DOI: 10.1002/adsc.202001311

Advanced Synthesis & Catalysis

Pauson-Khand Reactions with Concomitant C–O Bond Cleavage for the Preparation of 5,5- 5,6- and 5,7-Bicyclic Ring Systems

Ding Ma,[a] Naifeng Hu,[a] Junli Ao,[a, b] Shaoli Zang,[a, b] Guo Yu,[b] and Guangxin Liang[b,*]

[a] State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China
[b] School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, People's Republic of China
E-mail: lianggx@shanghaitech.edu.cn

Manuscript received: October 24, 2020; Revised manuscript received: January 25, 2021;
Version of record online: Februar 16, 2021

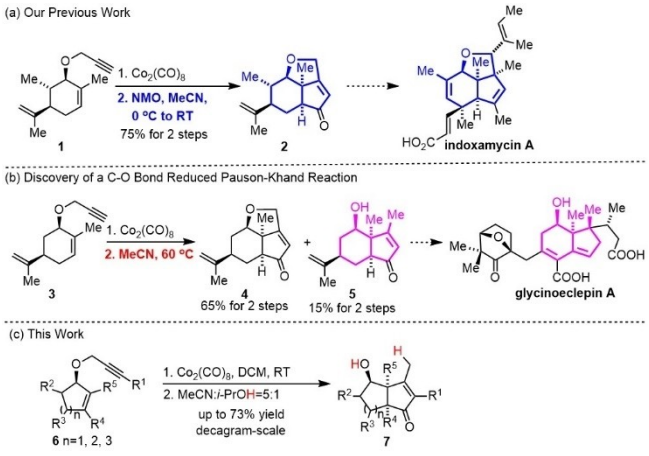
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001311

Abstract: Pauson-Khand reactions (PKR) with concomitant C–O bond cleavage have been developed for construction of 5,5- 5,6- and 5,7-bicyclic ring systems bearing complex stereochemistry. The chemistry generates intermolecular PKR-type products in an absolute regio- and stereochemical control which is hardly achievable through real intermolecular Pauson-Khand reactions. A mechanism for this Pauson-Khand reaction has been proposed based on deuterium labelling experiments.

Keywords: Pauson-Khand reaction; cyclopentenone; cobalt catalysis; C–O bond cleavage; bicyclo-carbocycles

The cobalt-mediated Pauson-Khand reaction (PKR) is an efficient, atom-economical[1] and conventional reaction for preparing densely functionalized cyclopentenone derivatives that are present in numerous bioactive molecules.[2] The PKR has been actively investigated since Khand and Pauson's first report in 1973.[3] Due to the difficulty in controlling the regio- and stereoselectivity in intermolecular reactions, intramolecular versions of Pauson-Khand reactions are much more widely used and frequently applied to the synthesis of complex natural products.[4] In our previous total synthesis of indoxamycin A,[5] we also demonstrated an efficient intramolecular Pauson-Khand reaction as a key strategy for the rapid construction of the 5,5,6-tricyclic ring system in the target molecule (Scheme 1a). Encouraged by this previous work, we initiated a new project aiming for the total synthesis of glycinoeclepin A[6] employing a very similar Pauson-Khand reaction in an early stage. Originally, we planned to reductively break the C–O bond of the product **4** in a subsequent step to access **5** in order to prepare the core of our target. However, to our surprise, **5** was generated directly as a minor product in a reaction without using NMO as an additive (Scheme 1b). Obviously, the C–O bond was cleaved during the reaction to yield an intermolecular PKR-type product. Direct access to this highly synthetically valuable product and the appealing mechanism behind it encouraged us to further investigate this unusual reductive Pauson-Khand reaction.

In the literature, there are only a handful of reports on C–O bond cleaved Pauson-Khand reactions.[7] In rare reports of relevant cases to our finding, Smits and co-workers described reductive cleavage of C–O bonds during Pauson-Khand reactions when cobalt-alkyne complexes were heated in SiO_2.[7a–c] In 2002, Krafft

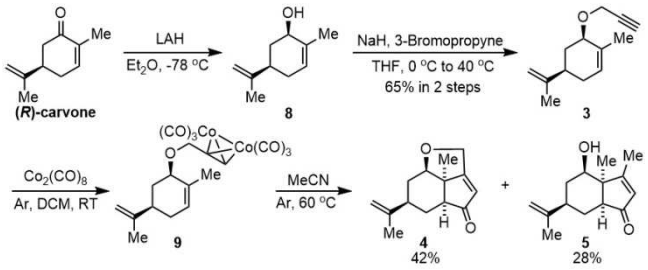


Scheme 1. The Discovery of a C–O Bond Cleaved Pauson-Khand Reaction.

and co-workers displayed a single example of a C–O bond cleaved product in 32% yield in their study on C–C double bond reduced Pauson-Khand reactions.[7g] Surprisingly, no comments or discussions was made on this unexpected interesting product. Silyl ether tethered enynes have also been reported to undergo C–O bond cleavage during Pauson-Khand reactions.[7h] Other C–O bond cleavage during Pauson-Khand reactions has been demonstrated in the use of vinyl esters as ethylene surrogates in PKR.[7e,f] Among numerous modifications and applications of the Pauson-Khand reaction over the past half century, this type of unusual C–O bond cleaved Pauson-Khand reactions have not drawn enough attention. Herein, we reported our development of this reaction into a general method for rapid construction of 5,5- 5,6- and 5,7-bicyclic ring systems. The resulting ring systems can bear multifarious stereochemical information, which are barely accessible via regular intermolecular Pauson-Khand reactions (Scheme 1c).

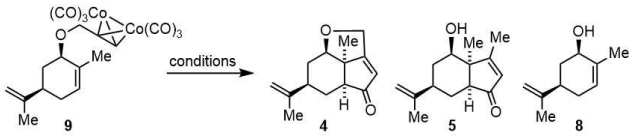
Our study started from repeating this Pauson-Khand reaction using a carefully confirmed cobalt-alkyne complex **9** which was derived from economic-friendly (*R*)-carvone (Scheme 2). The reduction of (*R*)-carvone with lithium aluminum hydride at −78 °C, followed by treatment of alcohol **8** with sodium hydride and 3-bromopropyne in THF, afforded alkyne **3** in 65% yield over two steps. The reaction of **3** with octacarbonyldicobalt (1.0 equiv.) in dichloromethane under argon atmosphere at room temperature provided cobalt-alkyne complex **9** which was purified by flash chromatography and characterized by NMR and IR spectroscopic analysis (see Supporting Information). When a solution of cobalt-alkyne complex **9** in MeCN was warmed to 60 °C under argon atmosphere, it produced the normal PKR product **4** in 42% yield along with the reductive PKR product **5** in 28% yield.

Based on the initial attempt, we further optimized the reaction conditions of solvent, reaction atmosphere, additive and temperature using purified cobalt-alkyne complex **9** as the substrate (Table 1). Comparison of 11 different solvents (Entries 1–11, Table 1) indicated that among the reaction media tested, MeCN (Entry 1) was the most effective for this reductive reaction process;



Scheme 2. Initial Attempt.

Table 1. Optimization of Reaction Conditions.



Entry	Solvents[a]	Atmosphere	Additives	Temp	Results
1	MeCN	Ar (1 atm)	–	60 °C	**4** (42%) **5** (28%)
2	PhCN	Ar (1 atm)	–	60 °C	**4** (45%) **5** (10%)
3	Toluene	Ar (1 atm)	–	60 °C	**4** (63%)
4	DMSO	Ar (1 atm)	–	60 °C	**4** (58%)
5	DMF	Ar (1 atm)	–	60 °C	**4** (45%)
6	DMAC	Ar (1 atm)	–	60 °C	**8** (65%)
7	Pyridine	Ar (1 atm)	–	60 °C	**8** (52%)
8	Acetone	Ar (1 atm)	–	60 °C	**8** (63%)
9	CH_3OH	Ar (1 atm)	–	60 °C	–
10	EtOH	Ar (1 atm)	–	60 °C	–
11	*i*-PrOH	Ar (1 atm)	–	60 °C	–
12	MeCN	CO (1 atm)	–	60 °C	**4** (45%) **5** (8%)
13	MeCN	CO (5 atm)	–	60 °C	**4** (52%)
14	MeCN	H_2 (1 atm)	–	60 °C	**4** (56%)
15	MeCN	H_2 (5 atm)	–	60 °C	**4** (52%)
16	MeCN	H_2 (5 atm) CO (5 atm)	–	60 °C	**4** (51%)
17	MeCN	Ar (1 atm)	H_2O[b]	60 °C	**4** (45%) **5** (15%)
18	MeCN	Ar (1 atm)	MeOH[b]	60 °C	**4** (55%) **5** (22%)
19	MeCN	Ar (1 atm)	EtOH[b]	60 °C	**4** (55%) **5** (20%)
20	MeCN	Ar (1 atm)	*i*-PrOH[b]	60 °C	**4** (15%) **5** (41%)
21	MeCN	Ar (1 atm)	*i*-PrOH[c]	60 °C	**4** (8%) **5** (51%)
22	MeCN	Ar (1 atm)	*i*-PrOH[c]	50 °C	**4** (5%) **5** (56%)
23	MeCN	Ar (1 atm)	*i*-PrOH[c]	40 °C	**4** (38%) **5** (15%)

[a] Reaction concentration: 0.1 mM.
[b] 10 equiv.
[c] MeCN:*i*-PrOH = 5:1; reaction concentration: 0.05 mM.

PhCN was another solvent in which C–O bond cleaved PKR product was observed, though with less ideal chemo-selectivity and yield (Entry 2); reactions in toluene, DMSO, and DMF (Entries 3–5) only produced the normal PKR product **4**; reactions in DMAC, pyridine, and acetone (Entry 6–8) only yielded the depropargylated product **8**; no reactions were observed in alcoholic solvents (Entries 9–11). Next, reactions in MeCN under different atmosphere (Entries 12–16) were tested. CO atmosphere generally suppressed the production of the C–O bond cleaved product **5** (Entry 12); Elevating the pressure of CO to 5 atm

completely shut down the production of **5**, with only the normal PKR product **4** observed (Entry 13); Meanwhile, H_2 atmosphere also suppressed the production of **5**; Reactions under either pure H_2 atmosphere or H_2/CO atmosphere only produced the normal PKR product **4** (Table 1, Entries 14–16).

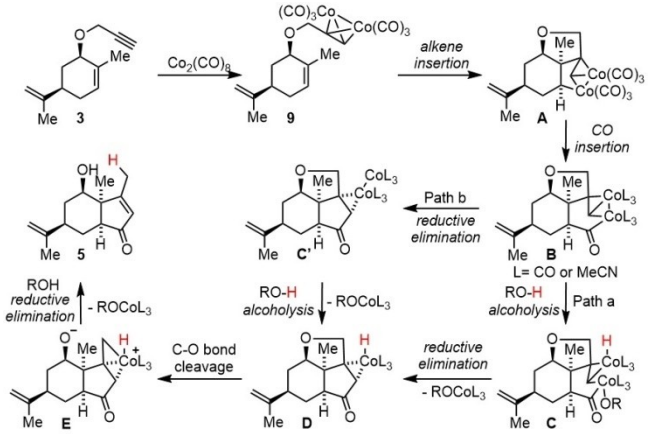
In the search of the best additives for the reductive cleavage of the C–O bond, we found that water or alcoholic solvents (Entries 17–20) were able to promote the C–O bond cleavage to generate **5**. It is interesting to note that both chemoselectivity and yield of **5** were significantly improved when isopropanol was used as an additive (Table 1, Entry 20). The yield of the desired product **5** was further increased when more *i*-PrOH (MeCN: *i*-PrOH = 5:1) was used in the reaction (Entry 21). Finally, the yield of **5** reached 56% when the reaction was performed at both a lower concentration (0.05 M) and a lower temperature (50 °C).

With the optimized reaction conditions in hand, we further investigated the substrate scope of the C–O bond cleaved PKR (Table 2). It turned out that the reaction was highly substrate-dependent. The substitution pattern and stereochemistry had a vital influence on the outcome of the reactions. Substrates **6a–c** afforded the C–O bond cleaved PKR products **7a–c** in 38–58% yields; while substrate **6d** and **6e** only produced the normal PKR product **7d** and **7e**. Substrate **6f**, the diastereoisomer of our primary substrate **3**, failed to undergo PKR and yielded a depropargylated product **epi-8** instead. This result illustrated the crucial contribution of the substrate configuration to the reaction. Besides syntheses of the above 5,6-carbocycles, 5,7-carbocycle **7g** could also be generated from substrate **6g** in 37% yield using this chemistry. Although the yield was not ideal, this reaction holds a great advantage for preparing such a synthetic challenging compound from a simple substrate **6g**. To our further delight, the C–O bond cleaved PKR was generally successful with cyclopentene substrates. Substrates **6h–m**, which contained various substitution patterns, all produced the corresponding 5,5-carbocycles in modest to good yields. Notably, the reaction of **6h**, which was carried out on a 5 g scale, achieved 73% yield. Again, the influence of stereochemistry of the substrate was observed. Although very similar to **6h** structurally, substrate **6n** only afforded depropargylated product **10** under our optimized reaction conditions.

To acquire more insights into the mechanism of this interesting reaction, we first tried to clarify the hydrogen source in this reductive process. Given the best performance of alcoholic additives in our optimization experiment, they were speculated to be the hydrogen source. To verify this assumption, we conducted a deuterium labelling experiment using various commercially available *d*-methanol as an additive (Table 3). Gratifyingly, the expected deuterated product **11** (Entry 1) was obtained with the addition of CD_3OD in the reaction mixture. Then two additional deuterium labelling conditions (Entries 2–3) were devised to determine whether the deuterium in the product **11** was stemmed from the methyl group or the hydroxyl group of the methanol. The results clearly indicated that hydrogen originated from the alkanol proton of the methanol. Meanwhile, considering that the association of the deuterium in **11** could either occur during the reaction or after it was quenched by proton sources, we also added CH_3OD after the disappearance of cobalt-alkyne complex **9** (Entry 4). No association of deuterium in the product indicated that the reductive cleavage of C–O bond took place during the reaction.

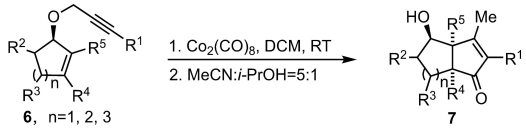
Based on the widely recognized Pauson-Khand reaction mechanism[8] and the deuterium labelling experiment, a plausible reaction mechanism for the C–O bond cleaved Pauson-Khand reaction was proposed (Scheme 3).

Taking substrate **3** as an example, we assumed that cobalt-alkyne complex **9** went through a well-accepted mechanism to convert to intermediate **B** via **A**. Given that Lewis base can accelerate the alcoholysis of carbonyl cobalt,[9] we speculated that MeCN might serve as a Lewis base to promote the alcoholysis of intermediate **B**, which breaks the Co–Co bond to form the cobalt-hydrogen species **C**. Subsequently, reductive elimination of carbonyl cobalt complex in **C** could furnish an intermediate **D** (Path a). Alternatively, the intermediate **B** could go through the same path in a regular Pauson-Khand reaction to reach intermediate **C'**. **C'** was then converted to the intermediate **D** through alcoholysis (Path b). We speculated that electrons on Co in the intermediate **D** could fill in the antibonding orbital of C–O bond to promote the heterolysis of C–O bond. Finally, the resulting intermediate **E** produces the C–O bond cleaved PKR



Scheme 3. A Proposed Reaction Mechanism.

Table 2. Reaction Scope of the C–O Bond Cleaved PKRs.[a]



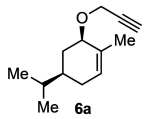
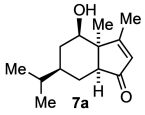
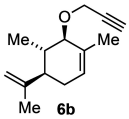
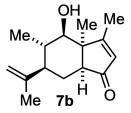
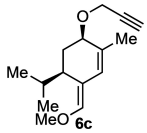
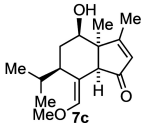
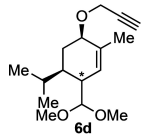
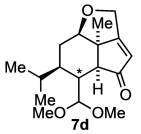
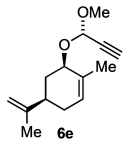
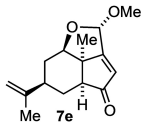
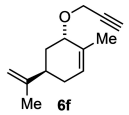
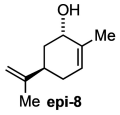
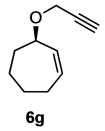
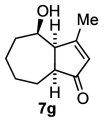
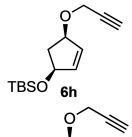
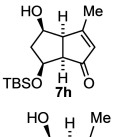
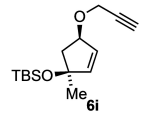
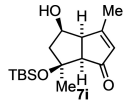
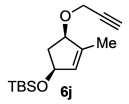
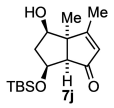
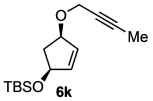
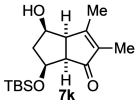
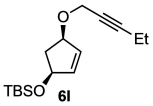
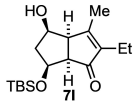
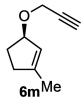
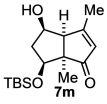
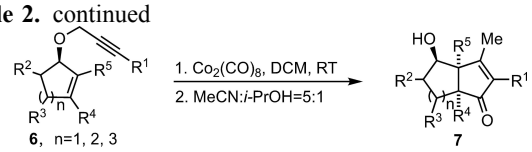
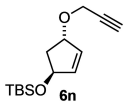
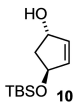
Substrates	Products	Yield[b]
 **6a**	 **7a**	58%
 **6b**	 **7b**	38%
 **6c**	 **7c**	45%
 **6d**	 **7d**	52%[c]
 **6e**	 **7e**	53%
 **6f**	 **epi-8**	69%
 **6g**	 **7g**	37%
 **6h**	 **7h**	73%[d]
 **6i**	 **7i**	48%
 **6j**	 **7j**	54%
 **6k**	 **7k**	49%
 **6l**	 **7l**	54%
 **6m**	 **7m**	55%

Table 2. continued



Substrates	Products	Yield[b]
 **6n**	 **10**	65%

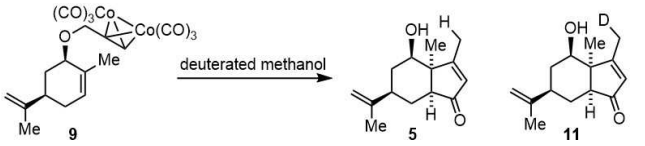
[a] Treatment of **6** (0.1–1.0 mmol) with octacarbonyldicobalt (1.0 equiv.) in dichloromethane (0.2 M) under argon atmosphere at room temperature provided cobalt-alkyne complex which was purified by flash chromatography. The solution of cobalt-alkyne complex in the mixed solvents (MeCN:*i*-PrOH = 5:1; 0.05 mM) was warmed to 50 °C (**6a–6f**) or 60 °C (**6g–6n**) under argon atmosphere to produce **7**.

[b] Isolated yield for two steps.

[c] Both substrate and product are a pair of inseparable diastereomers with a ratio of 3:2.

[d] Performed on 5.1 g (20.2 mmol) scale.

Table 3. Pauson-Khand Reactions in Deuterated Methanol.



Entry	*d*-Methanol	Results
1	CD_3OD[a]	**11** (> 90% deuteration)
2	CD_3OH[a]	**5**
3	CH_3OD[a]	**11** (> 90% deuteration)
4	CH_3OD[b]	**5**

[a] The solution of cobalt-alkyne complex **9** (0.05 mM) in a mixed solvent (MeCN:*d*-methanol = 5:1) was heated at 50 °C under argon atmosphere.

[b] The solution of cobalt-alkyne complex **9** in MeCN (0.05 mM) was heated at 50 °C under argon atmosphere; *d*-methanol was added after disappearance of cobalt-alkyne complex **9**.

product **5** through reductive elimination and ligand dissociation of the cobalt species.

In conclusion, we have discovered a C–O bond cleaved Pauson-Khand reaction and further developed it into a generic and efficient method for rapid construction of complex 5,5- 5,6- and 5,7-bicyclic ring systems bearing rich stereochemical information. These types of products are particularly difficult to access through regular intermolecular Pauson-Khand reactions. Deuterium labelling experiment revealed that the hydrogen was provided by the proton in an alcoholic solvent. Accordingly, a plausible mechanism of the reaction was proposed. Taken together, our

chemistry could serve as a solution to reach challenging intermolecular PKR type products using C–O bond as a temporary tether, which could inspire new applcations of Pauson-Khand reactions in the synthesis of complex molecules.

Experimental Section

Representative reaction procedure: The solution of **6h** (5.10 g, 20.24 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at 0 °C was added $Co_2(CO)_8$ (6.92 g, 20.24 mmol, 1.0 equiv.) in one portion under argon. After stirring for 30 min at the same temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EA = 100/1) to afford crude cobalt-alkyne complex as a brown oil. A solution of crude cobalt-alkyne complex in MeCN:*i*-PrOH = 5:1 (400 mL) was warmed to 60 °C under argon. After stirring for 5 h at 60 °C, the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EA = 20/1) to afford product **7h** (4.18 g, 14.81 mmol, 73% in two steps) as colorless oil.

Acknowledgements

We thank the National Key Research and Development Program of China (2017YFD0201404) and the National Natural Science Foundation of China (21772097, 21971122) for financial support.

References

[1] B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2] For selected reviews, see: a) S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.* **2016**, *116*, 5744–5893; b) D. J. Aitken, H. Eijsberg, A. Frongia, J. Ollivier, P. P. Piras, *Synthesis* **2013**, *46*, 1–24; c) K. Narasaka, T. Shibata, *Chem. Lett.* **1994**, *4*, 315–320; d) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2004**, 3377–3383.

[3] a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, *J. Chem. Soc. Perkin Trans. 1* **1973**, 975–977; b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977–981; c) *The Pauson-Khand Reaction; Scope, Variation and Applications*, R. R. Torres, Ed., Wiley: Chichester, **2012**; d) "Recent Advances in the Pauson-Khand Reaction", D. M. Lindsay, W. J. Kerr, in Cobalt Catalysis in *Organic Synthesis: Methods and Reactions*, M. Hapke, G. Hilt, Eds., Wiley-VCH: Weinheim, **2020**, Chapter 8, pp 259–285; e) I. Omae, *Appl. Organomet. Chem.* **2007**, *21*, 318–344; f) J. Blanco-Urgoiti, L. Añorbe, L. Pérez-Serrano, G. Dominguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32–42; g) K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263–3283; h) Y. K. Chung, *Coord. Chem. Rev.* **1999**, *188*, 297–341; i) N. E. Schore, *Org. React.* **1991**, *40*, 1–90; j) N. E. Schore, In *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, **1991**, vol. 5, pp1037–1064; k) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.

[4] For selected application of Pauson-Khand reaction in total synthesis: a) T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363; b) S. Min, S.-J. Danishefsky, *Angew. Chem. Int. Ed.* **2007**, *46*, 2199–2202; c) L. You, X.-T. Liang, L.-M. Xu, Y.-F. Wang, J.-J. Zhang, Q. Su, Y.-H. Li, B. Zhang, S.-L. Yang, J.-H. Chen, Z. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 10120–10123; d) A. Cabré, H. Khaizourane, M. Garçon, X. Verdaguer, A. Riera, *Org. Lett.* **2018**, *20*, 3953–3957; e) A. Vázquez-Romero, L. Cárdenas, E. Blasi, X. Verdaguer, A. Riera, *Org. Lett.* **2009**, *11*, 14, 3104–3107; f) V. Bernardes, N. Kann, A. Riera, A. Moyano, M. A. Pericas, A. E. Greene, *J. Org. Chem.* **1995**, *60*, 6670–6671.

[5] a) N. Hu, C. Dong, C. Zhang, G. Liang, *Angew. Chem. Int. Ed.* **2019**, *58*, 6659–6662; b) N. Hu, *Total Syntheses of (−)-Indoxamycin A and B*, Univ. Nankai, **2018**.

[6] a) T. Masamune, M. Anetai, M. Takasugi, N. Katsui, *Nature* **1982**, *297*, 495–496; b) T. Masamune, A. Fukuzawa, A. Furusaki, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001–1004.

[7] a) W. A. Smit, S. O. Simonyan, A. S. Shashkov, *Aka. nauk SSSR. Izve. Ser. Khim.* **1987**, 234–236; b) W. A. Smit, S. O. Simonyan, V. A. Tarasov, G. S. Mikaeclian, A. S. Gybin, I. I. Ibragimov, R. Caple, D. Froen, A. Kreager, *Synthesis* **1989**, 472–476; c) S. O. Simonian, W. A. Smit, A. S. Gybin, A. S. Shashkov, *Tetrahedron Lett.* **1986**, *27*, 1245–1248; d) J. Marco-Contelles, J. Ruiz-Caro, *Carbohydr. Res.* **2001**, *335*, 71–90; e) W. J. Kerr, M. McLaughlin, P. L. Pauson, S. M. Robertson, *Chem. Commun.* **1999**, 2171–2172; f) A. Cabré, X. Verdaguer, A. Riera, *Synthesis* **2017**, *49*, 3945–3951; g) M. E. Krafft, L. V. Boñaga, J. A. Wright, C. Hirosawa, *J. Org. Chem.* **2002**, *67*, 1233–1246; h) J. F. Reichwein, S. T. Iacono, M. C. Patel, B. L. Pagenkopf *Tetrahedron Lett.* **2002**, *43*, 3739–3741.

[8] a) P. Magnus, L. Principe, *Tetrahedron Lett.* **1985**, *26*, 4851–4854; b) P. Magnus, C. A. Exon, *Tetrahedron* **1985**, *41*, 5861–5869; c) M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc.* **2001**, *123*, 1703–1708.

[9] I. Kovács, F. Ungváry, *Coord. Chem. Rev.* **1997**, *161*, 1–32.

