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Synergistic $NaBH_4$-reduction/cyclization of 2-aroyl-cyclopropane-1-carboxylates: novel synthesis of 3-oxabicyclo[3.1.0]hexane derivatives

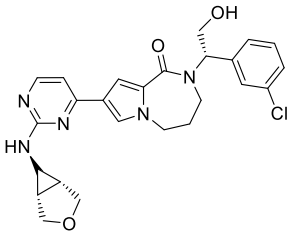
Jiaming Liu,[a] Lizhong Wang,[a,b] Xushun Qing,[a] Feixiang Zhang,[a] Ting Wang,[a] and Cunde Wang*[a]

Dedication ((optional))

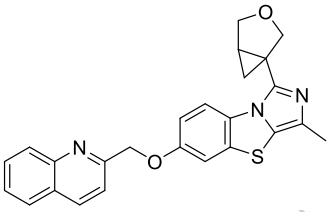
Abstract: The $NaBH_4$-reduction/cyclization of readily available 2-aroyl-1-cyano-3-arylcyclopropane-1-carboxylate compounds was investigated, which provides access to the stereoselective synthesis of 3-oxabicyclo[3.1.0]hexane derivatives in high yields.

Introduction

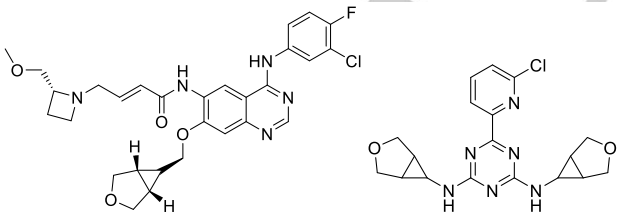
3-Oxabicyclo[3.1.0]hexane derivatives have attracted the attention of medicinal chemists for decades owing to their unique chemical properties. In particular, several 3-oxabicyclo[3.1.0]hexanes as core structures are found in many pharmacological compounds because of their interesting biological activities, they have been used as ERK2 kinase inhibitor,[1] selective PDE10A inhibitors,[2] leukotriene production inhibitors[3] for treatment of cardiovascular, inflammatory and other diseases, antitumor agents[4,5] and hepatitis C virus inhibitors[6] as illustrated in Figure 1.



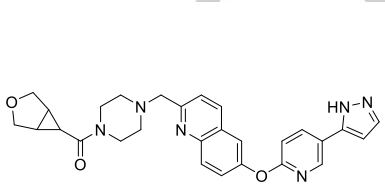
ERK2 kinase inhibitor[1]



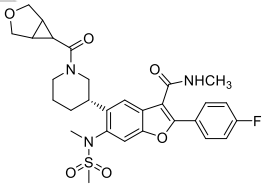
Selective PDE10A inhibitors[2]



Antitumor agents[4, 5]



Leukotriene production inhibitors[3]



Hepatitis C virus inhibitors[6]

Figure 1. Examples of 3-oxabicyclo[3.1.0]hexane-containing bioactive molecules.

The great pharmaceutical potential of this scaffold prompted us to search for new and efficient methods that would provide diversified structures in a minimum number of steps. Due to the biological importance, a lot of methods for the construction of 3-oxabicyclo[3.1.0]hexanes have been developed.[2] 3-Oxabicyclo[3.1.0]hexanes can be synthesized by various strategies, such as the Ireland−Claisen rearrangement procedure,[7,8] intramolecular cyclization of aryldiazoacetates,[9] Ru-catalyzed annulations,[10-12] Pd-promoted [2 + 1] cycloaddition between dihydrofuran derivatives with alkynes,[13] or Au-catalyzed cyclopropanation of substituted (allyloxy)sulfonium ylides.[14] Another interesting synthetic pathway, reported by Pathak and co-author, employs the formation of single diastereomeric substituted 3-oxabicyclo[3.1.0]hexanes from the corresponding vinyl selenone with nitromethane, malononitrile, and dimethyl malonate in the presence of ^{t}BuOK in THF at room temperature.[15] Despite the advances, the development of novel and efficient methods for the preparation of 3-oxabicyclo[3.1.0]hexanes with various structural features and substitution patterns, especially those containing cyano group, remains one of the hottest topics in synthetic chemistry. Herein, we report, to the best of our knowledge, a new and convenient synthesis of the 3-oxabicyclo[3.1.0]hexane derivatives by the synergistic $NaBH_4$-reduction/cyclization of readily available 2-aroyl-3-aryl-1-cyano cyclopropanecarboxylates.

Results and Discussion

Cyclopropane-1-carboxylate **1a** was readily prepared from ethyl (E)-3-(4-chloro-phenyl)-2-cyanoacrylate and 1-(2-(4-bromo-phenyl)-2-oxoethyl)pyridin-1-ium iodide according to the reported method[16] (Scheme 1). The structure of **1a** was shown in Scheme 1.[17] X-ray crystallographic analysis determined that product **1a** possess the *cis* relationship of the benzoyl and contiguous substituent ester group. 1-cyanopropane-1-carboxylates **1b-s** were prepared via the same method from the corresponding 1-(2-oxo-2-arylethyl) pyridin-1-ium and 2-cyano-

[a] Liu, Jiaming; Wang, Lizhong; Qing, Xushun; Zhang, Feixiang; Wang, Ting; Wang, Cunde
School of Chemistry and Chemical Engineering
Yangzhou University
180 Siwangting Street, Yangzhou 225002, P. R. China
E-mail: wangcd@yzu.edu.cn.
[b] Wang, Lizhong: Taizhou Polytechnic College, Taizhou 225300, P.R. China

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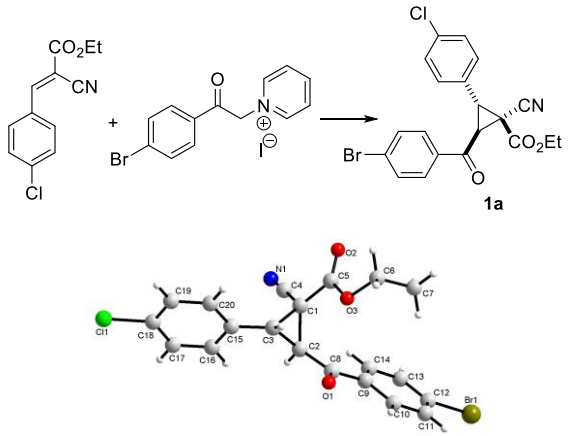
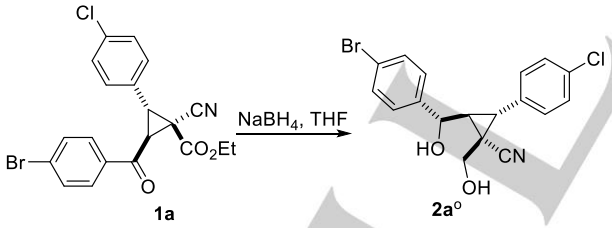
3-arylacrylates.

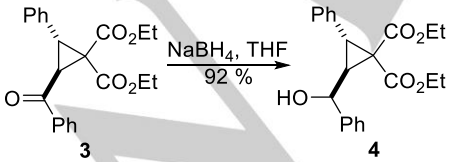


Scheme 1. Preparation of the starting material **1a**

Our investigation began with the reaction of ethyl 2-(4-bromobenzoyl)-1-cyano-3-(4-chlorophenyl)cycloprop- ane-1-carboxylate (**1a**) with $NaBH_4$ at room temperature for 3 h (Scheme 2). As expected, the reaction proceeded smoothly to afford the desired alcoholic product **2a**^{o} in a conversion of 100% based on TLC. After simple workup, the crude product was used directly to the following cyclization without further purification. Partial sample was purified by flash chromatography for the confirmation of the structure. The molecular structure of **2a**^{o} was elucidated from its spectroscopic analyses as described herein for **2a**^{o}. The mass spectrum of **2a**^{o} displayed the molecular ion peak at *m*/*z* = 391.95 (M+1), which is in good agreement with the proposed structure. The ^{1}H NMR spectrum of **2a**^{o} exhibited three signals at 5.77 *ppm*, 5.44 *ppm*, 4.59 *ppm* for Ar*CH*OH and *CH*$_2$OH, respectively. Characteristic ^{1}H chemical shift of Ar*CH*OH and *CH*$_2$OH unequivocally indicated the the carbonyl and ester group all were reduced. (see: *Supporting Information*).

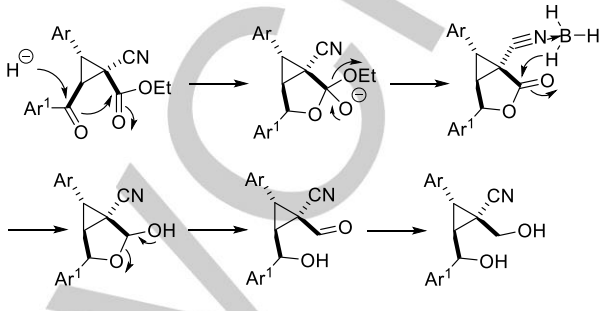


Scheme 2. The synergistic reduction of cyclopropane-1-carboxylate **1a**



Scheme 3. The reduction of cyclopropane-1,1-dicarboxylate **3**

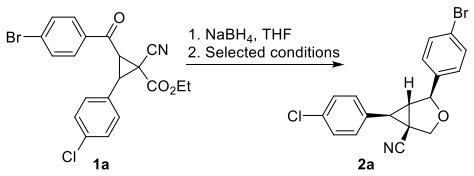
Somewhat surprisingly, cyclopropane-1,1-dicarboxylate **3**[18] was reduced using the same reduction system to give the product **4** which only carbonyl of ketone was reduced (Scheme 3). The reaction proved that a cyano group plays an important role in the synergistic reduction of cyclopropane-1-carboxylate **1a**. On the basis of stereoscopic evidence the comprehensible mechanism via the neighbouring-group participation and nitrile-borane complexes[19] was shown in Scheme 4 for an explanation of the synergistic reduction of carbonyl and ester group through the intermediate δ-butyrolactone to form a glycol.



Scheme 4. Tentative reaction mechanism of the synergistic reduction of carbonyl and ester

Our further investigations of the cyclization reaction focused on optimizing the reaction conditions of the intermediate glycol in the presence of different acid anhydride, bases and solvents. Without any base the cyclization reaction the intermediate glycol **2a**^{o} in the presence of Tf_2O using DCM as a solvent did not occur (Table 1, entry 1). To our delight, the reaction proceeded to give the desired product **2a** in 15 % yield when it was conducted in DCM with an equivalent NaOH (Table 1, entry 2). Thus, we screened a series of bases, including K_2CO_3, DBU, DABCO, Et_3N and DMAP (Table 1, entries 3−7), and the base DMAP was shown to be the most effective for this reaction.

Table 1. Optimization of reaction conditions in the synthesis of **2**[a]



Entry	Base (equiv)	Anhydride (equiv)	Solvent	t (h)	Yield (%)[a]
1	-	Tf_2O(2.0)	DCM	8	0
2	NaOH(1.0)	Tf_2O(2.0)	DCM	5	15
3	K_2CO_3(1.0)	Tf_2O(2.0)	DCM	5	12
4	DBU(1.0)	Tf_2O(2.0)	DCM	5	42
5	DABCO(1.0)	Tf_2O(2.0)	DCM	6	25
6	Et_3N(1.0)	Tf_2O(2.0)	DCM	6	13
7	DMAP(1.0)	Tf_2O(2.0)	DCM	5	95
8	DMAP(1.0)	Tf_2O(2.0)	$C_6H_5CH_3$	5	10
9	DMAP(1.0)	Tf_2O(2.0)	1,4-dioxane	7	32
10	DMAP(1.0)	Tf_2O(2.0)	DMF	5	0
11	DMAP(1.0)	Tf_2O(2.0)	EtOAc	5	0
12	DMAP(1.0)	Tf_2O(1.0)	DCM	8	82
13	DMAP(0.75)	Tf_2O(2.0)	DCM	5	89
14	DMAP(1.5)	Tf_2O(2.0)	DCM	5	93
15	DMAP(1.0)	Ac_2O(2.0)	DCM	5	0
16[b]	DMAP(1.0)	Tf_2O(2.0)	DCM	9	95

[a] Isolated yields. The reaction was carried out at room temperature unless otherwise mention. [b] at 0^{o}C

Based on this encouraging result, we then studied the effect of solvent on reaction, the reaction was carried out with different

solvents such as toluene, 1,4-dioxane, DMF and EtOAc, the solvents toluene and 1,4-dioxane gave the desired product **2a** in low yields (Table 1, entries 8, 9), however, DMF and EtOAc as solvents did not work (Table 1, entries 10, 11) and the intermediate glycol **2a**^{o} was yielded, screening of the solvents revealed that DCM was a good candidate. Further study on the effect of the amount of Tf_2O led to the observation that the reaction using 1.0 equiv Tf_2O afforded the yield of product **2a** in 82 % (entry 12). When the reaction was carried out using 0.75 equiv DMAP (Table 1, entry 13) or 1.5 equiv DMAP (Table 1, entry 14), the yield of product **2a** was slightly decreased. The replacement of Tf_2O with Ac_2O did not give the desired product **2a** (Table 1, entry 15), the intermediate glycol **2a**^{o} was recovered. Additionally, the reaction of the cyclopropane-1-carboxylate **1a** in the presence of Ac_2O and DMAP in DCM under refluxing gave the diester of glycol **2a**^{o} (see: *Supporting Information*). Reducing the temperature of the title reaction from room temperature to 0 ^{o}C afforded the same best result, as it should be needed the longer reaction time (Table 1, entry 16). Thus, we defined that the reaction of the cyclopropane-1-carboxylate **1a** was carried out with 2.0 equiv $NaBH_4$ firstly in THF at room temperature, then with 2.0 equiv Tf_2O and 1.0 equiv DMAP in DCM at room temperature for 5 h as the standard conditions (Table 1, entry 7). The structure of **2a** was shown in Figure 2.[17] X-ray crystallographic analysis determined that product **2a** possess *cis* two aryls and cyano at C(4), C(6) and C(1) of 3-oxabicyclo[3.1.0]hexane. On the basis of spectroscopic evidence the structure of compound **2a** was identified as *cis*-4-(4-bromophenyl)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2a**).

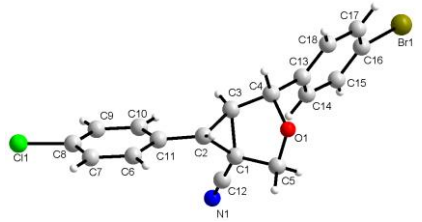
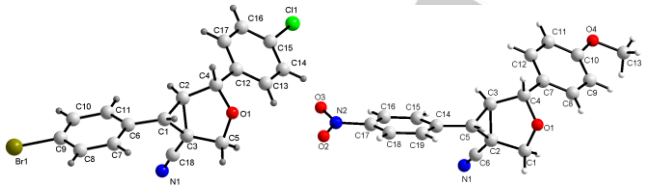


Figure 2. Molecular structure of 3-oxabicyclo[3.1.0]hexane-1-carbonitrile **2a**

The scope of this two-step transformation was then investigated under the standard conditions using different cyclopropane-1-carboxylates. The results are summarized in Table 2. A variety of cyclopropane-1-carboxylates **1a**–**s** underwent the formal cyclization with $NaBH_4$ and Tf_2O-DMAP system smoothly to deliver the targeted products. Variation of R^1 and R^2 substituents showed that the benzene rings with an electron-donating group (-OMe or -OAr) or an electron-withdrawing group (-Br, -Cl, $-NO_2$) as well as *o*-halo were well tolerated, producing the desired 3-oxabicyclo[3.1.0]hexane-1-carbonitriles in 92–96% yield.

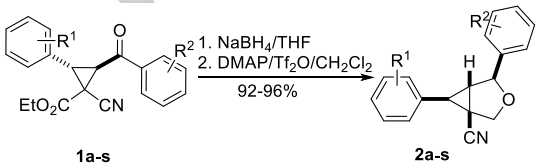
All corresponding substituted 3-oxabicyclo[3.1.0]hexane-1-carbonitriles were analyzed by their ^{1}H NMR, ^{13}C NMR and HRMS. Characteristic ^{1}H chemical shifts of 3-oxabicyclo[3.1.0]hexane-1-carbonitriles at δ ca 5.08(1H), 4.16 (1H), 4.06 (1H), 2.76 (1H), and 2.56 (1H), unequivocally indicated the exclusive chemical environment of 3-oxabicyclo[3.1.0]hexane-1-carbonitrile bicycle protons. Products 3-oxabicyclo[3.1.0]hexane-1-carbonitriles **2b** and **2p** were further characterized by single X-ray crystallography (Figure 3).[16]



2b **2p**

Figure 3. Molecular structure of 3-oxabicyclo[3.1.0]hexane-1-carbonitriles **2b** and **2p**

Table 2 Substrate scope of 1-cyanocyclopropane carboxylates.[a]



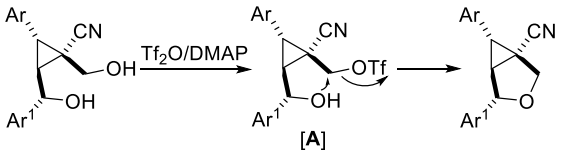
1a-s **2a-s**

Entry	R^1	R^2	Product	Yield (%)[b]
1	*p*-Cl	*p*-Br	**2a**	95
2	*p*-Br	*p*-Cl	**2b**	96
3	*p*-Br	*p*-CH_3O	**2c**	94
4	*o*-Br	*p*-Br	**2d**	92
5	*m*-Cl	*p*- Br	**2e**	92
6	*m*-Cl	H	**2f**	94
7	*m*-CH_3	H	**2g**	96
8	*m*-CH_3	*p*-CH_3O	**2h**	96
9	*o*-Br	*p*-CH_3O	**2i**	94
10	*m*-Cl	*p*-CH_3O	**2j**	96
11	*p*-Cl	*p*-CH_3O	**2k**	95
12	*p*-Cl	*p*-Cl	**2l**	95
13	*p*-PhO	*p*-Cl	**2m**	96
14	*m*-Cl	*p*-Cl	**2n**	94
15	*m*-Br	H	**2o**	92
16	*p*-O_2N	*p*-CH_3O	**2p**	92
17	*p*-(3-FC_6H_4O)	H	**2q**	95
18	*p*-Cl	H	**2r**	94
19	*o*-Cl	*p*-Br	**2s**	95

[a] Reaction conditions: (1)1-cyanocyclopropane-1-carboxylates **1a**-**s** (2 mmol), $NaBH_4$ (0.3026 g, 4mmol) and THF (15 mL), room temperature, 3-5 h; (2) 4-dimethylaminopyridine (0.2443 g, 2 mmol), trifluoromethanesulfonic anhydride (0.33 ml, 2 mmol), dried CH_2Cl_2 (10 mL), room temperature, 5 h.

[b] Isolated yields.

On the basis of the above experimental results together with related reports, the reaction mechanism of the cyclization of the glycol shown in Scheme 5 was proposed. In terms of tetrahydrofuran formations, the selective trifluoromethylsulfonation of the glycol with Tf_2O in the presence of DMAP gave firstly the intermediate δ-hydroxylbutyl trifluoromethylsulfonate [**A**],[20] then intramolecularly nucleophilic substitution afforded tetrahydrofuran.



Scheme 5. Tentative reaction mechanism of the cyclization of the glycol

Conclusions

In summary, we have presented the synergistic-$NaBH_4$-reduction/cyclization of readily available 2-aroyl-1-cyano-3-arylcyclopropane-1-carboxylate compounds, providing access to the selective synthesis of 3-oxabicyclo[3.1.0]hexane-1-carbonitrile derivatives. Due to the described pharmacological usefulness of 3-oxabicyclo[3.1.0]hexane-1-carbonitrile derivatives such simple reaction conditions and functional group tolerance is offering a new attractive method to access such structures. Therefore, from these results, it can be envisioned that this method will find many applications in medicinal chemistry.

Experimental Section

All melting points were determined in a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded in a Nicolet FT-IR 5DX spectrometer. The ^{1}H NMR (400 or 600 MHz) and ^{13}C NMR (100 or 150 MHz) spectra were recorded in a Bruker AV-400 spectrometer with TMS as internal reference in $CDCl_3$ solutions. The *J* values are given in hertz. Only discrete or characteristic signals for the ^{1}H NMR are reported. High-resolution ESI mass spectra were obtained on a UHR-TOF maXis (ESI) mass spectrometer. X-ray crystallographic analysis was performed with a SMART APEX-II diffractometer. Flash chromatography was performed on silica gel (230-400 mesh) eluting with ethyl acetate-hexanes mixture. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

General procedure for synthesis of 3-oxabicyclo[3.1.0]hexane-1-carbonitrile derivatives

To a solution of 2-aroyl-3-aryl-1-cyanocyclopropane-1-carboxylates **1a**-**s** (2 mmol) in THF (15 mL), $NaBH_4$ (0.3026 g, 4mmol) was added, the mixture was stirred at room temperature for 5 hrs, and the completion of reaction was confirmed by TLC (Hexanes/EtOAc, 8/1). Subsequently, the reaction was quenched by adding water (5mL), the solvent THF was removed by reduce pressure, the residues were extracted with dichloromethane (10 mL X 2). The organic phase was washed with water (10 mL) and brine (5 mL), and dried over anhydrate sodium sulfate. After removal of dichloromethane, the crude product was not purified further for the next step directly.

To the mixture of last crude product and 4-dimethylaminopyridine (0.2443 g, 2 mmol) in dried dichloromethane (10 mL) was added dropwise trifluoromethanesulfonic anhydride (0.33 ml, 2 mmol) at room temperature, the resultant mixture was stirred for 5 hrs, and the completion of reaction was confirmed by TLC (Hexanes/EtOAc, 8/1). Subsequently, the reaction was quenched by adding ice-water (5 mL), the mixture was separated, the aqueous phases were extracted with dichloromethane (10 mL X 2). The combined organic phase was washed with water (10 mL) and brine (5 mL), and dried over anhydrate sodium sulfate. After removal of dichloromethane, the crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/30) to give the desirable products **2a**-**s**.

(±) cis-4-(4-bromophenyl)-6-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbo nitrile (**2a**)

White solid, yield 95%; m.p. 170.2-171.0 °C (EA/PE); IR (KBr, cm^{-1}): v = 3056, 2927, 2877, 2236, 1741, 1490, 1418, 1076, 1008, 917, 819, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.50 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 9.8 Hz, 4H), 5.08 (s, 1H), 4.16 (d, *J* = 8.7 Hz, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 2.76 (d, *J* = 5.3 Hz, 1H), 2.56 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 136.8, 132.8, 131.1, 130.9, 127.9, 127.9, 126.7, 121.5, 115.6, 79.8, 67.9, 35.9, 29.8, 23.9; HRMS (ESI) calcd. for $C_{18}H_{13}BrClNO$ [(M+Na)$^+$]: 395.9767; Found: 395.9766.

(±) cis-6-(4-bromophenyl)-4-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbo nitrile (**2b**)

White solid, yield 96%; m.p. 170.3-171.0 °C (EA/PE); IR (KBr, cm^{-1}): v = 3055, 1985, 2875, 2298, 2231, 1904, 1794, 1571, 1487, 1408, 1303, 1256, 1188, 1066, 1005, 957, 858, 815, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.50 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 2.74 (d, *J* = 5.2 Hz, 1H), 2.54 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 136.4, 133.5, 131.6, 130.9, 128.3, 128.2, 126.5, 121.0, 115.6, 79.9, 68.0, 36.0, 30.0, 24.0; HRMS (ESI) calcd. for $C_{18}H_{13}BrClNO$ [(M+Na)$^+$]: 395.9767; Found: 395.9738.

(±) cis-6-(4-bromophenyl)-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0] hexane-1-carbo nitrile (**2c**)

White solid, yield 94%; m.p. 160.4-161.0 °C (EA/PE); IR (KBr, cm^{-1}): v = 2964, 2355, 2228, 1747, 1580, 1505, 1351, 1298, 1242, 1180, 1066, 960, 828, 747. ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.44 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.06 (s, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 3.77 (s, 3H), 2.75 (d, *J* = 5.2 Hz, 1H), 2.53 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 158.8, 131.9, 130.9, 130.0, 128.3, 126.7, 120.8, 115.9, 113.3, 80.2, 67.5, 54.3, 35.9, 29.9, 24.0; HRMS (ESI) calcd. for $C_{19}H_{16}BrNO_2$ [(M+Na)$^+$]: 392.0262; Found: 392.0285.

(±) cis-6-(2-bromophenyl)-4-(4-bromophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbo nitrile (**2d**)

White solid, yield 92%; m.p. 128.5-129.1 °C (EA/PE); IR (KBr, cm^{-1}): v = 3077, 2970, 2927, 2874, 2351, 2241, 1700, 1473, 1435, 1413, 1348, 1302, 1257, 1183, 1123, 1060, 1026, 961, 917, 886, 858, 816, 795, 774, 749, 731, 712, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.62-7.59 (m, 1H), 7.53-7.50 (m, 2H), 7.29-7.24 (m, 1H), 7.21 (s, 1H), 7.19 (s, 2H), 7.18-7.13 (m, 1H), 5.11 (s, 1H), 4.26 (d, *J* = 8.6 Hz, 1H), 4.08 (d, *J* = 8.6 Hz, 1H), 2.84 (d, *J* = 5.5 Hz, 1H), 2.72 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (*ppm*): 137.1, 132.4, 132.1, 131.1, 128.6, 128.0, 126.8, 126.6, 125.4, 121.6, 115.6, 79.9, 67.9, 35.8, 31.4, 23.9; HRMS (ESI) calcd. for $C_{18}H_{13}Br_2NO$ [(M+Na)$^+$]: 441.9241; Found: 441.9232.

(±) cis-4-(4-bromophenyl)-6-(3-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbo nitrile (**2e**)

White solid, yield 92%; m.p. 175.8-176.3 °C (EA/PE); IR (KBr, cm^{-1}): v = 3063, 2969, 2928, 2873, 2232, 1758, 1574, 1481, 1398, 1315, 1254, 1191, 1067, 1005, 957, 904, 871, 786, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.56-7.54 (m, 2H), 7.26-7.24 (m, 1H), 7.23 (s, 1H), 7.22-7.16 (m, 3H), 7.12-7.06 (m, 1H), 5.07 (s, 1H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.05 (d, *J* = 8.7 Hz, 1H), 2.77 (d, *J* = 5.2 Hz, 1H), 2.55 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 136.9, 134.6, 133.6, 131.1, 129.0, 127.1, 127.1, 126.8, 124.7, 121.6, 115.4, 79.9, 68.0, 35.8, 30.0, 24.0; HRMS (ESI) calcd. for $C_{18}H_{13}BrClNO$ [(M+Na)$^+$]: 395.9767; Found: 395.9752.

(±) cis-6-(3-chlorophenyl)-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2f**)

White solid, yield 94%; m.p. 125.6-126.1 °C (EA/PE); IR (KBr, cm^{-1}): v =

3066, 2970, 2925, 2860, 2351, 2234, 1701, 1600, 1483, 1450, 1348, 1214, 1059, 1039, 967, 929, 917, 889, 848, 808, 784, 775, 732, 703; ^{1}H NMR (400 MHz) δ (*ppm*): 7.37 (dd, *J* = 7.6 and 7.2 Hz, 2H), 7.31 (dd, *J* = 7.6 and 7.2 Hz, 3H), 7.24 (d, *J* = 6.1 Hz, 3H), 7.12-7.08 (m, 1H), 5.11 (s, 1H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 2.82 (d, *J* = 5.3 Hz, 1H), 2.56 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 158.8, 131.9, 130.9, 130.0, 128.3, 126.7, 120.8, 115.9, 113.3, 80.2, 67.5, 54.3, 35.9, 29.9, 24.0; HRMS (ESI) calcd. for $C_{18}H_{14}ClNO$ [(M+Na)$^+$]: 318.0662; Found: 318.0655.

(±) cis-4-phenyl-6-(m-tolyl)-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2g**)

White solid, yield 96%; m.p. 118.9-119.4 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3033, 2921, 1854, 2315, 2233, 1704, 1600, 1492, 1454, 1347, 1265, 1056, 1009, 967, 930, 843, 781, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.39-7.34 (m, 2H), 7.30 (dd, *J* = 7.4 and 7.1 Hz, 3H), 7.19 (d, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.10 (s, 1H), 4.15 (d, *J* = 8.6 Hz, 1H), 4.11 (d, *J* = 8.6 Hz, 1H), 2.82 (d, *J* = 5.3 Hz, 1H), 2.56 (d, *J* = 5.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 138.2, 137.4, 132.6, 127.9, 127.6, 127.5, 127.4, 125.2, 123.6, 116.1, 80.7, 68.1, 36.1, 30.6, 24.0, 20.4; HRMS (ESI) calcd. for $C_{19}H_{17}NO$ [(M+Na)$^+$]: 298.1208; Found: 298.1207.

(±) cis-4-(4-methoxyphenyl)-6-(m-tolyl)-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2h**)

White solid, yield 96%; m.p. 132.9-133.3 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3055, 2973, 2866, 2835, 2351, 2232, 1715, 1611, 1585, 1514, 1460, 1309, 1253, 1185, 1060, 1042, 1009, 962, 906, 863, 809, 787, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.23 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 7.8 and 7.8 Hz, 2H), 7.08 (s, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 1H), 4.10 (d, *J* = 8.6 Hz, 1H), 4.05 (d, *J* = 8.6 Hz, 1H), 3.77 (s, 3H), 2.78 (d, *J* = 5.3 Hz, 1H), 2.54 (d, *J* = 5.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 158.8, 137.4, 132.7, 130.3, 127.6, 127.6, 127.4, 126.8, 123.6, 116.3, 113.3, 80.3, 67.6, 54.3, 35.9, 30.5, 24.0, 20.4; HRMS (ESI) calcd. for $C_{20}H_{19}NO$ [(M+Na)$^+$]: 328.1313; Found: 328.1311.

(±) cis-6-(2-bromophenyl)-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2i**)

White solid, yield 96%; m.p. 130.6-131.0 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3099, 2971, 2657, 2455, 2340, 2245, 2175, 2056, 1908, 1696, 1517, 1274, 1184, 1069, 962, 827, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.24 (d, *J* = 8.1 Hz, 3H), 7.18 (t, *J* = 9.2 Hz, 2H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 2H), 5.09 (s, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 4.06 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 2.85 (d, *J* = 4.6 Hz, 1H), 2.71 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (*ppm*): 158.8, 132.7, 132.1, 130.2, 128.5, 128.0, 126.8, 126.6, 125.4, 116.0, 113.3, 80.2, 67.3, 54.3, 35.7, 31.3, 24.0; HRMS (ESI) calcd. for $C_{19}H_{16}BrNO_2$ [(M+Na)$^+$] : 392.0262; Found: 392.0239.

(±) cis--6-(3-chlorophenyl)-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane-1- carbonitrile (**2j**)

White solid, yield: 96%; m.p. 148.9-149.2 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3071, 2963, 2332, 2232, 1753, 1581, 1509, 1459, 1308, 1257, 1181, 1060, 877, 805, 702; ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.25-7.21 (m, 5H), 7.10 (d, *J* = 6.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 3.76 (s, 3H), 2.77 (d, *J* = 5.2 Hz, 1H), 2.54 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150MHz, $CDCl_3$) δ (*ppm*): 158.8, 134.9 133.6, 129.9, 129.0, 127.1, 127.0, 126.8, 124.7, 115.8, 113.3, 80.2, 67.5, 54.3, 35.8, 29.9, 24.1; HR-MS (ESI) calcd. for $C_{19}H_{16}ClNO_2$ [(M+Na)$^+$] : 348.0767; Found: 348.0757.

(±) cis-6-(2-chlorophenyl)-4-(4-methoxyphenyl)-3-oxabicyclo[3.1.0]hexane-1- carbonitrile (**2k**)

White solid, yield: 95%; m.p. 142.8-143.3 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 2967, 2919, 2230, 1611, 1583, 1514, 1498, 1463, 1440, 1352, 1308, 1061, 1029, 966, 878, 827, 775, 756,733, 705; ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.28 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 1H), 4.09 (d, *J* = 8.7 Hz, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 3.76 (s, 3H), 2.75 (d, *J* = 5.2 Hz, 1H), 2.54 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 159.8, 133.7, 132.4, 131.0, 129.0, 128.9, 127.7, 116.9, 114.3, 81.2, 68.4, 55.3, 36.9, 30.8, 25.0; HR-MS (ESI) calcd. for $C_{19}H_{16}ClNO_2$ [(M+Na)$^+$]: 348.0767, Found: 348.0757.

(±) cis-4,6-bis(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2l**)

White solid, yield: 95%; m.p. 164.5-165.2 ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3056, 2927, 2877, 2236, 1490, 1418, 1341,1260, 1076, 1008, 959, 917, 844, 819, 783, 721; ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.34 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.08 (s, 1H), 4.14 (d, *J* = 8.7 Hz, 1H), 4.05 (d, *J* = 8.7 Hz, 1H), 2.75 (d, *J* = 5.2 Hz, 1H), 2.55 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 136.4, 133.5, 132.9, 131.1, 128.2, 128.03, 128.02, 126.5, 115.6, 79.9, 68.0, 36.0, 29.9, 24.0; HRMS (ESI) calcd. for $C_{18}H_{13}Cl_2NO$ [(M+Na)$^+$]: 352.0272, Found: 352.0263.

(±) cis-4-(4-chlorophenyl)-6-(4-phenoxyphenyl)-3-oxabicyclo[3.1.0] hexane-1-carbonitrile (**2m**)

White solid, yield: 96%; m.p. 102.6-103.1ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3067, 2870, 2235, 1609, 1582, 1224, 1162, 1076, 1015, 965, 861, 807, 759; ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (dd, *J* = 7.2 and 7.5 Hz, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.05 (dd, *J* = 7.2 and 7.4 Hz, 1H), 6.95 (dd, *J* = 7.8 and 8.0 Hz, 3H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 5.06 (s, 1H), 4.13 (d, *J* = 8.7 Hz, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 2.74 (d, *J* = 5.2 Hz, 1H), 2.55 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 156.6, 155.7, 136.5, 134.5, 133.4, 129.1, 128.8, 128.1, 126.5, 122.5, 121.3, 118.0, 117.3, 117.2, 115.7, 79.9, 68.0, 35.9, 30.4, 24.1; HR-MS (ESI) calcd. for $C_{24}H_{18}ClNO_2$ [(M+Na)$^+$] : 410.0924, Found:410.0915.

(±) cis-6-(3-chlorophenyl)-4-(4-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1- carbonitrile (**2n**)

White solid, yield: 94%, m.p. 180.7-181.3ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3069, 2982, 2876, 2237, 1617, 1599, 1569, 1492, 1433, 1359, 1324, 1256, 1218, 1196, 1093, 1062, 1034, 1012, 958, 933, 908, 884, 865, 824, 796, 783, 766, 726, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.34 (d, *J* = 8.2 Hz, 2H), 7.27–7.23 (m, 3H), 7.22 (s, 2H), 7.09 (d, *J* = 6.0 Hz, 1H), 5.08 (s, 1H), 4.14 (d, *J* = 8.8 Hz, 1H), 4.05 (d, *J* = 8.7 Hz, 1H), 2.77 (d, *J* = 5.2 Hz, 1H), 2.55 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 136.3, 134.6, 133.7, 133.5, 129.0, 128.2, 127.2, 127.1, 126.5, 124.7, 115.5, 79.9, 68.0, 35.8, 30.0, 24.0; HR-MS (ESI) calcd. for $C_{18}H_{13}Cl_2NO$ [(M+Na)$^+$]: 352.0272, Found: 352.0259.

(±) cis-6-(3-bromophenyl)-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2o**)

White solid, yield: 92%; m.p. 133.7-134.5ºC (EA/PE); IR (KBr, cm^{-1}): ν = 3064, 2969, 2859, 2234, 1597, 1564, 1480, 1449, 1347, 1310, 1262, 1213, 1191, 1098, 1074, 1004, 967, 928, 915, 886, 849, 782, 773, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.38 (d, *J* = 6.8 Hz, 3H), 7.35 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 3H), 7.20-7.13 (m, 2H), 5.11 (s, 1H), 4.15 (d, *J* = 8.8 Hz, 1H), 4.10 (d, *J* = 8.7 Hz, 1H), 2.81 (d, *J* = 5.2 Hz, 1H), 2.56 (d,

J = 5.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (*ppm*): 137.9, 135.1, 130.1, 130.0, 129.3, 128.0, 127.6, 125.2, 121.8, 115.7, 80.6, 68.0, 36.0, 29.9, 24.2; HR-MS (ESI) calcd. for $C_{18}H_{14}BrNO$ [(M+Na)$^+$]: 362.0156, Found: 362.0146.

(±) cis-4-(4-methoxyphenyl)-6-(4-nitrophenyl)-3-oxabicyclo[3.1.0]hexane-1- carbonitrile (**2p**)

White solid, yield: 92%; m.p. 105.6-106.2°C (EA/PE); IR (KBr, cm^{-1}): v = 3076, 2980, 2877, 2236, 1612, 1598, 1151, 1347, 1245, 1178, 1069, 959, 858, 816, 745, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 8.19 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.11 (s, 1H), 4.15 (d, *J* = 8.8 Hz, 1H), 4.08 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H), 2.87 (d, *J* = 5.2 Hz, 1H), 2.67 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 137.15, 132.45, 132.16, 131.15, 128.67, 128.01, 126.88, 126.67, 125.41, 121.61, 115.68, 79.99, 67.93, 35.84, 31.46, 23.99; HR-MS (ESI) calcd. for $C_{19}H_{16}N_2O_4$ [(M+Na)$^+$]: 359.1008, Found: 359.1000.

(±) cis-6-(4-(3-fluorophenoxy)phenyl)-4-phenyl-3-oxabicyclo[3.1.0]hexane -1- carbonitrile (**2q**)

White solid, yield: 95%; m.p. 134.6-135.4°C(EA/PE); IR (KBr, cm^{-1}): v = 3065, 2859, 2232, 1610,1584, 1510, 1355, 1276, 1208, 1064, 966, 894, 825, 753, 697. ^{1}H NMR (600 MHz, $CDCl_3$) δ (*ppm*): 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.27 (t, *J* = 6.3 Hz, 4H), 7.12 (t, *J* = 9.3 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.93 (t, *J* = 8.9 Hz, 3H), 5.07 (s, 1H), 4.11 (d, *J* = 8.7 Hz, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 2.72 (d, *J* = 5.1 Hz, 1H), 2.52 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*ppm*): 155.9, 152.8 (d, *J* = 248.6 Hz), 143.0 (d, *J* = 11.9 Hz), 137.9, 129.7 (d, *J* = 3.9 Hz), 128.8, 128.0, 127.5, 125.1, 122.8 (d, *J* = 7.1 Hz), 122.4, 120.2, 116.3 (d, *J* = 80.2 Hz), 98.9, 80.6, 67.8, 36.0, 29.8, 24.1; HRMS (ESI) calcd. for $C_{24}H_{18}FNO_2$ [(M+Na)$^+$] : 394.1219, Found: 394.1211.

(±) cis-6-(4-chlorophenyl)-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carbonitrile (**2r**)

White solid, yield: 94%; m.p. 148.4-149.1°C (EA/PE); IR (KBr, cm^{-1}): v = 3038, 2958, 2880, 2232, 1895, 1757, 1552, 1493, 1351, 1303, 1190, 1067, 1005, 959, 877, 832, 766, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.38-7.34 (m, 2H), 7.32-7.30 (m, 2H), 7.29-7.27 (m, 2H), 7.18-7.16 (m, 2H), 7.16-7.14 (m, 1H), 5.12 (s, 1H), 4.15 (d, *J* = 8.7 Hz, 1H), 4.10 (d, *J* = 8.6 Hz, 1H), 2.79 (d, *J* = 5.3 Hz, 1H), 2.57 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 137.9, 132.8, 131.3, 128.0, 127.9, 127.5, 125.1, 115.8, 80.6, 67.9, 36.2, 29.9, 24.1; HR-MS (ESI) calcd. for $C_{18}H_{14}ClNO$ [(M+Na)$^+$]: 318.0662, Found: 318.0648.

(±) cis-4-(4-bromophenyl)-6-(2-chlorophenyl)-3-oxabicyclo[3.1.0]hexane-1- carbonitrile (**2s**)

White solid, yield: 95%; m.p. 110.8-111.7 °C (EA/PE); IR (KBr, cm^{-1}): 2981, 2879, 2240, 1617, 1566, 1482, 1414, 1342, 1257, 1189, 1138, 1064, 959, 873, 812, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*ppm*): 7.49 (d, *J* = 8.4 Hz, 2H), 7.44-7.37 (m, 1H), 7.26-7.18 (m, 4H), 7.18 (s, 1H), 5.09 (s, 1H), 4.22 (d, *J* = 8.6 Hz, 1H), 4.06 (d, *J* = 8.6 Hz, 1H), 2.83 (d, *J* = 5.5 Hz, 1H), 2.75 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*ppm*): 137.1, 134.8, 131.1, 130.7, 128.8, 128.4, 127.7, 126.8, 126.0, 121.6, 115.7, 79.9, 67.8, 35.4, 28.9, 23.7; HR-MS (ESI) calcd. for $C_{18}H_{13}BrClNO$ [(M+Na)$^+$] : 395.9767, Found: 395.9757.

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[1] J. T. Bagdanoff, R. Jain, W. Han, S. Zhu, A. M. Madiera, P. S. Lee, X. Ma, D. Poon, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3788.

[2] A. Banerjee, L. Narayana, F. A. Raje, D. V. Pisal, P. A. Kadam, S. Gullapalli, H. Kumar, S. V. More, M. Bajpai, R. R. Sangana, S. Jadhav, G. S. Gudi, N. Khairatkar-Joshi, R. R. T. Merugu, S. R. Voleti, L. A. Gharat, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6747.

[3] A. Abeywardane, J. Broadwater, S.R. Brunette, T.M. Kirrane, Jr., H. Razavi, R. Sibley, L.L. Smithkeenan, Q. Zhang, U.S. Pat. Appl. Publ., 20150018334, **2015**.

[4] W. Wang, X. Zhao, T. Li, Q. Tian, PCT Int. Appl., 2015007219, **2015**.

[5] J. Popovici-Muller, Z. Cai, D. Zhou, PCT Int. Appl., 2015003360, **2015**.

[6] S. He, Z. Lai, X. Dai, D. Xiao, PCT Int. Appl., 2014205592, **2014**.

[7] G. Ernouf, J.-L. Brayer, B. Folléas, J.-P. Demoute, C. Meyer, J. Cossy, *Org. Lett.* **2015**, *17*, 3786.

[8] B. Y. Wang, J. W. Huang, L. P. Liu, M. Shi, *Synlett*, **2005**, 421.

[9] E. D. Couch, T. J. Auvil, A. E. Mattson, *Chem. Eur. J.* **2014**, *20*, 8283.

[10] X. Zhou, I. Zafar, G. Dong, *Tetrahedron*, **2015**, *71*, 4478.

[11] a) S. T. R. Müller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, *20*, 495; b) A. F. G. Goldberg, R. A. Craig II, N. R. O'Connor, Brian. M. Stoltz, *Tetrahedron Lett*. **2015**, *56*, 2983.

[12] Y. Nakagawa, S. Chanthamath, K. Shibatomi, and S. Iwasa, *Org. Lett.* **2015**, *17*, 2792.

[13] K. L. Jeune, S. Chevallier-Michaud, D. Gatineau, L. Giordano, A. Tenaglia, H. Clavier, *J. Org. Chem.* **2015**, *80*, 8821.

[14] S. Klimczyk, X. Huang, H. Kählig, L. F. Veiros, N. Maulide, *J. Org. Chem.* **2015**, *80*, 5719.

[15] A. Bhaumik, T. Pathak, *J. Org. Chem.* **2015**, *80*, 11057.

[16] a) Q. F. Wang, X. K. Song, J. Chen, C. G. Yan, *J. Comb. Chem.* **2009**, *11*, 1007. b) J. Liu, F. Zhang, T. Wang, X. Qing, C. Wang, *J. Chem. Res.* **2016**, *40*, 694.

[17] Crystallographic data for ethyl 2-(4-bromobenzoyl)-1-cyano-3-(4-chloro phenyl)cyclopropane-1-carboxylate (**1a**), 3-oxabicyclo[3.1.0] hexane-1-carbonitriles **2a**, **2b**, **2p** have been deposited with the Cambridge Crystallographic Data Centre with the deposition number CCDC 1510846, 1469117, 1470498 and 1479693. These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax (+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

[18] a) J.-T. Li, Y. Cui, G.-F. Chen, Z.-L. Cheng, T.-S. Li, *Synth. Commun.* **2003**, *33*, 353. b) C.-B. Miao, M. Zhang, Z.-Y. Tian, H.-T. Xi, X.-Q. Sun, H.-T. Yang, *J. Org. Chem.* **2011**, *76*, 9809.

[19] A. Saito, Y. Kambara, T. Yagyu, K. Noguchi, A. Yoshimur, V. V. Zhdankin, *Adv. Synth. Catal.* **2015**, *357*, 667.

[20] a) S. J. Mantell, P. S. Ford, D. J. Watkin, G. W.J. Fleet, D. Brown, *Tetrahedron*, **1993**, *49*, 3343. b) J. R. Wheatley, C. J. F. Bichard, S. J. Mantell, J. C. Son, D. J. Hughes, G. W. J. Fleet, D. Brown, *J. Chem. Soc. Chem. Commun.* **1993**, 1065. c) Y. Takahashi, H. Nakayama, K. Katagiri, K. Ichikawa, N. Ito, T. Takita, T. Takeuchi, T. Miyake, *Tetrahedron Lett.* **2001**, *42*, 1053. d) T. Nemoto, T. Ohshima, M, Shibasaki, *Tetrahedron*, **2003**, *59*, 6889.

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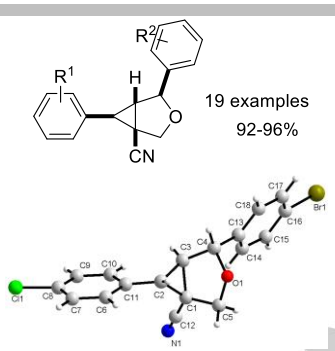

oxabicyclo[3.1.0]hexane

Jiaming Liu,[a] Lizhong Wang,[a,b] Xushun Qing,[a] Feixiang Zhang,[a] Ting Wang,[a] and Cunde Wang[a]*

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Synergistic $NaBH_4$-reduction/ cyclization of 2-aroyl-cyclopropane-1-carboxylates: novel synthesis of 3-oxabicyclo[3.1.0]hexane derivatives

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