



**HAL**  
open science

## Approach to pactamycin analogues using rhodium(II)-catalyzed alkene aziridination and C(sp<sup>3</sup>)-H amination reactions

Romain Rodrigues, Yanis Lazib, Julien Maury, Luc Neuville, David Leboeuf, Philippe Dauban, Benjamin Darses

### ► To cite this version:

Romain Rodrigues, Yanis Lazib, Julien Maury, Luc Neuville, David Leboeuf, et al.. Approach to pactamycin analogues using rhodium(II)- catalyzed alkene aziridination and C(sp<sup>3</sup>)-H amination reactions. *Organic Chemistry Frontiers*, 2018, 5 (6), pp.948-953. 10.1039/c7qo00878c . hal-02366206

**HAL Id: hal-02366206**

**<https://hal.science/hal-02366206v1>**

Submitted on 15 Nov 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Approach to pactamycin analogues using rhodium(II)-catalyzed alkene aziridination and C(sp<sup>3</sup>)—H amination reactions

Received 00th January 20xx,  
Accepted 00th January 20xx

Romain Rodrigues,<sup>a</sup> Yanis Lazib,<sup>a</sup> Julien Maury,<sup>a,b</sup> Luc Neuville,<sup>a</sup> David Leboeuf,<sup>b</sup> Philippe Dauban\*<sup>a</sup> and Benjamin Darses\*<sup>a</sup>

DOI: 10.1039/x0xx00000x

www.rsc.org/

Dirhodium(II)-catalyzed nitrene transfers have been used to prepare a novel synthetic platform bearing the triamino moiety present in pactamycin, jogyamycin and cranomycin. Catalytic intramolecular C(sp<sup>3</sup>)-H amination and alkene aziridination reactions, the latter followed by a nucleophilic aziridine ring opening, are the key steps of this strategy.

### Introduction

The genus *Streptomyces* has been a very productive source of biologically active molecules with original chemical structures. Among them, Pactamycin (Figure 1), which was first isolated from a fermentation broth of *Streptomyces pactum* var *pactum*, as a potential anticancer agent,<sup>1</sup> was the first member of a fascinating aminocyclopentitol family. This natural antibiotic displays antimicrobial activities against gram-positive and gram-negative bacteria, as well as *in vitro* and *in vivo* anti-proliferative activities, and anti-protozoal properties.<sup>2</sup> The general cytotoxic effect arises from the interaction of Pactamycin with a highly conserved region of the small ribosomal subunit, causing the inhibition of the protein synthesis and the cell's death.<sup>3</sup>

In 2000, an X-ray crystallography study has revealed the nature of the interactions between Pactamycin and the ribosomal 30S subunit of *Thermus thermophilus*,<sup>4</sup> allowing the identification of the functional groups responsible for the interaction with the ribosome small unit. Importantly, it can be highlighted that the C<sub>4</sub> site, bearing the OH and the methyl group, would not be involved in any stabilizing interaction, and it was later shown

that the absence of the methyl salicylate moiety does not modify the binding site between the ribosome and Pactamycin.<sup>5</sup>

In 2011, the Pactamycin analogues TM-025 and TM-026, obtained by bioengineering, exhibited an improved profile, displaying a greater cytotoxicity against *Plasmodium falciparum* as compared to mammalian cells, however, specific analog design by this method is prohibited.<sup>6</sup> Moreover, Jogyamycin,<sup>7</sup> and Cranomycin (also called 7-deoxypactamycin),<sup>8</sup> two very closely related natural products, also confirmed that minute modifications at C<sub>6</sub> and C<sub>7</sub> could modify both the toxicity and the selectivity.

The structural complexity of this aminocyclopentitol family and its relevant biological activities made its members stimulating targets for both synthetic and medicinal chemists. Different approaches to the partially functionalized core of Pactamycin or Jogyamycin have been thus reported.<sup>9,10</sup> More significantly, the first total synthesis of Pactamycin including 32 steps was reported in 2011 by the group of Hanessian,<sup>11</sup> followed two years later by a total synthesis completed in only 15 steps by the group of Johnson.<sup>12</sup>

These two successful strategies prompted each group to develop novel Pactamycin analogs.<sup>13</sup> These results, combined with the different X-ray crystallography information and the biosynthetic studies, afford valuable tools to design fine-tuned Pactamycin analogues with improved specific biological activity.

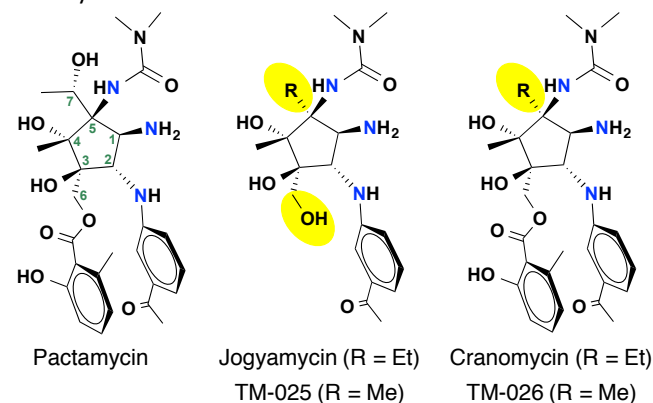
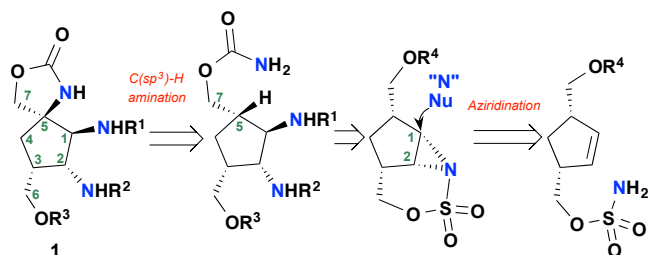


Figure 1 Pactamycin and biologically active aminocyclopentitols

<sup>a</sup> Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ. Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette, France.

E-mail: philippe.dauban@cnrs.fr, benjamin.darses@cnrs.fr

<sup>b</sup> Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Univ. Paris-Sud, Université Paris-Saclay, bâtiment 420, 91405 Orsay cedex, France



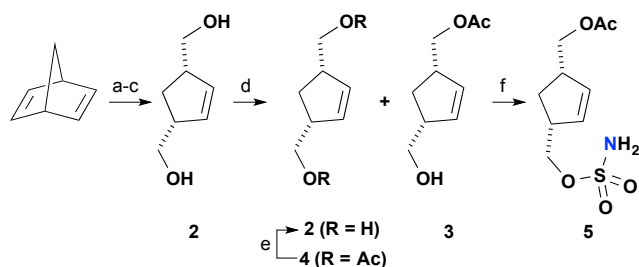
**Scheme 1** Building the triamino moiety of **1** via nitrene insertions

Over the last two decades, the field of nitrene addition reactions has considerably expanded.<sup>14</sup> Following the initial discovery that transition metal complexes can react with iminoiodinanes to form metallanitrenes, practical procedures were described for the *in situ* generation of iminoiodinanes. This breakthrough made possible the development of catalytic C(sp<sup>3</sup>)-H amination and alkene aziridination reactions, as methods of choice for the synthesis of complex nitrogen-containing natural and/or bioactive products.<sup>15</sup> Accordingly, we and others have identified that the triamino moiety of Pactamycin and derivatives, could be introduced using sequential nitrene insertion reactions.<sup>9b,f,g,10</sup> Indeed, the C<sub>1</sub>-C<sub>2</sub> 1,2-diamino moiety could result from the ring opening of an aziridine, obtained by the tethered alkene aziridination reported by Du Bois and our group,<sup>16</sup> while the C<sub>5</sub> tertiary amino group could be introduced by an intramolecular C(sp<sup>3</sup>)-H amination reaction (Scheme 1).<sup>17</sup> Herein we report the application of this strategy to the preparation of the advanced synthetic intermediate **1**, that could serve as a platform for the development simplified analogs of Pactamycin, Jogyamycin or Cranomycin. This intermediate could indeed allow tuning of the C<sub>7</sub> center, key to the biological activity, and afford a never reported series of compounds bearing a methylene at C<sub>4</sub>.<sup>18</sup>

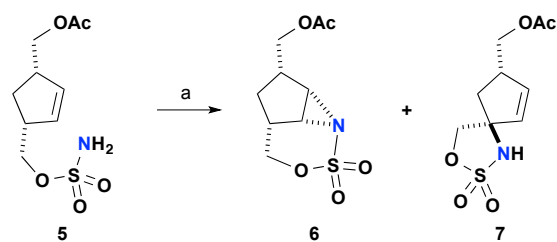
## Results and Discussion

### Preparation of the sulfamate **5**

Sulfamate **5** was identified as a first key intermediate in the synthesis of the pivotal product **1** (Scheme 2). Its preparation begins by the formation of the primary diol **2**, directly



**Scheme 2** Preparation of the nitrene precursor **5**. Reaction conditions: (a) OsO<sub>4</sub> 0.4 mol %, NMO, pyridine, *t*-BuOH/H<sub>2</sub>O reflux, 15h, 71%; (b) NaIO<sub>4</sub>, HCO<sub>2</sub>Me/H<sub>2</sub>O, 0 °C to rt, 1h; (c) LiAlH<sub>4</sub>, THF, 0 °C to rt, 2h, **2** 85% (2 steps); (d) Ac<sub>2</sub>O, Et<sub>3</sub>N, DCM, 0 °C to rt, 18h, **3** 53%, **2** 26% and **4** 20%; (e) MeONa, MeOH, rt, 18h, 2 99%; (f) ClSO<sub>2</sub>NCO, HCO<sub>2</sub>H, 0 °C to rt, 16h then **3**, DMA, pyridine, 0 °C to rt, 5h, **5** 90%. NMO = 4-methylmorpholine *N*-oxide; DMA = dimethylacetamide.



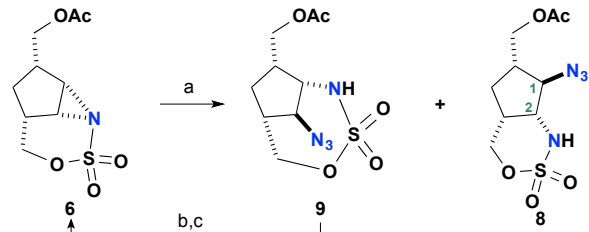
[Rh]	Loading	<b>6</b>	<b>7</b>
Rh <sub>2</sub> (esp) <sub>2</sub>	1 mol%	79%	10%
Rh <sub>2</sub> (OAc) <sub>4</sub>	1 mol%	82%	13%
Rh <sub>2</sub> (octanoate) <sub>4</sub>	1 mol%	71%	13%
Rh <sub>2</sub> (OCOCPh <sub>3</sub> ) <sub>4</sub>	1 mol%	87%	7%
Rh <sub>2</sub> (NHCOCF <sub>3</sub> ) <sub>4</sub>	1 mol%	96%	3%
<b>Rh<sub>2</sub>(NHCOCF<sub>3</sub>)<sub>4</sub></b>	<b>0.3 mol%</b>	<b>95%</b>	<b>3%</b>

**Scheme 3** Rhodium(II)-catalyzed aziridination. Reaction conditions: (a) [Rh], PhI(OAc)<sub>2</sub> 1.3 equiv., MgO 1.9 equiv., DCM, 0 °C to rt, see table.

accessible from norbornadiene following modification of the procedure reported by Rovis.<sup>19</sup> Thus, use of the low boiling point methyl formate as solvent was found to greatly facilitate the manipulation of the unstable dialdehyde obtained by oxidative cleavage of the dihydroxynorbornene intermediate, and subsequent reduction with LiAlH<sub>4</sub>. It indeed prevents the need of a tedious work up involving an extraction of the hydrophilic diol **2** from water. Classical conditions for acetylation, then, allowed us to obtain the mono acetylated compound **3** in 53% yield,<sup>20</sup> accompanied by 26% of recovered starting material **2** and 20% of diacetylated product **4**, the latter being used to regenerate **2** in quantitative yield. The nitrene precursor was finally isolated in 90% yield after the sulfamoylation reaction using sulfamoyl chloride, generated from chlorosulfonyl isocyanate.

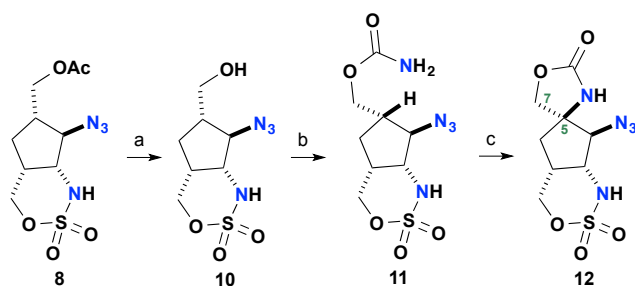
### Study of the aziridination reaction and the subsequent aziridine ring-opening

With this key precursor in hand, the first catalytic nitrene transfer of our strategy was envisaged. The intramolecular alkene aziridination was performed in the presence of 1.3 equivalents of PhI(OAc)<sub>2</sub> and 1 mol % of Rh<sub>2</sub>(esp)<sub>2</sub> (Scheme 3). Under these conditions, the expected aziridine **6** was isolated in 79% yield, accompanied by 10% of the tertiary C(sp<sup>3</sup>)-H amination product **7**. A rapid screening of the dirhodium(II)



**Scheme 4** Aziridine ring opening and recycling of **9**. Reaction conditions: (a) TMSN<sub>3</sub>, TBAF cat., MeCN, rt, **8** 63% and **9** 32%; (b) H<sub>2</sub>(g), Pd/C cat., AcOEt; (c) NaNO<sub>2</sub>/H<sub>2</sub>O, THF/AcOH, 0 °C to rt, **6** 42% (2 steps).

complexes allowed us to determine that Rh<sub>2</sub>(CF<sub>3</sub>CONH)<sub>4</sub> was

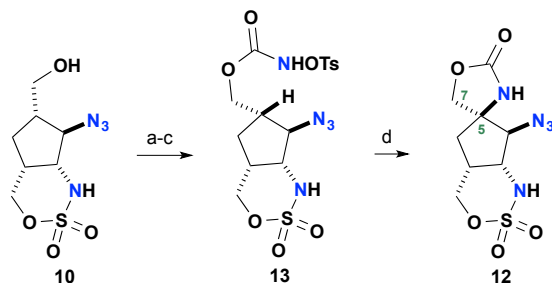


PhI(OR) <sub>2</sub>	Solvent	Time	<b>11</b>	<b>12</b>
PhI(OAc) <sub>2</sub>	TCE	16h	21%	18%
PhI(OAc) <sub>2</sub>	Benzene	16h	20%	12%
PhI(OAc) <sub>2</sub>	TCE	4 days	5%	5%
PhI(OPiv) <sub>2</sub>	Benzene	5h	50%	16%
PhI(OPiv) <sub>2</sub>	TCE	5h	48%	16%
<b>PhI(OPiv)<sub>2</sub></b>	<b>Benzene</b>	<b>16h</b>	<b>25%</b>	<b>20%</b>

**Scheme 5** Preparation of **11** and C(sp<sup>3</sup>)-H amination. Reaction conditions: (a) MeONa, MeOH, rt, 30 min., **10** 99%; (b) NaOCN, TFA, DCM, rt, 24h, **11** 66%; (c) Rh<sub>2</sub>(NHCOCF<sub>3</sub>)<sub>4</sub> 10 mol %, PhI(OR)<sub>2</sub> 1.5 equiv., MgO 3 equiv., solvent, 80 °C, see table. TCE = 1,1,2,2-tetrachloroethane.

the catalyst of choice to improve the chemoselectivity in favor of the aziridination product, the latter being isolated in 96% yield using this dirhodium(II) complex.<sup>21</sup> Moreover, the catalyst loading could be reduced to 0.3 mol % without any loss of efficiency.

The subsequent ring opening of the aziridine **6** proved to be more troublesome as the reaction with a nitrogen nucleophile showed poor regioselectivity. Extensive screening of nucleophiles, solvents, temperature and additives (see supplementary information for selected examples) led us to identify the combination of TMSN<sub>3</sub> and a catalytic amount of TBAF in MeCN as the best combination of reagents. The expected product **8** was thus isolated in 63%, but accompanied by 32% of the undesired regioisomer **9** (Scheme 4). Pleasingly, with the aim to recycle the latter, we found that reduction of the azide followed by diazotization of the resulting crude amine led to recover the starting aziridine **6** with a non-optimized yield of 42% over two steps. Formation of **6** results from the intramolecular substitution of the transient diazonium by the nitrogen of the sulfamate.<sup>22</sup>



**Scheme 6** C(sp<sup>3</sup>)-H amination using Lebel's protocol. Reaction conditions: (a) CDI, THF, rt, 3h; (b) NH<sub>2</sub>OH·HCl, pyridine, rt, 16h; (c) TsCl, Et<sub>3</sub>N, THF, 0 °C to rt, 6h, **13** 60% (3 steps); (d) Rh<sub>2</sub>(OCOCPH<sub>3</sub>)<sub>4</sub> 6 mol %, K<sub>2</sub>CO<sub>3</sub>, DCM, rt, **12** 10%.

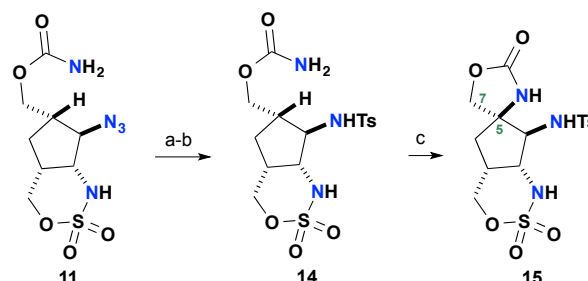
### Study of the intramolecular C(sp<sup>3</sup>)-H amination reaction in the presence of the cyclic sulfamate

We then planned to investigate the intramolecular C(sp<sup>3</sup>)-H amination of the tertiary C<sub>5</sub> center. Many nitrene sources are available to perform such a transformation,<sup>14g,j</sup> and in order to favour the formation of the expected 5-membered ring, we decided to introduce a carbamate as the nitrene precursor. Starting from compound **8**, the deacetylated intermediate **10** was obtained in nearly quantitative yield and subsequent carbamylation afforded **11** in 70% yield as the nitrene precursor for C(sp<sup>3</sup>)-H amination (Scheme 5).<sup>23</sup> Unfortunately, a screening of the reaction conditions only allowed reaching 20% of the expected product **12**, and 25% of recovered starting material.<sup>24</sup> Under all the tested reaction conditions, a high level of decomposition was observed.

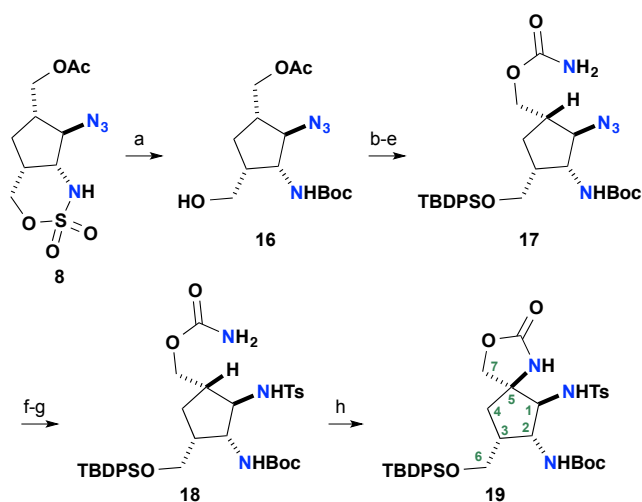
In order to try to improve the conversion, we turned our attention to the redox neutral conditions developed by Lebel.<sup>25</sup> The *N*-(sulfonyloxy)carbamate **13**, thus, was prepared from the alcohol **10** in 60% yield over 3 steps (Scheme 6). However, the C(sp<sup>3</sup>)-H amination reaction proved to be even less satisfying with only 10% of the expected product **12** isolated and no starting material recovery.

We identified the azido substituent as a potential unstable function responsible for the degradation of **14**, and, thus, decided to reduce this group and protect it as a sulfonamide. The resulting compound **14** was isolated in 72% over two steps (Scheme 7). Submitting the latter to different C(sp<sup>3</sup>)-H amination reaction conditions proved to be much more rewarding, the expected product **15** being isolated in 50% yield in the presence of 20 mol % of Rh<sub>2</sub>(CF<sub>3</sub>CONH)<sub>4</sub> and 1 equiv. of CF<sub>3</sub>CONH<sub>2</sub>. It is noteworthy that the degradation was limited, 46% of the starting material being recovered. However, the very low solubility of **14** in a broad range of solvents has impeded the improvement upon screening of the reaction conditions. Traces of product **15** were obtained in the presence of common rhodium complexes in acetonitrile, a solvent in which compound **14** is soluble.

We wondered whether the unexpected low turnover of the effective dirhodium complex could result from the presence of coordinating groups, likely to inhibit its catalytic activity. Accordingly, we have decided to remove the sulfamate moiety



**Scheme 7** Modification of the azide and C(sp<sup>3</sup>)-H amination. Reaction conditions: (a) H<sub>2</sub>(g), Pd/C cat., MeOH, rt, 30 min.; (b) TsCl, Et<sub>3</sub>N, DMAP cat., MeCN, rt, 4h, **14** 72% (2 steps); (c) TsCl, Et<sub>3</sub>N, THF, 0 °C to rt, 6h, **13** 60%; (d) Rh<sub>2</sub>(NHCOCF<sub>3</sub>)<sub>4</sub> 20 mol %, CF<sub>3</sub>CONH<sub>2</sub> 1 equiv., PhI(OAc)<sub>2</sub>, MgO, rt, 12h, **15** 50% and **14** 46%.



[Rh]	PhI(OR) <sub>2</sub>	Solvent	Time	18	19
Rh <sub>2</sub> (OAc) <sub>4</sub>	PhI(OAc) <sub>2</sub>	Benzene	15h	22%	54%
Rh <sub>2</sub> (NHCOCF <sub>3</sub> ) <sub>4</sub>	PhI(OAc) <sub>2</sub>	MeCN	15h	28%	58%
Rh <sub>2</sub> (OAc) <sub>4</sub>	PhI(OAc) <sub>2</sub>	TCE	15h	64%	22%
Rh <sub>2</sub> (esp) <sub>2</sub>	PhI(OAc) <sub>2</sub>	Benzene	18h	n.d.	48%
<b>Rh<sub>2</sub>(OAc)<sub>4</sub></b>	<b>PhI(OCOMe<sub>2</sub>Ph)<sub>2</sub></b>	<b>Benzene</b>	<b>18h</b>	<b>16%</b>	<b>63%</b>
Rh <sub>2</sub> (OAc) <sub>4</sub>	PhI(OCOMe <sub>2</sub> Ph) <sub>2</sub>	Benzene*	18h	26%	44%
Rh <sub>2</sub> (OAc) <sub>4</sub>	PhI(OCOMe <sub>2</sub> Ph) <sub>2</sub> **	Benzene	18h	10%	60%

\* 80 °C; \*\* PhI(OCOMe<sub>2</sub>Ph)<sub>2</sub> 3 equiv. and MgO 6 equiv.

**Scheme 8** Final strategy for C(sp<sup>3</sup>)-H amination. Reaction conditions: (a) Boc<sub>2</sub>O, DMAP cat., THF, rt, 1h, then phosphate buffer pH 8, 50 °C, 29h, **16** 74%; (b) TBDPSCI, imidazole, DMAP cat., DMF, 0 °C to rt, 96%; (c) MeONa, MeOH, 0 °C, 25 min., 94%; (d) Cl<sub>3</sub>CCONCO, DCM, 0 °C to rt, 30 min.; (e) K<sub>2</sub>CO<sub>3</sub>, MeOH, 50 min., **17** 97% (2 steps); (f) H<sub>2</sub>(g), Pd/C cat., MeOH, rt, 1h30; (g) TsCl, Et<sub>3</sub>N, DCM, rt, 1h, **18** 76% (2 steps); (h) [Rh] 10 mol %, PhI(OR)<sub>2</sub> 1.5 equiv., MgO 3 equiv., 50 °C.

and replace it by orthogonal protecting groups, prone to improve the solubility of our intermediates.

Therefore, after Boc activation of the nitrogen atom of **8**, hydrolysis afforded **16** in 74% over two steps, 14% of the Boc-protected sulfamate being also isolated (Scheme 8). Subsequent high yielding sequence of protection of the primary hydroxyl group as a silyl ether, acetyl group removal and carbamoylation led to the carbamate **17**. Repeating the azide reduction and Ts protection strategy delivered the more soluble C(sp<sup>3</sup>)-H amination precursor **18**. Indeed, extensive screening of the reaction conditions was possible with this intermediate. We found that the best conditions involve the use of 10 mol % of Rh<sub>2</sub>(OAc)<sub>4</sub> in benzene at 50 °C, and in the presence of the hypervalent iodine reagent PhI(OCOCMe<sub>2</sub>Ph)<sub>2</sub> subtly developed by Du Bois in the course of his mechanistic studies of the Rh<sub>2</sub>(esp)<sub>2</sub>-catalyzed reaction.<sup>26</sup> Under these conditions, the targeted pivotal product **19** (1 with R<sup>1</sup> = Ts; R<sup>2</sup> = Boc; R<sup>3</sup> = TBDPS) was obtained in 63% yield.

## Conclusions

In conclusion, we have designed a synthetic strategy from norbornadiene enabling the access to the novel platform **19** displaying the triamino moiety present in the

aminocyclopentitol congeners pactamycin, jogyamycin and cranomycin, with the correct relative stereochemistry. These aminated functional groups have been introduced by application of the synthetic nitrene chemistry and the dirhodium(II) catalysis: an intramolecular alkene aziridination followed by a nucleophilic aziridine ring opening delivers the 1,2 diamino motif whereas an intramolecular C(sp<sup>3</sup>)-H amination reaction allows for introducing the tertiary amino center.<sup>27</sup> Further work is currently under progress in our group to prepare new analogs of these bioactive natural products.

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgments

We wish to thank the Institut de Chimie des Substances Naturelles (fellowship to R. R.) and the French National Research Agency (program no INTER-NIT ANR-15-CE29-0014-01, and CHARMMMAT ANR-11-LABX-0039 fellowship to J. M.) for their support.

## Notes and references

- 1 A. D. Argoudelis, H. K. Jahnke and J. A. Fox, *Antimicrob. Agents Chemother.* **1962**, 191.
- 2 (a) B. K. Bhuyan, A. Dietz and C. G. Smith, *Antimicrob. Agents Chemother.* **1962**, 184; (b) F. R. White, *Cancer Chemother. Rep.* **1962**, **24**, 75; (c) B. K. Bhuyan *Biochem. Pharmacol.* **1967**, **16**, 1411; (d) K. Dobashi, K. Isshiki, T. Sawa, T. Obata, M. Hamada, H. Naganawa, T. Takita, T. Takeuchi and H. Umezawa *J. Antibiot.* **1986**, **39**, 1779; (e) E. S. Adama and K. L. Rinehart, *J. Antibiot.* **1994**, **47**, 1456. (f) K. Otoguro, M. Iwatsuki, A. Ishiyama, M. Namatame, A. Nishihara-Tsukashima, S. Shibahara, S. Kondo, H. Yamada and S. Omura, *J. Antibiot.* **2010**, **63**, 381; (g) M. E. Abugrain, W. Lu, Y. Li, J. D. Serrill, C. J. Brumsted, An. R. Osborn, A. Alani, J. E. Ishmael, J. X. Kelly and T. Mahmud, *ChemBiolChem* **2016**, **17**, 1585.
- 3 (a) G. Dinos, D. N. Wilson, Y. Teraoka, W. Szafarski, P. Fucini, D. Kalpaxis and K. H. Nierhaus, *Mol. Cell* **2004**, **13**, 113; (b) J. Egebjerg and R. A. Garrett *Biochimie* **1991**, **73**, 1145; (c) J. Woodcock, D. Moazed, M. Cannon, J. Davies and H. F. Noller, *EMBO J.* **1991**, **10**, 3099.
- 4 D. E. Brodersen, W. M. Clemons Jr., A. P. Carter, R. J. Morgan-Warren, B. T. Wimberly and V. Ramakrishnan, *Cell* **2000**, **103**, 1143.
- 5 D. S. Tourigny, I. S. Fernández, A. C. Kelley, R. R. Vakiti, A. K. Chattopadhyay, S. Dorich, S. Hanessian and V. Ramakrishnan, *J. Mol. Biol.* **2013**, **425**, 3907.
- 6 W. Lu, N. Roongsawang and T. Mahmud, *Chem. Biol.* **2011**, **18**, 425.
- 7 M. Iwatsuki, A. Nishihara-Tsukashima, A. Ishiyama, M. Namatame, Y. Watanabe, S. Handasah, H. Pranamuda, B. Marwoto, A. Matsumoto, Y. Takahashi, K. Otoguro and S. Omura, *J. Antibiot.* **2012**, **65**, 169.
- 8 S. Kondo, M. Shimura, M. Sezaki, K. Sato and T. Hara, *J. Antibiot. Ser. A* **1964**, **17**, 230.
- 9 (a) T. Tsujimoto, T. Nishikawa, D. Urabe and M. Isobe, *SYNLETT* **2005**, 433; (b) S. Knapp and Y. Yu, *Org. Lett.* **2007**, **9**, 1359; (c) N. Matsumoto, T. Tsujimoto, A. Nakazaki, M. Isobe and T. Nishikawa, *RSC Advances* **2012**, **2**, 9448; (d) J. T. Malinowski, S. J. McCarver and J. S. Johnson, *Org. Lett.* **2012**, **14**, 2878; (e) T. J. Haussener and R. E. Looper, *Org. Lett.* **2012**, **14**, 3632; (f) M. Yamaguchi, M. Hayashi, Y. Hamada and T. Nemoto, *Org. Lett.* **2016**, **18**, 2347; (g) A. Goto, S. Yoshimura, Y. Nakao, M. Inai, T. Asakawa, M. Egi, Y. Hamashima, M. Kondo and T. Kan, *Org. Lett.* **2017**, **19**, 3358; (h) N. Matsumoto, A.

- Nakazaki and T. Nishikawa, *SYNLETT* 2017, DOI: 10.1055/s-0036-1588495.
- 10 N. C. Gerstner, C. S. Adams, R. D. Grigg, M. Tretbar, J. W. Rigoli and J. M. Schomaker, *Org. Lett.* 2016, **18**, 284.
  - 11 (a) S. Hanessian, R. R. Vakiti, S. Dorich, S. Banerjee, F. Lecomte, J. R. DelValle, J. Zhang and B. Deschênes-Simard, *Angew. Chem. Int. Ed.* 2011, **50**, 3497; (b) S. Hanessian, R. R. Vakiti, S. Dorich, S. Banerjee and B. Deschênes-Simard, *J. Org. Chem.* 2012, **77**, 9458.
  - 12 (a) J. T. Malinowski, R. J. Sharpe and J. S. Johnson, *Science* 2013, **340**, 180; (b) R. J. Sharpe, J. T. Malinowski and J. S. Johnson, *J. Am. Chem. Soc.* 2013, **135**, 17990.
  - 13 (a) S. Hanessian, R. R. Vakiti, A. K. Chattopadhyay, S. Dorich and C. Lavallée, *Bioorg. Med. Chem.* 2013, **21**, 1775; (b) R. J. Sharpe, J. T. Malinowski, F. Sorana, J. C. Luft, C. J. Bowerman, J. M. DeSimone and J. S. Johnson, *Bioorg. Med. Chem.* 2015, **23**, 1849.
  - 14 Reviews: (a) P. Müller and C. Fruit, *Chem. Rev.* 2003, **103**, 2905; (b) M. M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.* 2008, **108**, 3379; (c) K. Huard and H. Lebel, *Chem. Eur. J.* 2008, **14**, 6222; (d) S. Fantauzzi, A. Caselli and E. Gallo, *Dalton Trans.* 2009, 5434; (e) T. G. Driver, *Org. Biomol. Chem.* 2010, **8**, 3831; (f) J. W. W. Chang, T. M. U. Ton and P. W. H. Chan, *Chem. Rec.* 2011, **11**, 331; (g) J. L. Roizen, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.* 2012, **45**, 911; (h) T. Uchida and T. Katsuki, *Chem. Rec.* 2014, **14**, 117; (i) R. J. Scamp, J. W. Rigoli and J. M. Schomaker, *Pure Appl. Chem.* 2014, **86**, 381; (j) J. Buendia, G. Grelier and P. Dauban, *Adv. Organomet. Chem.* 2015, **64**, 77. Selected recent relevant examples: (k) M. Ju, C. D. Weatherly, I. A. Guzei, J. M. Schomaker, *Angew. Chem. Int. Ed.* 2017, 56, 9944; (l) N. S. Dolan, R. J. Scamp, T. Yang, J. F. Berry, J. M. Schomaker, *J. Am. Chem. Soc.* 2016, **138**, 14658; (m) J. Buendia, G. Grelier, B. Darses, A. G. Jarvis, F. Taran, P. Dauban, *Angew. Chem.* 2016, **128**, 7656; (n) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem.* 2015, **7**, 987; (o) E. N. Bess, R. J. DeLuca, D. J. Tindall, M. S. Oderinde, J. L. Roizen, J. Du Bois, M. S. Sigman, *J. Am. Chem. Soc.* 2014, **136**, 5783; (p) J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem.* 2013, **125**, 11553; (q) Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem.* 2013, **125**, 1783; (r) T. M. U. Ton, C. Tejo, D. L. Y. Tiong and P. W. H. Chan, *J. Am. Chem. Soc.* 2012, **134**, 7344; (s) T. M. U. Ton, C. Tejo, S. Tania and P. W. H. Chan, *J. Org. Chem.* 2011, **76**, 4894; (t) J. W. W. Chang, T. M. U. Ton, S. Tania, P. C. Taylor and P. W. H. Chan, *Chem. Commun.* 2010, **46**, 922.
  - 15 Reviews: (a) D. Karila and R. H. Dodd, *Curr. Org. Chem.* 2011, **15**, 1507; (b) J. Egger and E. M. Carreira, *Nat. Prod. Rep.* 2014, **31**, 449; (c) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais and P. Dauban, *Chem. Commun.* 2017, **53**, 493; (d) D. Hazelard, P.-A. Nocquet and P. Compain, *Org. Chem. Front.* 2017, **4**, 2500.
  - 16 (a) F. Duran, L. Leman, A. Ghini, G. Burton, P. Dauban and R. H. Dodd, *Org. Lett.* 2002, **4**, 2481; (b) A. Estéoule, F. Duran, P. Retailleau, P. Dauban and R. H. Dodd, *Synthesis* 2007, 1251; (c) G. Malik, A. Estéoule, P. Retailleau and R. H. Dodd, *J. Org. Chem.* 2011, **76**, 7438; (d) P. M. Wehn, J. Lee and J. Du Bois, *Org. Lett.* 2003, **5**, 4823; (e) K. Guthikonda, P. M. Wehn, B. J. Caliendo and J. Du Bois, *Tetrahedron* 2006, **62**, 11331.
  - 17 C. G. Espino and J. Du Bois, *Angew. Chem. Int. Ed.* 2001, **40**, 598.
  - 18 A previous study showed that increasing the size of the substituent at position C<sub>4</sub> tends to lower the activity. See 8b
  - 19 M. J. Cook and T. Rovis, *J. Am. Chem. Soc.* 2007, **129**, 9302.
  - 20 For desymmetrization of **3** see: M. Mekrami and S. Sicsic, *Tetrahedron: Asymmetry* 2011, **22**, 1605.
  - 21 K. Guthikonda and J. Du Bois, *J. Am. Chem. Soc.* 2002, **124**, 13672.
  - 22 For a related transformation see: R. J. Alves, S. Castillon, A. Dessinges, P. Herczegh, J. C. Lopez, G. Lukacs, A. Olesker and T. T. Thang, *J. Org. Chem.* 1988, **53**, 4616.
  - 23 The carbamoylation reaction was performed using a mixture of NaOCN and TFA, because the use of the classical conditions involving trichloroacetyl chloroformate, led to lower yields, presumably because of the instability of compound **10** under basic conditions.
  - 24 Performing first the C(sp<sup>3</sup>)-H amination, then the aziridine ring opening only delivered the unwanted regioisomer during the opening step.
  - 25 (a) H. Lebel, K. Huard and S. Lectard, *J. Am. Chem. Soc.*, 2005, **127**, 14198; (b) K. Huard and H. Lebel, *Chem. Eur. J.* 2008, **14**, 6222.
  - 26 D. N. Zalatan and J. Du Bois, *J. Am. Chem. Soc.* 2009, **131**, 7558.
  - 27 On one hand, the resulting oxazolidinone could be converted to a 1,2-hydroxy urea motif following activation of the nitrogen with an acetyl group and a subsequent nucleophilic ring opening of the carbamate. Such conditions have been reported for the cleavage of similar spiro oxazolidinones at room temperature. See for example: (a) I. U. Khan, S. Kattela, A. Hassan, C. R. Duarte Correia, *Org. Biomol. Chem.* 2016, **14**, 9476; (b) T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta, T. Fukuyama, *Org. Lett.* 2008, **10**, 169. On the other hand, the key C2-aryl ring could be introduced via application of metal-catalyzed couplings or nucleophilic aromatic substitution. See for example: (c) J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.* 1996, **118**, 7215; (d) G. E. Job and S. L. Buchwald, *Org. Lett.* 2002, **4**, 3703.