Synthesis of 2′,3′-Cyclohexen Bicyclic Uridine Analogues Using Ring-Closure Metathesis

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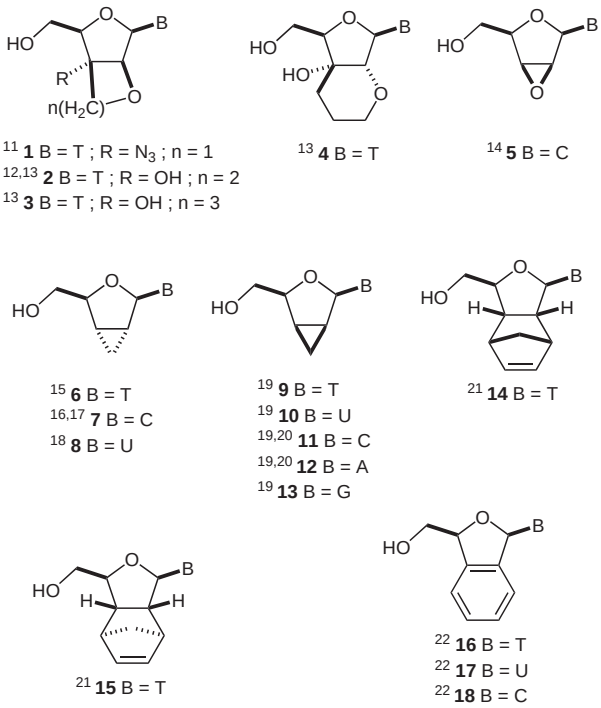
Abstract: The synthesis of two new 2′,3′-cyclohexen bicyclic uridine analogues is described. From 5′-protected uridine two successive tin radical-mediated allylations at 2′-C and 3′-C position followed by ring-closure olefin metathesis on the diene intermediate using Grubbs' catalyst led to the formation of the six-membered ring.

Key words: antivirals, nucleic acid analogues, radical allylation, ring-closure metathesis

Nucleoside analogues display a large range of biological activities as antiviral agents[1] against Human Immunodeficiency Virus (HIV),[2] Herpes Simplex Virus (HSV)[3] and Hepatitis B Virus (HBV)[4] and as antitumor agents.[5] A large number of 2′,3′-dideoxynucleoside analogues (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleoside analogues (d4Ns) are approved by the US Food and Drug Administration for the treatment of AIDS. The mechanism of action of ddNs and d4Ns require intracellular metabolization by cellular kinases into the corresponding 5′-triphosphate forms, which act as competitive inhibitors and/or chain terminators. Despite the wide number of nucleoside analogues reported, only a few effective compounds have been obtained. This inactivity may be due to either low intracellular metabolization into the corresponding nucleotide derivatives or lack of activity of such a nucleotide on the target enzyme. In the course of the search for new agents with a higher therapeutic index, the conformation equilibrium of nucleosides is considered as essential. The complete definition of the conformation of nucleosides usually involves the determination of three principal structural parameters:[6] (i) the glycosyl torsion angle (χ; *syn–anti* equilibrium); (ii) the torsion angle determining the orientation of the 5′-hydroxy group relative to C3′ (γ; +sc, ap, -sc equilibrium); (iii) the conformation of the furanose ring, i.e. its position on the pseudorotational cycle as determined by the phase angle of rotation (P). Therefore, conformationally restricted nucleoside analogues have served as useful model compounds for investigations of the conformational importance of enzyme–substrate interactions and physicochemical properties of nucleosides and nucleotides in solution.[7] Three different classes of conformationally restricted nucleoside analogues have been described: (i) bicyclic and tricyclic nucleosides having a bridge between two positions of the furanose ring;[8] (ii) cyclonucleosides having a bridge between the heterocyclic base and the furanose ring (χ, P);[9] (iii) cyclic phosphoesters having a bridge extending from the phosphorus atom of the nucleotide to either the heterocyclic base or the furanose ring (χ, γ).[10] In the case of bicyclic nucleosides the ring fusion to the 2′,3′-positions of the glycone moiety having either C,O-connection such as compounds **1**–**5**[11–14] or C,C-connection such as compounds **6**–**18**[15–22] have been reported for evaluation of either their antiviral activity or their ability to form duplex between an antisense oligonucleotide and the messenger RNA target (Figure 1).



[11] **1** B = T ; R = N_3 ; n = 1
[12,13] **2** B = T ; R = OH ; n = 2
[13] **3** B = T ; R = OH ; n = 3
[13] **4** B = T
[14] **5** B = C
[15] **6** B = T
[16,17] **7** B = C
[18] **8** B = U
[19] **9** B = T
[19] **10** B = U
[19,20] **11** B = C
[19,20] **12** B = A
[19] **13** B = G
[21] **14** B = T
[21] **15** B = T
[22] **16** B = T
[22] **17** B = U
[22] **18** B = C

Figure 1 Bicyclic nucleosides **1**–**18**.

As part of our drug-discovery program for antiviral agents having restricted conformation, we have recently reported the synthesis of the 1,3-dihydrobenzo[*c*]furan nucleoside

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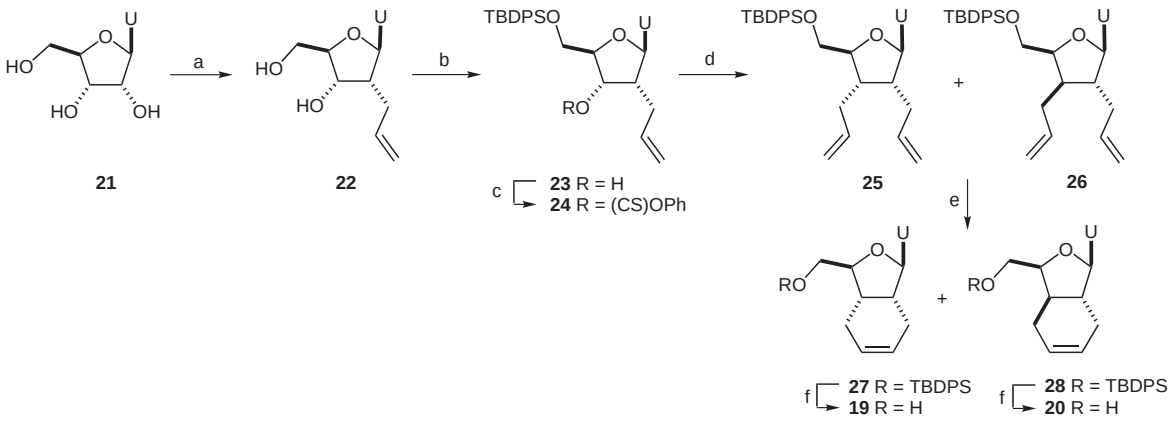
analogues **16**–**18** which had no significant anti-HIV activity.[23] One explanation for this result may be related to the steric effect of the benzene ring which does not allow the access of the triphosphate derivative to the enzyme nucleotide binding site. In view of this lack of activity we described herein the enantiomerically pure nucleoside analogues **19** and **20** having a cyclohexene ring in the 2′,3′-positions of the sugar residue. These novel compounds were expected to (i) retain the phosphorylation site; (ii) possess enhanced lipophilicity over ddN and d4N derivatives; (iii) have less steric effect than the benzo[*c*]furan analogues **16**–**18**. Furthermore, the diastereoisomeric nucleosides **19** and **20**, having *S* and *R* absolute configurations for the carbon atom C-3′, respectively, had different conformations (especially for P parameter) which will permit to contribute to the structure–activity relationship studies of our group and the others regarding antiviral nucleosides.

In this preliminary study the choice of uridine as starting material was dictated by the possibility at final stage to convert an advanced intermediate into its 5-methyl congener via 5-bromination and subsequent Pd-catalyzed cross-coupling reaction via trimethylaluminum[24] or into cytidine analogues via 4-triazolo intermediate[25] followed by treatment with concentrated ammonia. Access to the target molecules **19** and **20** from uridine would be straightforward via two successive free-radical allylations[26] with an appropriate C-2′- and C-3′-phenoxythiocarbonyl-substituted uridine leading to new C–C bond formation, followed by a well-established ring-closing metathesis (RCM)[27,28] reaction.

Radical allylation has proven to be an excellent tool to synthesize 2′- or 3′-C-substituted nucleoside derivatives giving high yields in a very practical synthetic route.[29] However, previous efforts had shown that stereoselective radical allylation at C-3′ in ribo series was more problematic compare to deoxyribo series (see ref. 6h). It should be pointed out that same difficulties were noted in the addition of styryltributyltin to 3′-C-centered radicals in ribo series: low yields and/or low diastereoselectivity.[30] We planned to take advantage of this fact for the preparation of the *cis*- and *trans*-diastereoisomers **19** and **20** which could be isolated pure after separation affording then enough material for preliminary biological evaluation.

Starting from uridine (**21**), the 2′-C-allyl-substituted nucleoside **22** was constructed on the basis of known methodology for preparing 2′-allyl-2′-deoxynucleosides.[29b] Selective protection of the primary hydroxyl group of **22** as a *tert*-butyldiphenylsilyl (TBDPS) ether afforded intermediate **23** in excellent yield, the stage was set to introduce the required allyl group at C-3′ position. Accordingly, exposure of **23** to phenyl chlorothiocarbonate (PTCCl) in the presence of *N*-hydroxysuccinimide (NOS), as described by Barton[31] in the case of hindered alcohol, proceeded smoothly to provide the corresponding thiocarbonate **24** in 91% yield. Using previous allylation procedure, no reaction took place and only starting material was recovered. The preparation of the 3′-*C*-allyluridine derivatives **25** and **26**, synthesized from thiocarbonate **24** by trapping the radical in the Barton deoxygenation with allyltributyltin was found to be much more delicate compare to the first one at C-2′ position. After considerable experimentations, it was found that the C-allylation reaction was best conducted at refluxing benzene with the use of 10 equivalents of allyltributyltin, 1 equivalent of 2,2′-azobis(isobutyronitrile) (AIBN) as initiator and 0.1 equivalents of tributyltin hydride[32] to give the desired key intermediates **25** and **26** in 51%[33] as a 75:25 mixture of *cis*- and *trans*-isomers **25** and **26** (vide infra), as well as 6% of reduced product (Scheme 1). In absence of tin hydride only starting material was recovered, prolonged reaction times (up to 14 h) led to degradation. On the basis of this result, it is reasonable to suggest that the formation of tributyltin radical in decent concentration due to the presence of more reactive tributyltin hydride with AIBN permitted to initiate the reaction with the thiocarbonyloxy group of **24**. Then, the tributyltin radical led to the classical fragmentation and afforded the alkyl radical on C-3′, which can react with the excess of allyltributyltin to yield the two diastereomeric diallyl derivatives **25** and **26**.



Scheme 1 *Reagents and conditions*: (a) ref. 29b; (b) TBDPSCl, imidazole, DMF, r.t., 12 h, 99%; (c) PTCCl, NOS, pyridine, toluene, 80 °C, 4 h, 91%; (d) Bu_3Sn-allyl, AIBN, Bu_3SnH, PhH, reflux, 14 h, 51%; (e) second-generation Grubbs'catalyst, CH_2Cl_2, r.t., 12 h, 65%; (f) NH_4F, MeOH, 60 °C, 12 h, 89%.

The modest stereoselectivity of the C-allylation could not be improved. In parallel, we briefly considered the possibility to use a double radical C-allylation on the 2′,3′-*O*-thionocarbonate-uridine as a shortest alternative to reach the diallyl intermediates **25** and **26**. Unfortunately all attempts failed, only 2′,3′-dideoxy-2′,3′-didehydrouridine (d4U) was isolated in low yield (22%) even when allyltributyltin was used as a solvent.[34] The mixture of the diallylated nucleosides **25** and **26** could not be efficiently separated by chromatography on silica gel column at this stage of the synthesis as well as the unprotected derivatives. The RCM reaction was carried on the later mixture with the Grubb's second-generation catalyst [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium] in CH_2Cl_2 at room temperature overnight at atmospheric pressure under nitrogen flux to afford the mixture of desired cyclohexene derivatives **27** and **28** in 65% yield after purification. Finally, cleavage of the silyl ether protecting group using conditions reported for nucleoside **3** led to the target molecules **19**[35] and **20**,[36] which were separated by preparative HPLC.[37]

The configuration of the diastereomeric products *cis*-**19** and *trans*-**20** was unambiguously assigned by a set of 1D and 2D NMR experiments, in particularly NOESY, COSY and HSQC between the proximal hydrogen atoms, on separated target molecules (see Figure 2).

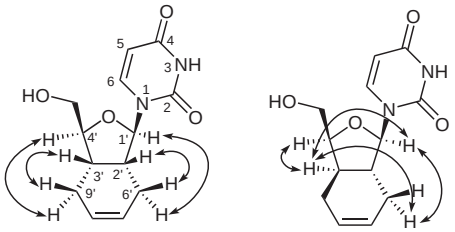


Figure 2 Selected NOE correlations for products *cis*-**19** and *trans*-**20**.

In conclusion, allyltributyltin(IV)-mediated radical C-allylation and RCM have been used successfully to provide an easy entry to a new family of bicyclic nucleosides. Extension of this work to the synthesis of other novel nucleosides, in particularly the corresponding thymine and cytosine series, and the results of modeling studies and biological tests will be reported in due course.

Acknowledgment

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References and Notes

(1) De Clercq, E. *J. Clin. Vir.* **2004**, *30*, 115.
(2) De Clercq, E. *Biochim. Biophys. Acta* **2002**, *1587*, 258.
(3) Brady, R. C.; Bernstein, D. I. *Antiviral Res.* **2004**, *61*, 73.
(4) Papatheodoridis, G. V.; Dimou, E.; Papadimitropoulos, V. *Am. J. Gastroenterology* **2002**, *97*, 1618.
(5) Matsuda, A.; Sasaki, T. *Cancer Sci.* **2004**, *95*, 105.
(6) (a) Saenger, W. *Principles of Nucleic Acid Structure*; Springer Verlag: New York, **1984**. (b) Altona, C.; Sundaraalingam, M. *J. Am. Chem. Soc.*; 1972, 94: , .
(7) (a) Russ, P.; Schelling, P.; Scapozza, L.; Folkers, G.; De Clercq, E.; Marquez, V. E. *J. Med. Chem.* **2003**, *46*, 5045. (b) Marquez, V. E.; Russ, P.; Alanso, R.; Siddiqui, M. A.; Shin, K. J.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H. *Nucleosides Nucleotides* **1999**, *18*, 521. (c) Kvaerno, L.; Nielsen, C.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2903.
(8) (a) Meldgaard, M.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3539. (b) Wengel, J. *Acc. Chem. Res.* **1999**, *32*, 301. (c) Leumann, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 841.
(9) (a) Yoshimura, Y.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1989**, *37*, 660. (b) Yagamata, Y.; Tomita, K.; Usui, H.; Sano, T.; Ueda, T. *Chem. Pharm. Bull.* **1989**, *37*, 1971. (c) Matsuda, A.; Ueda, T. *Nippon Kagaku Kaishi* **1981**, 845.
(10) (a) Sekine, M.; Kurasawa, O.; Shohda, K.; Seio, K.; Wada, W. *J. Org. Chem.* **2000**, *65*, 6515. (b) Sekine, M.; Kurasawa, O.; Shohda, K.; Seio, K.; Wada, W. *J. Org. Chem.* **2000**, *65*, 3571. (c) Le Clezio, I.; Escudier, J. M.; Vigroux, A. *Org. Lett.* **2003**, *5*, 161. (d) Le Clezio, I.; Gornitzka, H.; Escudier, J. M.; Vigroux, A. *J. Org. Chem.* **2005**, *70*, 1620.
(11) Sorensen, M. H.; Nielsen, C.; Nielsen, P. *J. Org. Chem.* **2001**, *66*, 4878.
(12) Nielsen, P.; Pfundheller, H. M.; Wengel, J. *Chem. Commun.* **1997**, 825.
(13) Nielsen, P.; Pfundheller, H. M.; Olsen, C. E.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3423.
(14) Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1988**, *31*, 1475.
(15) Sard, H. *Nucleosides Nucleotides* **1994**, *13*, 2321.
(16) Okabe, M.; Sun, R. C. *Tetrahedron Lett.* **1989**, *30*, 2203.
(17) Beard, A. R.; Butler, P. I.; Mann, J.; Partlett, N. K. *Carbohydr. Res.* **1990**, *205*, 87.
(18) Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2587.
(19) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685.
(20) Hong, J. H.; Chun, B. K.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 225.
(21) Hossain, N.; Plavec, J.; Thibaudeau, C.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 9079.
(22) Ewing, D. F.; Fahmi, N. E.; Len, C.; Mackenzie, G.; Pranzo, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3561.
(23) Egron, D.; Périgaud, C.; Gosselin, G.; Aubertin, A. M.; Faraj, A.; Sélouane, A.; Postel, D.; Len, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4473.
(24) (a) Obika, S.; Hari, Y.; Sugimoto, T.; Sekiguchi, M.; Imanishi, T. *Tetrahedron Lett.* **2000**, *41*, 8923. (b) Alauddin, M. M.; Conti, P. S. *Tetrahedron* **1994**, *50*, 1699. (c) Hirota, K.; Kitade, Y.; Kanbe, Y.; Isobe, Y.; Maki, Y. *Synthesis* **1993**, 213.
(25) Xu, Y.-Z.; Zheng, Q.; Swann, P. F. *J. Org. Chem.* **1992**, *57*, 3839.

(26) For recent reviews on radical-based reactions, see: (a) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251. (b) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; VCH: New York, **2001**. (c) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(27) For general reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (d) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199; and references cited therein.

(28) For recent examples of RCM in nucleosides field, see: (a) Chen, X.; Wiemer, D. F. *J. Org. Chem.* **2003**, *68*, 6597. (b) Borsting, P.; Freitag, M.; Nielsen, P. *Tetrahedron* **2004**, *60*, 10955. (c) Agrofoglio, L. A.; Amblard, F.; Nolan, S. P.; Charamon, S.; Gillaizeau, I.; Zevaco, T. A.; Guenot, P. *Tetrahedron* **2004**, *60*, 8397. (d) Freitag, M.; Thomassen, H.; Christensen, N. K.; Petersen, M.; Nielsen, P. *Tetrahedron* **2004**, *60*, 3775. (e) Busca, P.; Etheve-Quelquejeu, M.; Valéry, J.-M. *Tetrahedron Lett.* **2003**, *44*, 9131. (f) Montembault, M.; Bourgougnon, N.; Lebreton, J. *Tetrahedron Lett.* **2002**, *43*, 8091. (g) Ewing, D.; Glaçon, V.; Mackenzie, G.; Postel, D.; Len, C. *Tetrahedron Lett.* **2002**, *43*, 3503. (h) Ewing, D.; Glaçon, V.; Mackenzie, G.; Postel, D.; Len, C. *Tetrahedron* **2003**, *59*, 941.

(29) For radical allylation at C-2′, see: (a) Stork, G.; Zhang, C.; Gryaznov, S.; Schultz, R. *Tetrahedron Lett.* **1995**, *36*, 6387. (b) Cicero, D. O.; Neuner, P. J. S.; Franzese, O.; D'Onofrio, C.; Iribarren, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *7*, 861. (c) De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Synlett* **1993**, 733. (d) De Mesmaeker, A.; Lebreton, J.; Hoffmann, P.; Freier, S. M. *Synlett* **1993**, 677. (e) Chu, C. K.; Doboszewski, W. S.; Ullas, G. *J. Org. Chem.* **1989**, *54*, 2767. For radical allylation at C-3′, see: (f) Rozners, E.; Katkevica, D.; Bizdena, E.; Strömberg, R. *J. Am. Chem. Soc.* **2003**, *125*, 12125. (g) Batoux, N.; Benhaddou-Zerrouki, R.; Bressolier, P.; Granet, R.; Laumont, G.; Aubertin, A.-M.; Krausz, P. *Tetrahedron Lett.* **2001**, *42*, 1491. (h) De Mesmaeker, A.; Lesueur, C.; Bévière, M.-O.; Waldner, A.; Fritsch, V.; Wolf, R. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2790. (i) Fiandor, J.; Tam, S. Y. *Tetrahedron Lett.* **1990**, *31*, 597.

(30) An, H.; Wang, T.; Maier, M. A.; Manoharan, M.; Ross, B. S.; Cook, P. D. *J. Org. Chem.* **2001**, *66*, 2789.

(31) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619.

(32) Personal communication from Dr. Alain De Mesmaeker (Syngenta, Basel, Switzerland).

(33) **Representative Procedure for the Preparation of 3′-*C*-Allyluridine 25 and 26.**
A degassed solution of thiocarbonate **24** (1.0 g, 1.56 mmol), Bu_3SnAll (4.83 mL, 15.58 mmol, 10 equiv), AIBN (256 mg, 1.56 mmol, 1 equiv) and Bu_3SnH (45 mg, 0.16 mmol, 0.1 equiv) in distilled benzene (1.5 mL, 1 mol/L) was stirred overnight at reflux. The solvent was removed under reduced pressure and purification by flash chromatography (30% Et_2O–PE) afforded a mixture of diastereoisomers **25** and **26** (420 mg, 51%) as a white foam; 75% de [determined by HPLC performed using a Chrompack Inertsil column Intersil 250 × 3 mm with a flow of rate 1 mL/min (CH_2Cl_2), t_R = 10.5 min for minor diastereomer **26** and t_R = 11.1 min for major diastereomer **25**; R_f = 0.66 (30% Et_2O–PE, single spot with these conditions)]. MS (CI/NH_3): *m/z* 531(100) [M + NH_3]$^+$, 548.
Data for major diastereomer **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 9 H, *t*-Bu), 1.80–2.50 (m, 6 H, H-2′, H-3′, H-6′, H-6″, H-10′ and H-10″), 3.60 and 4.00 (part AB of ABX system, 2 H, *J* = 2.3 Hz, *J* = 2.4 Hz, *J* = 11.8 Hz, H-5′), 3.80 (m, 1 H, H-4′), 4.90–5.09 (m, 4 H, H-8′, H-9′, H-12′ and H-13′), 5.35 (d, 1 H, *J* = 8.2 Hz, H-5), 5.45–5.80 (m, 2 H, H-7′ and H-11′), 5.83 (d, 1 H, *J* = 4,3 Hz, H-1′), 7.25–7.75 (m, 10 H, 2 × Ph), 7.95 (d, 1 H, *J* = 8.2 Hz, H-6), 8.55 (br s, 1 H, N*H*-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3 [$(CH_3)_3C$-Si], 26.0 [$(CH_3)_3C$-Si], 29.6 (C-6′), 32.3 (C-10′), 38.3 (C-3′), 46.4 (C-2′), 63.5 (C-5′), 83.1 (C-4′), 87.8 (C-1′), 101.2 (C-5), 116.1 (C-8′), 116.3 (C-12′), 128.0–135.6 (2 × Ph), 129.2 (C-7′), 129.7 (C-11′), 139.4 (C-6), 149.3 (C=O), 162.1 (C=O) ppm.

(34) (a) Oba, M.; Suyama, M.; Shimamura, A.; Nishiyama, K. *Tetrahedron Lett.* **2003**, *44*, 4027. (b) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217. (c) Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 8502.

(35) Selected physico-chemical data for major diastereomer **19**: R_f = 0.23 (5% EtOH–CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 9.98 (br s, 1 H, NH), 8.30 (d, 1 H, *J* = 8.1 Hz, H_6), 5.76–5.72 (m, 2 H, $H_{7'}$ and $H_{8'}$), 5.69 (d, 1 H, *J* = 2.5 Hz, $H_{1'}$), 5.54 (d, 1 H, *J* = 8.1 Hz, H_5), 4.38 (br s, 1 H, OH), 3.98 (dd, 1 H, $J_{4'\text{-}5'}$ = 2.6 Hz and $J_{5'\text{-}5'}$ = 12.1 Hz, $H_{5'}$), 3.90 (dt, 1 H, $J_{4'\text{-}5'}$ = 2.6 Hz, $J_{3'\text{-}4'}$ = 7.9 Hz, $H_{4'}$), 3.82 (dd, 1 H, $J_{4'\text{-}5'}$ = 2.6 Hz and $J_{5'\text{-}5'}$ = 12.1 Hz, $H_{5'}$), 2.56 (m, 1 H, $H_{2'}$), 2.54 (m, 1 H, $H_{3'}$), 2.43–2.27 (m, 2 H, $H_{6'eq}$ and $H_{9'eq}$), 2.09–1.96 (m, 2 H, $H_{6'ax}$ and $H_{9'ax}$) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): δ = 163.2 (C4), 150.6 (C2), 140.5 (C6), 125.0 (C8′ or C7′), 124.3 (C8′ or C7′), 100.6 (C5), 89.2 (C1′), 84.9 (C4′), 60.5 (C5′), 40.2 (C2′), 32.2 (C3′), 22.9 (C6′), 22.9 (C9′) ppm. HRMS (ESI): *m/z* calcd for $C_{13}H_{16}N_2O_4Na$ [M + Na^+]: 287.1008; found: 287.1004.

(36) Selected physico-chemical data for minor diastereomer **20**: R_f = 0.26 (5% EtOH–CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 9.98 (br s, 1 H, NH), 8.15 (d, 1 H, *J* = 8.1 Hz, H_6), 5.88 (d, 1 H, *J* = 7.9 Hz, $H_{1'}$), 5.77 (m, 1 H, *J* = 11.9 Hz, $H_{8'}$), 5.71 (m, 1 H, *J* = 11.9 Hz, $H_{7'}$), 5.60 (d, 1 H, *J* = 8.1 Hz, H_5), 4.27 (br s, 1 H, OH), 4.22 (dt, 1 H, $J_{4'\text{-}5'}$ = 2.6, 3.3 Hz, $J_{3'\text{-}4'}$ = 6.6 Hz, $H_{4'}$), 3.89 (dd, 1 H, $J_{4'\text{-}5'}$ = 3.3 Hz and $J_{5'\text{-}5'}$ = 11.9 Hz, $H_{5'}$), 3.76 (dd, 1 H, $J_{4'\text{-}5'}$ = 2.6 Hz and $J_{5'\text{-}5'}$ = 11.9 Hz, $H_{5'}$), 2.38–2.28 (m, 2 H, $H_{2'}$ and $H_{3'}$), 2.28 (m, 1 H, $H_{6'eq}$), 2.30–2.20 (m, 2 H, $H_{9'ax}$ and $H_{9'eq}$), 2.00 (m, 1 H, $H_{6'ax}$) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): δ = 163.0 (C4), 150.8 (C2), 140.6 (C6), 126.8 (C8′), 125.7 (C7′), 101.8 (C5), 87.5 (C1′), 79.7 (C4′), 61.6 (C5′), 42.9 (C2′), 40.6 (C3′), 26.8 (C6′), 25.3 (C9′) ppm. HRMS (ESI): *m/z* calcd for $C_{13}H_{16}N_2O_4Na$ [M + Na^+]: 287.1008; found: 287.0995.

(37) Preparative HPLC was performed using a Chrompack Inertsil column Intersil 250 × 10 mm with a flow of rate 1 mL/min (CH_2Cl_2–MeOH, 95:5) with t_R = 31.0 min for minor diastereomer **20** and t_R = 34.8 min for major diastereomer **19**.