Advanced Synthesis & Catalysis

Title: An efficient synthesis of 6-oxa-spiro[3.4]octan-1-one derivates through 3-diazochroman-4-one and alkene

Authors: Meiling Xiao, Fuming Zhang, Zhe Du, and Bao-chun Ma

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701197

Link to VoR: http://dx.doi.org/10.1002/adsc.201701197

Advanced Synthesis & Catalysis **COMMUNICATION**

DOI: 10.1002/adsc.201

An efficient synthesis of 6-oxa-spiro[3.4]octan-1-one derivates through 3-diazochroman-4-one and alkene

Meiling Xiao [a], Fuming Zhang [a], Zhe Du [a], Baochun Ma [a],*

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China
E-mail: mabaochun@lzu.edu.cn

Received:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

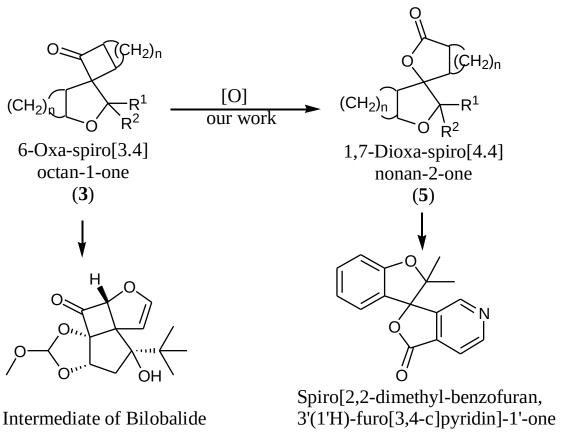
Abstract: Spiro[2, 2-dimethyl-benzofuran, bicyclo [4.2.0]octane]-7’-one with fused and spirocyclic oxygen-containing rigid skeleton structure is obtained via Wolff rearrangement and cycloaddition with good yields. Then spiro[2, 2-dimethyl-benzofuran, hexahydro-isobenzofuran-2’-one] is synthesized by further Baeyer-Villiger oxidation. These two kinds of products have a special fused and spirocyclic oxygen-containing rigid skeleton structure and are reported by our group.

Keywords: Spiro[3.4]octan-1-one; Wolff rearrangement; cycloaddition; α-diazo ketone; Baeyer-Villiger oxidation

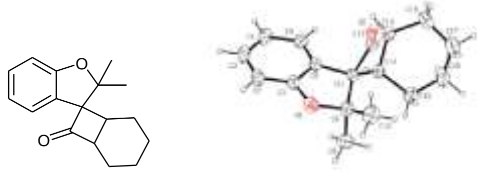
Fused and spirocyclic ring systems are key structural elements of numerous natural products.[1] Spirocyclic compounds, as conformationally restricted templates, have advantages for drug discovery due to their pre-organization.[2] Fused and spirocyclic ring systems containing oxygen heterocycles have attracted the attention of many research groups globally. 6-Oxa-spiro[3.4]octan-1-one, a valuable scaffold, including a strained cyclobutanone and furan motif connected by a quaternary carbon, has been widely involved in natural products and analogues. The extracts of Ginkgo biloba, have been employed as a therapeutic agent in Chinese folk medicine due to its healing function on diseases such as peripheral circulatory implication.[3] Bilobalide acts as an unusual compound extracted from Ginkgo biloba, and 6-oxa-spiro [3.4]octan-1-one plays an important role in the synthetic process of Bilobalide as a core skeleton (Scheme 1, **3**).[4] Compounds containing lactone motif are found extensively in natural products and are used in organic synthesis (Scheme 1, **5**).[5]

4-Chromanone and its derivatives widely exist in various natural products and play important roles in the synthesis of organic synthetic materials.[6] Therefore, 4-chromanone and its derivatives are attractive in their versatility. Thus, developing novel and efficient methods to synthesize these compounds are vital.

a. Representative products contain the core skeleton:



b. Our product **3aa**’s single-crystal X-ray diffraction:

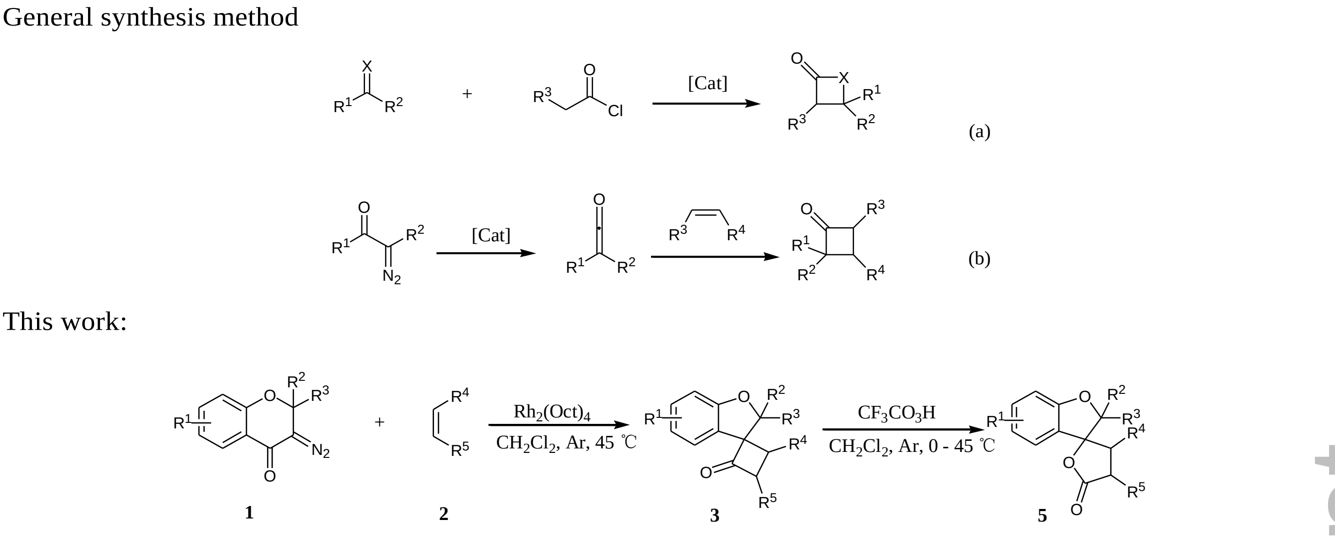


3aa

Crystal structure of **3aa**
CCDC-1571954

Scheme 1. Some representative products.

As part of our ongoing efforts toward the asymmetric synthesis of 3, 3’-biflavanones,[7] we have focused on the study of 4-chromanone, exclusively. In addition, we have reported the cyclopropenes of 3-diazochroman-4-one with phenylacetylene catalyzed by Rhodium (II) catalyst in good yield.[8] When we changed phenylacetylene to styrene at higher temperature, instead of expected cyclopropane product,[9] a new compound with spiro cyclobutanone motif as spiro[2,2-dimethyl-benzofuran, bicyclo[4.2.0]octane]-7’-one (Scheme 1, b, **3aa**) was obtained, and its structure was confirmed by single-



Scheme 2. The synthesis of the cyclobutanone.

crystal X-ray diffraction. Cyclobutanone, as the core structure of 6-oxa- spiro[3.4]octan-1-one, has been found in natural products and biologically active compounds.[10] The general methodologies to synthesize cyclobutanone were summarized in Scheme 2, (a), (b).[11] Staudinger [2+2] cycloaddition of ketenes with alkenes, offers a general method to an array of cyclobutanones and β-lactams.[12] Ketene, derived from 3-diazochroman-4-one, has a unique structure with more ring strain and has not been utilized as a substrate for [2+2] cycloaddition to synthesize fused and spirocyclic ring systems.

Herein, we reported the one-pot synthesis of fused and spirocyclic oxygen-containing cyclobutanone derivatives (**3aa** analogues), containing 6-oxa-spiro[3.4]octan-1-one as core skeleton based on 3-diazochroman-4-one and alkene (Scheme 2). Also, 1, 7-dioxa-spiro [4.4] nonan-2-one frameworks(**5**), which is a key intermediate in the synthesis of the nature product,[13] were obtained by the Baeyer-Villiger oxidation of the 6-oxa-spiro [3.4] octan-1-one(**3**). There are a number of known compounds which contain 1, 7-dioxa-spiro [4.4] nonan-2-one frameworks (Scheme 1, a). These two types of products contain a notable fused and spirocyclic oxygen-containing rigid skeleton structure are reported in this article.

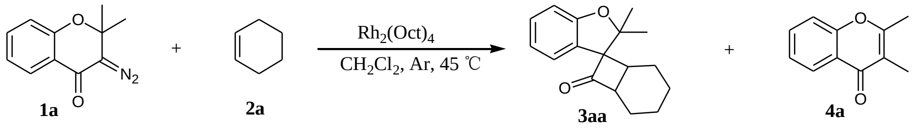
On the basis of the initial results, a number of different catalysts, solvents, and operating procedures were tested to optimize the reaction conditions (Table 1).

The thermal reactions of 3-diazochroman-4-one with cyclohexene were conducted at 110 ℃ according to standard Wolff condition (Table 1, entry 1), but the Wolff rearrangement did not occur as expected. The controlled experiment indicates the catalyst was necessary. Different catalysts were screened, Rhodium(II) could catalyze the reaction, other transition-mental catalysts, such as $Cu(OTf)_2$, $Cu_2(OAc)_4$, $Mn(OAc)_4$, $Zn(OAc)_4$, $Pd(OAc)_4$ could not proceed the reaction (Table 1, entry 2-6). When $Rh_2(OAc)_4$ and $Rh_2(Oct)_4$ were used as catalysts (Table 1, entry 7-15), it was observed that the temperature played an important role. At -20 ℃, 0 ℃, and 25 ℃, only 1, 2-shift product was detected with no product (**3**). Different solvents were screened. In CH_2Cl_2, at 45 ℃, the highest yield of **3aa** and the lowest 1, 2-shift product **4a** were obtained.[14] After sequential experiments, the reaction of **1** and **2** using $Rh_2(Oct)_4$ (0.1mol %) as a catalyst in CH_2Cl_2 (15 ml) at 45 ℃ afforded the expected **3aa** in 85% yield (Table 1, entry 7). In order to prevent the 1, 2-shift products, diazo **1** was dissolved in CH_2Cl_2 and was added to reaction system by slow addition through a syringe pump.

With the optimal reaction conditions in hand (Table 1, entry 7), the substrate scope was examined. First, the scope of diazo compounds **1** was tested (Scheme 3). When R^2 and R^3 both were small groups, the reaction had 85% and 80% yields (Scheme 3, **3aa** and **3ba**). Sterically hindered group decreased the yield (Scheme 3, such as **3ca**, **3ea,** and **3fa**). When R^2 and R^3 were different groups, a mixture of two kinds of conformational isomers was obtained (Scheme 3, **3ba**). Substrates **1d** and **1g** mainly underwent 1, 2-shift rearrangement to generate product **4** analogues, so **3da** and **3ga** were obtained in trace quantities. This result was consistent with our previous experiment.[8] When R^1 was an electron-donating group, higher yields were obtained (Scheme 3, such as **3ia**, and **3ka**). When R^1 was an electron-withdrawing group, the yields dropped (Scheme 3, such as **3la**, **3ma** and **3na**). As for the steric effect: when the adjacent position of benzene ring had a substituent, it would block the reaction (Scheme 3, **3ja**).

Next, the scope of alkene **2** was examined (Scheme 4). Various types of alkenes, including cycloalkenes, straight chain olefins, pyranoids and furans, were well tolerated. For cyclic olefins and straight chain olefins, good yields and stereo

Table 1. Optimization for the reaction conditions. a)

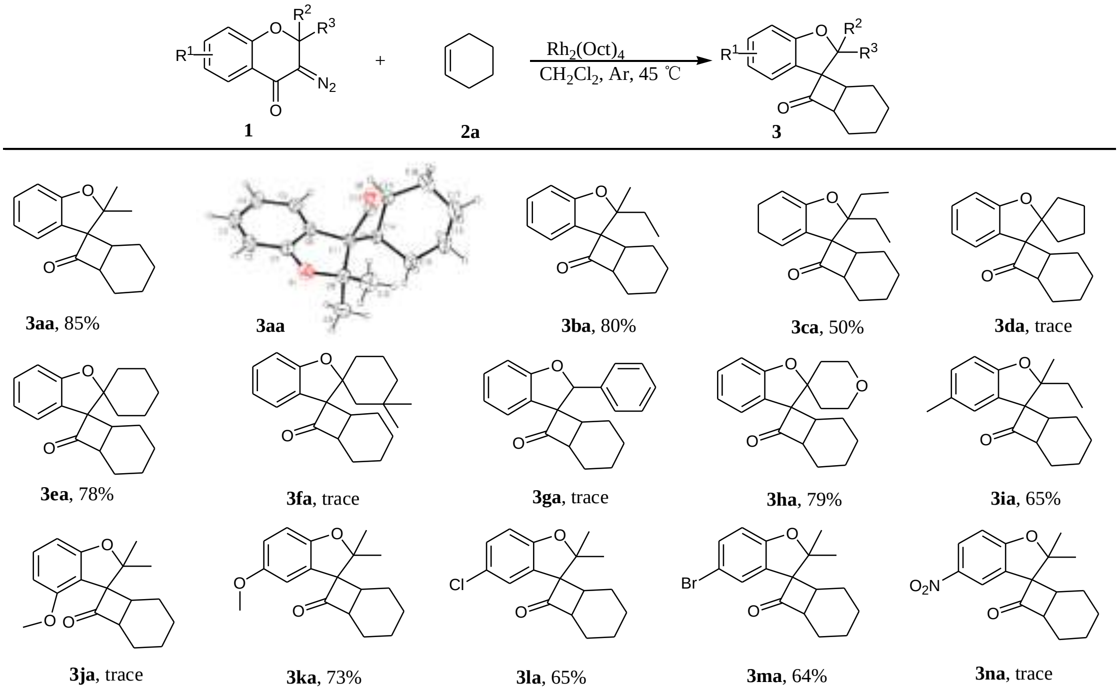


Entry	Catalyst	Solvent	Temp (℃)	3aa b) (%)	4a b) (%)
1	-	DMSO	110	-	30
2	$Cu(OTf)_2$	CH_2Cl_2	45	-	10
3	$Cu_2(OAc)_4$	CH_2Cl_2	45	-	10
4	$Mn(OAc)_4$	CH_2Cl_2	45	-	10
5	$Zn(OAc)_4$	CH_2Cl_2	45	-	10
6	$Pd(OAc)_4$	CH_2Cl_2	45	-	1
7	$Rh_2(Oct)_4$	CH_2Cl_2	45	85	5
8	$Rh_2(OAc)_4$	CH_2Cl_2	45	83	5
9	$Rh_2(Oct)_4$	CCl_4	-20	-	5
10	$Rh_2(Oct)_4$	$ClCH_2CH_2Cl$	80	8	40
11	$Rh_2(Oct)_4$	$ClCH_2CH_2Cl$	45	39	20
12	$Rh_2(Oct)_4$	*n*-hexane	45	47	25
13	$Rh_2(Oct)_4$	*n*-hexane	65	10	20
14	$Rh_2(Oct)_4$	CH_2Cl_2	-20	-	10
15	$Rh_2(Oct)_4$	CH_2Cl_2	0	-	15

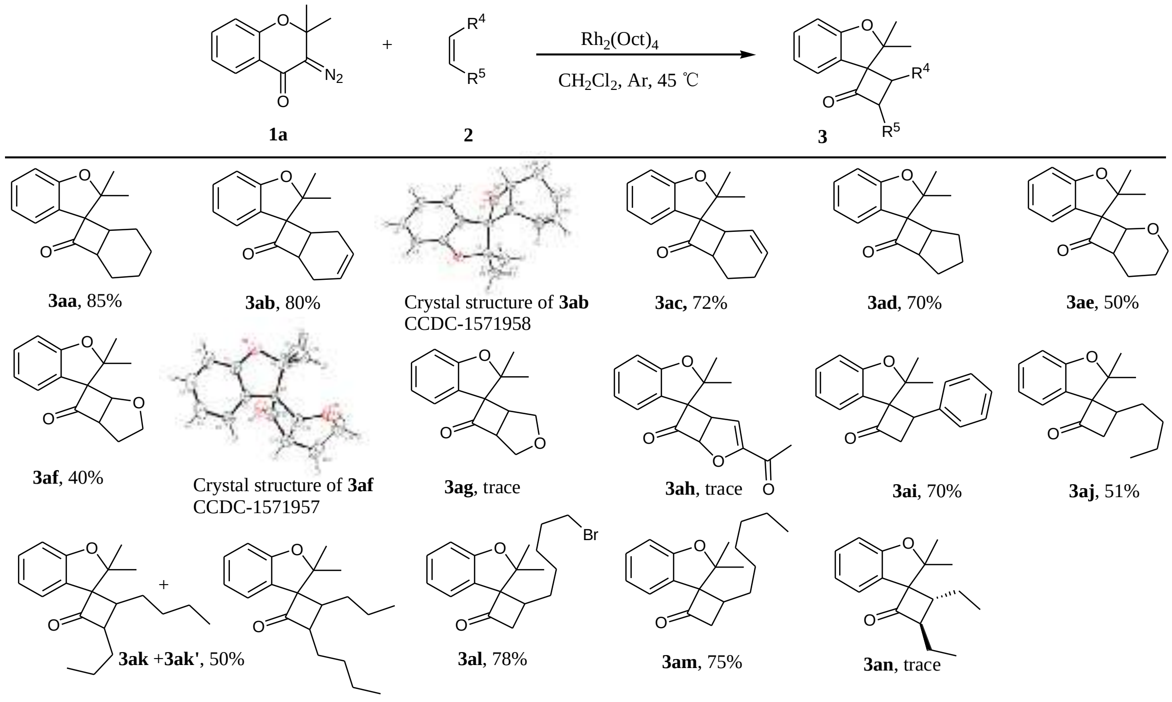
a) Reaction conditions: the reaction was carried out using **1** (1 mmol), **2** (5 mmol), and catalyst (0.1 mmol %) in the solvent (15 ml) under Ar protection.

b) Isolated yields.

selectivities were obtained (Scheme 4, **3aa-3ad**). Also, oxygen heterocyclic compounds also gave a moderate yield (Scheme 4, **3ae** and **3af**). Steric-hindrance effect and electron effect played an equally important role. The configuration of the alkene constituent was conserved in the cyclobutanone products. Di-substituted alkenes got acceptable yields (Scheme 4, **3aj**, **3ak**). When the size of two substitutes of cis olefin have no obvious differences, a mixture of two isomers was obtained (Scheme 4, **3ak** and **3ak'**). Tri-substituted alkenes groups could not react with diazo **1a** attribute to steric hindrance effect. The diastereoselectivity regulation was depended on the ketene substituents obviously. Z-alkenes were more



Scheme 3. Substrate scope of **1**.

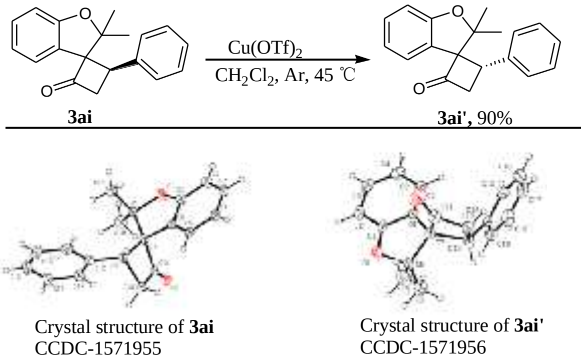


Scheme 4. Substrate scope of **2**.

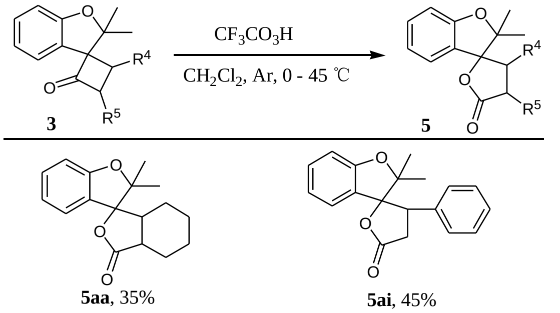
favorable over E-alkenes (Scheme 4, **3an**).[15]

Furthermore, Cu(OTf)$_2$ was able to reverse the diastereoselectivity for the reactions involving styrene. Product **3ai** was converted to its diastereoisomer **3ai'** in the presence of Cu(OTf)$_2$ in CH_2Cl_2 at 45 ℃ under an Ar atmosphere (Scheme 5).[16]

3aa and **3ai** were chosen as model substrates to explore the oxidation of cyclobutanone motif to γ-butyrolactone using CF_3CO_3H as an oxidant, the 6-oxa-spiro [3.4] octan-1-one could be transformed into the 1,7-dioxa-spiro [4.4] nonan-2-one scaffold (Scheme 6).



Scheme 5. The conversion of **3ai.**



Scheme 6. Baeyer-Villiger reaction of product **3**.

A plausible mechanism for this Wolff rearrangement and cycloaddition reaction is proposed in Figure 1. The reaction was presumably initiated by loss of nitrogen gas from **1** in the presence of Rh (II) forming benzofuran ketene intermediate through Wolff rearrangement, then captured by an alkene through [2+2] cycloaddition to give 6-oxa-spiro [3.4] octan-1-one.[17] This cycloaddition proceeded with regio-, stereo-, and often chemoselectivity, as a result of the orbital-controlled transformation in a concerted asynchronous mechanism.[18] Configuration is dependent on the ketene substituents.

In summary, we have developed a one-pot synthesis of 6-oxa-spiro [3.4] octan-1-one, an important core skeleton in spiro[2,2-dimethyl-

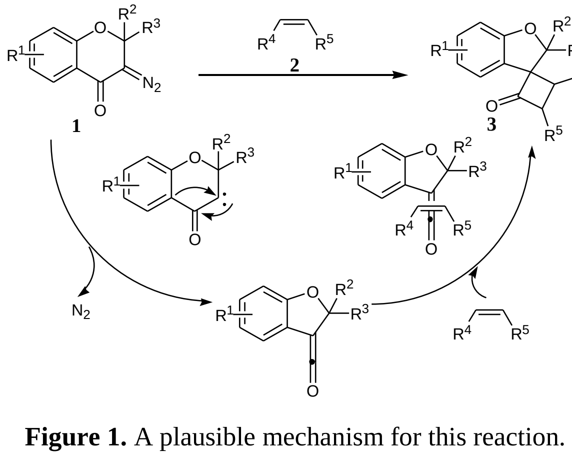


Figure 1. A plausible mechanism for this reaction.

benzofuran,bicyclo[4.2.0]octane]-7'-one based on 3-diazochroman-4-one and alkene. The process involved Rh (II)-catalyzed Wolff rearrangement/ [2+2] cycloaddition reaction. Also, the 1,7-dioxa-spiro[4.4]nonan-2-one motif, a crucial intermediate in the synthesis of the nature product, was procured through the Baeyer-Villiger oxidation of the 6-oxa-spiro[3.4]octan-1-one. These two kinds of products possess a special fused and spiro cyclic oxygen-containing rigid skeleton structure are reported in this article. A series of 3-diazochroman-4-one and alkene were evaluated and corresponding products were obtained in moderate to good yields. Considering its broad substrate scope and good functional group compatibility, this protocol may provide broad applications in organic synthesis.

Experimental Section

Typical Procedure for the Preparation of 3

Under an argon atmosphere, **1** (1 mmol, 1.0 equiv) in 15ml of CH_2Cl_2 was added slowly to a solution with stirring, of **2** (5 mmol, 5.0 equiv) and $Rh_2(Oct)_4$ (0.1 mol %) in CH_2Cl_2 (5 ml) at 45 ℃ over 15 h by syringe pump. The reaction was monitored by TLC. The reaction mixture was extracted three times with EtOAc and water. The combined organic layer was washed with saturated aqueous brine and dried over $MgSO_4$. The filtrate was then filtered and concentrated in vacuo. Further purification by a short silica gel column using petroleum ether (Ⅱ, 60-90 ℃) / EtOAc as eluent gave the corresponding product **3**. Some unique product of **3** requires separation with methylbenzene such as **3ba**, **3la**, **3ma**.

Typical Procedure for the Preparation of 5

To a 100 ml round-bottom bottle installed with an anhydrous calcium chloride tube condenser, 10 ml CH_2Cl_2 and 50% of H_2O_2 (2 ml, 20 mmol, 20.0 equiv) was added. Then trifluoroacetic acid anhydride (3.4 ml, 20 mmol, 20.0 equiv) was added into stirring solution, dropwise in 5 minutes in an ice/water bath. After 1 hour, the solution reached ambient temperature, **3** (1 mmol, 1.0 equiv) in 5 ml of CH_2Cl_2 was added to this mixture and refluxed for 1 hour. The reaction was monitored by TLC. Then the reaction mixture was extracted three times with CH_2Cl_2 and $NaHCO_3$ (10%), the combined organic layer was washed with saturated aqueous brine and dried over $MgSO_4$. The filtrate was then filtered and concentrated in vacuo. Further purification by a short silica gel column using petroleum ether (Ⅱ, 60-90 ℃) / EtOAc as eluent gave the corresponding product **5**. **5ai** needed to be separated by methylbenzene.

Supporting Information

Detailed descriptions of experimental procedures and their spectroscopic data, as well as the crystal structures, are presented in the Supporting Information. CCDC-1571954 (**3aa**), CCDC-1571955 (**3ai**), CCDC-1571956 (**3ai'**), CCDC-1571957 (**3af**) and CCDC-1571958 (**3ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Financial support by the National Natural Science Foundation of China (grant no 21572084, 21172098) and the Natural Science Foundation Program of Gansu Province (1506RJZA224). We thank Ms. Zheng min for her kind assistance and thank Mr. Paxtyn M. Fisher for English writing revision.

References

[1] a) B. M. Trost, D. A. Bringley, T. Zhang, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 16720-16735; b) D. J. Atkinson, D. P. Furkert, M. A. Brimble, *Tetrahedron* **2015**, *71*, 91-101; c) R. S. Coleman, J. M. Guernon, J. T. Roland, *Org. Lett.* **2000**, *2*, 277-280.

[2] a) P. Mykhailiuk, A. Kirichok, I. S. Iryna Shton, M. Kliachyna, I. Pishel, *Angew. Chem. Int. Ed.* **2017**, *56*, 8865-8869; b) B. J. Nie, L. H. Wu, R. F. Hu, Y. Sun, J. Wu, P. He, N. Y. Huang, *Synth. Commun.* **2017**, *47*, 1368-1374.

[3] a) Q. Yuan, C. W. Wang, J. Shi, Z. X. Lin, *J. Ethnopharmacol.* **2017**, *195*, 1-9; b) T. A. v. Beek, *J. Chromatogr. A* **2002**, *967*, 21-55; c) B. P. Le, M. M. Katz, N. Berman, T. M. Itil, A. M. Freedman, A. F. Schatzberg, *Jama* **1997**, *278*, 1327-1332.

[4] a) E. J. Corey, G. S. Wei, *J. Am. Chem. Soc.* **1987**, *109*, 7534-7536; b) M. T. Crimmins, D. K. Jung, J. L. Gray, *J. Am. Chem. Soc.* **1992**, *114*, 5445-5447; c) E. L. Chang, B. Bolte, L. Ping, A. C. Willis, M. G. Banwell, *J. Org. Chem.* **2016**, *81*, 2078-2086.

[5] a) E. J. Corey, M. C. Kang, *J. Am. Chem. Soc.* **1984**, *106*, 5384-5385 ; b) J. R. Dias, R. Ramachandra, *J. Org. Chem.* **1977**, *42*, 3584-3588; c) A. C. Albertsson, I. K. Varma, *Biomacromolecules* **2003**, *4*, 1466-1486.

[6] a) H. J. Kabbe, A. Widdig, *Angew. Chem. Int. Edit.* **2010**, *21*, 247-256; b) T. Ishikawa, Y. Oku, T. Tanaka, T. Kumamoto, *Tetrahedron Lett* **1999**, *40*, 3777-3780.

[7] W. D. Li, B. C. Ma, *Org. Lett.* **2005**, *36*, 271-274.

[8] J. Gong, Z. Zhao, F. Zhang, S. Wu, G. Yan, Y. Quan, B. Ma, *Org. Lett.* **2014**, *16*, 5524-5527.

[9] a) T. Sawada, M. Nakada, *Adv. Synth. Catal.* **2010**, *347*, 1527-1532; b) H. M. L. Davies, L. M. Hodges, *J. Org. Chem.* **2003**, *34*, 5683-5689; c) P. E. O'Bannon, W. P. Dailey, *J. Org. Chem.* **1989**, *54*, 3101-3105.

[10] a) T. P. Yoon, *ACS Catal.* **2013**, *3*, 895-902; b) V. M. Dembitsky, *Phytomedicine* **2014**, *21*, 1559-1581; c) B. M. Trost, P. H. Scudder, *J. Am. Chem. Soc.* **1977**, *99*, 7601-7610.

[11] a) C. M. Rasik, Y. J. Hong, D. J. Tantillo, M. K. Brown, *Org. Lett.* **2014**, *16*, 5168-5171; b) Y. Deng, L. A. Massey, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2017**, *56*, 7479-7483.

[12] a) M. R. Linder, J. Podlech, *Org. Lett.* **2001**, *3*, 1849-1851; b) Y. Q. Shi, L. D. Liao, P. He, Y. G. Hu, H. Cheng, S. Wang, J. J. Wu, *Synth. Commun.* **2016**, *46*, 1357-1363.

[13] a) S. Diethelm, C. S. Schindler, E. M. Carreira, *Org. Lett.* **2010**, *12*, 3950-3953; b) K. Ramakrishna, K. Kaliappan, *Synlett* **2011**, *2011*, 2580-2584.

[14] a) T. Ye, M. A. Mckervey, *Tetrahedron* **1992**, *48*, 8007-8022; b) S. H. Shin, D. Cizmeciyan, A. E. Keating, a. Saeed I. Khan, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **1997**, *119*, 1859-1868; c) K. Motschiedler, A. Gudmundsdottir, J. P. Toscano, M. Platz, M. A. Garcia-Garibay, *J. Org. Chem.* **1999**, *64*, 5139-5147.

[15] a) H. Staudinger, *Eur. J. Inorg. Chem.* **1905**, *38*, 1735-1739; b) S. Kitagaki, M. Anada, Osamu Kataoka, K. Matsuno, C. Umeda, A. Nobuhide Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417-1418; c) D. M. Hodgson, R. Glen, G. H. Grant, A. J. Redgrave, *Cheminform* **2003**, *68*, 581-586; d) H. Tsutsui, N. Shimada, T. Abe, M. Anada, M. Nakajima, S. Nakamura, H. Nambu, S. Hashimoto, *Adv. Synth. Catal.* **2007**, *349*, 521-526.

[16] CCDC-1571954 (**3aa**), CCDC-1571955 (**3ai**), CCDC-1571956 (**3ai'**), CCDC-1571957 (**3af**) and CCDC-1571958 (**3ab**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. The single crystal X-ray structures of **3aa, 3ai, 3ai', 3af** and **3ab** are included in the supporting information.

[17] a) I. G. Csizmadia, J. Font, O. P. Strausz, *J. Am. Chem. Soc.* **2002**, *90*, 1768-1769; b) S. Snyder, E. Corey, *J. Am. Chem. Soc* **2006**, *128*, 740-742; c) J. Deng, S. Zhou, W. Zhang, J. Li, R. Li, A. Li, *J. Am. Chem. Soc* **2014**, *136*, 8185-8188.

[18] J. Galvez, J. C. Castillo, J. Quiroga, M. Rajzmann, J. Rodriguez, Y. Coquerel, *Org. lett.* **2014**, *16*, 4126-4129.

COMMUNICATION

An efficient synthesis of 6-oxa-spiro[3.4]octan-1-one derivates through 3-diazochroman-4-one and alkene

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Meiling Xiao [a], Fuming Zhang [a], Zhe Du [a], Baochun Ma [a,*]