ORGANIC LETTERS

2013
Vol. 15, No. 21
5472–5475

Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (*S*)-SIRT1-Inhibitor IV

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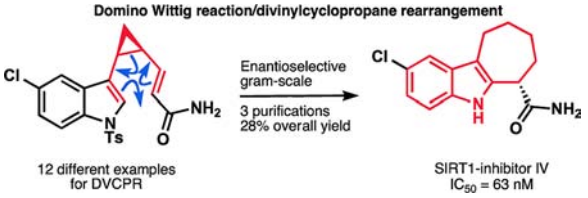
Received September 11, 2013

ABSTRACT



An enantioselective gram-scale synthesis of one of the most potent SIRT1-inhibitors has been accomplished by an unprecedented domino reaction sequence establishing the cyclohepta[*b*]indole core. This method was developed for application in natural product synthesis of a variety of indole alkaloids.

The cyclohepta[*b*]indole core, which occurs in a variety of indole alkaloids,[1] is associated with a broad spectrum of biological profiles ranging from anti-inflammation[2] and anti-aging[3] to anti-tuberculosis activities (Figure 1).[4] Among the pharmaceutically active compounds based on this structure motif, around two dozen patents have been issued within the past decade.[5] The SIRT1-inhibitor IV (**4**) shows outstanding biological activity and is therefore being heavily investigated. It belongs to a new class of histone deacetylase (HDAC) inhibitors and is involved in gene silencing via a new mode of action.[2b,6] Data shows that inhibition of SIRT1 enhances acetylation of p53.[2b,6] Compound **4** is one of the most potent compounds

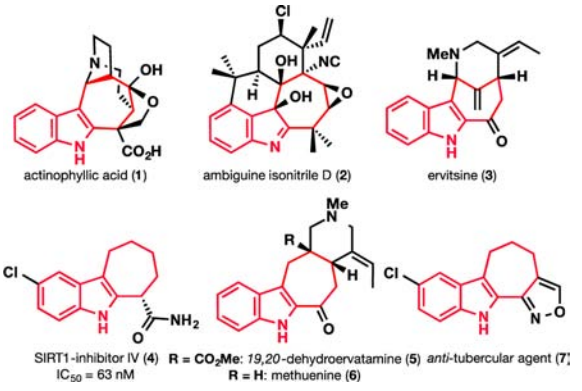


Figure 1. Compounds containing the cyclohepta[*b*]indole core.

‡ These authors contributed equally.

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10.1021/ol4026217
Published on Web 10/23/2013

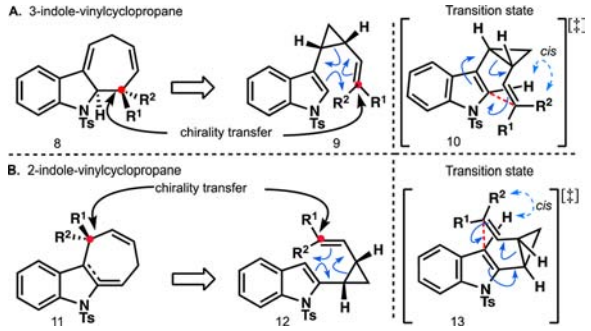


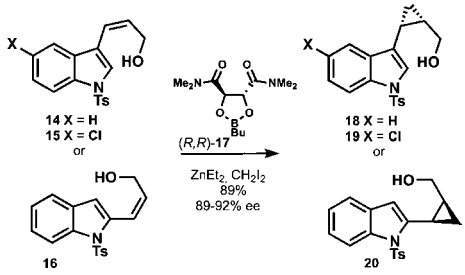
Figure 2. Chirality transfer in the indole−vinylcyclopropane rearrangement.

described, with IC_{50} values of 60−100 nM representing a 500-fold improvement over previously reported inhibitors.[2b]

This compound contains a single stereocenter and so far has only been synthesized as a racemate, which is separated by chiral HPLC. The two enantiomers differ drastically in their biological potency, with (*S*)-**4** (IC_{50} = 63 nM) being 365-fold more potent than (*R*)-**4** (IC_{50} = 23 μM), rendering an enantioselective access especially to the more potent (*S*)-**4** enantiomer utmost important.[2b]

Herein, we present an efficient, enantioselective, and gram-scale synthesis of SIRT1-inhibitor IV (**4**). In contrast to the established racemic route,[2b] which requires individual planning for derivative synthesis, our synthetic access is modular and therefore does not require additional steps or a change in synthetic planning to allow derivatization. This is crucial for library synthesis and rapid testing of a large variety of compounds. Our synthetic route rests upon a Wittig reaction/divinylcyclopropane rearrangement cascade.[7] To date, a few examples of racemic and only one example of an enantioselective synthesis of

Scheme 1. Enantioselective Cyclopropanation



cyclohepta[*b*]indole systems exist.[8] Our method tolerates a broad range of substituents at different positions of the seven-membered ring, making it a robust and general method to synthesize this structure motif (Figure 2). Since the key step constitutes a [3,3]-sigmatropic rearrangement,[9] each substituent can be introduced stereospecifically, which is not possible with any other method available to date. Our strategy relies upon a divinylcyclopropane rearrangement (DVCPR)[10] involving the indole moiety as a 2π-unit. This substrate type has previously not been reported in a DVCPR reaction, thus extending the scope of this reaction.[11] This reaction not only assembles the seven-membered ring, but due to orbital symmetry considerations,[12] chirality is transferred stereospecifically from the cyclopropane ring to the benzylic positions, which are very labile and therefore difficult to access in a stereoselective way by other methods (displayed in Figure 2).

The rearrangement can be carried out with a 2- or a 3-indole−vinylcyclopropane **9** or **12**. With both substrates, dearomatization of the indole core occurs in the course of the rearrangement, but only the 2-indole−vinylcyclopropane product rearomatizes spontaneously. The rearrangement temperatures vary with the substituents from 20 to 140 °C (see the Supporting Information). The transfer of chirality for both 2- and 3-indole−vinylcyclopropanes **9** and **12** is depicted in Figure 2. In the case of 3-indole−vinylcyclopropanes **9** (series A transition state **10**), it can be clearly seen that R^2 and the indole C2-proton will adopt the *cis*-stereorelationship on the seven-membered ring. The relative configuration is therefore governed by the geometry of the double bond; hence, a (*Z*)-double bond will give the *cis*-compound, whereas the (*E*)-double bond will give the *trans*-compound. The same holds true

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(10) (a) Davies, H. M. L. *Adv. Cycloaddit.* **1999**, *5*, 119. (b) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React. (N.Y.)* **1992**, *41*, 1. (c) Piers, E.; Burmeister, M. S.; Reissig, H. U. *Can. J. Chem.* **1986**, *64*, 180. (d) Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204.

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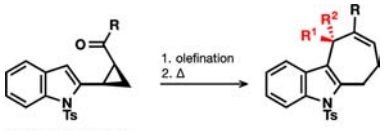
(12) Özkan, I.; Zora, M. *J. Org. Chem.* **2003**, *68*, 9635.

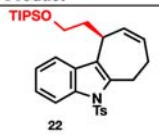
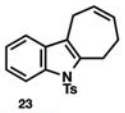
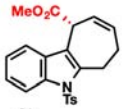
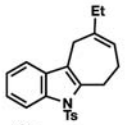
for 2-indole−vinylcyclopropanes **12** (series **B**, transition state **13**), but due to spontaneous aromatization in the course of the reaction, only one stereocenter is retained in the final product **11** (indicated with dashed line). The absolute stereochemistry in products **8** and **11** is governed by the stereocenters of the cyclopropane ring. Enantioselective Charette cyclopropanation of the easily accessible allylic alcohols (3 chemical operations/1 purification) **14**, **15**, and **16** (Scheme 1) with dioxaborolane **17** furnished the desired products **18**, **19**, and **20** with 89−92% ee.[13]

To validate this concept and to explore the scope of the domino sequence, a variety of olefins of type **9**/**12** were tested (Tables 1 and 2). The reaction is very robust, and tolerates a broad range of substituents (electron-rich and -deficient), which can be introduced at any position on the seven-membered ring. Even quaternary stereocenters are formed (compounds **25**, **31**, and **32**). Wittig adducts **9** and **12** cyclize in situ to deliver cyclohepta[*b*]indoles of type **8** and **11** in good to excellent yields.

Table 1. Substrate Scope of Cyclohepta[*b*]indole Synthesis (from 2-Indole−Vinylcyclopropyl Aldehyde)



21 (R = H), **48** (R = Et)
ee = 89–92%

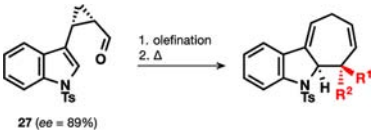
Entry	Product	*T* / °C	*ee* / %	Yield / %
1	 **22**	rt.	92	89
2	 **23**	rt.	—	71
3	 **24**	140	92	78
4	 **25**	140	89	65
5	 **26**	rt.	—	60

2-indole-vinylcyclopropyl aldehyde)

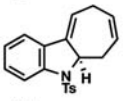
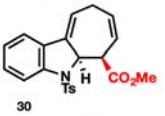
[a] For solvent and reaction time refer to the Supporting Information.

We then set out to apply our method to an enantioselective synthesis of the (*S*)-SIRT1-inhibitor IV (**4**). We envisioned that an enantioselective synthesis would present a special challenge, since it was well-known that the only stereocenter present in the molecule was prone to racemization, especially upon late-stage functional group interconversions at the carboxylic acid group. Therefore we decided to avoid this issue by directly introducing the carboxamide from the beginning.

Table 2. Substrate Scope of Cyclohepta[*b*]indole Synthesis (from 3-Indole−Vinylcyclopropyl Aldehyde)[a]



27 (*ee* = 89%)

Entry	Product	*T* / °C	*ee* / %	Yield / %
1	 **28**	80	89	70
2	 **29**	rt.	89	54
3	 **30**	80	89	76
4	 **31**	80	89	69
5	 **32**	80	89	73

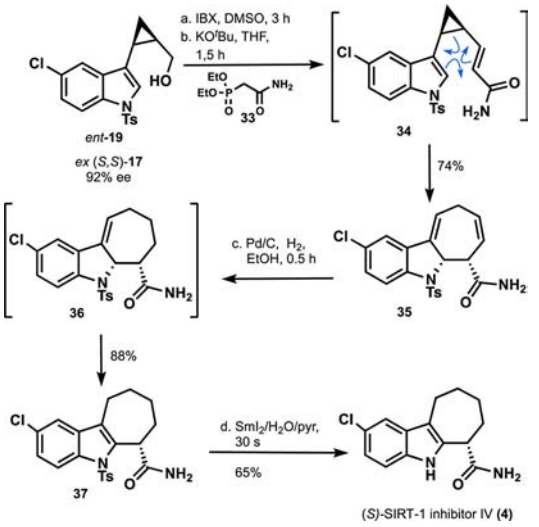
[a] For solvent and reaction time refer to the Supporting Information.

In order to synthesize the more potent (*S*)-SIRT1-inhibitor IV (**4**), we started our synthesis with the cyclopropantation using (*S,S*)-oxaborolane **17** (Scheme 2). Oxidation of *ent*-**19** to the corresponding aldehyde followed by Horner−Wadsworth−Emmons olefination with phosphonate **33** directly introduced the desired carboxamide and in situ divinylcyclopropane rearrangement gave cyclohepta[*b*]indole **35** in 74% yield. Hydrogenation of the double bond and concomitant aromatization with palladium on charcoal afforded precursor **37** in 88% yield. Removal of the tosyl group using samarium diiodide delivered (*S*)-SIRT1-inhibitor IV (**4**) with 92% ee and an overall yield of 28% with complete retention of the labile stereocenter.[14,15] It is important to note that even the exposure of **37** to magnesium and methanol did not result in racemization (as opposed to the treatment of the corresponding ester). For practical purposes it is important to note that the synthetic sequence requires only three purification steps and can be performed on a gram scale.

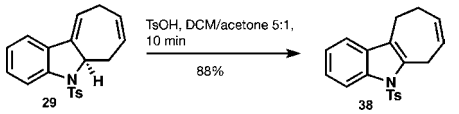
(13) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

(14) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503.

Scheme 2. Enantioselective Synthesis of (*S*)-**4**



Scheme 3. Aromatization of Cyclohepta[*b*]indoles from Indole−3-Vinylcyclopropane Adducts

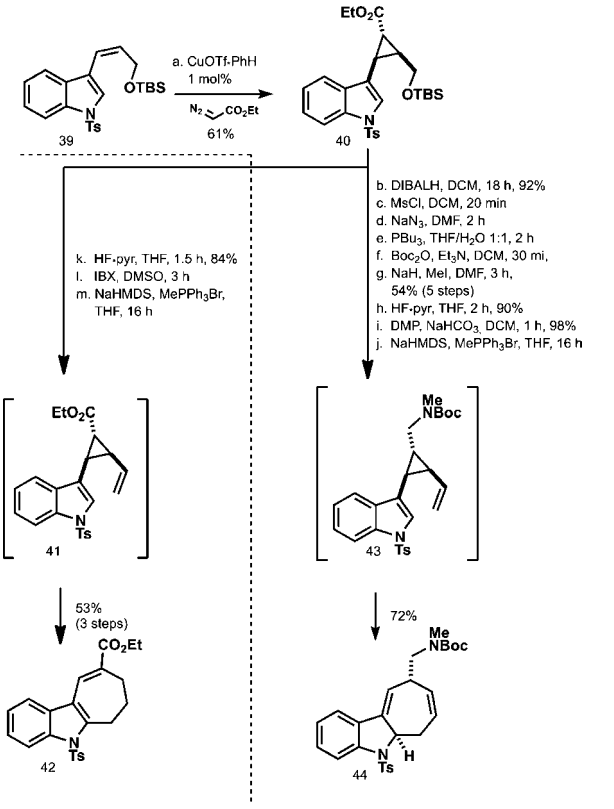


The enantiomeric excess of all our products was determined via chiral HPLC and to our delight corresponded to the optical purity of the cyclopropanation products, indicating not only complete transfer of chirality but proof that our method is mild enough to maintain the stereointegrity of the labile benzylic position.

As mentioned before, 3-indole−vinylcyclopropanes do not rearomatize spontaneously. Thus, **29** was exemplarily subjected to acidic conditions, upon which rearomatization to indole **38** took place (Scheme 3).

The scope of the reaction can even be extended by using a transition-metal-catalyzed cyclopropanation of **39** with ethyl diazoacetate (Scheme 4).[16] This is important for the application of this methodology to the synthesis of natural products depicted in Figure 1, which are currently pursued in our laboratories. The synthesis of tricycle **43**

Scheme 4. Extension of Substrate Scope



demonstrates the tolerance of heteroatoms in the system, serving as intermediates en route to methuenine (**6**).

Alternatively, compound **40** was deprotected, oxidized, and olefinated to give after rearrangement and spontaneous aromatization cyclohepta[*b*]indole.

In conclusion, we have accomplished the first enantioselective synthesis of the (*S*)-SIRT1-inhibitors **4** via a novel domino-Wittig/-divinylcyclopropane rearrangement sequence. Optical activity was introduced via Charette's asymmetric cyclopropanation and, in a divinylcyclopropane rearrangement, was transferred to the cyclohepta[*b*]indole core which is also a central structure motif of many other natural products. The scope of this domino process is very general, making a broad range of substituted cyclohepta[*b*]indoles accessible for further pharmacological testing.

Acknowledgment. We thank Dr. J. Fohrer, M. Rettstadt, D. Körtje, and Prof. E. Hofer for detailed 2D-NMR analysis and Dr. G. Dräger and R. Reichel for mass spectra. Financial support was generously granted by the Alexander von Humboldt foundation through a Sofja Kovalevskaja prize.

Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest

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