Asymmetric Catalysis Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 10521–10525
International Edition: doi.org/10.1002/anie.202101439
German Edition: doi.org/10.1002/ange.202101439

Concise Asymmetric Syntheses of Streptazone A and Abikoviromycin**

*Gustav J. Wørmer, Nikolaj L. Villadsen, Peter Nørby, and Thomas B. Poulsen**

Abstract: *Streptazone A and abikoviromycin are alkaloids that both feature an unusual arrangement of reactive functionalities within a compact tricyclic ring system. Here, we report a highly concise asymmetric synthesis of both natural products. The route first constructs another family member, streptazone B_1, using a rhodium-catalyzed distal selective allene-ynamide Pauson–Khand reaction. A regio- and enantioselective epoxidation under chiral phase-transfer catalytic conditions directly afforded streptazone A in 8 steps overall. In one additional step, a chemoselective, iridium-catalyzed reduction of the enaminone system then gave abikoviromycin. The reactivity of streptazone A towards a cysteine mimic, N-acetylcysteamine, was studied and revealed unanticipated transformations, including bis-thiol conjugation which may proceed via formation of a cyclopentadienone intermediate. With flexible access to these compounds, studies aimed to identify their direct biological targets are now possible.*

Natural products that feature unusual constellations of reactive chemical groups are fascinating outcomes of microbial biosynthesis and may constitute unique opportunities for discovering interesting biological activity.[1] The streptazones[2,3] (Figure 1A) are members of a larger family of piperidine alkaloids with diverse biological activity[4–11] sharing an interesting [4.3.0] bicyclic core (Figure 1A,B). In this family, streptazolin **3**[4,11a] has been the subject of sustained interest from several laboratories due to the challenging tricyclic urethane core structure.[12] We, however, have taken special interest in streptazone A (**1**) which is reported to be a potent inhibitor of liver cancer cell growth (HepG2, $GI_{50} = < 0.1\ \mu M$)[2] and features the unique constellation of an enaminone, a Michael acceptor, and a bis-allylic epoxide (Figure 1A). We were intrigued by the compact nature of the multiple electrophilic sites embedded in this small molecule ($MW = 177\ g\,mol^{-1}$) as well as the absence of information about direct biological targets. Here, we report the first asymmetric synthesis of (+)-streptazone A (**1**) in 8 steps, the assignment of its absolute configuration, and the discovery of conditions for selectively transforming **1** into abikoviromycin (**4**)[10] in a single operation. Finally, we uncover an unanticipated spectrum of thiol-reactivity inherent within the streptazone A ring system.

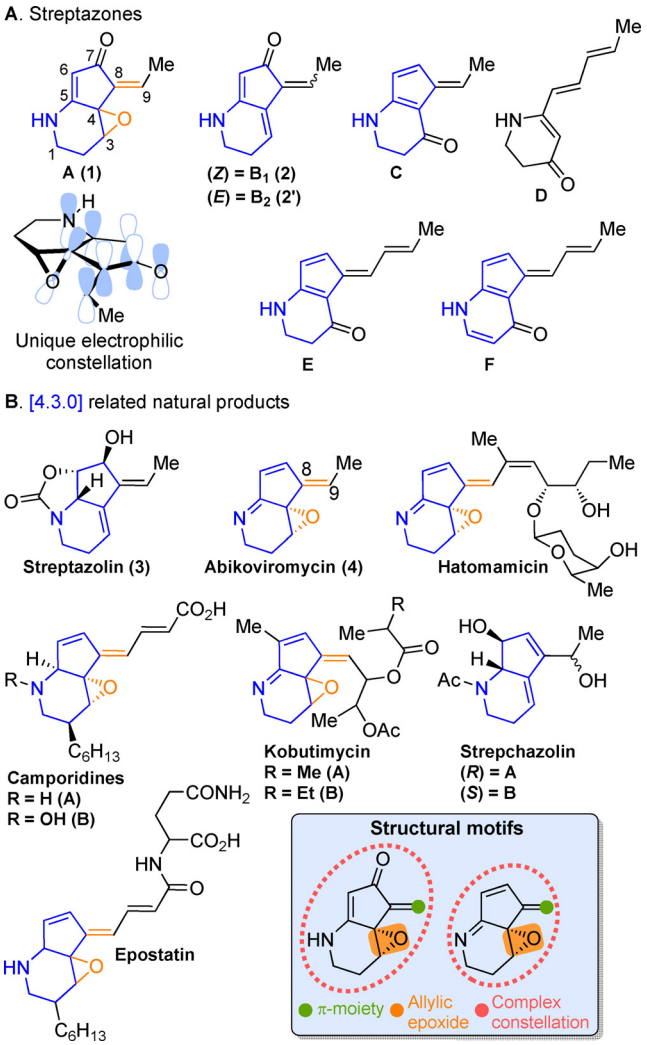


Figure 1. A) Chemical structures of streptazones and a graphic representation of antibonding molecular orbitals of streptazone A. B) Related [4.3.0] natural products.

In contrast to the plethora of syntheses of **3**, no synthesis has been reported for any epoxide-containing member of the family.[12] It has been proposed that an epoxide facilitates the formation of the [4.3.0] core by a ring-opening event during the biosynthesis of streptazone E[13] and the camporidines[9] (Figure 2A), however, the subsequent events that, for example, result in re-closure/re-installation of the epoxide, are not known in detail. Arguably, any synthetic strategies targeting this functionality are likely to be challenging due to the expected tendency for carbocation formation as a result of the

[*] G. J. Wørmer, Dr. N. L. Villadsen, Dr. P. Nørby, Prof. Dr. T. B. Poulsen
Department of Chemistry, Aarhus University
Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: thpou@chem.au.dk

[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/10.26434/chemrxiv.13293356.v1).

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202101439.

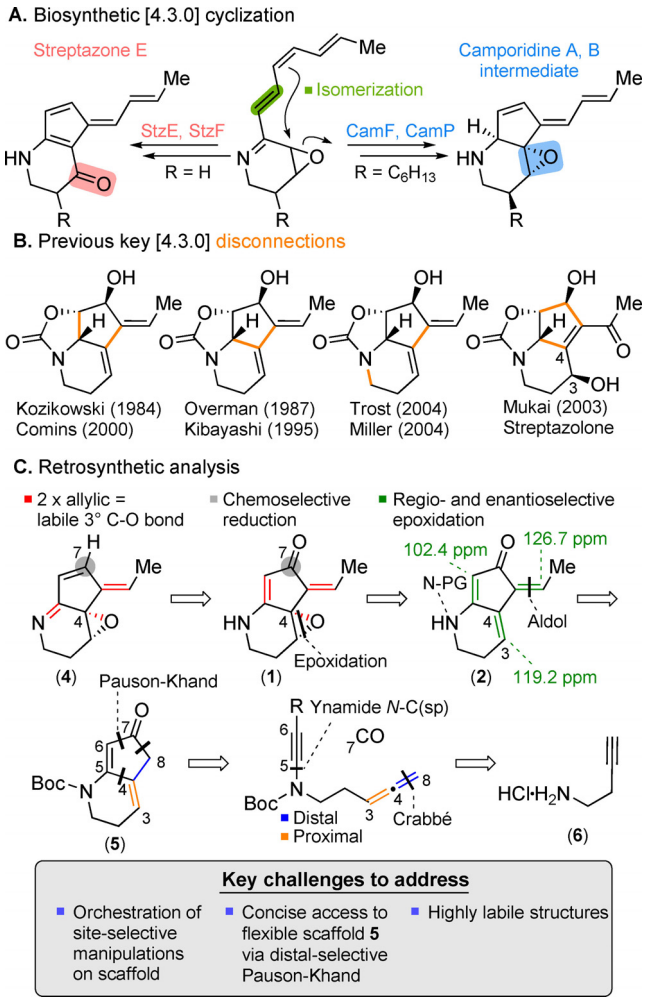
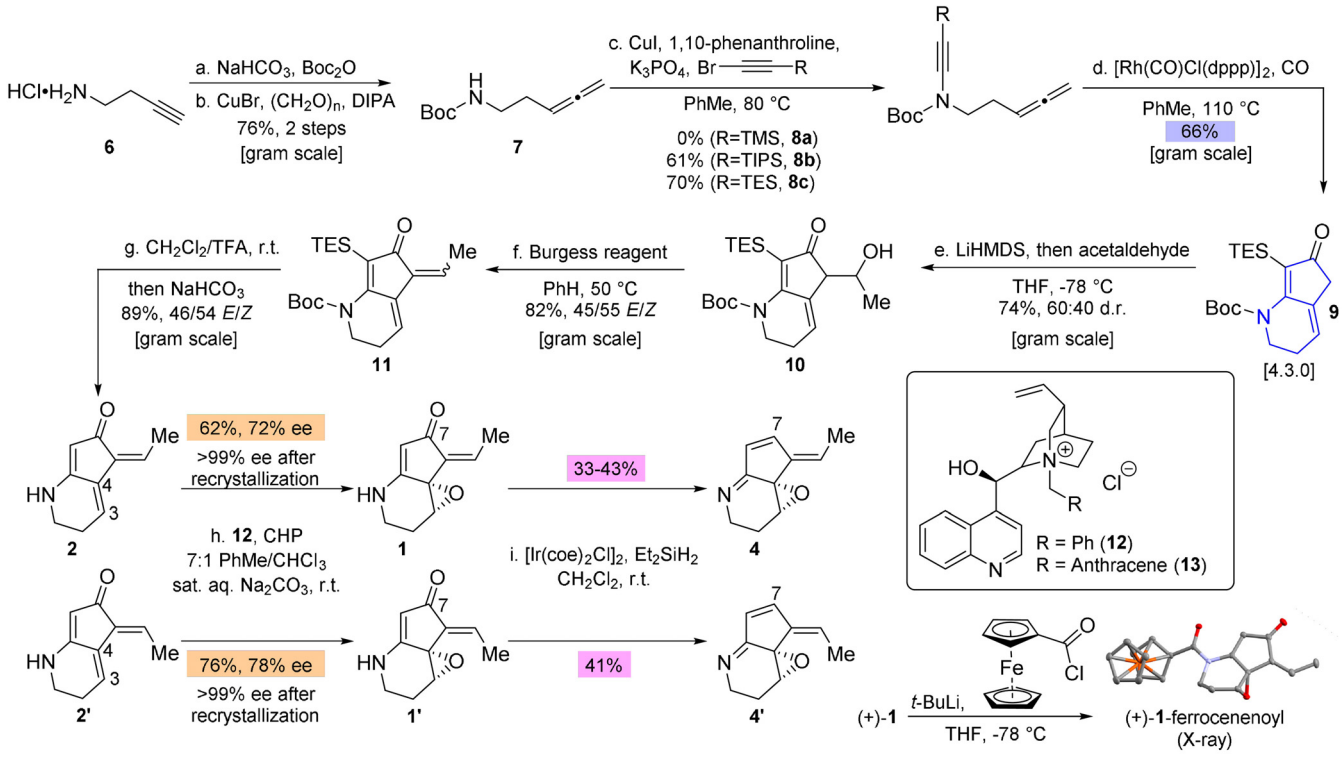


Figure 2. A) [4.3.0]-assembly during the biosynthesis of streptazone E and camporidine A and B. B) Different prior strategies towards streptazolin and streptazolone. C) Retrosynthetic analysis involving sequential transformations of three natural products.

double allylic tertiary position at C4 (Figure 1 A) which we speculate accounts for the severe instabilities reported for **4**.[10c] Mindful of the expected challenges associated with the epoxide, we pursued a strategy that would install this group at the final stages. Indeed, we realized the potential for developing an intriguingly direct approach in which streptazone B_1 (**2**) could be converted first to **1** and then further to **4** through sequential selective epoxidation and reduction (Figure 2 C). However, based on the reported ^{13}C NMR chemical shifts of **2**[2], the selective C3–C4 epoxidation was hard to predict and methodologies describing the subsequent enaminone-reduction were absent in the literature. Access to **2** would be possible via the simplified [4.3.0] bicyclic core **5** that was revealed by disconnecting the ethylidene sidechain (Figure 2 C).

This approach would also enable access to streptazone B_2 (**2′**) which is defined by (*E*)-configuration at the C8–C9-olefin (Figure 1 A) and provide a path towards the (*E*)-isomers of streptazone A and abikoviromycin—compounds currently uncharacterized from natural sources. To develop an efficient route to **5**, we judiciously evaluated the prior syntheses of streptazolin (**3**) and streptazolone (Figure 1 B, Figure 2 B) and found the intramolecular oxazolidinone Pauson–Khand cycloaddition utilized by Mukai and co-workers[12e] appealing, however, not directly applicable to our purpose. Instead, we envisioned that the olefin could be positioned advantageously by a distal selective intramolecular allene-ynamide Pauson–Khand cyclization (Figure 2 C), which, interestingly, is unprecedented in the literature for [4.3.0] scaffolds. Following ynamide and Crabbé disconnections, the analysis converged to commercial but-3-yn-1-amine hydrochloride **6** as an optimal starting material (Figure 2 C).

The synthesis was initiated using the Crabbé homologation[14] of **6** to deliver **7** in 76 % yield in multigram quantities over two steps (Scheme 1). Next, we turned our attention to establish the carbamate *N*–C(sp) bond. Several methodologies were evaluated[15] which generally failed to provide reproducible results for a scalable synthesis. Initial attempts based on TMS-bromoacetylene employing copper-catalyzed ynamide formation delivered the allene-ynamide **8a** in < 1 % yield, whereas the TIPS-bromoacetylene and the TES-bromoacetylene, resulting in **8b** and **8c**, respectively, performed significantly better after optimization (see the Supporting Information).[16] The intramolecular allene-ynamide Pauson–Khand cyclization was initially tested on all three ynamides (**8a**–**8c**) using $[Rh(CO)_2Cl]_2$ for regioselectively favoring the distal π-bond of the allene in the cyclization.[17–19] Furthermore, for safe handling of CO gas, we studied the reaction utilizing a two-chamber system developed by Skrydstrup and co-workers (see the Supporting Information).[20] Indeed, we found that the cyclization worked on all three substrates which establishes ynamides as functional precursors for rhodium-catalyzed Pauson–Khand cyclization to deliver [4.3.0] scaffolds. To our knowledge, only catalytic molybdenum has previously been employed in an intramolecular allene-ynamide cyclization, although to access [3.3.0] scaffolds.[21] In our hands, **8c** was balanced appropriately for both ynamide accessibility and performance in the early cyclization attempts. After evaluation of several distal selective catalysts (Scheme 1, step d), we found $[Rh(CO)Cl(dppp)]_2$ suitable for a scalable synthesis. With rapid access to the [4.3.0] core, installation of the C8-ethylidene group was achieved by LiHMDS and acetaldehyde treatment to afford a mixture (60:40 dr) of *β*-hydroxy ketones in 74 % yield. The diastereoisomers could readily undergo dehydration[22] using Burgess reagent to predominantly afford *syn*-eliminated *α*,*β*-unsaturated ketones **11** in 82 % yield as a 55:45 *cis*/*trans* mixture thereby allowing us to ultimately access the aforementioned uncharacterized geometric isomers. To our delight, protodesilylation and *N*-Boc deprotection could be achieved simultaneously using diluted TFA which upon basic work-up delivered streptazone B_1 (**2**) and streptazone B_2 (**2′**) in combined 89 % yield. Progressing forward, **2** and **2′** were separated by standard chromatography to study the direct epoxidation. Significant work was conducted in this particular transformation to probe the overall reactivity of the trisolefins in **2**/**2′** (see the Supporting Information). Generally, we found that electrophilic epoxidations using *m*-CPBA, DMDO etc. under different conditions delivered complex mixtures, presumably as a direct consequence of the more nucleophilic



Step d

Entry	Catalyst	Isolated (9/8c)
1	$[Rh(CO)_2Cl]_2$ (2.5 mol%)	24/0
2	$[Ir(cod)Cl]_2$ (2.5 mol%)	11/30
3	$[Ir(coe)_2Cl]_2$ (2.5 mol%)	11/12
4	$[Rh(cod)B(Ph)_4]$ (2.5 mol%)	32/5
5	$[Rh(CO)Cl(dppp)]_2$ (2.5 mol%)	56/0, (66/4)*

Screening was performed in two-chamber
* Conducted on 19.3 mmol scale

Step h

Entry	Conditions	Yield (2/1)#	ee%
1	*m*-CPBA, Jacobsen's $Mn^{(III)}$	0/trace	89
2	CHP, Shibasaki's La-BINOL	89/11*	0
3	CHP, DBU	28/23	-
4	CHP, TBAI	0/7	-
5	CHP, 12	0/56	76
6	CHP, 13	6/26	32

HNMR yield, * ratio between 2/1

Step i

Entry	Conditions	Result
1	Tf_2O then $Pd(OAc)_2$, TPP, Et_3N, HCO_2H	Decomposition
2	Tf_2O then $Pd(PPh_3)_4$, LiCl, Bu_3SnH	Decomposition
3	Schwartz reagent	1' recovered
4	$Zn(OAc)_2$, $(EtO)_3SiH$	1' recovered
5	$LiAlH(Ot\text{-}Bu)_3$, CuBr	1' recovered
6	Stryker's reagent, $PhMe_2SiH$	1' recovered
7	$[Ir(coe)_2Cl]_2$, Et_2SiH_2	1' recovered + 4'

Scheme 1. Synthesis of streptazone A and abikoviromycin. CCDC 2059610 for (+)-**1**-ferrocenenoyl.

enaminone system. Next, we tested Jacobsen's manganese-based system[23] (Scheme 1, step h, entry 1), which allowed us to identify **1** but unfortunately, the methodology failed to deliver improvement after substantial experimentation and was furthermore limited by irreproducible results on scales greater than 0.05 mmol. To our delight, we found that Shibasaki's lanthanum-BINOL system[24] (Scheme 1, step h, entry 2) also delivered **1**, although as a racemic mixture. Upon rational exclusion of each component in the system, it was clear that lanthanum was irrelevant for the epoxidation, while cumene hydroperoxide (CHP) at elevated temperature sluggishly could deliver **1** regioselectively. With catalytic DBU, we started to obtain promising results (Scheme 1, step h, entry 3) and conversion of **2** was further improved using TBAI as phase-transfer catalyst (PTC), although **1** was still only formed in small amounts (Scheme 1, step h, entry 4). This prompted us to investigate cinchona-based PTCs.[25] Gratifyingly, the yield of **2** increased significantly and stereoinduction was also obtained (Scheme 1, step h, entries 5 and 6). After further optimization (see the Supporting Information) we found that the commercial catalyst **12** could deliver **1** in 62% yield with 72% *ee* (>99% *ee* after recrystallization). Subsequent derivatization of (+)-**1** with ferrocene-COCl enabled us to determine the absolute configuration of (+)-**1** by X-ray crystallography. Streptazone B_2 (**2′**) could be converted to **1′** with equal efficiency.

The direct conversion from a free cyclic enaminone to the corresponding conjugated imine is to our knowledge not precedent in the literature. The transformation is complicated by several factors: 1) multiple sites in **1** are prone to alternate reductions, 2) facile over-reduction upon generation of the conjugated imine, 3) **4** is reportedly highly unstable.[10c] We decided to engage in a screen for reductive conditions utilizing the unnatural (*Z*)-olefin (**1′**) under the assumption that the overall outcome would be representative also for **1**. Our initial effort was based on the hypothesis that enaminones have increased electron density at the carbonyl group which should render the system more susceptible for *O*-activation. When **1′** was subjected to Tf_2O, we indeed observed *O*-triflation which was immediately subjected to reductive conditions under palladium catalysis (Scheme 1, step i, entries 1 and 2),[26,27] however, only decomposition of the starting material was observed. Next, we tested methodologies reported for secondary amide reduction (Scheme 1, step i, entries 3 and 4)[28,29] with neither indication of imine nor amine formation. Moreover, we evaluated the possibility of a 4-step sequence by initial copper hydride-catalyzed 1,4-reduction of the enaminone, triflation, reduction and lastly

relying on the reported enzymatic reoxidation to **4** by SF-973B oxidoreductase.[30–32] This idea, however, fell short of the goal already in the initial 1,4-reduction (Scheme 1, step i, entries 5 and 6). Finally, inspired by the recently reported total synthesis of herquline B and C by Baran and co-workers employing the iridium-diethylsilane system for amide reductions developed by Cheng and Brookhart, we found the conditions applicable to directly deliver the imine product **4′** (Scheme 1, step i, entry 7) (see the Supporting Information for evaluation of reductions).[33,34] In the case of **1**, the reduction proceeded slower but nonetheless afforded **4** in 43 % overall best yield, (see the Supporting Information for general stability of **4**). In the case of **1′**, simply increasing the reaction time pushed the reaction toward the dihydro adduct, whereas **1** required additional reductant to deliver dihydroabikoviromycin (see the Supporting Information), another [4.3.0] natural product.[6,35] Hence, the system may be employed to afford both the imine- and the amine [4.3.0] bicyclic classes by careful reaction control.

Finally, we investigated the electrophilic properties of **1** towards a biological thiol mimetic, *N*-acetylcysteamine, at physiological pH (Figure 3 A). Near complete conversion of **1** (95 % by HPLC, Figure 3 B) was obtained after 24 h thereby confirming the intrinsic reactivity of **1** towards thiols. Surprisingly, we were able to identify three major thiol-conjugates by analytical RP-HPLC, which we successfully isolated with the major product **14** corresponding to epoxide opening delivering a single diastereoisomer (Figure 3 A,B).

The epoxide was curiously opened at the tertiary position, not the secondary, and opening had occurred with inversion of configuration. We speculate that this reactivity is a direct

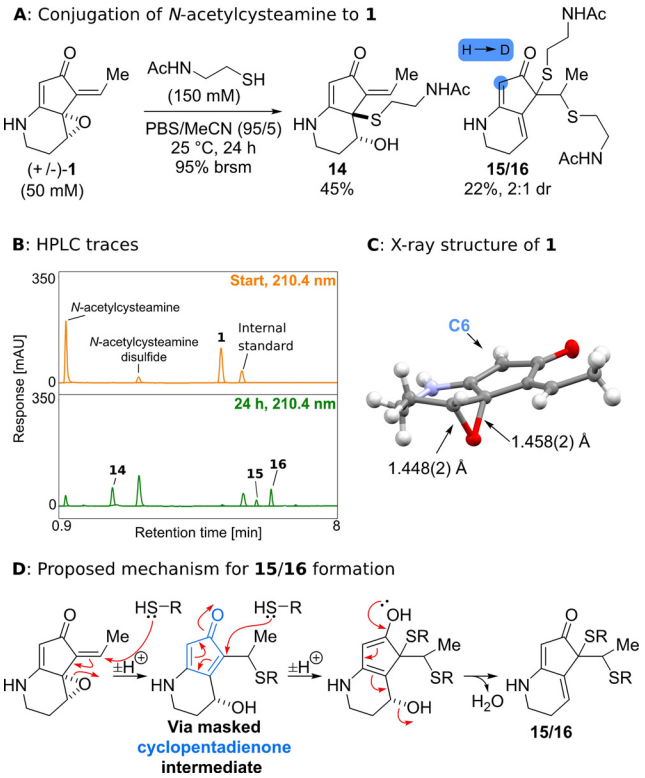


Figure 3. Studies of thiol-conjugation to streptazone A reveals dichotomous reactivity. CCDC 2059611 for (+/−)-**1**.

consequence of the double allylic contribution to the σ* C–O bond that in turn favors the tertiary carbon for incoming thiol-nucleophiles. In accord, crystallization of the natural product revealed that this particular C–O bond was slightly elongated (Figure 3 C). The remaining two products from the conjugation reaction corresponded to a set of diastereoisomers (**15**/**16**) and were unmistakably the products of double addition of *N*-acetylcysteamine (Figure 3 A,B). Again, we were surprised by the behavior of **1**, as it became evident from HMBC couplings, that **15**/**16** resulted from a completely different reaction path. We hypothesize that initial 1,4-addition induces epoxide opening, via the corresponding enolate, thereby unmasking a highly reactive cyclopentadienone electrophile (likely stabilized by the fused amine)[36] that undergoes a subsequent nucleophilic addition at the α-position and ultimately results in dehydration (Figure 3 D). To gain mechanistic insight, we conducted the conjugation in D_2O/CD_3CN and found that C6 had undergone full deuterium exchange, which could not be attributed to tautomerization of **1** nor was this observed for **14**, thereby suggesting that α-addition principally may be viewed as a 1,6-addition. To our knowledge, this is the first evidence supporting a masked cyclopentadienone natural product electrophile.

From a biological perspective, this data supports that **1** can act as a cysteine-reactive natural product and potentially also with the ability to facilitate cross-linking.[37] We anticipate that this highly peculiar reactivity will manifest itself in biological studies of this natural product family. Attempts to reproduce the reported toxicity against HepG2 cells were, in our hands, not successful with **1** (or **1′**). These observations, along with the observed intrinsic reactivity of **1**, underscores the importance of mapping the cellular targets of **1**.

In summary, we have developed the first syntheses of streptazone B_1/B_2, streptazone A, abikoviromycin and dihydroabikoviromycin in 7, 8, and 9 steps, respectively. The route also afforded access to geometric double-bond isomers of streptazone A and abikoviromycin, that may constitute members of this natural product family that are yet to be isolated. We discovered a new intramolecular Pauson–Khand cycloaddition performed on an allene-tethered ynamide substrate to deliver a bicyclo[4.3.0] core. Furthermore, we present a highly regioselective epoxidation employing chiral phase-transfer catalysis to epoxidize streptazone B_1 to A. This in turn enabled the direct reduction of the cyclic enaminone functionality using iridium catalysis to access abikoviromycin and dihydroabikoviromycin. Finally, we demonstrate that streptazone A possesses several electrophilic sites by in vitro thiol-conjugation studies which include formation of surprising double thiol-adducts that presumably are the result of a cyclopentadienone intermediate.

Acknowledgements

This work was supported by grants from the Novo Nordisk Foundation (grant NNF19OC0054782 to T.B.P.) and the Carlsberg Foundation (grant CF17-0800 to T.B.P.). We further thank the K. A. Jørgensen lab for access to chiral stationary phase UPC² and Anders Bodholt Nielsen and Dennis Wilkens

Juhl for technical assistance with NMR spectroscopy. Lastly, we thank the Troels Skrydstrup lab for technical assistance using the two-chamber system and Jens Christian Kondrup for scientific glassware design.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · electrophile · natural products · total synthesis · transition metal catalysis

[1] a) D. K. Nomura, T. J. Maimone, *Curr. Top. Microbiol. Immunol.* **2019**, *420*, 351 – 374; b) M. Gersch, J. Kreuzer, S. A. Sieber, *Nat. Prod. Rep.* **2012**, *29*, 659 – 682.
[2] C. Puder, P. Krastel, A. Zeeck, *J. Nat. Prod.* **2000**, *63*, 1258 – 1260.
[3] Q.-F. Liu, J.-D. Wang, X.-J. Wang, C.-X. Liu, J. Zhang, Y.-W. Pang, C. Yu, W.-S. Xiang, *J. Asian Nat. Prod. Res.* **2013**, *15*, 221 – 224.
[4] J. A. Perry, K. Koteva, C. P. Verschoor, W. Wang, D. M. Bowdish, G. D. Wright, *J. Antibiot.* **2015**, *68*, 40 – 46.
[5] T. Akiyama, S. Harada, F. Kojima, N. Kinoshita, M. Hamada, Y. Muraoka, T. Aoyagi, T. Takeuchi, *J. Antibiot.* **1998**, *51*, 253 – 260.
[6] a) H. Maruyama, S. Okamoto, Y. Kubo, G. Tsuji, I. Fujii, Y. Ebizuka, K. Furihata, Y. Hayakawa, H. Nagasawa, S. Sakuda, *J. Antibiot.* **2003**, *56*, 801 – 804; b) S. Takahashi, K. Serita, R. Enokita, T. Okaza, T. Haneishi, *Sankyo Kenkyusho Nenpo* **1986**, *38*, 105 – 108.
[7] K. Kanbe, H. Naganawa, Y. Okami, T. Takeuchi, *J. Antibiot.* **1992**, *45*, 1700 – 1702.
[8] H. Imai, S. Fujita, K. Suzuki, M. Morioka, T. Tokunaga, M. Shimizu, S. Kadota, T. Furuya, T. Saito, *J. Antibiot.* **1989**, *42*, 1043 – 1048.
[9] S.-H. Hong, Y. H. Ban, W. S. Byun, D. Kim, Y.-J. Jang, J. S. An, B. Shin, S. K. Lee, J. Shin, Y. J. Yoon, D.-C. Oh, *J. Nat. Prod.* **2019**, *82*, 903 – 910.
[10] Abikoviromycin has also been referred to as latumcidin in some earlier papers. In this manuscript we refer to the compound as abikoviromycin: a) Y. Sakagami, I. Yamaguchi, H. Yonehara, Y. Okimoto, S. Yamanouchi, K. Takiguchi, H. Sakai, *J. Antibiot. Ser. A* **1958**, *11*, 6 – 13; b) H. Umezawa, T. Tazaki, S. Fukuyama, *Jpn. Med. J.* **1951**, *4*, 331 – 346; c) A. Gurevich, M. Kolosov, V. Korobko, V. Onoprienko, *Tetrahedron Lett.* **1968**, *9*, 2209 – 2212; d) D. Mitchell, L. S. Liebeskind, *J. Am. Chem. Soc.* **1990**, *112*, 291 – 296.
[11] a) H. Drautz, H. Zahner, E. Kupfer, W. Kellerschierlein, *Helv. Chim. Acta* **1981**, *64*, 1752 – 1765; b) C.-L. Yang, Y.-S. Wang, C.-L. Liu, Y.-J. Zeng, P. Cheng, R.-H. Jiao, S.-X. Bao, H.-Q. Huang, R.-X. Tan, H.-M. Ge, *Mar. Drugs* **2017**, *15*, 244.
[12] a) A. P. Kozikowski, P. Uk Park, *J. Am. Chem. Soc.* **1985**, *107*, 1763 – 1765; b) C. J. Flann, L. E. Overman, *J. Am. Chem. Soc.* **1987**, *109*, 6115 – 6118; c) H. Yamada, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **1996**, *118*, 1054 – 1059; d) S. Huang, D. L. Comins, *Chem. Commun.* **2000**, 569 – 570; e) I. Nomura, C. Mukai, *Org. Lett.* **2002**, *4*, 4301 – 4304; f) B. M. Trost, C. K. Chung, A. B. Pinkerton, *Angew. Chem. Int. Ed.* **2004**, *43*, 4327 – 4329; *Angew. Chem.* **2004**, *116*, 4427 – 4429; g) F. Li, N. C. Warshakoon, M. J. Miller, *J. Org. Chem.* **2004**, *69*, 8836 – 8841.
[13] S. Ohno, Y. Katsuyama, Y. Tajima, M. Izumikawa, M. Takagi, M. Fujie, N. Satoh, K. Shin-ya, Y. Ohnishi, *ChemBioChem* **2015**, *16*, 2385 – 2391.
[14] a) M. Li, D. J. Dixon, *Org. Lett.* **2010**, *12*, 3784 – 3787; b) P. Crabbé, H. Fillion, D. André, J.-L. Luche, *J. Chem. Soc. Chem. Commun.* **1979**, 859 – 860.
[15] Selected examples: a) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1998**, *37*, 489 – 492; *Angew. Chem.* **1998**, *110*, 495 – 498; b) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368 – 2369; c) J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011 – 4014; d) F. M. Istrate, A. K. Buzas, I. D. Jurberg, Y. Odabachian, F. Gagosz, *Org. Lett.* **2008**, *10*, 925 – 928; e) S. J. Mansfield, R. C. Smith, J. R. J. Yong, O. L. Garry, E. A. Anderson, *Org. Lett.* **2019**, *21*, 2918 – 2922; f) N. Riddell, K. Villeneuve, W. Tam, *Org. Lett.* **2005**, *7*, 3681 – 3684.
[16] a) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151 – 1154; b) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem.* **2006**, *71*, 4170 – 4177; c) K. Dooleweerdt, H. Birkedal, T. Ruhland, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 9447 – 9450.
[17] K. M. Brummond, H. Chen, K. D. Fisher, A. D. Kerekes, B. Rickards, P. C. Sill, S. J. Geib, *Org. Lett.* **2002**, *4*, 1931 – 1934.
[18] S. Kitagaki, F. Inagaki, C. Mukai, *Chem. Soc. Rev.* **2014**, *43*, 2956 – 2978.
[19] A. S. Bayden, K. M. Brummond, K. D. Jordan, *Organometallics* **2006**, *25*, 5204 – 5206.
[20] P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061 – 6071.
[21] A. K. Gupta, D. I. Park, C. H. Oh, *Tetrahedron Lett.* **2005**, *46*, 4171 – 4174.
[22] P. Hjerrild, T. Tørring, T. B. Poulsen, *Nat. Prod. Rep.* **2020**, *37*, 1043 – 1064.
[23] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801 – 2803; b) B. D. Brandes, E. N. Jacobsen, *J. Org. Chem.* **1994**, *59*, 4378 – 4380.
[24] M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329 – 2330.
[25] a) J. C. Hummelen, H. Wynberg, *Tetrahedron Lett.* **1978**, *19*, 1089 – 1092; b) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599 – 1602; c) B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289 – 6300.
[26] S. Cacchi, E. Morera, G. Ortar, *Tetrahedron Lett.* **1984**, *25*, 4821 – 4824.
[27] W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033 – 3040.
[28] S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 1770 – 1771.
[29] D. J. A. Schedler, A. G. Godfrey, B. Ganem, *Tetrahedron Lett.* **1993**, *34*, 5035 – 5038.
[30] T. Focken, A. B. Charette, *Org. Lett.* **2006**, *8*, 2985 – 2988.
[31] B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Sclafani, R. W. Vivian, J. M. Keith, *Tetrahedron* **2000**, *56*, 2779 – 2788.
[32] T. Tsuruoka, T. Shomura, Y. Ogawa, N. Ezaki, H. Watanabe, S. Amano, S. Inouye, T. Niida, *J. Antibiot.* **1973**, *26*, 168 – 174.
[33] C. He, T. P. Stratton, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 29 – 32.
[34] C. Cheng, M. Brookhart, *J. Am. Chem. Soc.* **2012**, *134*, 11304 – 11307.
[35] a) J. Holmalahti, J. Mäki-Paakkanen, L. Kangas, A. von Wright, *Mutat. Res. Genet. Toxicol.* **1996**, *368*, 157 – 163; b) J. Holmalahti, O. Raatikainen, A. von Wright, H. Laatsch, A. Spohr, O. K. Lyngberg, J. Nielsen, *J. Appl. Microbiol.* **1998**, *85*, 61 – 68.
[36] J. D. Rainier, J. E. Imbriglio, *J. Org. Chem.* **2000**, *65*, 7272 – 7276.
[37] Y. Isobe, M. Okumura, L. M. McGregor, S. M. Brittain, M. D. Jones, X. Liang, R. White, W. Forrester, J. M. McKenna, J. A. Tallarico, M. Schirle, T. J. Maimone, D. K. Nomura, *Nat. Chem. Biol.* **2020**, *16*, 1189 – 1198.

Manuscript received: January 29, 2021
Accepted manuscript online: February 11, 2021
Version of record online: March 18, 2021

