Tetrahedron Letters 53 (2012) 3568–3572

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nucleophilic properties of a nonstabilized azomethine ylide derived from sarcosine and cyclohexanone. A novel domino reaction leading to substituted 4-aryl-2-pyrrolidones

Vladimir S. Moshkin [a,*], Vyacheslav Ya. Sosnovskikh [a], Gerd-Volker Röschenthaler [b]

[a] Department of Chemistry, Ural Federal University, pr. Lenina 51, 620083 Ekaterinburg, Russia
[b] School of Engineering and Science, Jacobs University Bremen, 28759 Bremen, Germany

ARTICLE INFO

Article history:
Received 7 February 2012
Revised 5 April 2012
Accepted 2 May 2012
Available online 11 May 2012

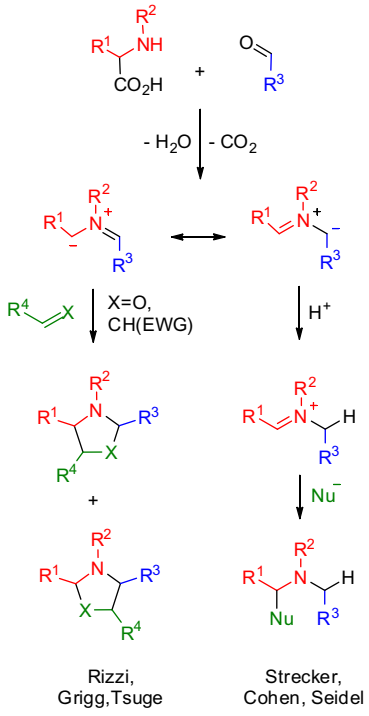
Keywords:
Nonstabilized asymmetric azomethine ylide
Domino reaction
4-Aryl-2-pyrrolidones
1,4-Nucleophilic addition
3-Substituted coumarins
[3+2] Cycloaddition

ABSTRACT

A nonstabilized asymmetric azomethine ylide derived from sarcosine and cyclohexanone reacts with 3-substituted coumarins and ethyl benzylidene malonate to give 4-aryl-2-pyrrolidones in moderate yields, and the adducts of classical 1,3-dipolar cycloadditions as the minor products. The main reaction proceeds via a domino process, starting with 1,4-nucleophilic addition to the conjugated double bond, and represents the first example of the nucleophilic properties of a nonstabilized azomethine ylide.

There are three main types of decarboxylative reactions of α-amino acids with carbonyl compounds, which proceed via the formation of intermediate nonstabilized azomethine ylides, and then depending on the reaction conditions, lead to different products. The first type is the Strecker amino acid degradation resulting in amino acetal formation, which hydrolyzes to give an aldehyde containing one carbon atom less than the starting amino acid.[1] However, in this case the intermediacy of a nonstabilized azomethine ylide is rare, and the process has no wide synthetic application.[1b,d,e] The second type are the [3+2] cycloadditions, which have been investigated extensively by Rizzi, Grigg, Tsuge, and others (Scheme 1).[2] The third type are 1,5- and 1,7-electrocyclizations of conjugated azomethine ylides.[3]

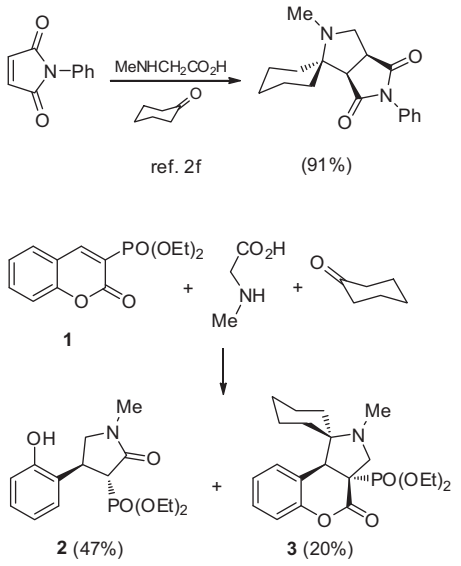
The 1,3-dipolar cycloaddition and electrocyclization reactions are carried out in an inert aprotic medium with the removal of water; the azomethine ylide either reacts with the dipolarophile or cyclizes intramolecularly, due to its inability to take part in ionic interactions. In contrast, Strecker amino acid degradation assisted by carbonyl compounds is performed in an alcoholic or aqueous medium, resulting in hydrolysis of the intermediate azomethine ylide with formation of an aldehyde. In 1979, Cohen reported on the reaction of proline with o-hydroxyacetophenones (a process similar to Strecker decarboxylation).[4] The azomethine ylide intermediate was able to deactivate its negative charge by



Scheme 1. Decarboxylative reactions of α-amino acids with carbonyl compounds.

* Corresponding author. Fax: +7 343 261 59 78.
E-mail address: mvslc@mail.ru (V.S. Moshkin).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.008

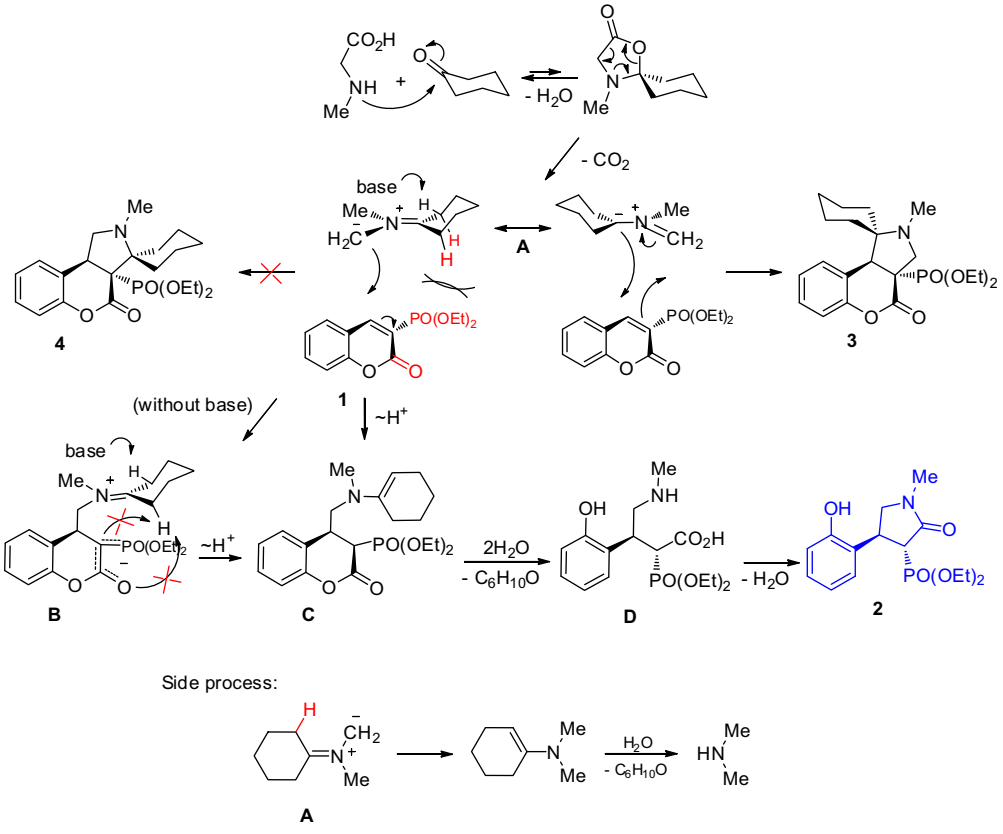


Scheme 2. Reactions of azomethine ylide derived from cyclohexanone and sarcosine.

protonation and demonstrated electrophilic properties relative to the internal nucleophile (phenolate anion). Only in the last 5 years has this chemistry achieved momentum.[5] In particular, Seidel expanded the reaction scope to various C-nucleophilic compounds and increased significantly the synthetic utility of azomethine ylides in non-pericyclic reactions.[6] It would be logical to assume the existence of nucleophilic properties in nonstabilized azomethine ylides, however, to the best of our knowledge, examples of such reactions have not been published to date.

In the course of our work on the reactions of nonstabilized azomethine ylides with 3-substituted coumarin,[7] we attempted the reaction with the asymmetric nonstabilized azomethine ylide derived from cyclohexanone and sarcosine. Surprisingly, only one reaction of this ylide was known previously[2f] in which *N*-(*p*-tolyl)maleimide gave the normal product of 1,3-dipolar cycloaddition in high yield (Scheme 2). Unexpectedly, we found that diethyl coumarin-3-phosphonate **1** (1 equiv) reacted with sarcosine (3 equiv) and cyclohexanone (1 equiv) in boiling toluene for 48 h to form pyrrolidone **2** as the main product (47%) and a second product of the classical [3+2] cycloaddition, **3** (20%).[8,9] Compounds **2** and **3** were isolated by column chromatography on silica gel and identified on the basis of ^{1}H, ^{31}P, and ^{13}C NMR, MS, IR and elemental analyses, as well as 2D ^{1}H–^{13}C HMQC, HMBC, and ^{1}H–^{1}H NOESY experiments. When this reaction was carried out in the presence of $(i\text{-Pr})_2NEt$ (DIPEA) (0.5 equiv) for 36 h followed by acidification with HCl (5 equiv), pyrrolidone **2** was isolated by simple filtration in 39% yield. In this case, the cycloaddition product **3** was obtained in a yield of 14% from the aqueous layer by neutralization with $NaHCO_3$ and subsequent flash chromatography on silica gel (Scheme 2).

Such an atypical property of this nonstabilized azomethine ylide is clearly associated with its structure as well as that of the activated alkene. The more nucleophilic center of the intermediate ylide **A** (Scheme 3) located on the terminal carbon atom, and favorable electronic orientation of the interacting molecules in the transition state of the reaction is associated with unfavorable steric interactions between the axial hydrogens and functional group of the coumarin. Additionally, ylide **A** contains hydrogens at the α-position which are able to eliminate with concomitant deactivation of the cationic center and loss of the dipolar properties of the azomethine ylide. The combination of these factors prevents formation of the 1,3-dipolar cycloaddition product with structure **4**.



Scheme 3. A plausible reaction route.

Instead, 1,4-nucleophilic addition to the activated double bond of the coumarin took place.

Due to the presence of water in the medium, enamine **C** underwent hydrolysis with regeneration of cyclohexanone. Next, the amino group of intermediate **D** attacks the carboxylic group and cyclization finishes the domino-process to give *trans*-substituted pyrrolidone **2**. This reaction represents a new approach to the synthesis of a 2-pyrrolidone ring, and 4-aryl-2-pyrrolidones are particularly interesting due to their biological activity. For example, commercial drugs such as phenotropil, cebaracetam, rolipram, and lidanserin contain this moiety.[10]

It should be noted that after boiling for 24 h the ratio of pyrrolidone **2** to pyrrolidine **3** was 2.4:1, and after 48 h was 2.7:1 (Table 1). It can be assumed that the formation of pyrrolidone **2** was catalyzed by the presence of a base which had formed by 1,3-dipolar cycloaddition and an intramolecular [1,4]-H shift in the azomethine ylide **A** (Scheme 3, side process). A threefold increase in the concentration of the reagents improved slightly the yield of the desired product and the rate of reaction increased (entry 3). Addition of 0.5 equiv of DIPEA resulted in a further increase in the reaction rate and the quantity of pyrrolidone **2** (entry 4). Based on these data, we concluded that the preliminary intermolecular deprotonation of ylide **A** or deactivation of the ionic centers after reaction with the coumarin is more likely than intramolecular 1,6- or 1,8-migration of the proton in intermediate **B**.

The experiment with the addition of 0.5 equiv of cyclohexanone led to the same ratio of products as with 1.0 equiv, but the reaction rate decreased, according to amount of starting coumarin (entries 4 and 6). Heating of sarcosine and diethyl coumarin-3-phosphonate without cyclohexanone led to no reaction, and therefore confirmed its participation in the formation of product **2**. Thus, it can be assumed that cyclohexanone is the catalyst for this domino reaction.

The ^{1}H NMR spectrum of compound **2** contained characteristic signals due to four protons of the pyrrolidone ring and shielded aromatic protons of the phenolic fragment (Fig. 1). Due to the different spatial environments, the ethoxy hydrogens were not equivalent and they had different chemical shifts and spin–spin couplings according to the ^{1}H NMR spectrum, as has been previously described for related structures.[11] An interesting feature of the structure of compound **2** is the presence of free phenolic hydroxy and phosphonate groups, which could in principle form a cyclic phosphate, however under these conditions this does not occur. A ^{1}H–^{13}C HMQC experiment was performed to assign the signals of the ^{13}C NMR spectrum and to provide additional confirmation of the location of the protons. The regiochemistry was confirmed by the ^{1}H–^{13}C HMBC experiment. Evidence for the *trans* arrangement of the two substituents in pyrrolidone **2** was obtained from the ^{1}H–^{1}H NOESY data, which showed clearly visible differences between the intensities of the benzylic proton cross-peaks with three vicinal neighbors.

To study the steric requirements and the scope of the process we carried out reactions of cyclohexanone and sarcosine with benzylidene malonate **5**, 3-ethoxycarbonylcoumarin (**6**), and 3-benzoylcoumarin (**7**) (Scheme 4). Substituted 4-aryl-2-pyrrolidones were obtained in all reactions, but each case had its own peculiarities. The reactions of diethyl benzylidene malonate (**5**) and 3-ethoxycarbonylcoumarin (**6**) were accompanied by nucleophilic attack of dimethylamine on the carbonyl groups and led to the pyrrolidones **8** and **9**, respectively. Dimethylamine evolves as a result of a side process (Scheme 3) and is an active nucleophile toward the carbonyls of the starting materials and intermediates. It should be noted that in the case of the phosphonate **1**, we did not detect even a trace of phosphoramide in view of the much lower susceptibility of the phosphonate group to nucleophilic attack by secondary amines. 3-Benzoylcoumarin (**7**) gave pyrrolidone **10** in equilibrium with its cyclic tautomer **10′** (ratio 85:15).[12]

Along with the pyrrolidones **8–10**, the adducts of 1,3-dipolar cycloaddition **11–13** were obtained in each reaction in 7–17% yields. Products **8–10** were isolated by column chromatography.

Table 1
^{31}P NMR spectroscopic analysis of the reaction products

Entry	Conditions	Solvent	Time (h)	Product ratio by ^{31}P NMR		
				2	**3**	**1**
1	1 equiv $C_6H_{10}O$	PhMe	24	2.4	1	3.6
2	1 equiv $C_6H_{10}O$	PhMe	48	2.7	1	1.1
3	Conc. increased threefold	PhMe	24	2.8	1	1.8
4	0.5 equiv $(i\text{-Pr})_2NEt$, 1 equiv $C_6H_{10}O$	PhMe	24	3.1	1	1.2
5	0.5 equiv $(i\text{-Pr})_2NEt$, 1 equiv $C_6H_{10}O$	PhMe	36	3.1	1	0.6
6	0.5 equiv $(i\text{-Pr})_2NEt$, 0.5 equiv $C_6H_{10}O$	PhMe	24	3.0	1	1.6
7	without $C_6H_{10}O$	PhMe	24	0	0	1
8	1 equiv $C_6H_{10}O$	*s*-BuOH	24	0	0	1
9	1 equiv $C_6H_{10}O$, 80 °C	DMSO	3	0	0	1
10	1 equiv $C_6H_{10}O$, 120 °C	DMSO	3	Complex mixture of products		

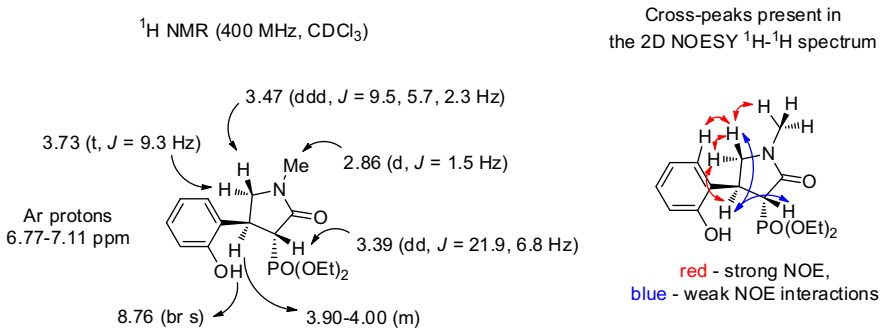
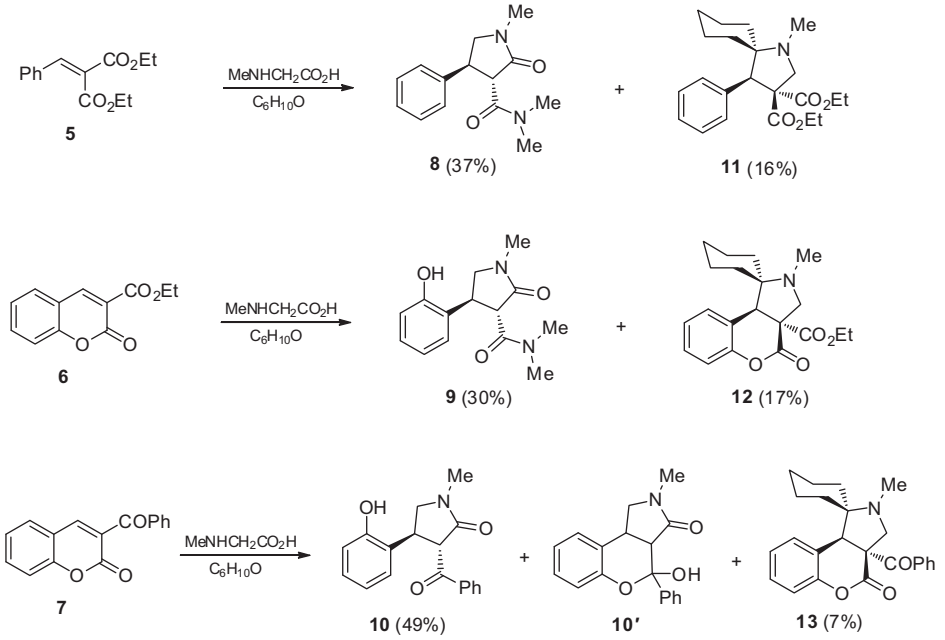


Figure 1. Spectral data of pyrrolidone **2**.



Scheme 4. Another examples of nucleophilic properties of the nonstabilized azomethine ylide.

Their ^{1}H NMR spectra resembled closely the spectrum of pyrrolidone **2** and contained characteristic signals for the four protons of the 2-pyrrolidone ring. Additionally, ^{13}C, $^{1}H–^{13}C$ HMQC and $^{1}H–^{1}H$ NOESY NMR spectra were recorded for compounds **8–13**.

Reactions of diethyl coumarin-3-phosphonate **1** and cyclohexanone with proline or glycine led to mixtures of more than five products, according to ^{31}P NMR spectroscopy. In the case of proline, this may be explained by the formation of additional diastereomers during the 1,3-dipolar cycloaddition and the presence of protons at the α-position of the pyrroline ring; in the case of glycine—a less stable N-protonated intermediate ylide. We conclude that further efforts should be directed to develop a more effective catalyst for this new reaction to increase the yield of the desired pyrrolidones and the scope of the amino acids.

Thus, we have reported a novel domino reaction consisting of two successive attacks of the methylaminomethyl anion species from sarcosine (via its C- and N-centers) to an activated alkene to give substituted pyrrolidones. The nucleophilic properties of nonstabilized azomethine ylides have been described for the first time, and continued studies are in progress.

Acknowledgment

This work was supported financially by the DFG RO 362/50/1.

References and notes

1. (a) Strecker, A. *Liebigs Ann. Chem.* **1862**, *123*, 363–365; (b) Schönberg, A.; Moubasher, R. *Chem. Rev.* **1952**, *50*, 261–277; (c) Dose, K. *Nature* **1957**, *179*, 734–735; (d) Baddar, F. G. *J. Chem. Soc.* **1949**, S163–S167; (e) Baddar, F. G. *J. Chem. Soc.* **1950**, 136–139.
2. (a) Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069–2072; (b) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180–181; (c) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182–183; (d) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49–51; (e) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703–2713; (f) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079–4089; (g) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231–344; (h) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517; (i) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105–1150; (j) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809; (k) Padwa, A.; Pearson, W. H. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, 2002; Vol. 59, 169–252.
3. (a) Anaç, O.; Güngör, F. Ş. *Tetrahedron* **2010**, *66*, 5931–5953; (b) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873–2888.
4. Cohen, N.; Blount, J. F.; Lopresti, R. J.; Trullinger, D. P. *J. Org. Chem.* **1979**, *44*, 4005–4007.
5. (a) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889–892; (b) Mao, H.; Wang, S.; Yu, R.; Lv, H.; Xu, R.; Pan, Y. *J. Org. Chem.* **2011**, *76*, 1167–1169; (c) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417; (d) Deb, I.; Coiro, D. J.; Seidel, D. *Chem. Commun.* **2011**, *47*, 6473–6475.
6. (a) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798–1799; (b) Das, D.; Richers, M. T.; Ma, L.; Seidel, D. *Org. Lett.* **2011**, *13*, 6584–6587; (c) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233–236.
7. Moshkin, V. S.; Sosnovskikh, V. Ya.; Slepukhin, P. A.; Röschenthaler, G.-V. *Mendeleev Commun.* **2012**, *22*, 29–31.
8. *General procedure*: A mixture of the corresponding coumarin or diethyl benzylidene malonate (1.0 mmol), cyclohexanone (0.10 g, 1.0 mmol), finely ground sarcosine (0.27 g, 3.0 mmol) and DIPEA (0.06 g, 0.5 mmol) was refluxed in dry toluene (3.3 mL) with magnetic stirring and removal of the water formed by means of a Dean–Stark trap. Refluxing was continued for 24–48 h. The resulting mixture was cooled to room temperature and filtered. The solution was evaporated in vacuo to give a viscous mixture of crude products, which were isolated by column chromatography on silica gel.
9. *Diethyl [(3R*,4S*)-4-(2-hydroxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl]phosphonate* (***2***): This compound was prepared from coumarin **1** according to the general procedure (48 h), except DIPEA was not employed. White crystals, yield 47%, mp 129–133 °C; IR: 3158, 1686, 1459, 1219, 1052, 1022, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, Me, J = 7.1 Hz), 1.28 (t, 3H, Me, J = 7.1 Hz), 2.86 (d, 3H, NMe, J = 1.5 Hz), 3.39 (dd, 1H, H-3, J = 21.9, 6.8 Hz), 3.47 (ddd, 1H, 5-C*H*H, J = 9.5, 5.7, 2.3 Hz), 3.73 (t, 1H, 5-CH*H*, J = 9.3 Hz), 3.90–4.00 (m, 1H, H-4), 3.99–4.11 (m, 2H, OCH_2), 4.19 (quin, 2H, OCH_2, J = 7.1 Hz), 6.77 (t, 1H, H-5′, J = 7.5 Hz), 6.96 (dd, 1H, H-3′, J = 8.0, 1.1 Hz), 7.04–7.11 (m, 2H, H-6′, H-4′), 8.76 (br s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3 (d, OCH_2*Me*, J = 6.2 Hz), 16.4 (d, OCH_2*Me*, J = 6.1 Hz), 30.0 (NMe), 35.3 (C4), 46.9 (d, C3, J = 143.5 Hz), 54.4 (d, C5, J = 7.1 Hz), 62.8 (d, OCH_2, J = 6.8 Hz), 63.5 (d, OCH_2, J = 6.5 Hz), 116.6 (C3′), 119.7 (C5′), 127.5 (d, C1′, J = 5.7 Hz), 128.6 (C6′), 128.7 (C4′), 155.2 (C2′), 169.5 (d, C2, J = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.54 ($PO(OEt)_2$). Anal. Calcd for $C_{15}H_{22}NO_5P{\cdot}0.5H_2O$: C, 53.57; H, 6.89; N, 4.16. Found: C, 53.52; H, 6.97; N, 4.20.
10. (a) Zvejniece, L.; Svalbe, B.; Veinberg, G.; Grinberga, S.; Vorona, M.; Kalvinsh, I.; Dambrova, M. *Basic Clin. Pharmacol. Toxicol.* **2011**, *109*, 407–412; (b) Kanes, S. J.; Tokarczyk, J.; Siegel, S. J.; Bilker, W.; Abel, T.; Kelly, M. P. *Neuroscience* **2007**, *144*, 239–246.
11. Janecki, T.; Wąsek, T. *Tetrahedron* **2004**, *60*, 1049–1055.
12. *(3S*,4S*)-3-Benzoyl-4-(2-hydroxyphenyl)-1-methylpyrrolidin-2-one and 4-hydroxy-2-methyl-4-phenyl-1,3a,4,9b-tetrahydrochromeno[3,4-c]pyrrol-3(2H)-one* (***10***): Pale-brown crystals, yield 49%, mp 82–87 °C; IR: 3159, 2927, 1660, 1455, 1259, 754, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (**10**, 85%) δ 2.94 (s, 3H, NMe), 3.63 (dd, 1H, C*H*H, J = 9.7, 6.6 Hz), 3.82 (dd, 1H, CH*H*, J = 9.7, 8.9 Hz), 4.30 (dt, 1H, H-4, J = 8.9, 6.9 Hz), 4.70 (d, 1H, H-3, J = 7.2 Hz), 6.85 (td, 1H, H-5′, J = 7.4, 1.1 Hz), 6.87 (dd, 1H, H-3′, J = 8.0, 1.1 Hz), 7.11 (ddd, 1H, H-4′, J = 8.0, 7.4, 1.6 Hz), 7.14 (dd, 1H, H-6′, J = 7.4, 1.6 Hz), 7.41 (tt, 2H, H-3″, H-5″, J = 7.7, 1.6 Hz), 7.54 (ddt, 1H, H-4″, J = 8.0, 6.9, 1.3 Hz), 8.04 (dd, 2H, H-2″, H-6″, J = 8.5, 1.3 Hz); (**10**′, 15%) δ 2.84 (s, 3H, NMe), 3.37 (d, 1H, C*H*H, J = 9.7 Hz), 3.48 (br d, 2H, H-3a, H-9b, J = 3 Hz), 3.84–3.89 (m, 1H, CH*H*), 6.92 (td, 1H, H-8, J = 7.5, 1.2 Hz), 7.03 (dd, 1H, H-6, J = 8.1,

1.2 Hz), 7.04 (dd, 1H, H-9, J = 7.7, 1.6 Hz), 7.17–7.22 (m, 1H), 7.26–7.30 (m, 3H), 7.46–7.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (**10**, 85%) δ 30.2 (Me), 36.8 (C4), 53.7 (C5), 57.7 (C3), 116.8 (C3′), 120.5 (C5′), 127.3 (C1′), 128.6 (C3″, C5″), 128.8 (C6′), 129.0 (C4'), 129.9 (C2″, C6″), 133.8 (C4″), 136.3 (C1″), 154.7 (C2′), 170.5 (C2), 197.1 (*C*OPh); (**10′**, 15%) δ 30.0 (NMe), 33.7, 46.8, 56.4 (C1), 98.8 (C4), 118.1 (C6), 122.0 (C8), 126.2, 127.7, 128.3, 128.8, 128.9, 173.7 (C3). Anal. Calcd for $C_{18}H_{17}NO_3 \cdot 0.75H_2O$: C, 70.00; H, 6.04; N, 4.54. Found: C, 70.35; H, 5.69; N, 4.38.