THE DIASTEREOSELECTIVE SYNTHESIS OF OXACEPHAMS FROM 1,3-*2H*-OXAZINES

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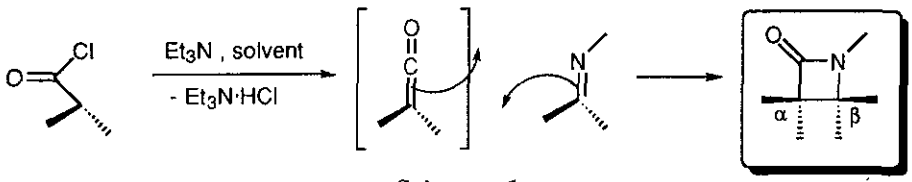
Abstract- Various oxacephams are obtained from symmetrically and unsymmetrically 2,2,5,5-substituted 1,3-*2H*-oxazines by the Staudinger reaction. The annulation reaction proceeds diastereoselectively with both synthons, as unequivocally determined by nmr spectroscopical analysis.

Though already many of β-lactams were prepared chemically or biologically and are in part used as antibiotics,[1] the chemistry of these compounds is still in development. This is undoubtedly due to the evolution of resistance effects in pathogenic microorganisms, which demand for new and possibly less toxic antibiotic compounds.



Scheme 1

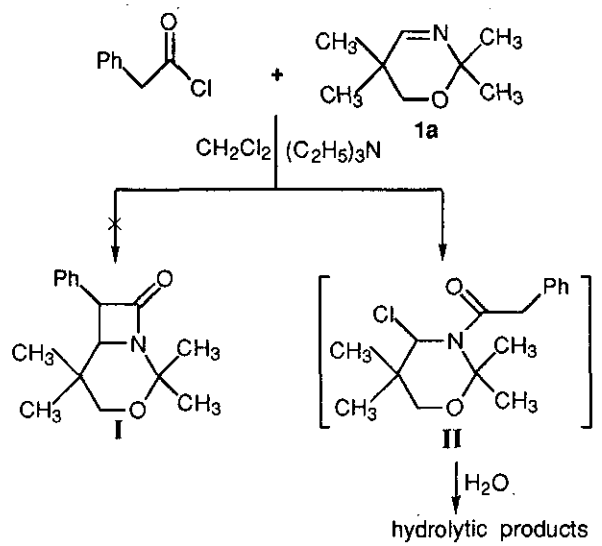
β-Lactams may be synthesized by different methods.[2] One of the first and probably easiest methods is the Staudinger reaction which condenses a substituted acetyl chloride and an imine compound in the presence of a base[3] as depicted in Scheme 1.

Extending our studies on the synthesis and chemistry of heterocyclic imines (1,3-thiazolines,[4] 1,3-oxazolines,[5] and 1,3-oxazines[6]) we were interested in the synthesis of β-lactam derivatives of 1,3-*2H*-oxazines using this method.

Results and discussion

The structural, experimental,[7] and stereochemical requirements[8] of the Staudinger reaction have been described previously. The dehydrohalogenation of acid chlorides with α hydrogens leads in basic media to ketene intermediates which then undergo a [2+2] cycloaddition with the Schiff base. Therefore factors that favor the formation of ketenes will enhance the annulation reaction .

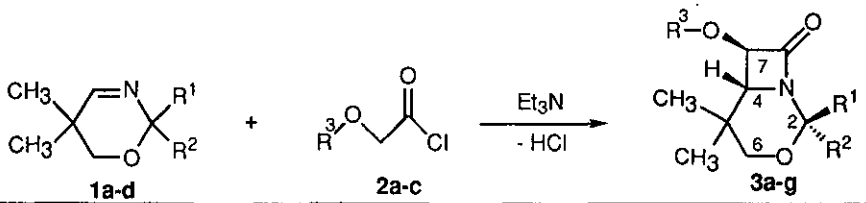
We studied reactions of acid chlorides with 1,3-oxazines under Staudinger conditions. The reaction of phenyl acetyl chloride with 2,2,5,5-tetramethyloxazine (**1a**) did not lead to the expected β-lactam (**I**), but



Scheme 2

afforded the *N*-acyliminium chloride (**II**). This is the typical product which arises from the addition of acid chlorides to the 1,3-thiazolines[9] and oxazolines[5] in the absence of base (Scheme 2). Here, the direct amidation of the imine bond by the acid chloride is obviously favored in comparison to the formation of a ketene.

As documented in literature,[10] 2-alkoxy- and 2-aryloxyacetyl chlorides are some appropriate sources for generation of ketenes in the course of Staudinger reaction. Hence, we treated methoxy-, phenoxy- and 4-chlorophenoxyacetyl chlorides with 1,3-oxazines (**1a-d**) in the cold and in the presence of equimolar amounts of triethylamine (Scheme 3). We thus obtained the corresponding oxacephams (**3a-g**) in moderate to excellent yields (Table 1).



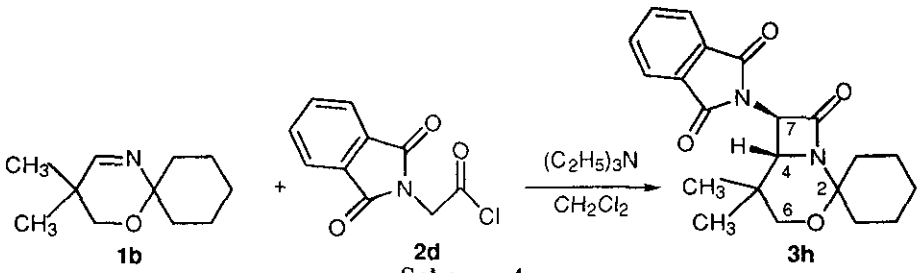
1	R^1	R^2
a	CH_3	CH_3
b	$-(CH_2)_5-$	
c	CH_3	H
d	*tert*-C_4H_9	H

2	R^3
a	CH_3
b	Ph
c	*p*-Cl-C_6H_4

3	R^1	R^2	R^3
a	CH_3	CH_3	Ph
b	$-(CH_2)_5-$		Ph
c	$-(CH_2)_5-$		CH_3
d	$-(CH_2)_5-$		*p*-Cl-C_6H_4
e	CH_3	H	*p*-Cl-C_6H_4
f	CH_3	H	Ph
g	*tert*-C_4H_9	H	*p*-Cl-C_6H_4

Scheme 3

With these results we next examined the reaction of phthaloylglycyl chloride (**2d**) as an acid chloride derivatives of *N*-protected α-amino acids possessing H_α.The addition of a solution of it to the prochiral imine (**1b**) afforded the racemic oxacepham (**3h**) in 55% yield (Scheme 4). Thus, the applied method proved to be capable of condensing a wide range of α-amino acids possessing H_α in *N*-protected form as ketene synthons with 1,3-*2H*-oxazines.



Scheme 4

The here presented S t a u d i n g e r reactions with racemic imines (**1c,d**) as well as with prochiral imines (**1a,b**) proceeded with an interesting stereochemistry. According to the literature acyclic prochiral imines did not demonstrate diastereoselectivity in the annulation with achiral acid chlorides.[2] Diastereoselectivity was first observed as asymmetric induction in chiral imines or acid chlorides.[11] Here the *cis* isomer was either the unique[12] or the major[13] diastereomer formed.

Cyclization of ketenes with the Schiff bases (**1**) generates two chiral centers C-4 and C-7 in the resultant azetidinones (**3**) (Scheme 3). Therefore two diastereomeric products are possible from the reaction of prochiral imines (**1a-b**). In the case of the chiral imines (**1c-d**) additional stereoisomers can be produced due to the presence of a stereogenic centre in position 2. We observed diastereoselectivity in both cases.

Table 1: Some selected data of the new oxacephams (**3a-h**).

3	yield[a]	*dr*[b]	mp[c]	ir[d]	ms[e]
a	60	>99:1	115	1751	276
b	80	>99:1	109	1751	316
c	45	>99:1	120	1754	254
d	90	>99:1	129	1750	350
e	63	>99:1:0	101	1757	296
f	50	>99:1:0	121	1751	262
g	80	>99:1:0	143	1750	338
h	55	>99:1	92	1753, 1780[f]	369

[a] in %, based on (**1a-d**). [b] diastereomeric ratio according to ^{1}H-nmr . [c] in °C, are uncorrected. [d] KBr, cm^{-1}, *C=O stretching*. [e] CI, *isobutane*, *m/e* [MH^+](100%). [f] -*N*(C=O)$_2$ stretching.

The nmr spectra of the reaction products (**3**) reveal that only one diastereoisomer had been formed. All of them show weak vicinal proton coupling constants of $J_{4,7}$ from 0 to 2.1 Hz between the two newly formed chiral centers. This is an indication for a *trans* orientation of protons H-4 and H-7, when compared to literature values for *cis*[14] and *trans*[15] configured β-lactams. However, the values of the dihedral angles between H-4 and H-7 in *cis* and in *trans* configured products would lead to comparable coupling constants, when one considers a Karplus-like relationship. The observed differences in coupling constants between *cis* and *trans* configured products therefore derive from anisotropic effects of the electronegative character of the substituents. These anisotropic effects depend themself on the stereochemistry of the compound and the coupling constants, therefore, do not seem to allow for an unequivocal assignment. Additionally, in the here reported products the observed range in the coupling constants of about 2 Hz is nearly as broad as the reported differences[14,15] between *cis* and *trans* isomers. An independent and unequivocal assignment of the stereochemistry in the new oxacephams was performed by NOE studies on compound (**3a**) as a model for the products of the prochiral and on compound (**3f**) as a model for the products of the chiral imines.

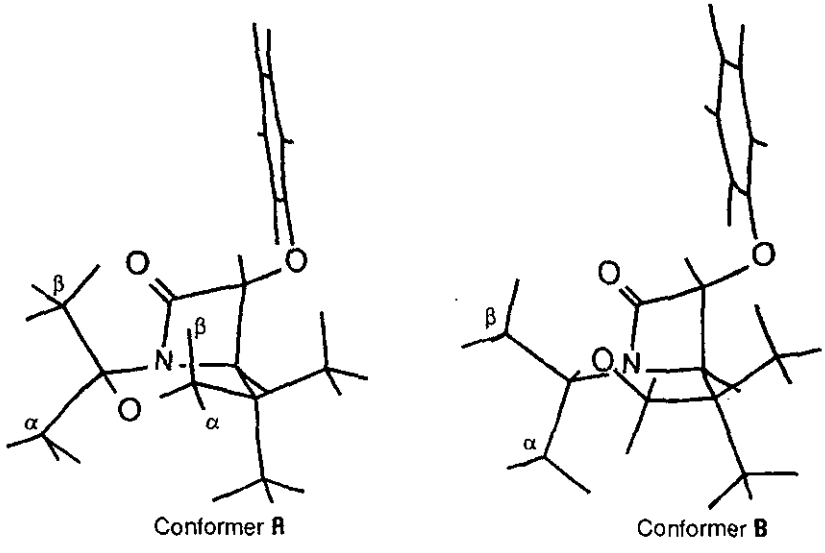
Table 2. The intensities of NOE contacts in compound (**3a**) and (**3f**)[a]

diagonal peak	cross peak	3a	3f	diagonal peak	cross peak	3a	3f
	Me2β	3.8	—		H-4	4.1	3.2
	Me5β	7.9	9.7		H-6α	19.6	22.5
H-7	Me5α	3.2	4.6	H-6β	Me2α	7.7	10.5
	HAr	5.1	4.5		Me5β	2.1	5.2
	H-4	2.1	2.5		Me5α	4.9	9.9
H-4	H-2,2'Ar	6.5	3.4		H-6β	19.6	22.5
H-2	Me2	—	8.2	H-6α	Me2β	4.2	—
	Me5β	—	3.6		Me5β	5.5	9.8
	H6β	4.1	3.2		Me5α	4.9	9.0
H-4	Me2α	3.0	5.6	Me2β	Me2α	7.1	—
	Me5α	4.0	6.2	Me5β	Me5α	1.9	—

[a] Intensities are given in % relative to the diagonal peak of H-7.

The two dimensional NOE spectra of (**3a**) show NOE contacts between numerous protons (Table 2). There is a small but observable NOE contact between H-7 and H-4 . Since the distance between these protons is approximately 2.4 Å in a *cis* isomer and 3.1 Å in a *trans* product, this relatively small NOE can be considered to indicate a *trans* relationship. A conclusive analysis, however, was possible by evaluating the NOE enhancements between H-7 and the methyl groups. NOE contacts to both methyl groups at C-5 and to one methyl group at C-2 clearly indicate the presence of the *trans* isomer. These contacts are not probable in

a *cis* isomer, as is revealed by regarding the possible conformations of the product. For the synthesized oxacephams two conformational arrangements (**A**) and (**B**) with *endo* and *exo* oriented -C-O-C- fragments are probable (Scheme 5). In conformer (**A**) the six membered ring adopts a $^{6}T_{O}$ conformation whereas the *exo* orientation in conformer (**B**) leads to a $^{O}T_{5}$ conformation of this ring. Calculations with the TRIPOS force field revealed that (**A**) is the energetically favored conformer with -5.0 kcal/mol energy difference to conformer (**B**). All observed NOE enhancements are in agreement with a *trans* configured product and, moreover, indicate that most of the products adopt the minor energy conformer (**A**). This was concluded from the NOE contacts that involve the H-6 protons. In conformer (**A**) H-6α bisects the angle to both Me-5 groups and should thus qualitatively lead to comparable effects in both Me-5 groups and an NOE effect to only the upper Me-2β group. This is observed in the experiment. On the other hand, some of the NOE enhancements of H-6β and a too strong NOE effect H-7/Me-5α are not as unequivocally indicating the existence of a single conformation. We are aware that NOE contacts to freely rotating methyl groups may not be as easily transformed into unequivocal distance information, due to possible differences between movements of the whole molecule and fragments. But we think that these effects can be taken as a qualitative indication of the existence of mainly one conformer (**A**) and a minor proportion of conformer (**B**).



Scheme 5: The endo(**A**) and exo(**B**) conformers of (**3a**).

The annulation products of the chiral imines (**3e-g**) exhibit the same stereochemistry in the oxacepham ring as the product from prochiral imines, which is evident from the nmr shift and coupling pattern. The results of the NOE measurements of the former products (**3a**) facilitated also the stereochemical assignment in the chiral position 4 of **3e-g.** Through the NOESY spectra of **3a** as well as of **3f** an unequivocal assignment of methyl groups situated at the upper (β) and lower site (α) and the methylene protons in

position 6 was possible. As might be expected from the differences in chemical shifts induced by the carbonyl group in the oxacepham ring the β-site methyl groups and protons are shifted downfield as compared to the α-site groups. This effect is very profound in position 2, where the difference in chemical shift is nearly 1 ppm. The differences in Me-5's are smaller (about 0.4 ppm).

From the absence of the downfield resonances for the methyl and tert-butyl groups in the spectra of **3a-d** we conclud that the isomer with this group in the α- position and therefore a *trans* relationship of protons H-4 and H-2 has been formed. This assignment was ascertained by the NOESY spectra of **3f**, which gave nearly identical results to **3a.** Also the conformational analysis performed by calculation and evaluation of the NOE's led to the same results as in **3a** ; i.e. that conformer comparable to (**A**) is favored over a (**B**)-like conformer.

The diastereoselective formation of a *trans* configuration of H-2 and H-4 in the unsymmetrically substitued oxacephams (**3e-f**) is in agreement with results published by Ugi[16] and Martens[7]. Ugi interpreted his results by assuming that a nucleophilic attack proceeds *anti* to the bulky group in position 2 of the oxazine. This results in only one diastereoisomer, because the unsymmetric 1,3-2*H*-oxazines like **1c** preferentially adopt a half-chair conformation with the C2-alkyl group in an equatorial position.

EXPERIMENTAL

Melting points were determined in an open capillary tube on a Dr. Linström instrument and were uncorrected. The elemental analyses were carried out on a Carlo Erba (MOD 1104). The ir spectra were recorded on a Beckman spectrophotometer (IR 4220). The nmr spectra were recorded either on a Bruker AM300 or a ARX500 spectrometer at 300 and 500 MHz for ^{1}H and 121 MHz and 75 MHz, respectively, for ^{13}C. NOE measurements were performed at the ARX500 instrument in benzene-d_6 as 2D NOESY spectroscopy applying standard Bruker software. Mixing times of 200, 400, and 800 ms were used, the data given in table 2 correspond to a mixing time of 800 ms. Molecular Modeling was performed on Iris Indigo Silicon Graphics computers with the programme package SYBYL. Several energy minimisations were performed from different starting geometries and let to two distinct conformers (**A** and **B**) with energy differences of -5.0 kcal/mol for **3a** and -5.5 kcal /mol for **3f**. Mass spectroscopy was peformed on a Finnigan MAT 212 (data system SS 300) apparatus. The 1,3-oxazines[6,17] *N*-phthaloylglycine[18] and its acid chloride[19] were prepared according to the literature.

β-Lactams (3a-h); General Procedure: A solution of imines (**1a-d**) (10 mmol) and triethylamine(20 mmol) in dry dichloromethane(20 ml) was cooled to 0°C and then a dry dichloromethane solution(10 ml) of acid chlorides (**2a-d**) (10 mmol) was added dropwise to it. The reaction mixture was kept under stirring overnight at room temperature and then an aqueous saturated solution of ammonium chloride(20 ml) was added. The organic phase was seperated and the water phase was extracted with dichloromethane(3×20 ml). The recombined organic phases were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. Addition of ether followed by standing in refrigarator gave the fine colorless crystals of (**3a-h**) which were filtered off and washed with little ice cooled ether and dried in *vacuo*.

rac-2,2,5,5-Tetramethyl-7-phenoxy-3-oxa-1-azabicyclo[4.2.0]octan-8-one (**3a**): ^{1}H-Nmr ($CDCl_3$/δ): 0.95(s, 3H, CH_3-5α); 1.15(s, 3H, CH_3-5β); 1.46(s, 3H, CH_3-2α); 1.79(s, 3H, CH_3-2β); 3.31(d, $J_{6\alpha,6\beta}$=12.1 Hz, H-6α); 3.56(d, $J_{6\alpha,6\beta}$=12.1 Hz, H-6β); 3.47(s, 1H, H-4); 5.07(s, 1H, H-7); 7.00-7.08, 7.27-7.34(m, 5H, Ar-H) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 18.83(CH_3-5α); 21.88(CH_3-5β); 22.74(CH_3-2α); 26.31(CH_3-2β); 31.23(C-5); 61.91(C-4); 70.41(C-6); 82.59(C-7); 82.95(C-2); 115.80, 122.28, 129.53, 157.35(Ar-C); 161.36 (C=O) ppm. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.41; H, 7.92; N, 4.94.

Racemic oxacepham **3b**: ^{1}H-Nmr ($CDCl_3$/δ): 0.94(s, 3H, CH_3-5α); 1.15(s, 3H, CH_3-5β); 1.37-1.51, 1.58-1.70, 1.82-2.04, 2.34-2.40, 3.05-3.10(m, 10H, cyclohexyl-CH_2); 3.28(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6α); 3.54(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6β); 3.46(s, 1H, H-4); 5.04(s, 1H, H-7); 6.99-7.08, 7.27-7.32(m, 5H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 19.04(CH_3-5α); 22.78CH_3-5β); 21.50, 21.68, 25.05, 29.93, 34.88(cyclohexyl-CH_2); 45.77(C-5); 61.37(C-4); 69.69(C-6); 82.36(C-7); 84.51(C-2); 115.81, 122.23, 129.52, 157.39(Ar-C); 161.52 (C=O) ppm. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.34; H, 7.99; N, 4.44. Found: C, 72.10; H, 8.19; N, 4.80.

Racemic oxacepham **3c**: ^{1}H-Nmr ($CDCl_3$/δ): 0.92(s, 3H, CH_3-5α); 1.05(s, 3H, CH_3-5β); 1.44-1.48, 1.72-1.83, 1.98-2.05, 2.30 - 2.38(m, 10H, cyclohexyl-CH_2); 3.22(d, $J_{4,7}$=1.1 Hz, H-4), 3.25(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6α); 3.49(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6β); 3.46(s, 3H, CH_3O); 4.31(d, $J_{4,7}$=1.1 Hz, H-7) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 18.89(CH_3-5α); 22.65(CH_3-5β); 21.47, 21.67, 25.05, 29.94, 31.19 (cyclohexyl-CH_2); 34.82(C-5) ; 57.71(C-4); 60.66(CH_3O); 69.73(C-6); 84.22(C-2); 85.40(C-7); 175.70(C=O) ppm. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.36; H, 9.16; N, 5.53. Found: C, 65.98; H, 9.23; N, 5.44.

Racemic oxacepham **3d**: ^{1}H-Nmr ($CDCl_3$/δ): 0.94(s, 3H, CH_3-5α); 1.13(s, 3H, CH_3-5β); 1.38-1.68, 1.80-2.03, 2.31-2.39, 3.06-3.13(m, 10H, cyclohexyl-CH_2); 3.28(d, $J_{6\alpha,6\beta}$=12.1 Hz, H-6α); 3.54(d, $J_{6\alpha,6\beta}$=12.1 Hz, H-6β); 3.46(s, 1H, H-4); 4.97(s, 1H, H-7); 6.99-7.02, 7.24-7.27(2m, 4H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 19.06(CH_3-5α); 22.76(CH_3-5β); 21.49, 21.68, 25.04, 29.94, 34.88(cyclohexyl-CH_2); 45.78(C-5); 61.25(C-4); 69.64(C-6); 82.56(C-7); 117.23, 118.42, 129.40, 130.01(Ar-C); 179.3(C=O) ppm. Anal. Calcd for $C_{19}H_{24}NO_3Cl$: C, 65.30; H, 6.93; N, 4.01. Found: C, 65.12; H, 7.12; N, 4.38.

rac-7-(4-Chlorophenoxy)-2,5,5-trimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (**3e**): ^{1}H-Nmr ($CDCl_3$/δ): 0.99(s, 3H, CH_3-5α); 1.14(s, 3H, CH_3-5β); 1.41(d, ^3J=6.2 Hz, 3H, CH_3-2); 3.26(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6α); 3.58(d, $J_{6\alpha,6\beta}$=12.1 Hz, H-6β); 3.53(d, $J_{6\alpha,6\beta}$=1.2 Hz, H-4); 5.03(d, $J_{6\alpha,6\beta}$=1.2 Hz, 1H, H-7); 5.46(q, ^3J=6.2 Hz, 1H, H-2); 6.98-7.04, 7.23-7.27 (2m, 4H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3$/δ): 17.08(CH_3-5α); 19.40, 23.56(CH_3-5β, CH_3-2); 31.58(C-5); 61.03(C4-); 69.43(C-6); 73.76(C-7); 83.48 (C-2); 116.60, 117.99, 127.33, 128.96, 129.45, 155.90(Ar-C); 162.12 (C=O) ppm. Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 61.00; H, 6.15; N, 4.75. Found: C, 60.86; H, 6.23; N, 4.65.

rac-2,5,5-Trimethyl-7-phenoxy-3-oxa-1-azabicyclo[4.2.0] octan-8-one (**3f**): ^{1}H-Nmr ($CDCl_3/\delta$): 1.01(s, 3H, CH_3-5α); 1.16(s, 3H, CH_3-5β); 1.44(d, ^3J=6.0 Hz, 3H, CH_3-2); 3.28(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6α); 3.59(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6β); 3.55(s, 1H, H-4); 5.11(s, 1H, H-7); 5.49(q, ^3J=6.1 Hz, 1H, H-2); 7.01-7.09, 7.28-7.35(m, 5H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3/\delta$): 17.14(CH_3-5α); 19.43, 23.66(CH_3-5β, CH_3-2); 31.67(C-5); 61.22(C-4); 69.56(C-6); 73.77 (C-7); 82.95(C-2); 115.71, 122.35, 129.62, 157.36(Ar-C); 162.48 (C=O) ppm. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.36. Found: C, 69.10; H, 7.19; N, 5.27.

rac-7-(4-Chlorophenoxy)-5,5-dimethyl-2-tert-butyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (**3g**): ^{1}H-Nmr ($CDCl_3/\delta$): 0.99[s, 9H, $C(CH_3)_3$]; 1.05(s, 3H, CH_3-5α); 1.22(s, 3H, CH_3-5β); 3.18(d, $J_{6\alpha,6\beta}$=11.6 Hz, H-6α); 3.46(d, $J_{6\alpha,6\beta}$=11.6 Hz, H-6β); 3.57(d, $J_{6\alpha,6\beta}$=1.5 Hz, H-4); 5.00(d, $J_{6\alpha,6\beta}$=1.5 Hz, H-7); 4.65(s, 1H, H-2); 7.08(d, ^3J= 8.8 Hz, 2H, Ar-H); 7.26 (d, ^3J=8.8 Hz, 2H, Ar-H) ppm. ^{13}C-Nmr ($CDCl_3/\delta$): 21.52(CH_3-5α); 27.35(CH_3-5β); 24.92[C($\underline{C}H_3$)$_3$]; 33.25, 37.20[C-5, $\underline{C}(CH_3)_3$]; 64.35(C-4); 73.55(C-6); 82.19(C-7); 89.01(C-2); 117.46, 127.39, 129.44, 155.92(Ar); 165.79(C=O) ppm. Anal. Calcd for $C_{18}H_{24}NO_3Cl$: C, 64.07; H, 7.17; N, 4.15. Found: C, 64.29; H, 7.00; N, 4.19.

Racemic oxacepham (**3h**): ^{1}H-Nmr ($CDCl_3/\delta$): 0.91(s, 3H, CH_3-5α); 1.34(s, 3H, CH_3-5β); 1.04-1.70, 1.82-1.97, 2.16-2.40(m, 10H, cyclohexyl-CH_2); 3.32(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6α); 3.57(d, $J_{6\alpha,6\beta}$=12.0 Hz, H-6β); 3.64(d, $J_{6\alpha,6\beta}$=2.1 Hz, H-4); 5.14(d, $J_{6\alpha,6\beta}$=2.1 Hz, 1H, H-7); 7.72-7.77, 7.83-7.88(2m, 4H, Ar-CH) ppm. ^{13}C-Nmr ($CDCl_3/\delta$): 18.52, 22.39 (2×CH_3); 21.60, 21.67, 25.14, 29.96, 31.79(cyclohexyl-CH_2); 34.93(C-5); 56.08(C-4); 59.31(C-7); 84.96(C-6); 123.61, 124.07, 131.77, 134.30, 134.39(Ar-C); 159.63, 160.21, 167.00(3×C=O) ppm. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.45; H, 6.57; N, 7.61. Found: C, 68.23; H, 6.72; N, 7.49.

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