, N 8.80; found C 53.34, H 8.11, N 8.46.

(+)-Leucinol Series: (1*S*)-*N*-(1-*iso*-Butyl-2-hydroxyethyl)-3,3-dimethoxypropanamide (**4**) (1.16 g, 5.0 mmol) and PTSA (142 mg, 0.75 mmol, 0.15 equiv.) in CH_2Cl_2 (33 mL, *c* = 0.15 M) were refluxed for 9 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **14** as three diastereomers **a**,**b**,**c** (251 mg, 0.62 mmol, 25%, ratio 8:42:50).

14-Membered Ring 14a: White crystals, m.p. 196−198 °C (ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3390 cm^{-1}, 1660. − ^1H NMR ($CDCl_3$): δ = 0.95 (d, 12 H, 4 CH_3, *J* = 6.3 Hz), 1.35 (m, 2 H, H-8B, H-8′B), 1.60 (m, 4 H, H-8A, H-8′A, H-9, H-9′), 2.54 (dd, 2 H, H-6B, H-6′B, *J* = 16.5, 2.2 Hz), 2.75 (dd, 2 H, H-6A, H-6′A, *J* = 16.5, 7.9 Hz), 3.38 (s, 6 H, 2 OCH_3), 3.47 (dd, 2 H, H-2B, H-2′B, *J* = 9.4, 2.8 Hz), 3.67 (dd, 2 H, H-2A, H-2′A, *J* = 9.4, 2.8 Hz), 4.23 (dtt, 2 H, H-3, H-3′, *J* = 8.8, 6.1, 2.8 Hz), 4.78 (dd, 2 H, H-7, H-7′, *J* = 7.9, 2.2 Hz), 6.47 (d, 2 H, 2 NH, *J* = 8.8 Hz). − ^{13}C NMR ($CDCl_3$): δ = 22.6 (2 CH_3), 22.9 (2 CH_3), 25.2 (C-9, C-9′), 39.4 (C-6, C-6′), 41.0 (C-8, C-8′), 46.7 (C-3, C-3′), 54.9 (2 OCH_3), 64.6 (C-2, C-2′), 99.7 (C-7, C-7′), 167.8 (2 CO). − MS (CI): *m/z* (%) = 441 (3) [MK^+], 403 (100) [MH^+], 371 (44) [MH^+ − CH_3OH], 202 (24) [M/2 + H^+], 146 (23), 117 (22), 113 (33), 102 (21), 88 (16), 77 (14), 73 (100), 57 (100).

14-Membered Ring 14b: White crystals, m.p. 131−133 °C (ether). − $[\alpha]_D^{25}$ = −35.8 (*c* = 1.1 $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3440 cm^{-1}, 3380, 1665. − COSY ^1H-^1H NMR ($CDCl_3$): δ = 0.92 (d, 6 H, 2 CH_3, *J* = 6.5 Hz), 0.93 (d, 6 H, 2 CH_3′, *J* = 6.5 Hz), 1.35 (ddd, 1 H, H-8B, *J* = 13.5, 8.1, 5.8 Hz), 1.39 (ddd, 1 H, H-8′B, *J* = 13.5, 7.5, 6.4 Hz), 1.53 (m, 1 H, H-8′A), 1.56 (m, 1 H, H-8A), 1.64 (m, 2 H, H-9, H-9′), 2.50 (dd, 1 H, H-6B, *J* = 16.8, 1.7 Hz), 2.52 (ABX, AB part, 2 H, H-6′B, H-6′A, *J* = 13.4, 9.3, 2.1 Hz, Δν = 14.3 Hz), 2.79 (dd, 1 H, H-6A, *J* = 16.8, 8.7 Hz), 3.34 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 3.39 (br. d, 1 H, H-2′B, *J* = 9.3, 0.5 Hz), 3.42 (dd, 1 H, H-2B, *J* = 9.1, 2.7 Hz), 3.72 (dd, 1 H, H-2′A, *J* = 9.3, 2.6 Hz),

3.82 (dd, 1 H, H-2A, J = 9.1, 1.4 Hz), 4.23 (m, 1 H, H-3), 4.25 (m, 1 H, H-3′), 4.73 (ABX, X part, 1 H, H-7′, J = 9.3, 2.1 Hz), 4.74 (dd, 1 H, H-7, J = 8.7, 1.7 Hz), 5.88 (d, 1 H, NH′, J = 9.1 Hz), 6.96 (d, 1 H, NH, J = 9.4 Hz). − HMQC ^{1}H-^{13}C NMR ($CDCl_3$): δ = 22.3, 22.6, 22.9, 23.0 (4 CH_3), 24.9, 25.1 (C-9, C-9′), 39.0 (C-6), 40.7 (C-8), 41.3 (C-8′), 42.1 (C-6′), 46.3 (C-3′), 46.9 (C-3), 52.6, 54.8 (2 OCH_3), 63.8 (C-2′), 70.3 (C-2), 99.6 (C-7), 101.5 (C-7′), 167.7 (CO), 168.5 (CO′). − MS (CI): m/z (%) = 403 (100) [MH^+], 371 (44) [$MH^+ - CH_3OH$], 202 (29) [M/2 + H^+], 234 (80), 160 (89), 146 (100), 57 (100).

14-Membered Ring 14c: White crystals, m.p. 140−142 °C (ether). − $[\alpha]_D^{25}$ = −19.5 (c = 0.93, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3445 cm^{-1}, 3390, 1660. − ^{1}H NMR ($CDCl_3$): δ = 0.92 (d, 6 H, 2 CH_3, J = 6.5 Hz), 0.94 (d, 6 H, 2 CH_3, J = 6.5 Hz), 1.38 (ddd, 2 H, H-8B, H-8′B, J = 13.9, 7.5, 6.5 Hz), 1.51 (ddd, 2 H, H-8A, H-8′A, J = 13.9, 8.5, 6.5 Hz), 1.62 (nonuplet, 2 H, H-9, H-9′, J = 6.5 Hz), 2.54 (ABX, AB part, 4 H, H-6B, H-6′B, H-6A, H-6′A, J = 13.9, 8.3, 1.8 Hz, Δν = 10.9 Hz), 3.32 (s, 6 H, 2 OCH_3), 3.51 (dd, 2 H, H-2B, H-2′B, J = 9.3, 2.6 Hz), 3.70 (dd, 2 H, H-2A, H-2′A, J = 9.3, 2.6 Hz), 4.17 (dddt, 2 H, H-3, H-3′, J = 9.0, 8.5, 7.5, 2.6 Hz), 4.65 (ABX, X part, 2 H, H-7, H-7′, J = 8.3, 1.8 Hz), 6.35 (d, 2 H, 2 NH, J = 9.0 Hz). − ^{13}C NMR ($CDCl_3$): δ = 22.5 (2 CH_3), 22.8 (2 CH_3), 24.9 (C-9, C-9′), 40.8 (C-8, C-8′), 41.6 (C-6, C-6′), 47.0 (C-3, C-3′), 52.8 (2 OCH_3), 69.6 (C-2, C-2′), 101.2 (C-7, C-7′), 168.4 (2 CO). − MS (CI): m/z (%) = 403 (100) [MH^+], 371 (44) [$MH^+ - CH_3OH$], 291 (23), 234 (80), 202 (29) [M/2 + H^+], 160 (89), 146 (98), 57 (100). − $C_{20}H_{38}N_2O_6$ (402.54): calcd. C 59.67, H 9.52, N 6.96; found C 59.40, H 9.38, N 6.99.

(−)-Phenylalaninol Series: (1*S*)-*N*-(1-Benzyl-2-hydroxyethyl)-3,3-dimethoxypropanamide (**5**) (1.34 g, 5.0 mmol) and PTSA (95 mg, 0.50 mmol, 0.1 equiv.) in CH_2Cl_2 (33 mL, c = 0.15 M) were refluxed for 9 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **15** as three diastereomers **a**,**b**,**c** (466 mg, 0.99 mmol, 40%, ratio 6:36:58).

14-Membered Ring 15a: White crystals, m.p. 222−224 °C (methanol). − $[\alpha]_D^{25}$ = −54.1 (c = 0.73, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3390 cm^{-1}, 1665. − ^{1}H NMR ($CDCl_3$): δ = 2.47 (dd, 2 H, H-6B, H-6′B, J = 15.5, 2.0 Hz), 2.70 (dd, 2 H, H-6A, H-6′A, J = 15.5, 6.6 Hz), 2.85 (dd, 2 H, H-8B, H-8′B, J = 13.5, 8.5 Hz), 3.01 (dd, 2 H, H-8A, H-8′A, J = 13.5, 5.6 Hz), 3.32 (s, 6 H, 2 OCH_3), 3.38 (dd, 2 H, H-2B, H-2′B, J = 9.5, 4.0 Hz), 3.76 (dd, 2 H, H-2A, H-2′A, J = 9.5, 3.0 Hz), 4.30 (m, 2 H, H-3, H-3′), 4.64 (dd, 2 H, H-7, H-7′, J = 6.6, 2.0 Hz), 6.68 (br. d, 2 H, NH, N′H, J = 8.0 Hz), 7.20−7.40 (m, 10 H, 10 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 37.8 (C-8, C-8′), 40.3 (C-6, C-6′), 50.1 (C-3, C-3′), 54.4 (2 OCH_3), 65.4 (C-2, C-2′), 100.3 (C-7, C-7′), 126.7 (2 Ar-CH), 128.5 (4 Ar-CH), 129.4 (4 Ar-CH), 138.0 (2 Ar-C), 168.9 (2 CO).

14-Membered Ring 15b: White crystals, m.p. 194−197 °C (methanol). − $[\alpha]_D^{25}$ = −21.9 (c = 1.0, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3440 cm^{-1}, 3385, 1660. − COSY ^{1}H-^{1}H NMR ($CDCl_3$): δ = 2.47 (dd, 1 H, H-6B, J = 16.1, 1.8 Hz), 2.48 (ABX, AB part, 2 H, H-6′B, H-6′A, J = 13.8, 8.7, 2.1 Hz, Δν = 28.3 Hz), 2.76 (dd, 1 H, H-6A, J = 16.1, 7.9 Hz), 2.90 (m, 4 H, 2 H-8, 2 H-8′), 3.24 (dd, 1 H, H-2′B, J = 9.6, 4.8 Hz), 3.31 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.34 (dd, 1 H, H-2B, J = 8.8, 3.0 Hz), 3.80 (dd, 1 H, H-2A, J = 8.8, 2.5 Hz), 3.82 (dd, 1 H, H-2′A, J = 9.6, 3.0 Hz), 4.34 (m, 1 H, H-3), 4.47 (m, 1 H, H-3′), 4.63 (dd, 1 H, H-7, J = 7.9, 1.8 Hz), 4.65 (ABX, X part, 1 H, H-7′, J = 8.7, 2.1 Hz), 5.91 (d, 1 H, NH′, J = 8.5 Hz), 7.00 (d, 1 H, NH, J = 8.5 Hz), 7.20−7.35 (m, 10 H, 10 Ar-H). − HMQC ^{1}H-^{13}C NMR ($CDCl_3$): δ = 38.0 (C-8, C-8′), 39.9 (C-6), 42.1 (C-6′), 49.6 (C-3, C-3′), 53.7 and 53.8 (2 OCH_3), 65.1 (C-2′), 68.3 (C-2), 100.0 (C-7), 101.6 (C-7′), 126.5 (Ar-CH), 126.9 (Ar-CH), 128.3 (2 Ar-CH), 128.7 (2 Ar-CH), 129.2 (2 Ar-CH), 129.8 (2 Ar-CH), 137.3, 138.2 (2 Ar-C), 167.9 (CO), 168.5 (CO′). − MS (CI): m/z (%) = 471 (100) [MH^+], 439 (47) [$MH^+ - CH_3OH$], 236 (34) [M/2 + H^+], 146 (37), 107 (71), 57 (100).

14-Membered Ring 15c: White crystals, m.p. 178−180 °C (methanol). − $[\alpha]_D^{25}$ = −32.2 (c = 1.6, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3440 cm^{-1}, 3390, 1660. − ^{1}H NMR ($CDCl_3$): δ = 2.55 (d, 4 H, H-6B, H-6′B, H-6A, H-6′A, J = 4.4 Hz), 2.92 (ABX, AB part, 4 H, H-8A, H-8′A, H-8B, H-8′B, J = 13.5, 8.8, 5.5 Hz, Δν = 24.3 Hz), 3.34 (s, 6 H, 2 OCH_3), 3.47 (dd, 2 H, H-2B, H-2′B, J = 9.3, 3.0 Hz), 3.71 (dd, 2 H, H-2A, H-2′A, J = 9.3, 3.2 Hz), 4.34 (m, 2 H, H-3, H-3′), 4.63 (*pseudo* t, 2 H, H-7, H-7′, J = 4.4 Hz), 6.47 (br. d, 2 H, NH, NH′, J = 8.9 Hz), 7.20−7.35 (m, 10 H, 10 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 37.6 (C-8, C-8′), 41.5 (C-6, C-6′), 50.1 (C-3, C-3′), 53.8 (2 OCH_3), 67.7 (C-2, C-2′), 101.4 (C-7, C-7′), 126.5 (2 Ar-CH), 128.4 (4 Ar-CH), 129.4 (4 Ar-CH), 137.7 (2 Ar-C), 168.3 (2 CO). − MS (CI): m/z (%) = 471 (100) [MH^+], 439 (40) [$MH^+ - CH_3OH$], 236 [23, [M/2 + H^+], 218 (19), 107 (30), 102 (19), 73 (46), 57 (83).

15b/15c (52:48): $C_{26}H_{34}N_2O_6$ (470.57): calcd. C 66.36, H 7.28, N 5.95; found C 66.38, H 7.30, N 5.78.

(−)-Norephedrine Series: (1*S*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-3,3-dimethoxypropanamide (**6**) (1.34 g, 5.0 mmol) and PTSA (95 mg, 0.50 mmol, 0.1 equiv.) in CH_2Cl_2 (25 mL, c = 0.20 M) were refluxed for 8 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **16** as three diastereomers **a**,**b**,**c** (567 mg, 1.20 mmol, 48%, ratio 30:53:17) and the ketal lactam **20** as two diastereomers **a**,**b** (61 mg, 0.26 mmol, 5%, ratio 60:40).

14-Membered Ring 16a: Yellow crystals, m.p. 77−79 °C (cyclohexane). − $[\alpha]_D^{25}$ = −81.0 (c = 1.1, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3410 cm^{-1}, 1660. − ^{1}H NMR ($CDCl_3$): δ = 1.06 (d, 6 H, CH_3, CH_3′, J = 6.8 Hz), 2.77 (ABX, AB part, 4 H, H-6B, H-6A, H-6′B, H-6′A, J = 16.0, 3.6, 1.2 Hz, Δν = 6.1 Hz), 3.39 (s, 6 H, OCH_3, OCH_3′), 4.23 (dqd, 2 H, H-3, H-3′, J = 7.3, 6.8, 2.7 Hz), 4.55 (ABX, X part, 2 H, H-7, H-7′, J = 3.6, 1.2 Hz), 5.16 (d, 2 H, H-2, H-2′, J = 2.7 Hz), 7.24 (d, 2 H, NH, NH′, J = 7.3 Hz), 7.29−7.42 (m, 10 H, 10 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3, CH_3′), 40.6 (C-6, C-6′), 50.1 (C-3, C-3′), 56.5 (OCH_3, OCH_3′), 78.0 (C-2, C-2′), 98.6 (C-7, C-7′), 126.8 (4 Ar-CH), 128.0 (2 Ar-CH), 128.7 (4 Ar-CH), 137.3 (2 Ar-C), 167.9 (2 CO). − MS (FAB^+): m/z (%) = 493 (100) [MNa^+], 461 (14) [$MNa^+ - CH_3OH$], 439 (4) [$MH^+ - CH_3OH$], 265 (7), 236 (3) [M/2 + H^+], 218 (7), 204 (9), 173 (7), 160 (12), 134 (24), 115 (37).

14-Membered Ring 16b: Yellow crystals, m.p. 81−84 °C (cyclohexane). − $[\alpha]_D^{25}$ = −89.9 (c = 1.3, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3390 cm^{-1}, 1660, 1605. − COSY ^{1}H-^{1}H NMR ($CDCl_3$): δ = 0.99 (d, 3 H, CH_3′, J = 7.1 Hz), 1.12 (d, 3 H, CH_3, J = 6.8 Hz), 2.65 (br. d, 2 H, H-6B, H-6′B, J = 15.4 Hz), 2.77 (dd, 1 H, H-6′A, J = 15.6, 6.7 Hz), 2.83 (dd, 1 H, H-6A, J = 15.4, 6.1 Hz), 3.19 (s, 3 H, OCH_3′), 3.33 (s, 3 H, OCH_3), 4.13 (dqd, 1 H, H-3, J = 8.1, 6.8, 2.0 Hz), 4.49 (d, 1 H, H-7, J = 6.1, 0.5 Hz), 4.50 (m, 1 H, H-3′), 4.86 (d, 1 H, H-2, J = 2.0 Hz), 4.89 (dd, 1 H, H-7′, J = 6.7, 1.8 Hz), 5.10 (d, 1 H, H-2′, J = 3.0 Hz), 6.62 (d, 1 H, NH′, J = 8.8 Hz), 7.51 (d, 1 H, NH, J = 8.1 Hz), 7.25−7.45 (m, 10 H, 10 Ar-H). − HMQC ^{1}H-^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3), 14.8 (CH_3′), 40.8 (C-6), 41.8 (C-6′), 49.0 (C-3′), 50.8 (C-3), 54.9 (OCH_3), 55.1 (OCH_3′), 77.5 (C-2′), 81.6 (C-2), 98.1 (C-7), 102.2 (C-7′), 126.7 (2 Ar-CH), 127.4 (2 Ar-CH), 127.7 (Ar-CH), 128.2 (2 Ar-CH), 128.3 (Ar-CH), 128.6 (2 Ar-CH), 136.5 (Ar-C′), 139.5

(Ar-C), 168.2 (CO), 168.5 (CO′). − MS (EI): *m/z* (%) = 471 (61) [MH$^+$], 439 (67) [MH$^+$ − CH_3OH], 409 (6), 364 (17), 332 (5), 258 (42), 236 (23) [M/2 + H$^+$], 203 (44), 160 (16), 118 (42), 85 (46), 58 (100), 44 (93).

14-Membered Ring 16c: Yellow crystals, m.p. 98−100 °C (cyclohexane). − $[\alpha]_D^{25}$ = −69.3 (*c* = 2.2, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3380 cm^{-1}, 1655, 1600. − ^{1}H NMR ($CDCl_3$): δ = 1.07 (d, 6 H, CH_3, CH_3′, *J* = 6.9 Hz), 2.65 (dd, 2 H, H-6B, H-6′B, *J* = 15.7, 5.2 Hz), 2.77 (dd, 2 H, H-6A, H-6′A, *J* = 15.7, 2.6 Hz), 3.33 (s, 6 H, OCH_3, OCH_3′), 4.47 (dqd, 2 H, H-3, H-3′, *J* = 9.0, 6.9, 2.9 Hz), 4.83 (d, 2 H, H-2, H-2′, *J* = 2.9 Hz), 4.95 (dd, 2 H, H-7, H-7′, *J* = 5.2, 2.6 Hz), 7.05 (br. d, 2 H, NH, NH′, *J* = 9.0 Hz), 7.25−7.47 (m, 10 H, 10 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 14.8 (CH_3, CH_3′), 40.9 (C-6, C-6′), 47.9 (C-3, C-3′), 54.6 (OCH_3, OCH_3′), 80.7 (C-2, C-2′), 100.0 (C-7, C-7′), 127.2 (4 Ar-CH), 127.7 (2 Ar-CH), 128.2 (4 Ar-CH), 137.3 (2 Ar-C), 167.8 (CO, CO′). − MS (FAB$^+$): *m/z* (%) = 493 (45) [MNa$^+$], 439 (10) [MH$^+$ − CH_3OH], 236 (7) [M/2 + H$^+$], 218 (9), 207 (23), 204 (12), 186 (9), 160 (12), 133 (100) − HRMS (FAB$^+$): calcd. for ($C_{26}H_{34}N_2O_6$ + H$^+$) 471.2495, found 471.2505.

7-Membered Ring 20a: Oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 1665 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.05 (d, 3 H, CH_3, *J* = 7.0 Hz), 2.90 (ddd, 1 H, H-6B, *J* = 15.1, 4.4, 0.8 Hz), 3.08 (dd, 1 H, H-6A, *J* = 15.1, 4.4 Hz), 3.40 (s, 3 H, OCH_3), 3.73 (dqd, 1 H, H-3, *J* = 7.5, 7.0, 2.7 Hz), 5.01 (t, 1 H, H-7, *J* = 4.4 Hz), 5.10 (d, 1 H, H-2, *J* = 2.7 Hz), 6.51 (d, 1 H, NH, *J* = 7.5 Hz), 7.25−7.44 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 44.3 (C-6), 52.1 (C-3), 56.0 (OCH_3), 74.1 (C-2), 96.4 (C-7), 126.8, 127.9, 128.4 (5 Ar-CH), 138.8 (Ar-C), 172.4 (CO). − MS (CI): *m/z* (%) = 274 (3) [MK$^+$], 236 (99) [MH$^+$], 204 (11), 194 (3), 143 (4), 135 (3), 73 (4), 57 (100).

7-Membered Ring 20b: Oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 1660 cm^{-1} − ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, 3 H, CH_3, *J* = 7.0 Hz), 2.96 (dt, 1 H, H-6B, *J* = 15.8, 2.0 Hz), 3.09 (dd, 1 H, H-6A, *J* = 15.8, 8.7 Hz), 3.48 (s, 3 H, OCH_3), 3.58 (qdd, 1 H, H-3, *J* = 7.0, 6.9, 2.1 Hz), 4.82 (dd, 1 H, H-7, *J* = 8.7, 2.0 Hz), 4.93 (d, 1 H, H-2, *J* = 2.1 Hz), 6.71 (br. d, 1 H, NH, *J* = 6.9 Hz), 7.28−7.45 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3), 46.0 (C-6), 53.6 (C-3), 56.3 (OCH_3), 81.2 (C-2), 100.6 (C-7), 126.1, 126.4, 128.5 (5 Ar-CH), 136.2 (Ar-C), 170.0 (CO).

Amino Ethanol Series: *N*-(2-Hydroxyethyl)-3,3-dimethoxypropanamide (**7**) (1.77 g, 10.0 mmol) and PTSA (190 mg, 1.00 mmol, 0.1 equiv.) in CH_2Cl_2 (67 mL, *c* = 0.15 M) were refluxed for 6 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **17** as two diastereomers **b**,**c** (492 mg, 1.69 mmol, 34%, ratio 38:62) and the ketal lactam **21** (14 mg, 0.10 mmol, 1%).

14-Membered Ring 17b: White crystals, m.p. 248−250 °C (methanol). − ^{1}H NMR ($CDCl_3$): δ = 2.61 (ABX, AB part, 4 H, H-6A, H-6B, H-6′A, H-6′B, *J* = 15.0, 8.3, 2.0 Hz, Δν = 43.1 Hz), 3.37 (s, 6 H, 2 OCH_3), 3.42 (m, 2 H, H-3B, H-3′B), 3.47 (ddd, 2 H, H-2B, H-2′B, *J* = 9.7, 6.8, 2.6 Hz), 3.65 (dddd, 2 H, H-3A, H-3′A, *J* = 14.0, 7.5, 6.8, 3.0 Hz), 3.84 (ddd, 2 H, H-2A, H-2′A, *J* = 9.7, 6.7, 3.0 Hz), 4.77 (ABX, X part, 2 H, H-7, H-7′, *J* = 8.3, 2.0 Hz), 6.73 (br. s, 2 H, 2 NH). − ^{13}C NMR ($CDCl_3$): δ = 39.0 (C-3, C-3′), 40.6 (C-6, C-6′), 53.9 (2 OCH_3), 64.6 (C-2, C-2′), 100.6 (C-7, C-7′), 168.8 (CO, CO′). − MS (CI): *m/z* (%) = 291 (42) [MH$^+$], 259 (100) [MH$^+$ − CH_3OH], 227 (2), 146 (2) [M/2 + H$^+$].

14-Membered Ring 17c: White crystals, m.p. 170−172 °C (methanol) − IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 3460, 1660. − ^{1}H NMR ($CDCl_3$): δ = 2.59 (ABX, AB part, 4 H, H-6A, H-6B, H-6′A, H-6′B, *J* = 14.7, 8.2, 1.8 Hz, Δν = 34.5 Hz), 3.20 (ddd, 2 H, H-3B, H-3′B, *J* = 14.1, 9.2, 2.9 Hz), 3.35 (s, 6 H, 2 OCH_3), 3.55 (ddd, 2 H, H-2B, H-2′B, *J* = 9.5, 9.2, 2.1 Hz), 3.78 (dddd, 2 H, H-3A, H-3′A, *J* = 14.1, 7.5, 4.5, 2.1 Hz), 3.83 (ddd, 2 H, H-2A, H-2′A, *J* = 9.5, 4.5, 2.9 Hz), 4.69 (ABX, X part, 2 H, H-7, H-7′, *J* = 8.2, 1.8 Hz), 6.73 (br. s, 2 H, 2 NH). − XHCORR ^{1}H-^{13}C NMR ($CDCl_3$): δ = 39.2 (C-3, C-3′), 41.1 (C-6, C-6′), 53.4 (2 OCH_3), 66.1 (C-2, C-2′), 100.9 (C-7, C-7′), 169.1 (CO, CO′). − MS (CI): *m/z* (%) = 291 (9) [MH$^+$], 259 (73) [MH$^+$ − CH_3OH], 198 (6), 146 (16) [M/2 + H$^+$], 57 (100). − $C_{12}H_{22}N_2O_6$ (290.32): calcd. C 49.65, H 7.64, N 9.65; found C 49.26, H 7.42, N 9.55.

7-Membered Ring 21: Oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 3430 cm^{-1}, 2940, 2840, 1675. − ^{1}H NMR ($CDCl_3$): δ = 2.79 (ddd, 1 H, H-6B, *J* = 14.5, 5.1, 1.8 Hz), 2.97 (dd, 1 H, H-6A, *J* = 14.5, 1.5 Hz), 3.18 (dddd, 1 H, H-3B, *J* = 15.8, 6.8, 5.1, 1.1 Hz), 3.42 (s, 3 H, OCH_3), 3.55 (dddd, 1 H, H-3A, *J* = 15.8, 9.1, 4.8, 1.1 Hz), 3.68 (ddd, 1 H, H-2B, *J* = 12.8, 5.1, 1.1 Hz), 3.99 (dd, 1 H, H-2A, *J* = 12.8, 9.1, 1.1. Hz), 4.75 (dd, 1 H, H-7, *J* = 5.1, 1.5 Hz), 6.24 (br. s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 44.0 (C-6), 44.6 (C-3), 55.6 (OCH_3), 62.6 (C-2), 96.6 (C-7), 173.6 (CO). − MS (CI): *m/z* (%) = 146 (100) [MH$^+$], 63 (33), 57 (100).

Dimethylamino Ethanol Series: *N*-(2-Hydroxyethyl-1,1-dimethyl)-3,3-dimethoxypropanamide (**8**) (1.03 g, 5.0 mmol) and PTSA (190 mg, 1.00 mmol, 0.2 equiv.) in benzene (33 mL, *c* = 0.15 M) were refluxed for 17 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the diketal bislactam **18** as two diastereomers **b**,**c** (108 mg, 0.31 mmol, 12%, ratio 55:45).

14-Membered Ring 18b: White crystals, m.p. 158−160 °C (ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3450 cm^{-1}, 3380, 1665. − ^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 6 H, 2 CH_3), 1.38 (s, 6 H, 2 CH_3), 2.51 (ABX, AB part, 4 H, H-6B, H-6′B, H-6A, H-6′A, *J* = 14.6, 8.3, 1.9 Hz, Δν = 39.8 Hz), 3.31 (s, 6 H, 2 OCH_3), 3.41 (d, 2 H, H-2B, H-2′B, *J* = 9.2 Hz), 3.69 (d, 2 H, H-2A, H-2′A, *J* = 9.2 Hz), 4.70 (ABX, X part, 2 H, H-7, H-7′, *J* = 8.3, 1.9 Hz), 6.28 (s, 2 H, 2 NH). − ^{13}C NMR ($CDCl_3$): δ = 23.2 (2 CH_3), 24.5 (2 CH_3), 42.2 (C-6, C-6′), 53.0 (2 OCH_3), 53.6 (C-3, C-3′), 73.3 (C-2, C-2′), 100.8 (C-7, C-7′), 168.6 (2 CO). − MS (FAB$^+$): *m/z* (%) = 369 (63) [MNa$^+$], 347 (35) [MH$^+$], 315 (100) [MH$^+$ − CH_3OH], 174 (61) [M/2 + H$^+$], 156 (33), 142 (56), 116 (41), 100 (24).

14-Membered Ring 18c: White crystals, m.p. 145−146 °C (ether). − IR ($CHCl_3$): $\tilde{\nu}$ = 3380 cm^{-1}, 1665. − ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 6 H, 2 CH_3), 1.41 (s, 6 H, 2 CH_3), 2.54 (ABX, AB part, 4 H, H-6B, H-6′B, H-6A, H-6′A, *J* = 14.9, 7.1, 2.2 Hz, Δν = 44.1 Hz), 3.24 (d, 2 H, H-2B, H-2′B, *J* = 9.4 Hz), 3.36 (s, 6 H, 2 OCH_3), 3.83 (d, 2 H, H-2A, H-2′A, *J* = 9.4 Hz), 4.70 (ABX, X part, 2 H, H-7, H-7′, *J* = 7.1, 2.2 Hz), 6.38 (s, 2 H, 2 NH). − ^{13}C NMR ($CDCl_3$): δ = 23.4 (2 CH_3), 24.4 (2 CH_3), 41.9 (C-6, C-6′), 53.5 (C-3, C-3′), 54.2 (2 OCH_3), 72.8 (C-2, C-2′), 101.3 (C-7, C-7′), 168.5 (2 CO). − MS (FAB$^+$): *m/z* (%) = 369 (63) [MNa$^+$], 347 (35) [MH$^+$], 315 (100) [MH$^+$ − CH_3OH], 174 (61) [M/2 + H$^+$], 156 (33), 142 (56), 116 (41), 100 (24).

18b/18c (16:84): $C_{16}H_{30}N_2O_6$ (346.43): calcd. C 55.47, H 8.73, N 8.09; found C 55.29, H 8.66, N 7.94.

2-Amino Phenol Series.− 7-Membered Ring Ketal Lactam 22: *N*-(2-Hydroxyphenyl)-3,3-dimethoxypropanamide (**9**) (180 mg, 0.80 mmol) and PTSA (15 mg, 0.08 mmol, 0.1 equiv.) in CH_2Cl_2 (5 mL, *c* = 0.16 M) were refluxed for 8 h. Chromatography with cyclohexane/ethyl acetate (gradient: 100:0→0:100) afforded the ketal lactam **22** (100 mg, 0.52 mmol, 65%). − White crystals, m.p. 161−163 °C (methanol). − IR ($CHCl_3$): $\tilde{\nu}$ = 3400 cm^{-1}, 1680, 1690, 1605. −

^{1}H NMR ($CDCl_3$): δ = 2.77 (ABMX, AB part, 2 H, H-6B, H-6A, *J* = 13.7, 8.3, 4.9, 1.0 Hz, Δν = 10.8 Hz), 3.63 (s, 3 H, OCH_3), 5.48 (ABMX, M part, 1 H, H-7, *J* = 8.3, 4.9 Hz), 7.03−7.18 (m, 4 H, 4 Ar-H), 8.65 (ABMX, X part, 1 H, NH, *J* = 1.0 Hz). − ^{13}C NMR ($CDCl_3$): δ = 40.5 (C-6), 56.2 (OCH_3), 105.6 (C-7), 122.3 (C-8), 124.4 (C-10), 125.2 (C-11), 126.2 (C-9), 131.2 (C-3), 145.7 (C-2), 169.9 (CO). − MS (FAB^+): *m*/*z* (%) = 387 (7) [2 M + H^+], 194 (100) [MH^+], 162 (39) [$MH^+ - CH_3OH$], 120 (24).

(−)-Ephedrine Series: (1*S*,2*R*)-*N*-(2-Hydroxy-2-methyl-1-phenylethyl)-3,3-dimethoxy-*N*-methylpropanamide (**10**) (428 mg, 1.52 mmol) and PTSA (43 mg, 0.23 mmol, 0.15 equiv.) in CH_2Cl_2 (10 mL, *c* = 0.15 M) were refluxed for 9 h. Chromatography with diethyl ether/methanol (gradient: 100:0→90:10) afforded the ketal lactam **23** as two diastereomers **a**,**b** (143 mg, 0.57 mmol, 38%, ratio 30:70).

7-Membered Ring 23a: Yellow oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, 3 H, CH_3, *J* = 7.2 Hz), 2.95 (dd, 1 H, H-6B, *J* = 15.1, 3.2 Hz), 3.06 (s, 3 H, NCH_3), 3.10 (dd, 1 H, H-6A, *J* = 15.1, 3.2 Hz), 3.33 (s, 3 H, OCH_3), 3.48 (qd, 1 H, H-3, *J* = 7.2, 1.6 Hz), 4.94 (*pseudo* t, 1 H, H-7, *J* = 3.2 Hz), 5.25 (br. s, 1 H, H-2), 7.30−7.45 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 10.5 (CH_3), 36.2 (NCH_3), 44.7 (C-6), 55.6 (OCH_3), 62.0 (C-3), 72.9 (C-2), 96.7 (C-7), 125.8−128.4 (5 Ar-CH), 140.0 (Ar-C), 169.7 (CO).

23a,b: MS (CI): *m*/*z* (%) = 499 (11) [2 M + H^+], 250 (100) [MH^+], 57 (100). − MS (FAB^+): *m*/*z* (%) = 523 (11), 505 (33) [2 M + Li^+], 409 (27), 397 (21), 313 (33), 256 (100) [MLi^+], 250 (13) [MH^+], 218 (19) [$MH^+ - CH_3OH$], 160 (90), 154 (41), 136 (66), 107 (34).

7-Membered Ring 23b: Yellow oil. − $[\alpha]_D^{25}$ = −84.1 (*c* = 1.1; $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1628 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.17 (d, 3 H, CH_3, *J* = 7.5 Hz), 2.96 (dd, 1 H, H-6B, *J* = 15.6, 0.9 Hz), 3.07 (s, 3 H, NCH_3), 3.09 (dd, 1 H, H-6A, *J* = 15.6, 9.0 Hz), 3.45 (qd, 1 H, H-3, *J* = 7.5, 1.3 Hz), 3.48 (s, 3 H, OCH_3), 4.69 (dd, 1 H, H-7, *J* = 9.0, 0.9 Hz), 4.91 (br. s, 1 H, H-2), 7.28−7.40 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_3), 37.4 (NCH_3), 46.5 (C-6), 56.3 (OCH_3), 63.1 (C-3), 79.8 (C-2), 100.9 (C-7), 125.8−128.4 (5 Ar-CH), 139.5 (Ar-C), 169.3 (CO). − MS (FAB^+): *m*/*z* (%) = 505 (21) [2 M + Li^+], 313 (11), 256 (100) [MLi^+], 250 (16) [MH^+], 218 (40) [$MH^+ - CH_3OH$], 160 (46), 154 (37), 148 (31), 137 (30). − HRMS (FAB^+): calcd. for ($C_{14}H_{19}NO_3$ + H^+) 250.1443, found 250.1452.

(+)-Pseudoephedrine Series. − 7-Membered Ring Ketal Lactam 24: (1*S*,2*S*)-*N*-(2-Hydroxy-2-methyl-1-phenylethyl)-3,3-dimethoxy-*N*-methylpropanamide (**11**) (562 mg, 2.0 mmol) and PTSA (95 mg, 0.50 mmol, 0.25 equiv.) in CH_2Cl_2 (13 mL, *c* = 0.15 M) were refluxed for 47 h. Chromatography with diethyl ether/methanol (gradient: 100:0→80:20) afforded the ketal lactam **24** as a yellow oil (95 mg, 0.38 mmol, 19%). − $[\alpha]_D^{25}$ = −14.8 (*c* = 1.3, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1635 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.17 (d, 3 H, CH_3, *J* = 6.8 Hz), 2.81 (dd, 1 H, H-6B, *J* = 14.4, 4.2 Hz), 2.92 (dd, 1 H, H-6A, *J* = 14.4, 9.5 Hz), 2.98 (s, 3 H, NCH_3), 3.20 (s, 3 H, OCH_3), 3.53 (dq, 1 H, H-3, *J* = 9.2, 6.8 Hz), 4.70 (d, 1 H, H-2, *J* = 9.2 Hz), 4.95 (dd, 1 H, H-7, *J* = 9.5, 4.2 Hz), 7.30−7.45 (m, 5 H, 5 Ar-H). − ^{13}C NMR ($CDCl_3$): δ = 16.0 (CH_3), 35.0 (NCH_3), 41.5 (C-6), 55.1 (OCH_3), 63.0 (C-3), 74.5 (C-2), 98.6 (C-7), 127.2, 128.3, 128.7 (5 Ar-CH), 140.8 (Ar-C), 167.6 (CO). − MS (FAB^+): *m*/*z* (%) = 505 (11) [2 M + Li^+], 313 (17), 256 (100) [MLi^+], 250 (23) [MH^+], 218 (33) [$MH^+ - CH_3OH$], 160 (40), 154 (56), 136 (40), 107 (23), 91 (24). − HRMS (FAB^+): calcd. for ($C_{14}H_{19}NO_3$ + H^+) 250.1443, found 250.1462.

(+)-Prolinol Series: (2*S*)-1-(3,3-Dimethoxypropanoyl)-2-hydroxymethylpyrrolidine (**12**) (217 mg, 1.00 mmol) and PTSA (19 mg, 0.10 mmol, 0.1 equiv.) in CH_2Cl_2 (7 mL, *c* = 0.14 M) were refluxed for 9 h. Chromatography with diethyl ether/methanol (gradient: 100:0→70:30) afforded the diketal bislactam **19** (4 mg, 0.01 mmol, 2%) and the ketal lactam **25** as two diastereomers **a**,**b** (102 mg, 0.55 mmol, 55%, ratio 42:58).

14-Membered Ring 19: Oil − IR ($CHCl_3$): $\tilde{\nu}$ = 1635 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.88 (m, 2 H, H-8B, H-8′B), 2.01 (m, 4 H, H-9B, H-9A, H-9′B, H-9′A), 2.19 (m, 2 H, H-8A, H-8′A), 2.38 (dd, 2 H, H-6B, H-6′B, *J* = 12.5, 2.0 Hz), 2.81 (dd, 2 H, H-6A, H-6′A, *J* = 12.5, 9.3 Hz), 3.37 (s, 6 H, 2 OCH_3), 3.51 (*pseudo* t, 2 H, H-10B, H-10′B, *J* = 7.8 Hz), 3.62 (m, 2 H, H-10A, H-10′A,), 3.65 (dd, 2 H, H-2B, H-2′B, *J* = 9.5, 1.1 Hz), 4.14 (dd, 2 H, H-2A, H-2′A, *J* = 9.5, 2.4 Hz), 4.17 (m, 2 H, H-3, H-3′), 4.77 (dd, 2 H, H-7, H-7′, *J* = 9.3, 2.0 Hz). − XHCORR ^{1}H-^{13}C NMR ($CDCl_3$): δ = 25.0 (C-9, C-9′), 28.7 (C-8, C-8′), 40.1 (C-6, C-6′), 48.7 (C-10, C-10′), 53.3 (2 OCH_3), 56.9 (C-3, C-3′), 69.6 (C-2, C-2′), 103.6 (C-7, C-7′), 168.0 (2 CO). − MS (CI): *m*/*z* (%) = 371 (84) [MH^+], 339 (41) [$MH^+ - CH_3OH$], 186 (9) [M/2 + H^+], 154 (3).− MS (FAB^+): *m*/*z* (%) = 377 (100) [MLi^+], 345 (12) [$MLi^+ - CH_3OH$], 186 (13) [M/2 + H^+], 160 (9), 154 (12), 136 (11).

7-Membered Ring 25a: Yellow oil. − $[\alpha]_D^{25}$ = +51.4 (*c* = 3.2, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1635 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.48 (dddd, 1 H, H-8B, *J* = 12.6, 10.2, 8.7, 6.8 Hz), 1.71 (m, 1 H, H-9B), 1.84 (dtt, 1 H, H-9A, *J* = 13.2, 6.7, 3.3 Hz), 2.10 (dtd, 1 H, H-8A, *J* = 12.6, 6.7, 3.5 Hz), 2.75 (dd, 1H, H-6B, *J* = 14.8, 1.0 Hz), 2.87 (dd, 1 H, H-6A, *J* = 14.8, 8.4 Hz), 3.33 (dd, 1 H, H-2B, *J* = 12.7, 8.8 Hz), 3.34 (m, 1 H, H-10B), 3.40 (s, 3 H, OCH_3), 3.68 (ddd, 1 H, H-10A, *J* = 11.9, 7.9, 3.3 Hz), 3.88 (tdd, 1 H, H-3, *J* = 8.8, 6.7, 1.7 Hz), 3.94 (dd, 1 H, H-2A, *J* = 12.7, 1.7 Hz), 4.49 (dd, 1 H, H-7, *J* = 8.4, 1.0 Hz). − XHCORR ^{1}H-^{13}C NMR ($CDCl_3$): δ = 22.7 (C-9), 29.8 (C-8), 46.4 (C-6), 47.1 (C-10), 56.0 (2 OCH_3), 58.8 (C-3), 70.1 (C-2), 100.1 (C-7), 168.5 (CO). − MS (FAB^+): *m*/*z* (%) = 377 (37) [2 M + Li^+], 345 (30), 313 (19), 192 (100) [MLi^+], 186 (60) [MH^+], 160 (60), 154 (53) [$MH^+ - CH_3OH$], 136 (62), 112 (21).

7-Membered Ring 25b: Yellow oil. − $[\alpha]_D^{25}$ = −132.4 (*c* = 3.0, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 1640 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.47 (dddd, 1 H, H-8B, *J* = 12.8, 10.7, 8.6, 6.8 Hz), 1.68 (m, 1 H, H-9B), 1.83 (dddt, 1 H, H-9A, *J* = 12.8, 6.8, 6.4, 3.2 Hz), 2.10 (dtd, 1 H, H-8A, *J* = 12.8, 6.4, 3.2 Hz), 2.73 (dd, 1 H, H-6B, *J* = 14.4, 4.4 Hz), 2.89 (dd, 1 H, H-6A, *J* = 14.4, 1.4 Hz), 3.31 (s, 3 H, OCH_3), 3.32 (ddd, 1 H, H-10B, *J* = 12.0, 10.0, 6.4 Hz), 3.50 (dd, 1 H, H-2B, *J* = 12.7, 1.2 Hz), 3.66 (m, 1 H, H-10A), 3.66 (dd, 1 H, H-2A, *J* = 12.7, 9.2 Hz), 3.92 (dddd, 1 H, H-3, *J* = 9.2, 8.6, 6.4, 1.2 Hz), 4.69 (dd, 1 H, H-7, *J* = 4.4, 1.4 Hz). − XHCORR ^{1}H-^{13}C NMR ($CDCl_3$): δ = 23.2 (C-9), 29.6 (C-8), 44.9 (C-6), 46.6 (C-10), 55.3 (OCH_3), 58.6 (C-3), 64.7 (C-2), 96.4 (C-7), 168.4 (CO). − MS (CI): *m*/*z* (%) = 371 (42) [2 M + H)$^+$], 186 (99) [MH^+], 57 (100). − MS (FAB^+): *m*/*z* (%) = 377 (69) [2 M + Li^+], 371 (8) [2 M + H^+], 192 (100) [MLi^+], 186 (59) [MH^+], 160 (8), 154 (33) [$MH^+ - CH_3OH$], 112 (63). − HRMS (FAB^+): calcd. for ($C_9H_{15}NO_3$ + H^+) 186.1130, found 186.1118.

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