Organic LETTERS

Letter

pubs.acs.org/OrgLett

Reaction of Corey Ylide with α,β-Unsaturated Ketones: Tuning of Chemoselectivity toward Dihydrofuran Synthesis

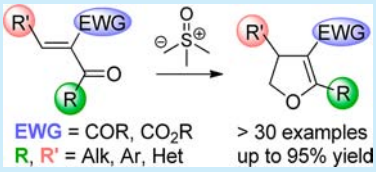
Alexey O. Chagarovsky,[†,‡] Ekaterina M. Budynina,*[,†,‡] Olga A. Ivanova,[†] Elena V. Villemson,[†] Victor B. Rybakov,[†] Igor V. Trushkov,[†,‡] and Mikhail Ya. Melnikov[†]

[†]Department of Chemistry, M.V. Lomonosov Moscow State University, Leninskie gory 1-3, Moscow 119991, Russia

[‡]Laboratory of Chemical Synthesis, Federal Research Center of Pediatric Hematology, Oncology and Immunology, Samory Mashela. 1, Moscow 117997, Russia

Supporting Information

ABSTRACT: A straightforward, efficient, and reliable approach to synthetically valuable 2,3-dihydrofurans via a reaction between Corey ylide and α,β-unsaturated ketones has been developed. The use of simple and widely spread starting materials as well as mild reaction conditions and scalability provide a broad scope of 2,3-dihydrofurans.

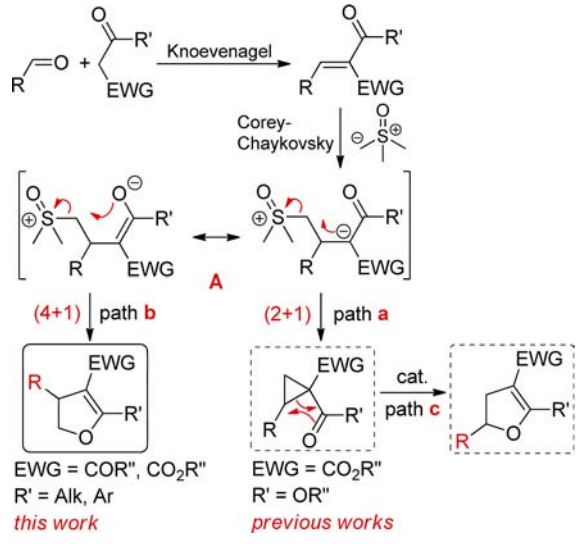


The evolution of synthetic organic chemistry is mostly due to the design of new reagents which allow development of original synthetic methods. Meanwhile, the unexplored potential of seemingly well-known reagents allows for unexpected processes to be revealed that lead to a significantly different outcome in comparison with established reactivity.

In our research, dimethylsulfoxonium methylide was found to be such a reagent. It is widely known as Corey ylide, the reactions of which with carbonyl and thiocarbonyl compounds, imines, or electrophilic alkenes (Corey−Chaykovsky reaction) constitute a powerful approach to three-membered carbo- and heterocycles.[1] In recent years, this ylide is intensively used for the synthesis of a representative subclass of donor−acceptor (DA) cyclopropanes, namely 2-substituted cyclopropane-1,1-diesters, whose usefulness is mainly defined by their reactivity in various ring-opening reactions, (3+*n*)-cycloadditions, and annulations to unsaturated compounds.[2] Synthesis of such cyclopropanes, among which there is a great variety of 2-alkyl-, aryl-, heteroaryl-, alkenylcyclopropane-1,1-diesters, is based on the well-proven, highly efficient, and easily scalable sequence of Knoevenagel/Corey−Chaykovsky reactions starting from commercially or synthetically accessible aldehydes and malonic esters (path **a** in Scheme 1). By contrast, the reactivity of Corey ylide toward alkenes derived from other readily available and commonly used active methylene compounds, such as 1,3-diketones, β-ketoesters, nitroacetates, and malononitrile, still remains essentially unknown. Currently, there are only a few examples of DA cyclopropane synthesis via a Corey ylide reaction with some vinylidene ketoesters.[3] Meanwhile, introduction of other types of electrophilic alkenes derived from different active methylene compounds into a reaction with Corey ylide could significantly enhance the method variability and facilitate a high diversity of DA cyclopropanes.

However, our initial experiment with a product of acetylacetone-to-benzaldehyde condensation led to a conceptually different result, namely chemoselective 2,3-dihydrofuran formation (path **b** in Scheme 1).[4]

Scheme 1



In our opinion, this reactivity tuning is mainly provided by the electron-withdrawing ability of α-substituent EWG, the increase of which enhances anion delocalization in intermediate **A** and favors (4 + 1)-annulation through O-attack (path **a**) rather than (2 + 1)-annulation *via* C-attack (path **b**). Based on this hypothesis, we designed the general route to 3,4,5-trisubstituted 2,3-dihydrofurans and developed a very simple practical method for the synthesis of representatives of these synthetically useful and biologically important heterocycles[5] from various 1,3-diketones and β-ketoesters. This new

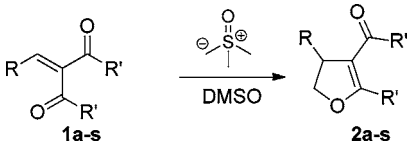
Received: March 24, 2014
Published: May 12, 2014

   dx.doi.org/10.1021/ol500877c | *Org. Lett.* 2014, 16, 2830−2833

approach based on the discussed (4 + 1)-annulation provides broad substituent variability and can serve as a viable and low-cost alternative to existing methods for the preparation of the similar dihydrofurans.[6] A proposed approach to 3,4,5-trisubstituted 2,3-dihydrofurans can be considered to be complementary to the well-known synthesis of 2,4,5-trisubstituted 2,3-dihydrofurans via the corresponding cyclopropane isomerization[7] (path **c** in Scheme 1). Here we report the results of our research.

To study the scope of the disclosed reaction, we used a broad series of 2-ylidene-1,3-diketones **1** which were synthesized from commonly used alkyl, alkenyl, aryl, hetaryl aldehydes and acetylacetone or other common 1,3-diketones. In all cases, reaction between equimolar amounts of alkenes **1** and Corey ylide proceeded as a (4 + 1)-annulation affording exclusively 3,4,5-trisubstituted 2,3-dihydrofurans **2** in good isolated yields (Table 1). No traces of the corresponding cyclopropanes or

Table 1. Synthesis of Dihydrofurans 2 from 1,3-Diketones 1[a]



1a-s **2a-s**

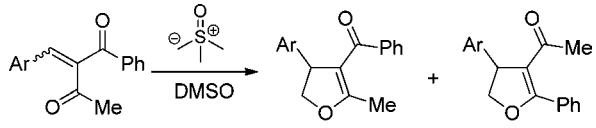
entry	1,2	R	R′	*t* (h)	yield, %[b]
1	**a**	Ph	Me	2	89 (95)[c]
2	**b**	4-MeOC$_6$H$_4$	Me	2	82
3	**c**	4-Me$_2$NC$_6$H$_4$	Me	2	77
4	**d**	3,4,5-(MeO)$_3$C$_6$H$_4$	Me	2	68
5	**e**	2,4,6-(MeO)$_3$C$_6$H$_4$	Me	2	72
6	**f**	biphenyl-4-yl	Me	2	80
7	**g**	4-O$_2$NC$_6$H$_4$	Me	2	70
8	**h**	2-Fu	Me	1	57
9	**i**	2-Th	Me	1	62
10	**j**	2-pyridyl	Me	1	53
11	**k**	1-Bn-3-Ind	Me	0.3	61
12	**l**	PhCH=C(Me)	Me	2	70
13	**m**	4-MeOC$_6$H$_4$CH=CH	Me	2	75
14	**n**	Me	Me	1	64
15	**o**[d]	Ph	Ph	2	82
16	**p**	4-Me$_2$NC$_6$H$_4$	Ph	2	77
17	**q**	2-Th	Ph	2	71
18	**r**	Ph	Et	2	64
19	**s**	2-Th	Et	2	68

[a]Reaction conditions: **1** (1.0 mmol), ylide (1.05 mmol), DMSO (9 mL), rt. [b]Isolated yield after column chromatography. [c]Yield of **2a** after distillation when reaction was performed in 7.0 g (37.2 mmol) scale. [d]Structure of **2o** was unambiguously proved by X-ray analysis (CCDC no. 924444).

products of their isomerization, namely 2,4,5-trisubstituted 2,3-dihydrofurans, were formed. Depending on **1** lability, the reaction time was varied between 2 h and 20 min. Substituents with different electronic effects in the benzene ring had no significant influence on the reaction efficiency (entries 1−7), while diketones **1h−k** containing heteroaromatic groups at the *β*-position as well as alkyl-substituted diketone **1n** gave dihydrofurans **2h−k,n** in slightly lower yields (entries 8−11, 14). Dienes **1l,m** were also applicable for this transformation allowing for further potential structural modifications. Variation of substituents at the 1,3-dicarbonyl moiety of **1** did not lead to noticeable changes in the yields of dihydrofurans **2** (entries 1, 15, 18 and 9, 17, 19). The yield loss mainly arose during product isolation by column chromatography due to the moderate stability of **2** on silica. Scaling up the loading and isolating the product more completely by distillation provided a gain in reaction outcome (entry 1).

For diketones **1t,u** which contain two different acyl groups (4 + 1)-annulations via both carbonyl *O*-atoms were equally probable processes that afforded two isomeric dihydrofurans **2t,t′** and **2u,u′** in an equimolar ratio (Scheme 2).

Scheme 2

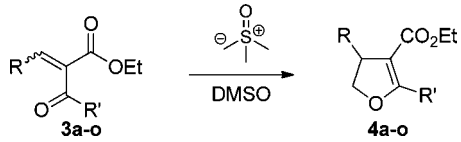


1t,u

2t,2t': Ar = Ph, 82% (1:1)
2u,2u': Ar = 2-Th, 68% (1:1)

Our further efforts were directed toward extension of this reaction to other *α,β*-unsaturated ketones bearing a strong acceptor at the *α*-position. Thus, we focused on *α*-acyl acrylates **3** that can be easily synthesized from various commercially or synthetically available *β*-ketoesters. The series **3a−o** was studied in reactions with Corey ylide, revealing mainly chemoselective formation of dihydrofurans **4a−o** (Table 2). The same tendency as in the case of diketones **1** was observed for the reaction efficiency of ketoesters **3** depending on substituents at the carbonyl group or *β*-position. A decrease in chemoselectivity was found only for the reaction of *β*-alkyl or

Table 2. Synthesis of Dihydrofurans 4 from 1,3-Ketoesters 3[a]



3a-o **4a-o**

entry	3,4	R	R′	*t* (h)	yield, %[b]
1	**a**	Ph	Me	2	75 (92)[c]
2	**b**	4-MeOC$_6$H$_4$	Me	2	91
3	**c**	4-Me$_2$NC$_6$H$_4$	Me	1	74
4	**d**	4-FC$_6$H$_4$	Me	2	83
5	**e**	3-O$_2$NC$_6$H$_4$	Me	2	76
6	**f**	2-Th	Me	1	69
7	**g**[d]	1-Bn-3-Ind	Me	0.3	52
8	**h**	Ph	Ph	1	81
9	**i**	4-Me$_2$NC$_6$H$_4$	Ph	1	84
10	**j**	2-Th	Ph	2	63
11	**k**	Ph	2-Th	2	70
12	**l**	2-Th	2-Th	1	59
13	**m**	Me	Me	1.5	57[e]
14	**n**	4-MeOC$_6$H$_4$CH=CH	Me	2	42[e]
15	**o**	Ph	*i*-Pr	2	80

[a]Reaction conditions: **3** (1.0 mmol), ylide (1.05 mmol), DMSO (9 mL), rt. [b]Isolated yields after column chromatography. [c]Yield of **4a** after distillation when reaction was performed in 6.0 g (27.5 mmol) scale. [d]Structure of **4g** was unambiguously proved by X-ray analysis (CCDC no. 917373). [e]**4m,n** were formed together with isomeric cyclopropanes, ethyl 1-acetyl-2-methylcyclopropanecarboxylate and 1-acetyl-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]cyclopropanecarboxylate, in 75:25 and 85:15 ratio, respectively.

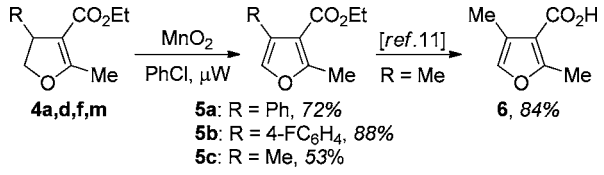
dx.doi.org/10.1021/ol500877c | *Org. Lett.* 2014, 16, 2830−2833

alkenyl-substituted α-acyl acrylates **3m,n** where the corresponding cyclopropanes were formed as side products (entries 13, 14).

2,3-Dihydrofurans are synthetically significant precursors for the construction of more complex structures with useful properties, including synthetic and natural bioactive compounds. Among the evident applications of dihydrofurans, their role as key intermediates for the straightforward synthesis of such ubiquitous compounds as furans and tetrahydrofurans can be named. Thereto, the presence of a donor−acceptor substituted C−C double bond in structures of types **2** and **4** provides an especial opportunity for simple modifications via both electrophilic and nucleophilic, cycloaddition, *etc.*

The synthetic utility of obtained dihydrofurans was primarily demonstrated via the development of a dihydrofuran-to-furan oxidation procedure. For this purpose, we tried several well-known methods of aromatization, such as Pd-catalyzed dehydrogenation[8] and oxidation with DDQ[9] or MnO_2,[10] for the model compounds **4a,d,f,m** under various reaction conditions. The best yields of the corresponding furan-3-carboxylates **5a−d** were achieved when **4** were heated with activated MnO_2 at 130 °C under microwave irradiation (Scheme 3). The developed procedure can be successfully

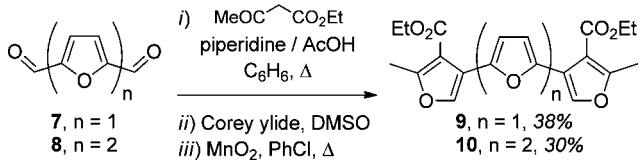
Scheme 3



applied in the synthesis of 2,4-dimethylfuran-3-carboxylic acid (**6**)[11] whose α-L-rhamnopyranoside isolated from culture broth of *Streptomyces* sp. was shown to inhibit α-hydroxysteroid dehydrogenase.[12]

Moreover, involvement of furan-2,5-dicarbaldehyde (**7**) and 2,2′-difuran-5,5′-dicarbaldehyde (**8**) into an assembly of Knoevenagel/Corey−Chaykovsky/dihydrofuran-to-furan oxidation reactions was successfully applied for the synthesis of oligofurans **9** and **10** connected via 2,2′ and 2,3′ C−C bonds in three- and four-ring sequences (Scheme 4). Currently,

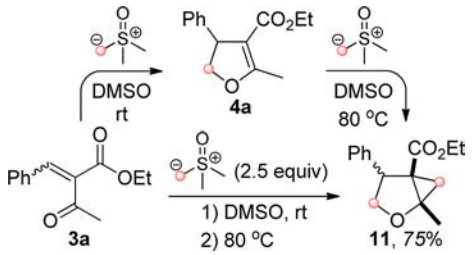
Scheme 4. Oligofurans Synthesis



oligofurans with 2,3′ bonding are novel unique compounds; however, the related oligofurans with 2,2′ connections were considered as promising materials for solar cells, OLEDs, OFETs, *etc.*[13]

An elegant approach to 2-oxycyclopropanecarboxylates, one of the subclasses of DA cyclopropanes,[14] was designed on the basis of the Corey−Chaykovsky reaction with participation of obtained dihydrofurans. Thus, a model experiment with **4a** led to cyclopropa[*b*]tetrahydrofuran **11** (Scheme 5). Evidently, this cyclopropanation can be combined with dihydrofuran **4a**

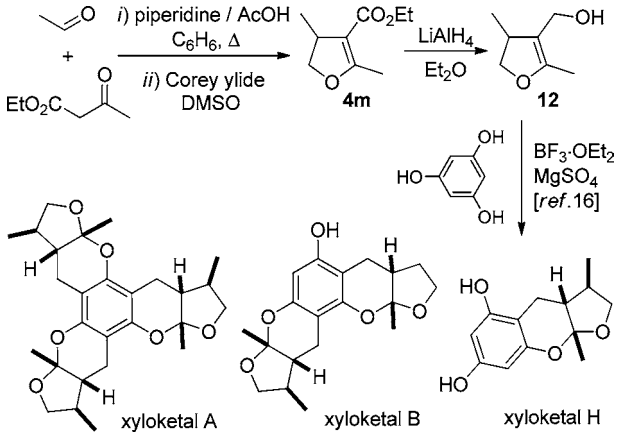
Scheme 5. Sequential and One-Pot Double Corey−Chaykovsky Reaction in Synthesis of Donor−Acceptor Cyclopropane 11



synthesis in a one-pot procedure allowing for cyclopropa[*b*]-tetrahydrofuran **11** construction directly from alkene **3a**.

In regard to the synthesis of natural compounds, dihydrofuran **4m** derived from acetaldehyde and ethyl acetoacetate can be easily reduced to alcohol **12** which was previously transformed to xyloketals A, B, H[15] (Scheme 6), originating from mangrove fungus *Xylaria* sp.[16] and exhibiting a broad range of biological activities.[15b,16b,17]

Scheme 6. Formal Synthesis of Xyloketals



In conclusion, we have disclosed a new reactivity of Corey ylide toward α,β-unsaturated ketones providing chemoselective synthesis of 2,3-dihydrofurans via (4 + 1)-annulation in contrast to common (2 + 1)-annulation leading to cyclopropane derivatives. An electron-withdrawing group at the α-position of the used ketones was found to be responsible for this chemoselectivity switch. Easy availability and variability of the reagents as well as mild reaction conditions and scalability allowed us to develop an efficient straightforward method for the synthesis of a wide range of 3,4,5-trisubstituted 2,3-dihydrofurans. Easy modifiability of the central dihydrofuran ring, the C−C double bond, and side substituents makes the resulting 2,3-dihydrofurans relevant reagents for producing potentially useful structures, including natural and pharmacologically valuable compounds. Further investigations on the scope of the described (4 + 1)-annulation as well as the synthetic application of dihydrofurans are in progress now.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR, IR, MS spectra, elemental analyses, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol500877c | *Org. Lett.* 2014, 16, 2830−2833

AUTHOR INFORMATION

Corresponding Author

*E-mail: ekatbud@kinet.chem.msu.ru.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Russian Scientific Foundation for support of this work. The NMR measurements were carried out in the Laboratory of Magnetic Tomography and Spectroscopy, Faculty of Fundamental Medicine of Moscow State University.

REFERENCES

(1) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364. (b) Gololobov, Yu. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609−2651.

(2) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321−347. (c) Agrawal, D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471−6488. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051−3060. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353−3374. (f) Mel'nikov, M. Ya.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293−301. (g) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969−2984. (h) Wang, Z. *Synlett* **2012**, 2311−2327. (i) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804−818.

(3) (a) Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 1952−1955. (b) Aujard, I.; Röme, D.; Arzel, E.; Johansson, M.; de Vos, D.; Sterner, O. *Bioorg. Med. Chem.* **2005**, *13*, 6145−6150. (c) Yamashita, M.; Okuyama, K.; Kawajiri, T.; Takada, A.; Inagaki, Y.; Nakano, H.; Tomiyama, M.; Ohnaka, A.; Terayama, I.; Kawasaki, I.; Ohta, S. *Tetrahedron* **2002**, *58*, 1497−1505. (d) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979−5989.

(4) Similar reactivity of Corey ylide, however mainly as a side-reaction, was previously observed in the cyclopropane synthesis from α-sulfur or −selenium-substituted α,β-unsaturated ketones: (a) Redon, S.; Leleu, S.; Pannecoucke, X.; Franck, X.; Outurquin, F. *Tetrahedron* **2008**, *64*, 9293−9304. (b) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565−4568.

(5) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, 4929−4949.

(6) (a) Lin, H.; Shen, Q.; Lu, L. *J. Org. Chem.* **2011**, *76*, 7359−7369. (b) Wu, M.-Y.; Wang, M.-Q.; Li, K.; Feng, X.-W.; He, T.; Wang, N.; Yu, X.-Q. *Tetrahedron Lett.* **2011**, *52*, 679−683. (c) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590−3593. (d) Kitagaki, S.; Shibata, D.; Mukai, C. *Tetrahedron Lett.* **2007**, *48*, 1735−1738. (e) Ghosh, C. K.; Biswas, S.; Sahana, S. *Indian J. Chem.* **1993**, *32B*, 630−636. (f) Johnson, C. R.; Lockard, J. P.; Kennedy, E. R. *J. Org. Chem.* **1980**, *45*, 264−271.

(7) For recent selected examples, see: (a) Huang, P.; Zhang, R.; Liang, Y.; Dong, D. *Org. Lett.* **2012**, *14*, 5196−5199. (b) Wang, H.; Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 4316−4319. (c) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573−576.

(8) Maiti, S.; Perumal, P. T.; Menendez, J. C. *Tetrahedron* **2010**, *66*, 9512−9518.

(9) Garzino, F.; Meou, A.; Brun, P. *Helv. Chim. Acta* **2002**, *85*, 1989−1998.

(10) Yang, Z.; Fan, M.; Mu, R.; Liu, W.; Liang, Y. *Tetrahedron* **2005**, *61*, 9140−9146.

(11) Wenkert, E.; Khatuya, H.; Klein, P. S. *Tetrahedron Lett.* **1999**, *40*, 5171−5174.

(12) Hu, J.-F.; Wunderlich, D.; Sattler, I.; Härtl, A.; Papastavrou, I.; Grond, S.; Grabley, S.; Feng, X.-Z.; Thiericke, R. *J. Antibiot.* **2000**, *53*, 944−953.

(13) Jin, X.-H.; Sheberla, D.; Shimon, L. J. W.; Bendikov, M. *J. Am. Chem. Soc.* **2014**, *136*, 2592−2601.

(14) For recent examples, see: (a) Haveli, S. D.; Roy, S.; Gautam, V.; Parmar, K. C.; Chandrasekaran, S. *Tetrahedron* **2013**, *69*, 11138−11143. (b) Kaschel, J.; Schneider, T. F.; Schirmer, P.; Maass, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem.* **2013**, 4539−4551. (c) Ramakrishna, B.; Sridhar, P. R. *Org. Lett.* **2013**, *15*, 4474−4477. (d) Truong, P. M.; Mandler, M. D.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 3278−3281. (e) Wilsdorf, M.; Leichnitz, D.; Reissig, H.-U. *Org. Lett.* **2013**, *15*, 2494−2497. (f) Gladow, D.; Reissig, H.-U. *Synthesis* **2013**, *45*, 2179−2187. (g) Beyzavi, M. H.; Lentz, D.; Reissig, H.-U.; Wiehe, A. *Eur. J. Org. Chem.* **2013**, 269−282.

(15) (a) Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427−1429. (b) Xu, Z.; Li, X.; Xiang, Q.; Pei, Z.; Liu, X.; Lu, B.; Chen, L.; Wang, G.; Pang, J.; Lin, Y. *J. Med. Chem.* **2010**, *53*, 4642−4653.

(16) (a) Liu, X.; Xu, F.; Zhang, Y.; Liu, L.; Huang, H.; Cai, X.; Lin, Y.; Chan, W. *Russ. Chem. Bull.* **2006**, *55*, 1091−1092. (b) Lin, Y.; Wu, X.; Feng, S.; Jiang, G.; Luo, J.; Zhou, S.; Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingröver, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252−6256.

(17) (a) Chen, W.-L.; Qian, Y.; Meng, W.-F.; Pang, J.-Y.; Lin, Y.-C.; Guan, Y.-Y.; Chen, S.-P.; Liu, J.; Pei, Z.; Wang, G.-L. *Biochem. Pharmacol.* **2009**, *78*, 941−950. (b) Zhao, J.; Li, L.; Ling, C.; Li, J.; Pang, J.-Y.; Lin, Y.-C.; Liu, J.; Huang, R.; Wang, G.-L.; Pei, Z.; Zeng, J. *Brain Res.* **2009**, *1302*, 240−247.