A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

Title: Total synthesis of (−)-Indoxamycins A and B

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201902043
Angew. Chem. 10.1002/ange.201902043

Link to VoR: http://dx.doi.org/10.1002/anie.201902043
http://dx.doi.org/10.1002/ange.201902043

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10.1002/anie.201902043

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COMMUNICATION

Total synthesis of (−)-Indoxamycins A and B

Naifeng Hu, Changming Dong, Cuifang Zhang, Guangxin Liang*

Abstract: Concise total syntheses of (−)-indoxamycins A and B are reported. The chemistry features a 7-step preparation of a highly congested [5.5.6] tricyclic advanced common intermediate from a readily available *R*-carvone derivative. Key steps involve a Pauson-Khand reaction for rapid construction of a basic scaffold bearing a quaternary carbon, a copper catalyzed Michael addition for introduction of another adjacent all-carbon quaternary stereocenter, and a tandem retro-oxa-Michael addition/1, 2-addition/oxa-Michael addition for installation of a trisubstituted olefin side chain. The synthetic strategy allows for easy access to both enantiomers of this family of natural products and their analogs from cost-effective starting material through straightforward chemical transformations.

Indoxamycins A − F (Figure 1) were isolated from a saline culture group of marine-derived actinomyces by Sato and co-workers in 2009.[1] As a novel class of polyketide natural products, indoxamycins A − F contain a highly congested [5.5.6] tricyclic cage-like carbon skeleton featuring six contiguous stereogenic centers, including three all carbon quaternary centers, two of which are vicinal, and bear an α, β-unsaturated carboxylic acid and a trisubstituted olefin suspended on the core structure.

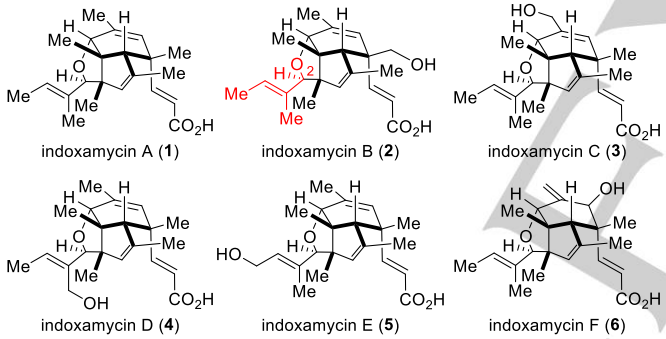
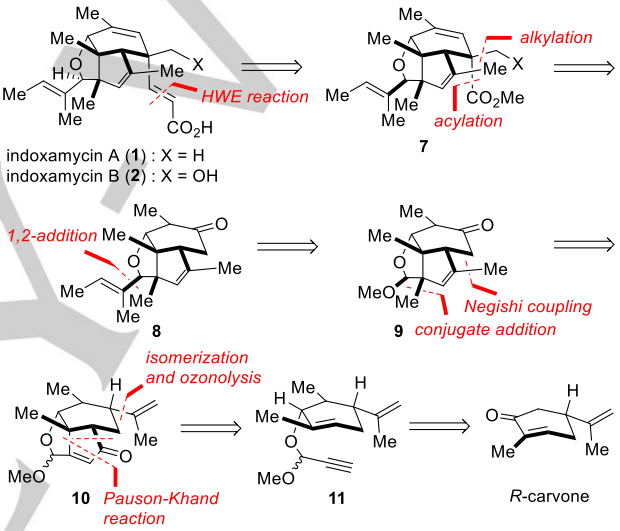


Figure 1. Structures of indoxamycins A−F.

Owing to their elegant molecular structures and reported anti-tumor biological activities,[1] indoxamycins have attracted significant synthetic attention. To date, two brilliant approaches to their syntheses have been reported. In 2012, Carreira and co-worker reported the first total synthesis.[2] Taking indoxamycin B (**2**, Figure 1) as a target, they applied a series of modern metal-catalyzed reactions and [3, 3]-sigmatropic rearrangements to construct the densely functionalized tricyclic core framework. Their pioneer work also led to the structural reassignment of the family of natural products, with both the originally proposed stereochemistry at C2 position and the geometry of the trisubstituted olefin in the side chain (highlighted in red) being revised. In 2013 and 2014, Ding and co-workers accomplished a collective asymmetric total synthesis of all six members of indoxamycins and validated the structural revision for other members proposed by Carreira.[3] Herein, we report our concise asymmetric total syntheses of indoxamycins A and B (**1** and **2,** Figure 1) starting from economic friendly *R*-carvone.[4]



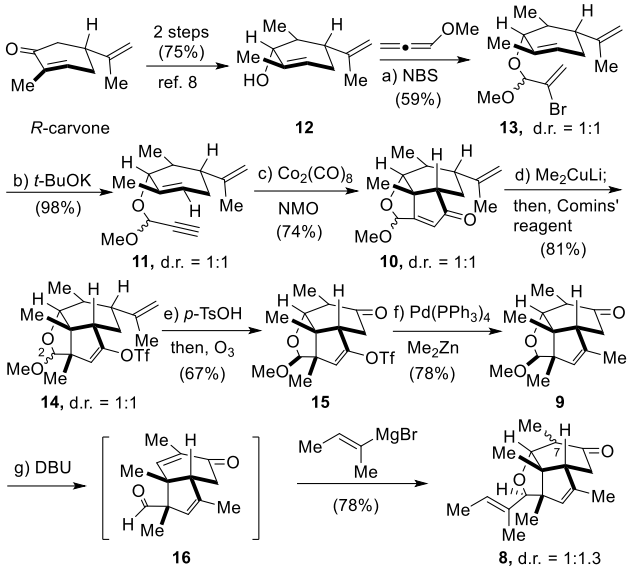
Scheme 1. Retrosynthetic analysis.

Our retrosynthetic analysis is depicted in Scheme 1. We rationalized that either indoxamycin A or B could be synthesized from advanced intermediate **7** bearing characteristic X group, whose distinctive all-carbon quaternary center could be established from a common precursor **8** through stereoselective acylation and alkylation reactions controlled by the convex nature of the substrate. Encouraged by Ding's work,[3] we reasoned that the trisubstituted alkene side chain in **8** could be installed through a substrate-controlled tandem retro-oxa-Michael addition/1, 2-addition/oxa-Michael addition[5] from **9**. The intermediate **9** could be generated by a sequence of reactions including copper catalyzed conjugated addition, Negishi coupling,[6] and ozonolysis following isomerization of an isopropenyl group. The [5.5.6] tricyclic framework in **10** could be rapidly constructed through an intramolecular Pauson-Khand reaction[7] of enyne **11**, which could be readily obtained from *R*-carvone.

[*] N. Hu, C. Dong, C. Zhang, Prof. G. Liang
State Key Laboratory of Elemento-organic Chemistry
College of Chemistry
Nankai University
Tianjin 300071 (China)
E-mail: lianggx@nankai.edu.cn

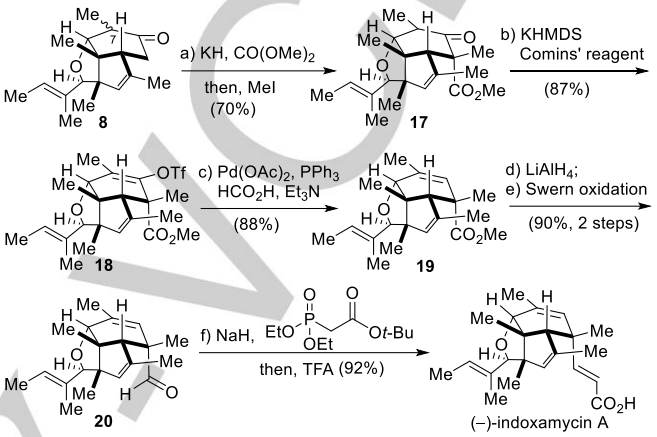
Supporting information and the ORCID identification number for the author(s) of this article can be found under:

10.1002/anie.201902043



Scheme 2. Preparation of the common intermediate **8**. Reagent and conditions: (a) NBS (2.0 equiv), methoxyallene (2.0 equiv), CH_2Cl_2, −20 °C to rt, 6 h, 59%; (b) *t*-BuOK (1.0 equiv), 18-crown-6 (0.05 equiv), pentane, rt, 5 h, 98%; (c) $Co_2(CO)_8$ (1.0 equiv), CH_2Cl_2, 0 °C, 1 h, then, NMO (6.0 equiv), MeCN, 0 °C to rt, 12 h, 74%; (d) MeLi (3.0 equiv), CuI (1.5 equiv), Et_2O, −20 °C to rt, Comins' reagent (1.5 equiv), 81%; (e) *p*-TsOH (1.0 equiv), PhMe, 70 °C, 5 h, then $NaHCO_3$ (1.0 equiv), O_3, CH_2Cl_2, −78 °C, then Me_2S, 67%; (f) Me_2Zn (3.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF, 0 °C, 78%; (g) DBU (0.2 equiv), 4 Å MS, THF, 80 °C, 2 h, then −78 °C, (*E*)-2-butenyl-2-magesium bromide (1.3 equiv), 0.5 h, 78%. NBS = *N*-bromosuccinimide, NMO = 4-methylmorpholine *N*-oxide, DBU = 1, 8-diazabicyclo [5.4.0]-7-undecene, MS = molecular sieve.

Our synthesis started from a literature documented carvone derivative **12** (Scheme 2), which was readily prepared on multi-decagram scale in 75% yield through a methylation and reduction sequence.[8] The starting material **12** reacted with methoxyallene in the presence of NBS,[9] furnishing acetal **13** as a pair of diastereoisomers in 59% yield. Subsequent elimination using *t*-BuOK afforded enyne **11** in 98% yield, setting the stage for a Pauson-Khand reaction. Gratifyingly, this key desired reaction went very smoothly, producing the rather complex [5.5.6] tricyclic compound **10** bearing a quaternary carbon in 74% yield.[10] Such a Pauson-Khand reaction strategy allowed for rapid assemble of the basic scaffold of the natural products in only 3 steps from **12** in a stereoselective fashion. Copper-mediated conjugate addition of MeLi followed by triflation of the enolate intermediate with Comins' reagent in Et_2O afforded **14** in 81% yield. What is worth noting is that Et_2O was essential for this one-pot transformation. Desired product was obtained in very low yield when THF was used as solvent.[11] Subsequently, treatment of **14** with *p*-TsOH[12] resulted in complete isomerization of a double-substituted olefin to a more stable tetra-substituted one, which was subjected to ozonolysis to yield a ketone **15** in 67% yield. Simultaneously, the ketal stereogenic center at C2 position isomerized to give a single diastereoisomer under such acidic conditions. Ketone **15** readily underwent Negishi coupling to produce alkene **9** in 78% yield upon exposure to $Pd(PPh_3)_4$ (10 mol%) in THF with Me_2Zn.[13] After extensive screening of bases (*t*-BuOK, NaOMe, LDA, Et_3N, DABCO, DBU), we found that **9** underwent retro-Michael reaction[14] cleanly when exposed to DBU in the presence of 4 Å MS to afford an unstable aldehyde **16**, which gradually decomposed upon purification. Fortunately, in situ treatment of **16** with (*E*)-2-butenyl-2-magesium bromide[15] generated the desired tricyclic product **8** as a pair of diastereoisomers (d.r. = 1:1.3 at C7) in 87% yield. At this stage, we have achieved a 9-step multi-gram scale preparation of an advanced common intermediate possessing majority of the structural features in the natural products from *R*-carvone.



Scheme 3. Total synthesis of (−)-indoxamycin A. Reagent and conditions: (a) KH (30% w/w in mineral oil, 3.0 equiv), $CO(OMe)_2$ (5.0 equiv), THF, reflux, then MeI (5.0 equiv), 0 °C, 4 h, 70%; (b) KHMDS (2.0 equiv), Comins' reagent (1.5 equiv), THF, −78 °C, 1 h, 87%; (c) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), HCO_2H (10 equiv), Et_3N (12 equiv), THF, 70 °C, 1 h, 88%; (d) $LiAlH_4$ (2.0 equiv), THF, 60 °C, 1 h; (e) oxalyl chloride (2.0 equiv), DMSO (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 °C, 1.5 h, 90% for two steps; (f) NaH (3.0 equiv), *tert*-butyl diethylphosphonoacetate (3.0 equiv), THF, 70 °C,1.5 h, then TFA, CH_2Cl_2, rt, 5 h, 92% for two steps. KHMDS = potassium bis(trimethylsily)amide.

With compound **8** readily available in hand, we proceeded to synthesize indoxamycin A (Scheme 3). Acylation of **8** under KH/dimethyl carbonate[16] conditions generated potassium enolate salt, which was in situ methylated with MeI furnishing a desired all carbon quaternary center to deliver **17** as a single diastereoisomer in 70% yield thanks to the excellent stereochemical control of the methylation reaction and the simultaneous isomerization at C7 position under the basic reaction conditions. Generation of potassium enolate with KHMDS followed by addition of Comins' reagent[17] gave corresponding enol triflate **18** in 87% yield. Subsequent Pd-catalyzed reductive detriflation[18] gave alkene **19** in 88% yield, which was then converted into aldehyde **20** in 90% overall yield through a standard reduction/oxidation operation. Eventually, Horner-Wadsworth-Emmons (HWE) olefination[19] on **20** followed by in situ removal of *t*-butyl group yielded (−)-indoxamycin A in 92% yield.

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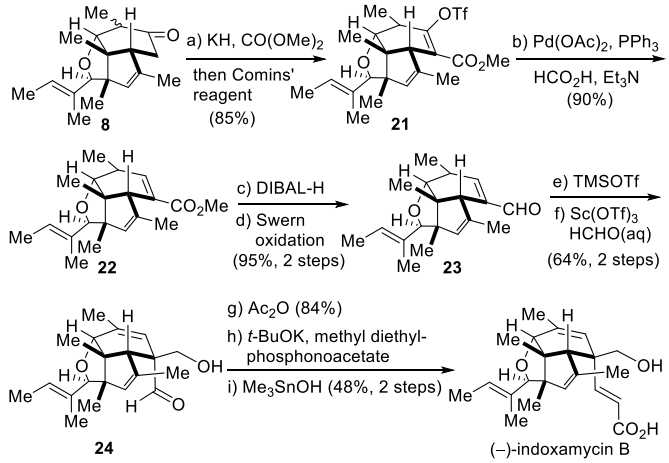

Scheme 4. Total synthesis of (−)-indoxamycin B. Reagent and conditions: (a) KH (3.0 equiv), $CO(OMe)_2$ (5.0 equiv), THF, reflux, then Comins' reagent, 0 °C, 1.5 h, 85%; (b) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), HCO_2H (10 equiv), Et_3N (12 equiv), THF, 70 °C, 1 h, 90%; (c) DIBAL-H (2.5 equiv), CH_2Cl_2, −78 °C, 0.5 h; (d) oxalyl chloride (1.5 equiv), DMSO (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 °C, 1 h, 95% for two steps; (e) TMSOTf (2.5 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; (f) $Sc(OTf)_3$ (0.1 equiv), HCHO (37% wt%, 10 equiv), THF, rt, 0.6 h, 64% for two steps; (g) Ac_2O (2.0 equiv), pyridine (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 0.5 h, 84%; (h) *t*-BuOK (2.0 equiv), **24** (3.0 equiv), THF, rt, 48 h, 59% (88% brsm); (i) Me_3SnOH (2.0 equiv), 1,2-dichloroethane, 90 °C, 20 h, 80%. DIBAL-H = diisobutylaluminium hydride, TMSOTf = trimethylsilyl trifluoromethanesulfonate, DMAP = 4-dimethylaminopyridine.

With the successful completion of (−)-indoxamycin A, we envisaged that (−)-indoxamycin B could be synthesized from the common intermediate **8** applying the same alkylation strategy. However, either exclusive O-alkylation or no reaction was observed after investigations on several bases (K_2CO_3, Cs_2CO_3, Et_3N, DBU, etc) with alkylation reagent $BzOCH_2I$. The unsuccessful trials drove us to look into an aldol reaction approach. Although reactions between 1, 3-dicarbonyl compounds and formaldehyde to construct quaternary carbon centers are well documented in the literature, we were unfortunate to find that a variety of conditions such as [$KHCO_3$/HCHO (aq.)],[20] [$Yb(OTf)_3$, $(CH_2O)_n$],[21] (LiHMDS /benzotriazolylmethanol),[22] either gave complex mixtures or caused decomposition of the starting material. Eventually, we were able to conquer this challenge using a Mukaiyama aldol reaction[23] approach (Scheme 4). First, triflation of the potassium enolate derived from **8** in the presence of KH produced enol triflate **21** in 85% yield. The enol triflate readily underwent Pd-catalyzed reductive detriflation, generating α,β-unsaturated ester **22** in 90% yield. A reduction and oxidation sequence gave rise to aldehyde **23** in good yield, which was subjected to TMSOTf/Et_3N, affording a dienol silyl ether with a trisubstituted olefin in place. Subsequent Mukaiyama aldol reaction with formaldehyde in aqueous media[24] catalyzed by $Sc(OTf)_3$ formed the desired quaternary carbon center, delivering alcohol **24** in 64% yield in two steps. After acetylation of the primary hydroxyl group in **24**, HWE reaction was conducted. Owing to the steric hindrance around the aldehyde, low conversion of the reaction was observed. Several bases (NaH, *n*-BuLi, *t*-BuOK) were studied to promote this reaction, and *t*-BuOK proved to be relatively effective to produce the corresponding unsaturated ester in 59% (88% brsm) yield. Lastly, following an effective neutral condition (Me_3SnOH)[25] identified by Ding and co-workers in their syntheses, we were able to hydrolyze methyl ester as well as the acetate to afford (−)-indoxamycin B in 48% yield in two steps.

In conclusion, a concise and efficient route for the total syntheses of (−)-indoxamycins A and B has been developed. The key features of our chemistry included a Pauson-Khand reaction for quick construction of a tricyclic basic scaffold bearing an all-carbon quaternary center, a copper mediated Michael addition to furnish another adjacent quaternary carbon center, a tandem retro-oxa-Michael addition/1,2-addition/oxa-Michael addition to efficiently install the suspended trisubstituted olefin, as well as a Mukaiyama aldol reaction in aqueous media to accomplish a challenging all carbon quaternary center in indoxamycin B. Starting from *S*-carvone, the described strategy could be readily applicable to the syntheses of (+)-indoxamycins A and B, whose bioactivities we believe are totally worth investigation.[26] Relevant studies will be reported in due courses.

Acknowledgements

We thank the National Key Research and Development Program of China (2017YFD0201404) and the National Natural Science Foundation of China (21772097, 21572104) for financial support.

Keywords: indoxamycins • polyketides • Pauson-Khand reaction • tandem reaction • total synthesis

[1] S. Sato, F. Iwata, T. Mukai, S. Yamada, J. Takeo, A. Abe, H. Kawahara, *J. Org. Chem.* **2009**, *74,* 5502.

[2] (a) O. F. Jeker, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51,* 3474; *Angew. Chem.* **2012**, *124,* 3531. (b) O. F. Jeker, *Ph.D. Dissertation*, ETH, Zurich (Switzerland), **2013**.

[3] (a) C. He, C.-L. Zhu, Z.-F. Dai, C.C. Tseng, H.-F. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 13256; *Angew. Chem.* **2013**, *125*, 13498. (b) C. He, C.-L. Zhu, B.-N. Wang, H.-F. Ding, *Chem. Eur. J.* **2014,** *20*, 15053; (c) C. He, C.-L. Zhu, H.-F. Ding, *Synlett* **2014**, *25*, 1487.

[4] For a recent review on total syntheses using carvone, see: Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753.

[5] For reviews on tandem reactions, see: (a) R. A. Bunce, *Tetrahedron* **1995**, *51,* 13103; (b) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; (c) A. Padwa, *Pure Appl. Chem.* **2004**, *76,* 1933; for a review on oxa-Michael reaction, see: (d) J.-L. Hu, M. Bian, H.-F. Ding, *Tetrahedron Lett.* **2016**, *57*, 5519.

[6] (a) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98,* 6729; (b) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, 683; (c) E. Negishi, *Acc. Chem. Res.* **1982**, *15,* 340; (d) E. Erdik, *Tetrahedron* **1992**, *48*, 9577.

[7] (a) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977; (b) P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855; for representative reviews on Pauson-Khand reaction, see: (c) K. Krohn, *Org. Synth. Highlights* **1991**, 137; (d) N. E. Schore, *Org. React.* **1991**, *40*, 1; (e) O. Geis, H. G. Schmalz, *Angew. Chem. Int. Ed.* **1998**, *37*, 911; *Angew. Chem.* **1998**, *110*, 955. (f) K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263; (g) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32; for representative total syntheses featuring Pauson-Khand reactions, see: (h) T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, *119*, 4353; (i) Q. Xiao, W.-W. Ren,

10.1002/anie.201902043

Z.-X. Chen, T.-W. Sun, Y. Li, Q.-D. Ye, J.-X. Gong, F.-K. Meng, L. You, Y.-F. Liu, M.-Z. Zhao, L.-M. Xu, Z.-H. Shan, Y. Shi, Y.-F. Tang, J.-H. Chen, Z. Yang, *Angew. Chem. Int. Ed.* **2011**, *50*, 7373; *Angew. Chem.* **2011**, *123*, 7511. (j) Q. Liu, G.-Z. Yue, N. Wu, G. Lin, Y.-Z. Li, J.-M. Quan, C.-C. Li, G.-X. Wang, Z. Yang, *Angew. Chem. Int. Ed.* **2012**, *51*, 12072; *Angew. Chem.* **2012**, *124*, 12238. (k) L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding, P. S. Baran, *Science* **2013**, *341*, 878; (l) 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; (m) K. V. Chuang, C. Xu, S. E. Reisman, *Science* **2016**, *353*, 912; (n) D.-D. Liu, T.-W. Sun, K.-Y. Wang, Y. Lu, S.-L. Zhang, Y.-H. Li, Y.-L. Jiang, J.-H. Chen, Z. Yang, *J. Am. Chem. Soc*. **2017**, *139*, 5732; (o) Z.-H. Huang, J. Huang, Y.-Z. Qu, W.-B. Zhang, J.-X. Gong, Z. Yang, *Angew. Chem. Int. Ed.* **2018**, *57*, 8744; *Angew. Chem.* **2018**, *130*, 8880.

[8] (a) A. Srikrishna, D. Vijaykumar, *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2583; (b) Y. Chen, T. Ju, *Org. Lett.* **2011**, *13*, 86.

[9] (a) O. Moriya, M. Okawara, Y. Ueno, *Chem. Lett.* **1984**, *13*, 1437; (b) C. J. Forsyth, J. Clardy, *J. Am. Chem. Soc.***1990**, *112*, 3497.

[10] S. Shambayati, W. E. Crewel, S. L. Schreiber, *Tetrahedron Lett*. **1990**, *31*, 5289.

[11] B. Christenson, G. Hallnemo, C. Ullenius, *Tetrahedron* **1991**, *47*, 4739.

[12] (a) T. Hudlicky, M. G. Natchus, G. Sinai-Zingde, *J. Org. Chem.* **1987**, *52*, 4641; (b) D.-S. Hsu, C.-C. Liao, *Org. Lett.* **2003**, *5*, 4741.

[13] (a) J. Ramharter, J. Mulzer, *Org. Lett.* **2009**, *11*, 1151; (b) L.-Z. Liu, J.-C. Han, G.-Z. Yue, C.-C. Li, Z. Yang, *J. Am. Chem. Soc*. **2010**, *132*, 13608.

[14] (a) J.-D. Wu, K.-S. Shia, H.-J. Liu, *Tetrahedron Lett*, **2001**, *42*, 4207; (b) P. Ceccherelli, M. Curini, M. C. Marcotullio, B. L. Mylari, E. Wenkert, *J. Org. Chem.* **1986**, *51*, 1505; (c) P. P. Seth, N. I. Totah, *Org. Lett.* **2000**, *2*, 2507; (d) K. M. Rupprecht, J. Boger, K. Hoogsteen, R. B. Nachbar, J. P. Springer, *J. Org. Chem.* **1991**, *56*, 6180.

[15] (a) F. Sate, H. Ishikawa, M. Sato, *Tetrahedron Lett*. **1981**, *22*, 85; (b) C. M. Garner, M. E. Prince, *Tetrahedron Lett*. **1994**, *35*, 2463.

[16] K. C. Nicolaou, M. P. Jennings, P. Dagneau, *Chem. Commun.* **2002**, 2480.

[17] D. L. Comins, A. Dehghani, *Tetrahedron Lett*. **1992**, *33*, 6299.

[18] S. Cacchi, E. Morera, G. Ortar, *Tetrahedron Lett.* **1984**, *25*, 4821.

[19] For representative reviews on HWE reaction, see: (a) J. Boutagy, R. Thomas, *Chem. Rev.* **1974**, *74*, 87; (b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863; (c) K. C. Nicolaou, M. W. Härter, J. L. Gunzner, A. Nadin, *Liebigs Ann./Recueil* **1997**, 1283; (d) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698.

[20] B. D. Schwartz, D. P. Tilly, R. Heim, S. Wiedemann, C. M. Williams, P. V. Bernhardt, *Eur. J. Org. Chem.* **2006**, 3181.

[21] K. C. Nicolaou, P. K. Sasmal, A. J. Roecker, X.-W. Sun, S. Mandal, A. Converso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3443; *Angew. Chem.* **2005**, *117*, 3509.

[22] (a) G. Deguest, L. Bischoff, C. Fruit, F. Marsais, *Org. Lett.* **2007**, *9*, 1165; (b) K. C. Nicolaou, L. Shi, M. Lu, M. R. Pattanayak, A. A. Shah, H. A. Ioannidou, M. Lamani, *Angew. Chem. Int. Ed.* **2014**, *53*, 10970; *Angew. Chem.* **2014**, *126*, 11150.

[23] (a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011; (b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503; (c) T. Mukaiyama, *Org. React.* **1982**, *28*, 203. For representative reviews on Mukaiyama aldol reaction, see: (d) E. M. Carreira, *Comprehensive Asymmetric Catalysis I-III* **1999**, *3*, 997; (e) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; *Angew.Chem.* **2013**, *125*, 9256; (f) M. Kalesse, M. Cordes, G. Symkenberga, H.-H. Lu, *Nat. Prod. Rep.* **2014**, *31*, 563; (g) S. B. Jennifer Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097; *Angew.Chem.* **2013**, *125*, 9267; (h) J. I. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109; *Angew.Chem.* **2013**, *125*, 9280.

[24] (a) S. Kobayashi, C*hem. Lett.* **1991**, *20*, 2187; (b) S. Kobayashi, *Synlett* **1994**, *1994*, 689; For reviews on lanthanide triflate in organic synthesis, see: (c) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15; (d) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227; (e) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954; (f) T. Kitanosonoa, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 3095.

[25] (a) R. L. E. Furlán, E. G. Mata, O. A. Mascaretti, *J. Chem. Soc. Perkin Trans.1* **1998**, 355; (b) R. L. E. Furlán, E. G. Mata, O. A. Mascaretti, C. Pena, M. P. Coba, *Tetrahedron* **1998**, *54*, 13023; (c) K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378; *Angew. Chem.* **2005**, *117*, 1402.

[26] For representative examples of interesting bioactivities of enantiomers of natural products, see: (a) D. L. Boger, J. Hong, *J. Am. Chem. Soc.* **2001**, *123*, 8515; (b) A. Fürstner, K. Reinecke, H. Prinz, H. Waldmann, *ChemBioChem* **2004**, *5*, 1575; (c) M. M. Logan, T. Toma, R. Thomas-Tran, J. Du Bois, *Science* **2016**, *354*, 865.

10.1002/anie.201902043

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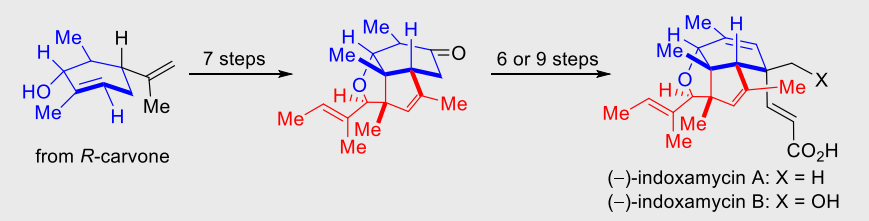

*Naifeng Hu, Changming Dong, Cuifang Zhang, Guangxin Liang**

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Total synthesis of (−)-indoxamycins A and B

Concise total synthesis of (−)-indoxamycins A and B are described. Highlights of this work include a Pauson-Khand reaction, a tandem retro-oxa-Michael addition/1,2-addition/oxa-Michael addition and a Mukaiyama aldol reaction.

[a] Title(s), Initial(s), Surname(s) of Author(s) including Corres