Enantioselective *Michael* Addition of the 2-(1-Ethylpropoxy)acetaldehyde to *N*-[(1*Z*)-2-Nitroethenyl]acetamide – Optimization of the Key Step in the Organocatalytic Oseltamivir Synthesis

by **Viktória Hajzer**[a]), **Attila Latika**[a]), **Július Durmis**[a]), and **Radovan Šebesta***[b])

[a]) *Synkola*, Mlynská dolina CH-2, SK-84215 Bratislava, Slovakia
[b]) Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina CH-2, SK-84215 Bratislava (phone: +421-2-60296208; fax: +421-2-60296337; e-mail: radovan.sebesta@fns.uniba.sk)

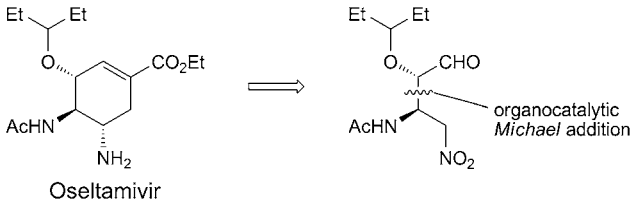
Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Organocatalytic *Michael* addition of alkoxyacetaldehyde **1** to N-protected 2-nitroethene-1-amine **2** (*Scheme 2*) is a key step in the synthesis of an important antiviral agent, oseltamivir. Screening of a large array of structurally diverse acids as potential promoters led to the identification of several useful acidic additives for this reaction (*Tables 1–4*). Also other reaction parameters were investigated with the aim of improving the diastereoselectivity of the *Michael* addition, while maintaining high enantiomer purity and yield (*Tables 5* and *6*).

Introduction. – Oseltamivir phosphate is an active ingredient of *Tamiflu*®, one of the most potent antiviral drugs, which is used against various strains of influenza, including variant H5N1 [1]. Oseltamivir belongs to a group of neuraminidase inhibitors, which prevents the release of influenza virus from cells [2]. The potential threat of an influenza pandemic resulted in great attention of both academia and industry to find a viable synthesis of oseltamivir. The result of this interest are several syntheses of oseltamivir, which have been developed recently [3]. Oseltamivir is currently produced by *Hoffmann-La Roche Ltd.* [4], by means of a modified synthesis originally developed by *Gilead Sciences* [5]. The *Roche* process uses shikimic acid as a starting material. Also several other syntheses start from chiral starting materials [6]. The reliance on supply of natural material is one of the weak points of this approach [7]. The assembly of a cyclohexene core by an organocatalyzed domino reaction, *Enders*' triple cascade [8], served as inspiration for the development of an alternative route to oseltamivir based on organocatalysis. The enantioselective organocatalytic approach to oseltamivir was pioneered by *Hayashi* and co-workers [9]. The oseltamivir skeleton was built from simple achiral starting materials in the presence of a chiral organocatalyst. *Hayashi* and co-workers' elegant strategy was applied also to other secondary-amine organocatalysts [10]. The key step of this approach was an asymmetric organocatalytic *Michael* addition of an alkoxyacetaldehyde to a nitroacrylate, followed by a *Horner–Wadsworth–Emmons* reaction to complete the assembly of the cyclohexene core of oseltamivir. Although other organocatalytic syntheses of oseltamivir have been developed [11], the approach based on the *Michael*

addition seems to be the most straightforward. The disadvantage of *Hayashi* and co-workers' approach is the necessity to transform an ester group into an amino group *via* a potentially hazardous azide. An improvement was suggested by *Ma* and co-workers, who used N-protected 2-nitroethenes-1-amines as substrates for the *Michael* addition to circumvent the *Curtius* rearrangement [12]. This strategy was applied also in other oseltamivir syntheses (*Scheme 1*) [13]. Both these strategies rely on the *Michael* addition as a key step to obtain an important intermediate with high diastereoisomer and enantiomer purity. Enantioselectivities are generally high, but diastereoselectivities are often medium, at best.

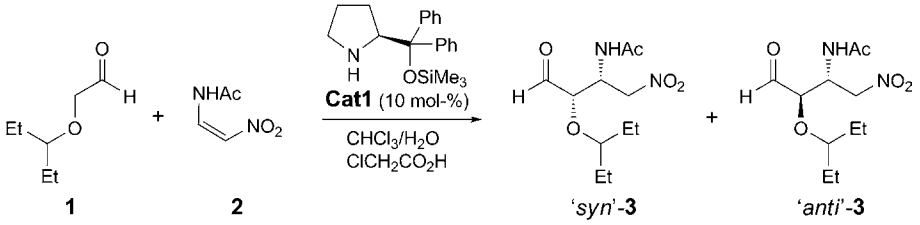
Scheme 1



In this context we decided to study the organocatalytic *Michael* addition of 2-(1-ethylpropoxy)acetaldehyde (**1**) to *N*-[(1*Z*)-2-nitroethenyl]acetamide (**2**). Several parameters influencing this addition reaction were evaluated, but particular attention was devoted to the effect of the additive.

Results and Discussion. – As a starting point, we chose our previous results from the *Michael* addition of aldehyde **1** to alkene derivative **2** (*Scheme 2*) [13a]. In the presence of the *Hayashi–Jorgensen* catalyst (**Cat1**), this reaction led to compound **3** as a mixture of the '*syn*' and '*anti*'-isomer. The '*syn*'-**3** is the advanced intermediate required for the oseltamivir synthesis. Therefore, in an attempt to increase the diastereoselectivity of the *Michael* addition in favor of *'syn'*-**3**, we investigated the influence of several reaction parameters. Previously, the highest diastereoselectivity (*'syn'*/*'anti'* 4:1) was achieved in a two-phase system $CHCl_3/H_2O$ 1.5:1 (*v*/*v*) with an excess of aldehyde **1** and 10 mol-% of catalysts **Cat1**. Chloroacetic acid (20 mol-%) was used as an additive (*Scheme 2*). Similar results were obtained also by *Ma* and co-workers with benzoic acid in neat $CHCl_3$ [12].

Scheme 2



Various acidic additives have been suggested to promote organocatalytic *Michael* additions [14]. It seems, however, that none of them is universally applicable. Therefore, we decided to investigate the influence of an additive as the first reaction parameter (*Table 1*). Without any acidic additive, the reaction proceeded slowly, and the *'syn'*/*'anti'* ratio was also low, with *'anti'*-**3** being the major product (*Entry 1*). Conversion dramatically increased when acetic acid was used as the additive, but the dr was only 1.7:1 (*Entry 2*). Interestingly, the desired *'syn'*-**3** isomer was now dominant. The best results were obtained with chloroacetic acid (*Entry 3*). Stronger acids, such as dichloroacetic acid, gave worse results, and the reaction with trichloroacetic acid did not work at all (*Entries 4* and *5*).

Table 1. *Initial Screening of the* Michael *Addition of Aldehyde* **1** *with Alkene Derivative* **2** *in the Presence of Additives of Varying Acidity*

Entry	Additive	pK_a[a])	dr (*'syn'*/*'anti'*)	Conversion [%]
1	–	–	0.7:1	9
2	MeCOOH	4.76	1.7:1	97
3	$ClCH_2COOH$	2.85	4.9:1	92
4	$Cl_2CHCOOH$	1.48	3.5:1	20
5	Cl_3CCOOH	0.70	–	0

[a]) pK_a Values were taken from *Wiliams* pK_a table, which can be accessed at the Organic Division of the American Chemical Society (http://www.chem.wisc.edu/areas/organic/index-chem.htm).

Realizing that chloroacetic acid provided the best results, we screened an array of substituted acetic acids for the *Michael* addition of aldehyde **1** and alkene derivtive **2** (*Table 2*) with substituted acetic acids. The results with other haloacetic acids were similar to that obtained with chloroacetic acid (*Entries 1–4*). The highest diastereoselectivities *'syn'*/*'anti'* 5.9:1 and 5.6:1 were obtained with 2-(4-chlorophenyl)- and 2-(4-bromophenyl)-2-hydroxyacetic acids, respectively (*Entries 11* and *12*). However, conversions were lower in these experiments. The most promising results, in terms of diastereoselectivity, enantioselectivity, and conversion, were obtained with racemic mandelic acid (*Entry 5*).

Several other additives with acidic properties were tested too. Additives, such as boric acid, L-proline, glycine, *Amberlite* and ethylenediaminetetraacetic acid (= *N*,*N*′-ethane-1,2-diylbis[*N*-(carboxymethyl)glycine]; EDTA) gave low diastereoselectivities, slightly in favor of *'anti'*-**3** (*Table 3*). Only benzoic acid afforded isomer *'syn'*-**3** as a major product with a *'syn'*/*'anti'* ratio of 2.3:1.

Seebach, *Hayashi* and co-workers identified 4-nitrophenol as another effective additive for the addition of aldehydes to nitrostyrenes [15]. However, in the reaction of aldehyde **1** with nitroalkene derivative **2**, 4-nitrophenol performed less well (*Table 4*, *Entry 1*). Similar results were obtained also with 2-methyl-4-nitrophenol. Interestingly, in the presence of the more acidic 2,4- or 2,6-dinitrophenols, the diastereoselectivity markedly increased (*Entries 3* and *4*). Further increase of the acidity of the additive was detrimental to the reaction (*Entries 5* and *6*).

Screening a range of acidic additives suggests that there is an optimal pK_a range for a good additive in the reaction of aldehyde **1** with nitroalkene derivative **2**. Only

Table 2. Michael *Addition of Aldehyde* **1** *with Alkene Derivative* **2** *in the Presence of Substituted Acetic Acids as Additives*

Entry	Additive	pK_a	dr (*'syn'*/*'anti'*)	ee *'syn'*-**3** [%]	ee *'anti'*-**3** [%]	Conversion [%][a])
1	FCH_2COOH	2.10	4.6 : 1	94	68	94
2	$ClCH_2COOH$	2.85	4.3 : 1	95	77	97 (75)
3	$BrCH_2COOH$	2.69	4.8 : 1	96	77	82
4	ICH_2COOH	3.12	3.6 : 1	98	77	94
5	*rac*-PhCH(OH)COOH	3.85	5.0 : 1	94	86	74
6	$HOCH_2CO_2H$	3.83	1.2 : 1	n.d.	n.d.	72
7	$BrCH_2CH_2CO_2H$		2.2 : 1	n.d.	n.d.	97
8	$PhCH_2CO_2H$		3.0 : 1	n.d.	n.d.	90
9	$PhCHBrCO_2H$	2.4	4.7 : 1	90	79	60
10	4-Br–$C_6H_4CH_2CO_2H$	4.17	3.2 : 1	90	65	69
11	4-Br–$C_6H_4CH(OH)CO_2H$	3.14	5.6 : 1	90	85	49
12	4-Cl–$C_6H_4CH(OH)CO_2H$	3.14	5.9 : 1	90	84	48

[a]) Yield of isolated **3** in parentheses.

Table 3. Michael *Addition of Aldehyde* **1** *with Alkene Derivative* **2** *in the Presence of Various Acidic Additives*

Additive	dr (*'syn'*/*'anti'*)	ee *'syn'*-**3** [%]	ee *'anti'*-**3** [%]	Conversion [%]
H_3BO_3	0.73 : 1	n.d.	n.d.	28
$PhCO_2H$	2.3 : 1	n.d.	n.d.	90
L-Proline	0.8 : 1	n.d.	n.d.	45
Glycine	0.76 : 1	25	60	18
Amberlite	0.91 : 1	n.d.	n.d.	54
EDTA	0.73 : 1	n.d.	n.d.	7

additives with a pK_a from 2 to 4 afforded good results. *Michael* additions to nitrostyrenes proceed well also with less acidic additive such as 4-nitrophenol; on the other hand, a less reactive *Michael* acceptor, such as alkene derivative **2**, requires a more acidic additive. Furthermore, the additive seems to stabilize a transition state leading to *'syn'*-**3** better than the one leading to *'anti'*-**3**, as manifested in the higher diastereoselectivity ratio of the reaction.

Interestingly, the reaction time also influenced the diastereoselectivity of the *Michael* addition (*Table 5*). Particularly in experiments with bromoacetic acid as additive, the *'syn'*/*'anti'* ratio decreased with longer time. These results suggest that compound **3** epimerized under acidic conditions. This is unfortunate for practical applications, as prolonging the reaction time results in higher conversions.

Another reaction parameter with influence on the diastereoselectivity of the reaction of aldehyde **1** with alkene derivative **2** was the amount of H_2O in the reaction medium (*Table 6*). The highest diastereoselectivity was achieved in the presence of a minimum amount of H_2O with the additive chloroacetic acid, but at the expense of the conversion. The H_2O content had a lower influence in experiments when *rac*-mandelic acid was used as the additive.

Table 4. Michael *Addition of Aldehyde* **1** *with Alkene Derivative* **2** *in the Presence of Phenolic Additives*

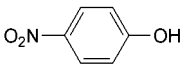
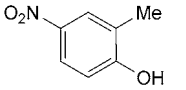
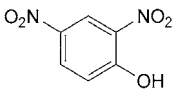
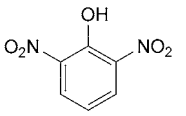
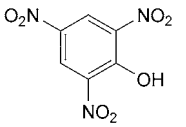
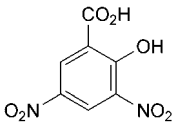
Entry	Additive	pK_a	dr (‘*syn*’/‘*anti*’)	ee ‘*syn*’-**3** [%]	ee ‘*anti*’-**3** [%]	Conversion [%]
1		7.15	2.5 : 1	89	62	86
2		–	2.2 : 1	87	66	80
3		3.96	6 : 1	94	62	84
4		3.97	5.9 : 1	94	72	66
5		0.38	n.d.	n.d.	n.d.	0
6		–	n.d.	n.d.	n.d.	0

Table 5. *Influence of Reaction Time on the* Michael *Addition of Aldehyde* **1** *to Alkene Derivative* **2**

Additive	Time [min]	dr (‘*syn*’/‘*anti*’)	ee ‘*syn*’-**3** [%]	ee ‘*anti*’-**3** [%]	Conversion [%]
rac-PhCH(OH)COOH	30	5.0 : 1	94	33	86
	60	4.8 : 1	94	89	83
	120	4.9 : 1	92	94	83
$BrCH_2COOH$	30	6.0 : 1	n.d.	n.d.	67
	60	5.8 : 1	n.d.	n.d.	75
	120	4.2 : 1	96	68	90

Other parameters, such as a higher amount of additive or gradual addition of excess of aldehyde **1** had only a small effect on the *Michael* addition of aldehyde **1** with alkene derivative **2**.

Conclusions. – An acidic additive influences the diastereoselectivity of the *Michael* reaction leading to the oseltamivir intermediate **3**. The most efficient additives are chloro- and bromoacetic acid, *rac*-mandelic acid, and 2,4-dinitrophenol. These additives give a high diastereoselectivity in favor of the desired ‘*syn*’-isomer, high

Table 6. *Effect of H_2O Content in the Reaction Medium for the Reaction of Aldehyde* **1** *and Alkene* **2**

Additive	H_2O [ml][a])	dr ('syn'/'anti')	ee *'syn'*-**3** [%]	ee *'anti'*-**3** [%]	Conversion [%]
$ClCH_2COOH$	0.1	6.4 : 1	n.d.	n.d.	48
	0.5	4.1 : 1	n.d.	n.d.	61
	1.0	3.5 : 1	n.d.	n.d.	80
	2.0	3.0 : 1	n.d.	n.d.	89
rac-PhCH(OH)COOH	0.05	5.3 :1	92	86	54
	0.5	5.0 :1	94	84	85
	1.0	5.5 :1	94	82	87
	2.0	5.3 :1	95	81	89

[a]) Reaction medium composed of $CHCl_3$ (2 ml) and a specified amount of H_2O.

enantiomer purity, and high conversion. Too strong as well as too weak acids hamper the reaction. Even more striking is the influence of the acidity of the additive on the diastereoselectivity of the *Michael* addition. Longer reaction times are detrimental to the diastereoselectivity. Further research of the reaction conditions as well as computational investigation of possible transition states are underway in our laboratory.

Experimental Part

1. *General.* Flash chromatography (FC): *Acros* silica gel *60A* (SiO_2; 0.035–0.070 nm). TLC: silica gel *60 F_{254}* plates (*Merck*); prep. TLC with gel *60 F_{254}* plates (SiO_2, 2 mm; *Merck*). HPLC: *Chiralcel-OD-H* column (*Daicel Chemical Industries*) hexane/^{i}PrOH as mobile phase, and UV detection for the determination of enantiomer excesses (ee); t_R in min. NMR Spectra: *Varian-300* instrument; at 300 (^{1}H) and 75 MHz (^{13}C); δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *LCMS-IT-TOF* spectrometer (*Shimadzu*, Kyoto, Japan), with an *Ascentis C_{18}* column and H_2O/MeCN gradient elution within 33 min; in m/z.

2. Michael *Addition: General Procedure.* A soln. of *N*-[(1*Z*)-2-nitroethenyl]acetamide (**2**; 0.25 mmol, 32.5 mg) in $CDCl_3$ (0.75 ml) was cooled in an ice-bath. Freshly distilled 2-(1-ethylpropoxy)-acetaldehyde (**1**; 0.375 mmol, 49 mg), an aq. soln. of additive (0.05 mmol, in 1 ml), and organocatalyst **Cat1** (0.025 mmol, 8.1 mg) were mixed with $CDCl_3$ (0.25 ml) and added to the mixture. The reaction mixture was stirred for 2 h (or for the specified time) at 0° (ice-water bath); then an aliquot (0.6 ml) was taken directly into an NMR tube and analyzed. The residue was derivatized for HPLC analysis, see *Sect. 3* below for details.

Data of 'syn'-**3**: ^{1}H-NMR (300 MHz, $CDCl_3$): 9.65 (*t*, *J* = 0.6, 1 H); 6.04 (br. *d*, *J* = 8.5, 1 H); 5.11–5.02 (*m*, 1 H); 4.58 (*d*, *J* = 6.5, 2 H); 4.08 (*dd*, *J* = 0.3, 3.3, 1 H); 3.41 (*quint.*, *J* = 5.8, 1 H); 1.99 (*s*, 3 H); 1.62–1.49 (*m*, 4 H); 0.98–0.87 (*m*, 6 H). MS: 261.13 ($[M+H]^+$, $C_{11}H_{21}N_2O_5^+$; calc. 261.30).

Data of 'anti'-**3**: ^{1}H-NMR (300 MHz, $CDCl_3$): 9.61 (*d*, *J* = 3.1, 1 H); 6.11 (br. *d*, *J* = 8.8, 1 H); 4.85–4.50 (*m*, 3 H); 3.95 (*dd*, *J* = 3.1, 8.0, 1 H); 3.27 (*quint.*, *J* = 5.5, 1 H); 2.00 (*s*, 3 H); 1.57–1.42 (*m*, 4 H); 0.95–0.84 (*m*, 6 H). MS: 261.13 ($[M+H]^+$, $C_{11}H_{21}N_2O_5^+$; calc. 261.30).

The *Figure* shows a typical NMR spectrum of '*syn*'/'*anti*' **3**, the expanded region (δ(H) 9.5–9.8 exhibiting the aldehydic protons used for the determination of the diastereoselectivity.

N-*[2-(1-Ethylpropoxy)-1-(nitromethyl)-3-oxopropyl]acetamide* (**3**): *Large Scale Preparation.* A soln. of **2** (5.0 mmol, 0.65 g) in $CHCl_3$ (20 ml) was cooled in an ice-bath to 0°. Then freshly distilled **1** (7.5 mmol, 977 mg), distilled H_2O (20 ml) cooled to 0–3°, and a mixture of bromoacetic acid (1.0 mmol, 139 mg) with organocatalyst **Cat1** (0.5 mmol, 163 mg) in $CHCl_3$ (10 ml) cooled to 0° were added carefully, so that the temp. of the mixture dids not rise above 2°. After 4 h stirring at 0°, the reaction was

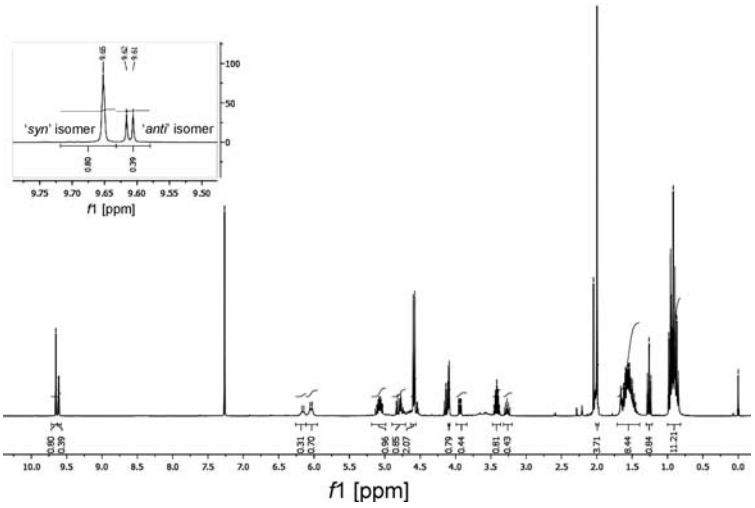
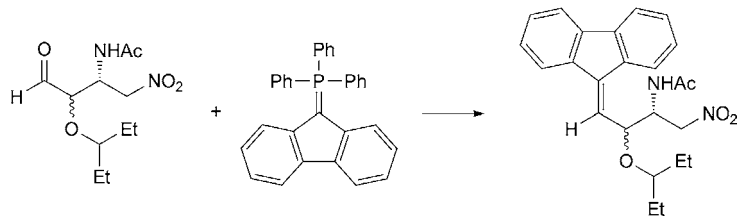


Figure. *NMR Spectrum of the mixture of* 'syn'-**3** *and* 'anti'-**3**

quenched with cold sat. aq. NH_4Cl soln. (50 ml). The mixture was stirred for 5 min, then the aq. phase extracted with $CHCl_3$ (5×15 ml), the combined org. phase dried (Na_2SO_4) and concentrated, and the crude mixture purified by FC (SiO_2 (95 g), hexane/AcOEt 1:1): **3** (914 mg, 70%), *'syn'/'anti'* 2.8:1; ee (*'syn'*) 92 % and ee (*'anti'*) 24%.

3. N-*[2-(1-Ethylpropoxy)-3-(9*H*-fluoren-9-ylidene)-1-(nitromethyl)propyl]acetamide for HPLC Analysis.* Into a soln. of **3** (0.019 mmol, 5 mg) in $CHCl_3$ (0.077 ml), 9*H*-fluoren-9-ylidentriphenylphosphorane (0.023 mmol, 10 mg) in toluene (0.5 ml) was added. The resulting soln. was stirred for 1 h at 100°. After cooling, an aliquot (0.25 ml) was taken and separated by prep. TLC (SiO_2, hexane/AcOEt 2:1). HPLC (*Chiralcel OD-H*, hexane/^{i}PrOH 85:15, 0.75 ml/min, 259 nm): t_R (*'syn'*-isomer) 25.82 and 15.78 min, t_R (*'anti'*-isomer) 12.81 and 10.06 (*Scheme 3*).

Scheme 3



N-*[(1*S*,2*S*)-2-(1-Ethylpropoxy)-3-(9*H*-fluoren-9-ylidene)-1-(nitromethyl)propylacetamide* ('syn'-*Isomer):* ^{1}H-NMR (300 MHz, $CDCl_3$): 7.77–7.61 (*m*, 4 H); 7.44–7.27 (*m*, 4 H); 6.42 (*d*, *J* = 9.3, 1 H); 5.95 (br. *d*, *J* = 8.7, 1 H); 5.46 (*dd*, *J* = 4.1, 9.3, 1 H); 4.93–4.84 (*m*, 1 H); 4.78 (*dd*, *J* = 6.0, 12.7, 1 H); 4.71 (*dd*, *J* = 7.0, 12.7, 1 H); 4.34–4.21 (*m*, 1 H); 3.36 (*quint.*, *J* = 5.5, 1 H); 1.94 (*s*, 3 H); 1.57–1.43 (*m*, 4 H); 0.91–0.86 (*m*, 6 H). MS: 431.18 ($[M + Na]^+$, $C_{24}H_{28}N_2NaO_4^+$; calc. 431.19).

'anti'-*Isomer.* ^{1}H-NMR (300 MHz, $CDCl_3$): 7.98–7.95 (*m*, 1 H); 7.76–7.65 (*m*, 3 H); 7.44–7.28 (*m*, 4 H); 6.45 (*d*, *J* = 8.6, 1 H); 6.21 (br. *d*, *J* = 8.8, 1 H); 5.38 (*dd*, *J* = 5.9, 8.6, 1 H); 4.92 (*dd*, *J* = 6.4, 12.8,

1 H); 4.84 – 4.76 (*m*, 1 H); 4.66 (*dd*, *J* = 3.5, 12.8, 1 H); 4.34 – 4.25 (*m*, 1 H); 3.30 (*quint.*, *J* = 5.4, 1 H); 1.91 (*s*, 3 H); 1.53 – 1.41 (*m*, 4 H); 0.92 – 0.82 (*m*, 6 H). MS: 431.18 ($[M+Na]^+$, $C_{24}H_{28}N_2NaO_4^+$; calc. 431.19).

REFERENCES

[1] W. Lew, X. Chen, C. U. Kim, *Curr. Med. Chem.* **2000**, *7*, 663.
[2] I. M. Lagoja, E. De Clercq, *Med. Res. Rev.* **2008**, *28*, 1.
[3] J. Magano, *Chem. Rev.* **2009**, *109*, 4398; J. Magano, *Tetrahedron* **2011**, *67*, 7875; M. Shibasaki, M. Kanai, K. Yamatsugu, *Israel J. Chem.* **2011**, *51*, 316.
[4] S. Abrecht, M. C. Federspiel, H. Estermann, R. Fischer, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi, U. Zutter, *Chimia* **2007**, *61*, 93; M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi, A. G. Zwahlen, *Org. Proc. Res. Dev.* **1999**, *3*, 266.
[5] J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545.
[6] J. Weng, Y.-B. Li, R.-B. Wang, F.-Q. Li, C. Liu, A. S. C. Chan, G. Lu, *J. Org. Chem.* **2010**, *75*, 3125; J. S. Ko, J. E. Keum, S. Y. Ko, *J. Org. Chem.* **2010**, *75*, 7006; J.-J. Shie, J.-M. Fang, C.-H. Wong, *Angew. Chem., Int. Ed.* **2008**, *47*, 5788.
[7] V. Farina, J. D. Brown, *Angew. Chem., Int. Ed.* **2006**, *45*, 7330.
[8] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature (London, U.K.)* **2006**, *441*, 861.
[9] H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru, Y. Hayashi, *Chem. – Eur. J.* **2010**, *16*, 12616; H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.
[10] H. Shen, K.-F. Yang, Z.-H. Shi, J.-X. Jiang, G.-Q. Lai, L.-W. Xu, *Eur. J. Org. Chem.* **2011**, *2011*, 5031.
[11] N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Tetrahedron* **2009**, *65*, 3239; C. Suttibut, Y. Kohari, K. Igarashi, H. Nakano, M. Hirama, C. Seki, H. Matsuyama, K. Uwai, N. Takano, Y. Okuyama, K. Osone, M. Takeshita, E. Kwon, *Tetrahedron Lett.* **2011**, *52*, 4745; H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano, Y. Kohari, *Chem. Commun.* **2010**, *46*, 4827.
[12] S. Zhu, S. Yu, Y. Wang, D. Ma, *Angew. Chem., Int. Ed.* **2010**, *49*, 4656.
[13] a) J. Rehák, M. Hut'ka, A. Latika, H. Brath, A. Almássy, V. Hajzer, J. Durmis, S. Toma, R. Šebesta, *Synthesis* **2012**, *44*, 2424; b) J. Weng, Y.-B. Li, R.-B. Wang, G. Lu, *ChemCatChem* **2012**, *4*, 1007.
[14] A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas, *Org. Lett.* **2004**, *6*, 2527; T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558; M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6; S. Saha, S. Seth, J. N. Moorthy, *Tetrahedron Lett.* **2010**, *51*, 5281; Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50; K. Shibatomi, A. Narayama, Y. Abe, S. Iwasa, *Chem. Commun.* **2012**, *48*, 7380.
[15] K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719.

Received September 14, 2012