HETEROCYCLES, Vol. 104, No. 3, 2022, pp. 524 - 540. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 25th November, 2021, Accepted, 20th December, 2021, Published online, 4th January, 2022
DOI: 10.3987/COM-21-14599

DEVELOPMENT OF A SCALABLE SYNTHESIS OF SIRT1 MODULATOR MACROCYCLES

János Tatai,[a] Márk Molnár,[a] Maud Villeneuve,[b] Laure Haberkorn,[b] and Miklós Nyerges[a]*

[a]Servier Research Institute of Medicinal Chemistry, 7 Záhony utca, 1031, Budapest, Hungary, [b]Institut de Recherches Servier, 3 rue de la République, 92150 Suresnes, France; E-mail: miklos.nyerges@servier.com

Abstract – An improved multigram route to key intermediate **26** for macrocyclic SIRT1 modulators has been developed. The increasing demand for this key intermediate caused the rerouting of the initial discovery route resulted in increase of overall yield to 8.3% over 8 steps, with the elimination of some tedious chromatographic purifications, and the substitution of critical reaction steps, which hindered a feasible scale-up. The key modification was the introduction of the microwave assisted intramolecular Suzuki reaction for the macrocyclization step, which provided in a reliable and reproducible manner of the targeted product **40**. This newly developed synthetic access to this first described macrocyclic ring system was capable of ensuring the supply of our medicinal chemistry program.

INTRODUCTION

SIRT1 is a NAD^+-dependent histone deacetylase that catalyses the transfer of acetyl group from the side-chain of acetyllysine to the ADP-ribose moiety of NAD^+. It has been extensively studied since its wide variety of physiological functions and the potential benefits of the modulation of sirtuins in human diseases, including cancer, metabolic disorders, and neurodegeneration.[1] The development of small molecules to regulate SIRT1 activity is of great interest in pharmaceutical research. Therefore, the synthesis of chemical modulators (inhibitors and activators) of the sirtuin-catalyzed deacetylation reaction have been actively pursued during the past few years.[2]

Even simple molecules as resveratrol[3] or some 1,4-dihydropyridine derivatives[4] exert an interesting SIRT1 modulating property and to date two molecules, APL-1202[5] and SEN-0014196[6] have been reported to be in various phases of clinical studies (Figure 1).

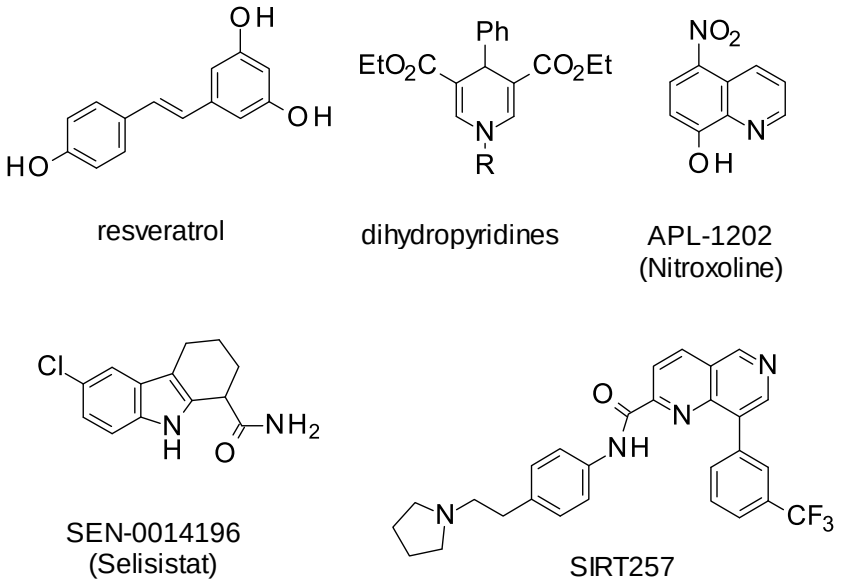
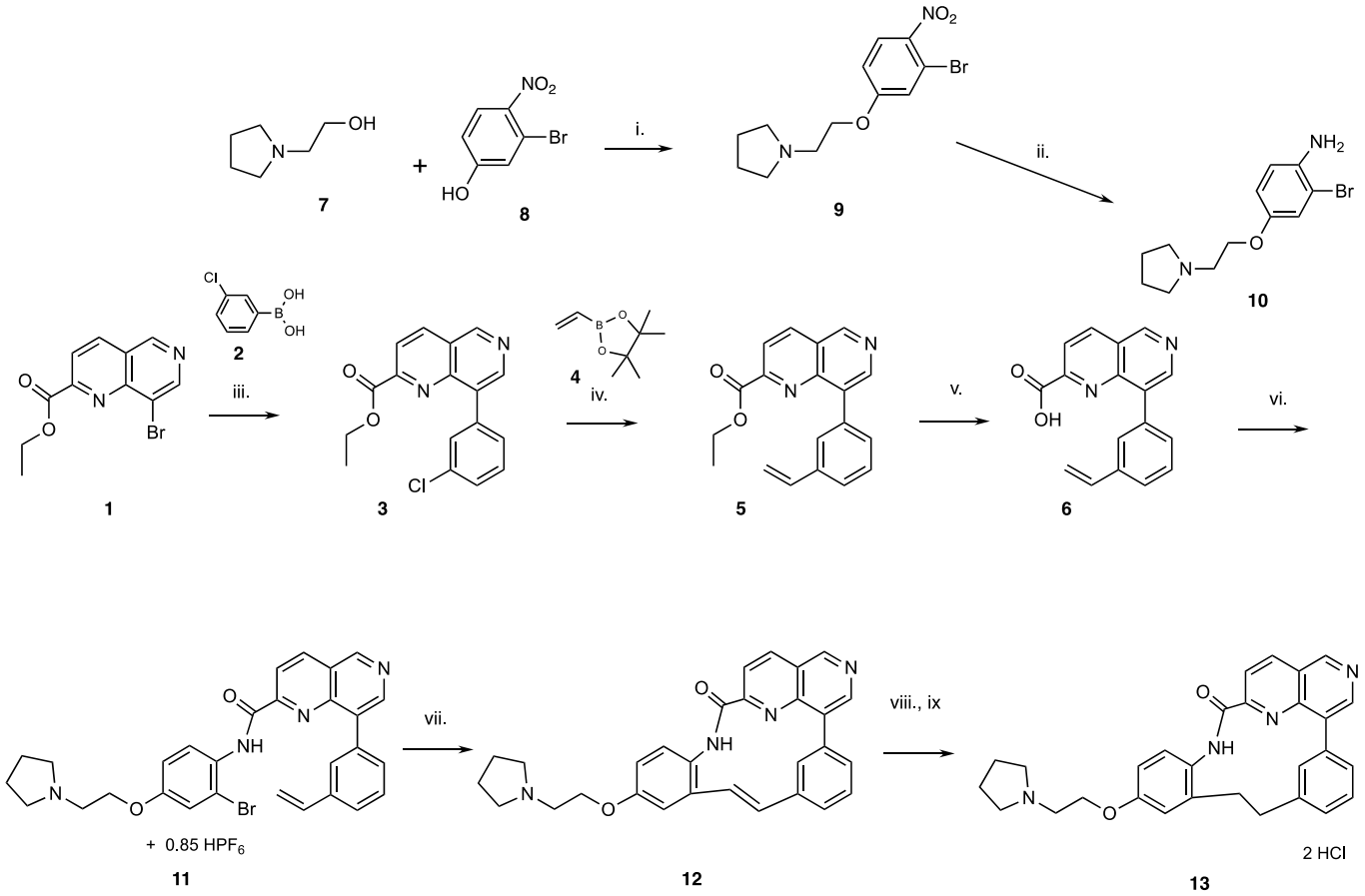


Figure 1. Reported SIRT1 modulators

During the early stages of our research project after the review and evaluation of the existing literature on active molecules, we decided to synthesize a macrocyclic variation of the SIRT257 molecule. The original molecule, that was previously described as the lead compound in an existing patent application,[7] was used as a reference molecule in our studies, and we hoped to achieve improved pharmacokinetic properties with our modifications.

Our exploratory 6+2 steps synthetic pathway to obtain a simple, cyclized analogue of SIRT257 is described in Scheme 1. Ethyl 8-bromo-1,6-naphthyridine-2-carboxylate[8] (**1**) was reacted with 3-chlorophenylboronic acid (**2**) in the presence of Pd catalyst and the product (**3**) underwent a consecutive Suzuki coupling with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**4**) resulting in the formation of styrene derivative **5**. The hydrolysed form of **5** was then reacted with the aniline **10** (which was previously synthesized in a 2-step reaction from 3-bromo-4-nitrophenol (**8**)) in the presence of TBTU, yielding the amide **11**.

An intramolecular Heck reaction, that is otherwise not widely reported to be used for similar purpose, was performed to carry out the macrocyclization step to successfully form the intermediate **12**. The robustness of the reaction was not completely satisfying as the yields obtained varied between 30 and 54% following a tedious purification process. However, the next step, a simple looking double bond reduction turned out to be even more troublesome and limiting in the synthetic sequence as several attempts of catalytic hydrogenation have failed. A rarely used, old reduction method worked only, using a large excess (30 equivalents) of tosylhydrazide, yielding the expected product in a yield not higher than 35%. The final, pharmacologically active form of the compound (**13**) was obtained after the salt formation with hydrochloric acid.

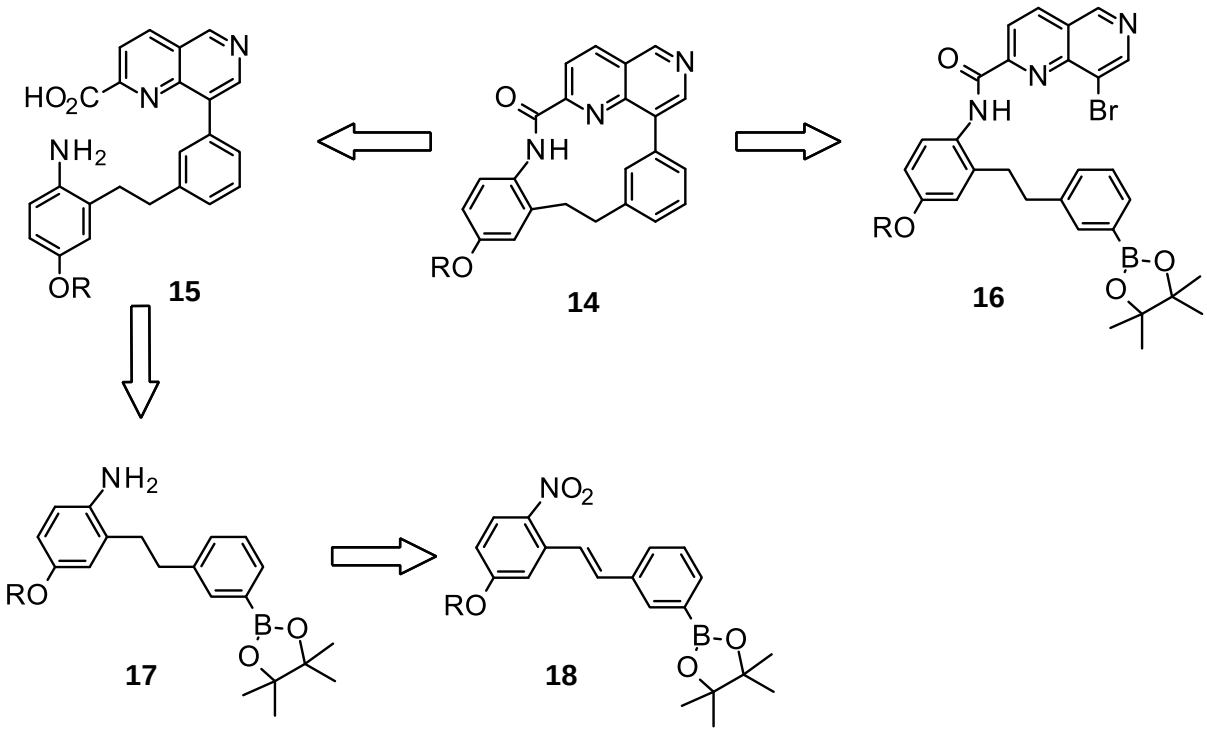


Scheme 1. *Reagents and conditions:* i. Ph_3P, DEAD, THF (66%); ii. NH_4Cl, Fe, *i*-PrOH (95%); iii. $PdAmphosCl_2$, KF, dioxane/H_2O (66%); iv. $PdAmphosCl_2$, KF, dioxane/H_2O (62%); v. NaOH, EtOH (81%); vi. HBTU, TEA, DMF (99%); vii. $Pd(OAc)_2$, PPh_3, TEA, DMF (30 – 54%); viii. $TsNHNH_2$ (30 eq.), Et_3N, THF (35%); ix. 1N HCl, MeCN/H_2O, Lyoph.

The aim of early scale-up group was to develop a convenient, scalable route that leads to macrocycle **13**, besides, to add an easily removable protecting group on the phenolic hydroxyl could allowing us for the rapid optimization of the side chain in parallel with other pharmacological tests.

RESULTS AND DISCUSSION

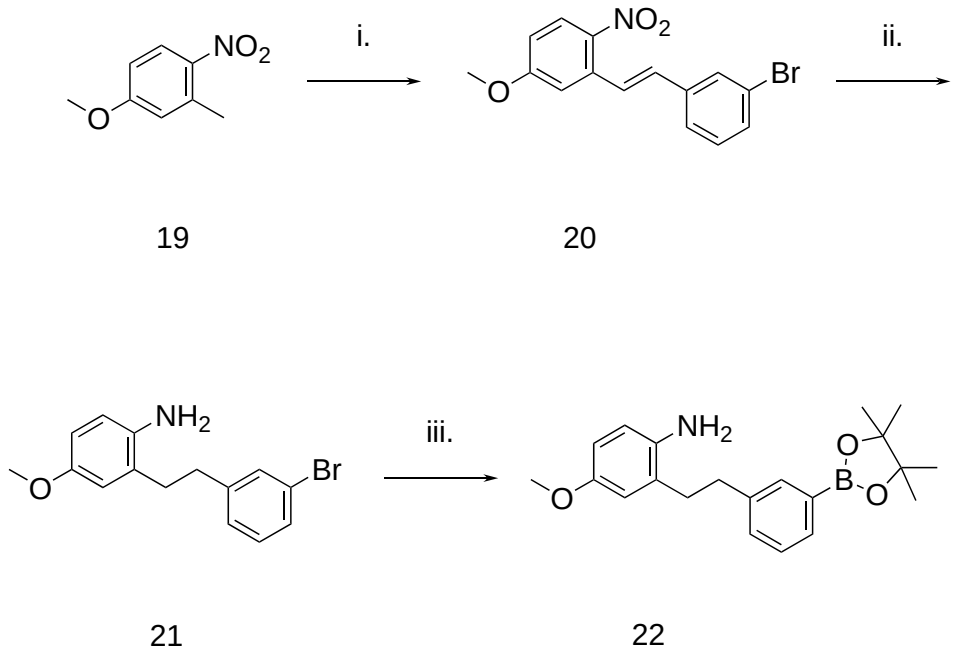
We envisaged that the two most challenging steps could be avoided if an ethylene linker was set up early in the synthesis and we decided to perform a comparison between the widely used intramolecular amide formation and the less known intramolecular Suzuki coupling. Both approaches needed a common key intermediate aniline **17**, which was selected as our first target compound (Scheme 2).



Scheme 2. Retrosynthetic analysis of macrocycle **14**

Our first set of experiments started with the Knoevenagel type condensation[9] of 4-methoxy-2-methyl-1-nitrobenzene (**19**) with 3-bromobenzaldehyde in the presence of sodium ethoxide to form the nitrostilbene derivative **20** in a moderate yield.

The next step, a catalytic hydrogenation was once again more difficult than expected. When the reaction was carried out in the presence of either Pd/C, PtO_2 or Raney Ni catalysts, the desired compound was problematic to be separated from the complex mixture formed. The transformation was however successfully carried out with *in situ* generated nickel boride (from nickel chloride and sodium borohydride) resulting in the formation of **21** in an acceptable yield.[10] The Suzuki-Miyaura reaction of **21** with bis(pinacolato)diboron worked well under standard conditions and the planned key intermediate **22** was formed in good yield (Scheme 3).

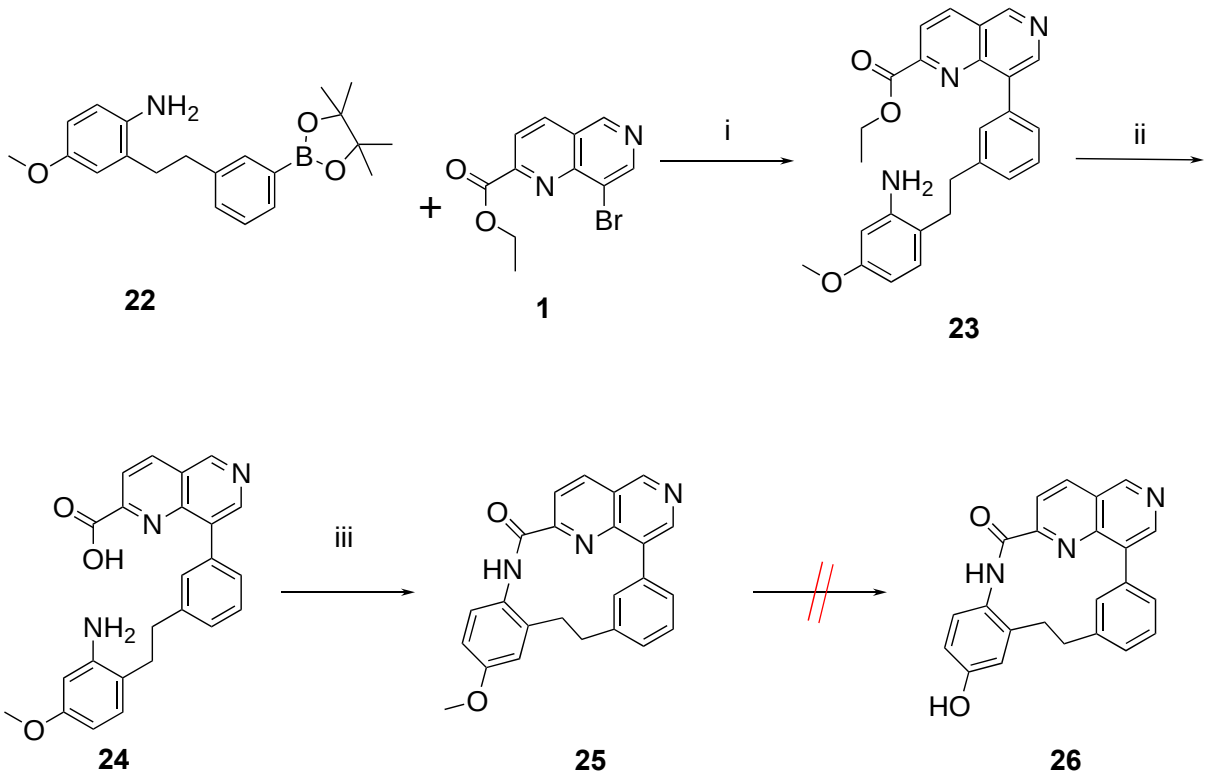


Scheme 3. *Reagents and conditions:* i. 3-bromobenzaldehyde, NaOEt, DMSO, EtOH (30%); ii. $NiCl_2$, $NaBH_4$ THF, MeOH (53%), iii. $Pd(dppf)Cl_2$, bis(pinacolato)diboron, KOAc, dioxane, water (62%).

With an adequate amount of **22** in hand it becomes possible to test the alternative macrocyclization pathway in order to avoid the original, unfavourable Heck reaction/reduction sequence.

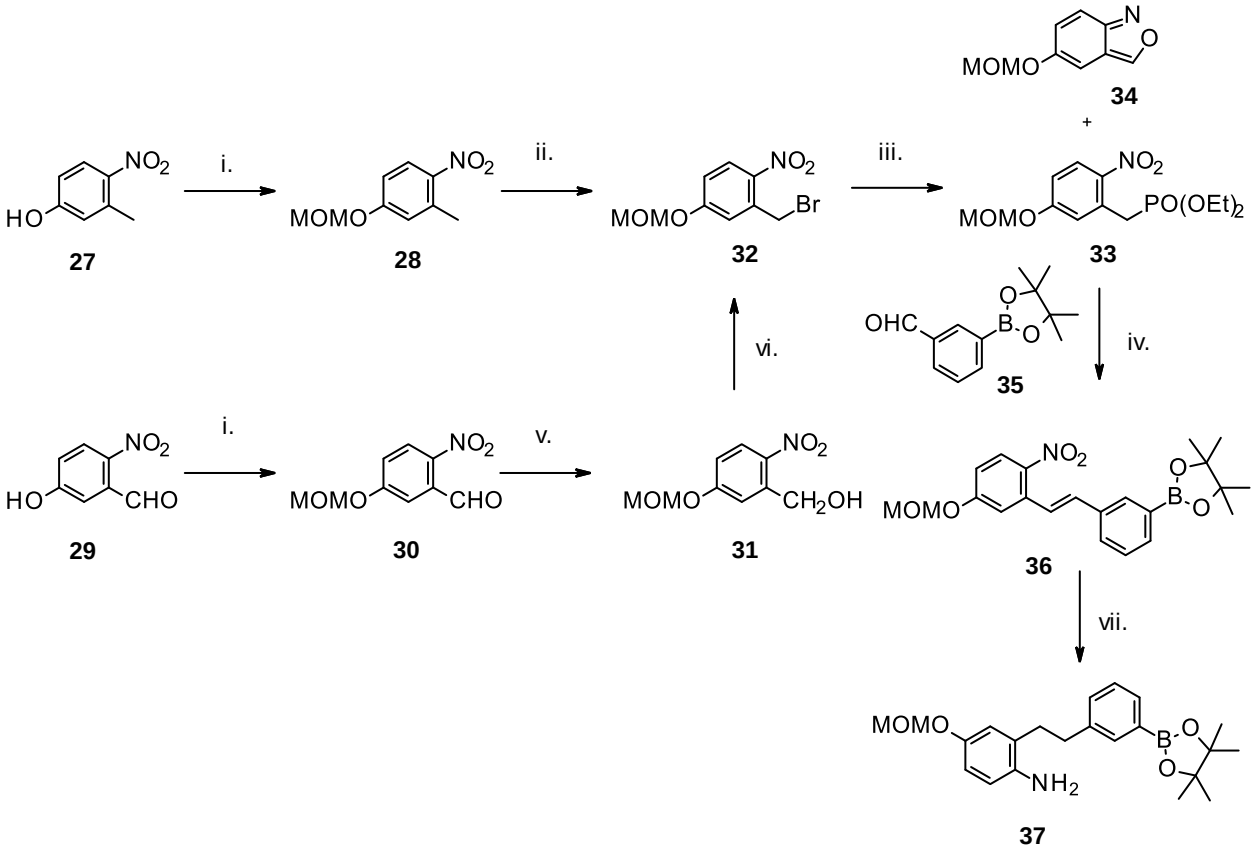
To proceed, the Suzuki reaction of **22** with ethyl 8-bromo-1,6-naphthyridine-2-carboxylate (**1**) was performed and after the hydrolysis of ester **23**, the intramolecular amidation of **24** was attempted. After several attempts with various peptide coupling agents (CDI, TBTU, HATU etc.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) proved to be the most effective for this macrocyclization. Adding the diluted solution of **24** in DCM dropwise to a solution of the activating agent (EDC) and base at room temperature resulted in the formation of the product **25**, however, only in a moderate yield (26%).

Several attempts were performed to prepare the target free phenol **26** by the selective *O*-demethylation of the aryl methyl ether **25**. Despite the plethora of methods described in the literature none of them resulted in the deprotection of this heterocycle: the use of Brønsted or Lewis acids, like HBr,[11] BBr_3,[12] $BF_3 \cdot Et_2O$,[13] $AlCl_3$,[14] or TMSCl-NaI[15] led to a complex mixture of products (only a minor amount of the desired product was detected by HPLC-MS), while no reaction occurred with nonacidic, strongly nucleophilic reagents (NaSEt[16] LiCl-DMF,[17] NaCN[18]).



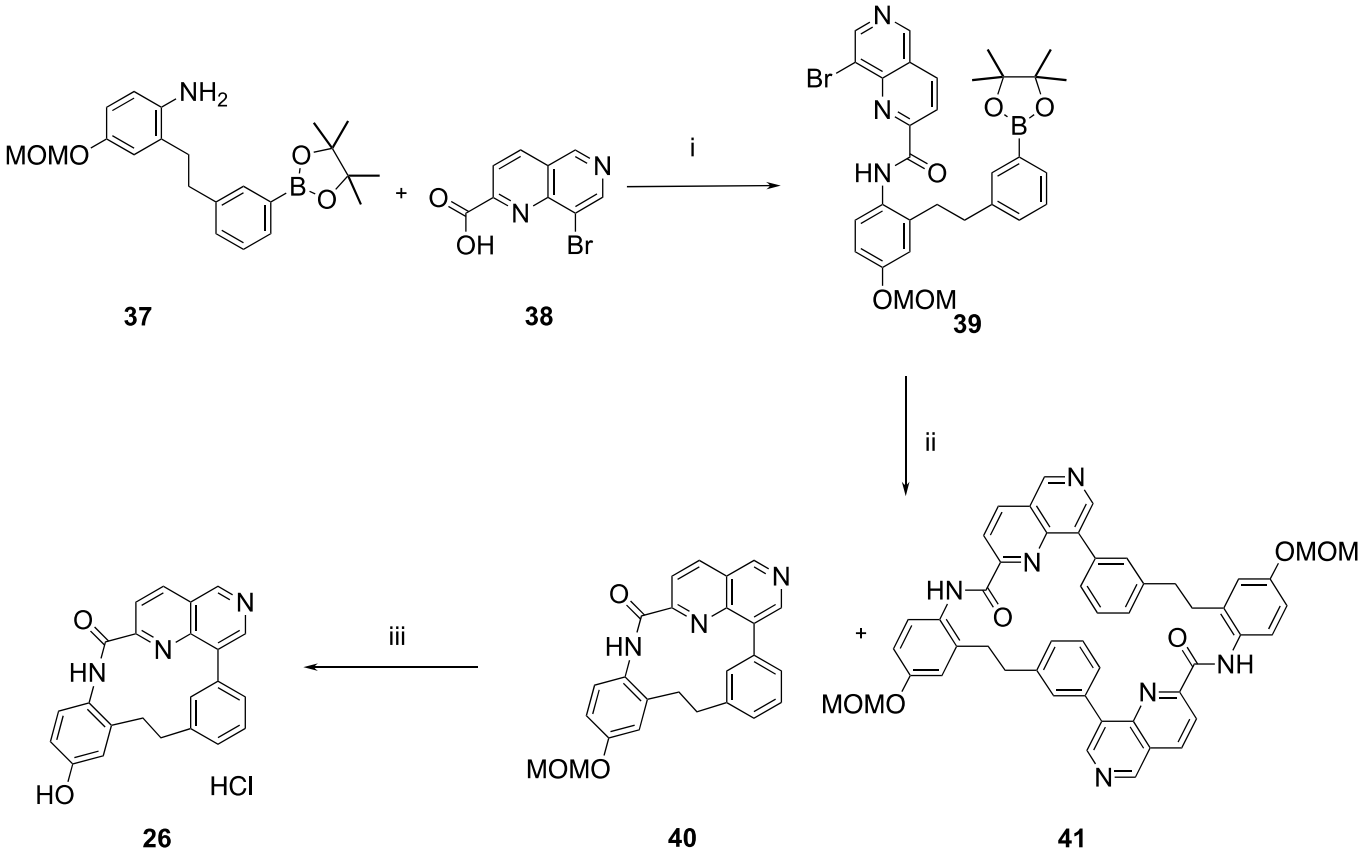
Scheme 4. *Reagents and conditions:* i. $Pd(PPh_3)_2Cl_2$, KF, dioxane, water (66%), ii. LiOH, THF, water (71%), iii. CDI, DCM, pyridine (26%).

A different synthetic approach was also investigated. This set of reactions started with the introduction of the more easily removable methoxymethyl protecting group to 3-methyl-4-nitrophenol to give **28**. It soon became clear however, that the originally planned selective radical mono-bromination of the methyl group of **28** is not scalable, so an alternative pathway was developed. Aldehyde **29** was found to be a suitable (and available) starting material. In three simple steps the key intermediate **32** was easily obtained on a 50-gram scale. The Arbuzov reaction of **32** with triethyl phosphite gave the expected Horner-Wittig reagent **33**, with a slightly decreased yield experienced as a result of the removal of the benzoxazole by-product **34** formed. The (*E*)-olefin **36** was synthesized smoothly, and was subsequently reduced with hydrogen in the presence of Pd/C. Both the olefinic double bond and the nitro group were reduced smoothly in this case, providing our envisaged key intermediate **37** in six steps, in an overall yield of 30% (Scheme 5).



Scheme 5. *Reagents and conditions:* i. MOMCl, NaH, DMF, 0 °C (**28**: 82%, **30**: 94%); ii. NBS, CH_2Cl_2 (56%); iii. $P(OEt)_3$, toluene (**33**: 71%, **34**: 5%); iv. $KOBu^t$, DMF (61%); v. $NaBH_4$, MeOH, THF (98%); vi. CBr_4, PPh_3, DCM (76%) vii. H_2, Pd/C, MeOH, THF (99%).

Based on our initial observations on the slow macrocyclization described in Scheme 4 (more than 24 h on 0.1 g scale) and due to the challenging deadline for the delivery of **26**, we decided to prepare the amide **39**, which was expected to be cyclized to **40** *via* an intramolecular Suzuki reaction.[19] After a short screening of conditions for this transformation we concluded that the reaction is best to be performed under microwave conditions at elevated temperatures above the boiling point of the selected solvent system, and it was indeed resulted in the formation of the expected product with an acceptable profile. With the usage of the automatic sample changer of our microwave reactor, all of the prepared final intermediate was cyclized overnight in 30 portions. The combined reaction mixtures were combined and purified on column chromatography to give the macrocyclic product **40** in a satisfactory overall yield on gram scale. The main by-product was the "dimer" **41** which could have been supressed with a higher dilution rate. The removal of the protecting group now easily provided us the target molecule **26** in the requested quantity (Scheme 6), which was used for the support of our medicinal chemistry program. Due to the obtained pharmacological results from the synthesized derivatives, further scale-up of this reaction sequence was not requested, so the conditions were not optimized further.



Scheme 6. *Reagents and conditions:* i. EDC.HCl, pyridine (86%); ii. $Pd(PPh_3)_2Cl_2$, KF, dioxane, water, microwawe, 130 °C (**40**: 32%, **41**: 6%), iii. HCl. MeOH, dioxane, water (87%).

In conclusion we have developed a new synthetic route to obtain macrocyclic intermediate **26**, supporting our medicinal chemistry program at Servier targeting macrocyclic analogues of SIRT 257. The microwave-mediated Suzuki-macrocyclization step[19] described above, resulted in the formation of a 13-membered heterocyclic ring, that is rarely exemplified in the chemical literature. The further investigation of this chemistry was abandoned due to changes in the project priorities.

EXPERIMENTAL

Organic solutions were dried over magnesium sulphate and concentrated under diminished pressure at 40 °C. Purification by column chromatography was performed using a Teledyne Isco CombiFlash® Rf system with RediSep Rf Gold™ columns. The NMR spectra were recorded on Bruker 500 MHz and 400 MHz spectrometers, ^{13}C-NMR spectra were recorded at 125 MHz and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal. High-resolution mass spectra (HRMS) were determined on an Agilent 6230 TOF LC/MS spectrometer.

2-[(*E*)-2-(3-Bromophenyl)ethenyl]-4-methoxy-1-nitrobenzene (20): To a solution of 3-methyl-4-nitroanisole (16.7 g, 0.1 mol) and 3-bromobenzaldehyde (11.7 mL, 0.1 mol) in dry DMSO

(700 mL), a solution of freshly prepared sodium ethoxide in dry EtOH solution (0.4 M, 100.0 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, poured into ice (3 kg) and was stirred overnight. The solid was filtered off and recrystallized from EtOH (310 mL) to give **20** (10.13 g, 30%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 8.08 (d, 1H, *J* = 9.0 Hz, H-6), 7.84 (br s, 1H, H-2'), 7.66 (d, 1H, *J* = 16.0 Hz, NO_2PhCH), 7.63 (d, 1H, *J* = 7.9 Hz, H-6'), 7.53 (d, 1H, *J* = 7.9 Hz, H-4'), 7.38 (t, 1H *J* = 7.9 Hz, H-5'), 7.35 (d, 1H, *J* = 3.0 Hz, H-3), 7.29 (d, 1H, *J* = 16.0 Hz, BrPhCH), 7.09 (dd, 1H *J* = 9.0 and 3.0 Hz, H-5), 3.94 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 163.3 (q), 141.3 (q), 139.5 (q), 135.5 (q), 132.1 (CH), 131.5 (CH), 131.4 (CH), 130.0 (CH), 128.0 (CH), 126.4 (CH), 126.4 (CH), 122.7 (q), 114.8 (CH), 113.3 (CH), 56.7 (CH_3). GC-MS (*m/z*): (EI) calcd for $C_{15}H_{12}BrNO_3$ $[M]^+$: 333.0, found 333.1.

2-[2-(3-Bromophenyl)ethyl]-4-methoxyaniline (21): To a suspension of 2-[(*E*)-2-(3-bromophenyl)ethenyl]-4-methoxy-1-nitrobenzene (**20**, 5.1 g, 15.2 mmol) and nickel chloride (2.0 g, 15.5 mmol) in a mixture of THF (25 mL) and MeOH (25 mL), sodium borohydride (1.2 g, 31.9 mmol) was added portionwise at 0 °C. The reaction mixture was allowed to attain room temperature and was stirred for 4 h. It was poured into water (100 mL), extracted with CH_2Cl_2 (2 x 300 mL), the combined organic phases were washed with brine (200 mL), dried and concentrated. The residue was purified by column chromatography (heptane → EtOAc) to give the title product (2.50 g, 53%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 7.53 (br s, 1H, H-2'), 7.37 (d, 1H, *J* = 7.8 Hz, H-4'), 7.29 (d, 1H, *J* = 7.8 Hz, H-6'), 7.24 (t, 1H, *J* = 7.8 Hz, H-5'), 6.58 (d, 1H, *J* = 9.0 Hz, H-6), 6.56 (d, 1H, *J* = 2.9 Hz, H-3), 6.53 (dd, 1H, *J* = 9.0 and 2.9 Hz H-5), 4.50 (s, 2H, NH_2), 3.60 (s, 3H, CH_3), 2.83-2.78 (m, 2H, BrPhCH_2), 2.71-2.65 (m, 2H, CH_2). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 151.4 (q), 145.5 (q), 131.8 (CH), 130.8 (CH), 129.1 (CH), 128.2 (CH), 126.5 (q), 116.2 (CH), 115.5 (CH), 112.6 (CH), 55.7 (CH_3), 34.5 (CH_2), 33.2 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_{15}H_{17}BrNO$ $[M+H]^+$: 306.0494, found 306.0490.

4-Methoxy-2-{2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}aniline (22): A mixture of 2-[2-(3-bromophenyl)ethyl]-4-methoxyaniline (**21**, 1.7 g, 5.5 mmol), bis(pinacolato)diboron (1.5 g, 6.1 mmol), potassium acetate (1.6 g, 16.5 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.20 g, 0.28 mmol) in degassed 1,4-dioxane (27 mL) was refluxed overnight. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and concentrated. The residue was purified by column chromatography (heptane → heptane/EtOAc 4/1) to give **22** (1.2 g, 61%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 7.60 (br s, 1H, H-2'), 7.50 (d, 1H, *J* = 7.6 Hz, H-4'), 7.43 (d, 1H, *J* = 7.6 Hz, H-6'), 7.30 (t, 1H, *J* = 7.6 Hz, H-5'), 6.58 (d, 1H, *J* = 3.0 Hz, H-3), 6.57 (d, 1H, *J* = 8.6 Hz, H-6), 6.52 (dd, 1H, *J* = 8.6 and 3.0 Hz, H-5), 4.47 (br s, 2H, NH_2), 3.60 (s, 3H, OCH_3), 2.84-2.79 (m, 2H, BPhCH_2), 2.71-2.65 (m, 2H, CH_2), 1.29 (s, 12H 4 x CH_3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 151.4 (q), 141.9 (q), 140.2 (q), 135.0 (CH), 132.4 (CH), 132.2 (CH), 128.7 (q), 128.2 (CH), 126.9 (q), 116.2 (CH), 115.4 (CH), 112.5 (CH), 84.0 (2 x q), 55.6 (CH_3), 34.9

(CH_2), 33.5 (CH_2), 25.2 (4 x CH_3). HRMS (*m/z*): (ESI) calcd for $C_{21}H_{29}BNO_3$ $[M+H]^+$: 354.2240, found 354.2223.

Ethyl 8-{3-[2-(2-amino-5-methoxyphenyl)ethyl]phenyl}-1,6-naphthyridine-2-carboxylate (23): A mixture of 4-methoxy-2-{2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}aniline (**22**, 1.20 g, 3.4 mmol), ethyl 8-bromo-1,6-naphthyridine-2-carboxylate (**1**, 1.10 g, 3.7 mmol), potassium fluoride (0.59 g, 10.20 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.12 g, 0.17 mmol) in a mixture of degassed 1,4-dioxane (40 mL) and water (10 mL) was refluxed for 6 h under nitrogen. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and concentrated. The residue was purified by column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 3/7) to give **23** (0.95 g, 66%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 9.53 (s, 1H, H-5), 8.90 (s, 1H, H-7), 8.86 (d, 1H, *J* = 8.4 Hz, H-4), 8.29 (d, 1H, *J* = 8.4 Hz, H-3), 7.83 (s, 1H, H-2'), 7.67 (d, 1H, *J* = 7.5 Hz, H-6'), 7.45 (t, 1H, *J* = 7.5 Hz, H-5'), 7.40 (d, 1H, *J* = 7.5 Hz, H-4'), 6.61 (d, 1H, *J* = 3.0 Hz, H-6"), 6.58 (d, 1H, *J* = 8.4 Hz, H-3"), 6.54 (dd, 1H, *J* = 8.4 and 3.0 Hz, H-4"), 4.51 (br s, 2H, NH_2), 4.38 (q, 2H, *J* = 7.1 Hz, *CH*$_2$$CH_3$), 3.59 (s, 3H, OCH_3), 2.95-2.90 (m, 2H, CH_2), 2.83-2.78 (m, 2H, NH_2PhCH_2), 1.32 (t, 3H, *J* = 7.1 Hz, CH_2*CH*$_3$). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 164.8 (q), 153.2 (CH), 152.2 (q), 151.4 (q), 147.2 (CH), 147.0 (q), 142.3 (q), 140.1 (q), 139.0 (CH), 135.2 (q), 133.6 (q), 131.8 (CH), 128.8 (2 x CH), 128.4 (CH), 126.8 (q), 124.2 (q), 122.7 (CH), 116.2 (CH), 115.4 (CH), 112.5 (CH), 62.3 (CH_2), 55.7 (CH_3), 35.1 (CH_2), 33.7 (CH_2), 14.5 (CH_3). HRMS (*m/z*): (ESI) calcd for $C_{26}H_{26}N_3O_3$ $[M+H]^+$: 428.1974, found 428.1963.

8-{3-[2-(2-Amino-5-methoxyphenyl)ethyl]phenyl}-1,6-naphthyridine-2-carboxylic acid (24): To a solution of ethyl 8-{3-[2-(2-amino-5-methoxyphenyl)ethyl]phenyl}-1,6-naphthyridine-2-carboxylate (**23**, 0.95 g, 2.23 mmol) in THF (6 mL), a solution of lithium hydroxide monohydrate (0.47 g, 11.15 mmol) in water (6 mL) was added and it was stirred for 1 h at room temperature. The reaction mixture was concentrated, the residue was dissolved in water (5 mL), the pH was adjusted to 5 with aqueous 1 M hydrochloric acid. The precipitated solid was filtered off and dried *in vacuo* to give the **24** carboxylic acid (0.63 g, 71%). ^{1}H-NMR (400 MHz, DMSO$_{d6}$): δ ppm 9.51 (s, 1H, H-5), 8.86 (s, 1H, H-7), 8.83 (d, 1H, *J* = 8.5 Hz, H-4), 8.27 (d, 1H, *J* = 8.5 Hz, H-3), 7.78 (br s, 1H, H-2'), 7.66 (d, 1H, *J* = 7.6 Hz, H-6'), 7.44 (t, 1H, *J* = 7.6 Hz, H-5'), 7.38 (d, 1H, *J* = 7.6 Hz, H-4'), 6.70 (d, 1H, *J* = 8.7 Hz, H-3"), 6.67 (d, 1H, *J* = 2.9 Hz, H-6"), 6.59 (dd, 1H, *J* = 8.7 and 2.9 Hz, H-4"), 3.62 (s, 3H, CH_3), 2.96-2.89 (m, 2H, CH_2), 2.86-2.80 (m, 2H, CH_3OPhCH_2), CO_2H and NH_2 not visible. ^{13}C-NMR (100 MHz, DMSO$_{d6}$): δ 166.9 (q), 153.5 (q), 153.2 (CH), 152.6 (q), 147.1 (CH), 147.0 (q), 142.3 (q), 138.7 (CH), 135.4 (q), 133.8 (q), 131.6 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 124.1 (q), 122.8 (CH), 117.6 (CH), 115.6 (CH), 112.6 (CH), 55.7 (CH_3), 35.2 (CH_2), 33.6 (CH_2), 2 x C (q) not visible. HRMS (*m/z*): (ESI) calcd for $C_{24}H_{22}N_3O_3$ $[M+H]^+$: 400.1661, found 400.1644.

13-Methoxy-11,16-dihydro-1,18-etheno-5,9-(metheno)pyrido[4,3-*e*][1,4]benzodiazacyclopentadecin-17(10*H*)-one (25): To a suspension of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.29 g, 1.50 mmol) in a mixture of CH_2Cl_2 (5 mL) and pyridine (0.61 mL, 7.5 mmol), a solution of 8-{3-[2-(2-amino-5-methoxyphenyl)ethyl]phenyl}-1,6-naphthyridine-2-carboxylic acid (**24**, 0.20 g, 0.50 mmol) in a mixture of CH_2Cl_2 (5 mL) and pyridine (0.61 mL, 7.5 mmol) was added dropwise at room temperature over a period of 10 h, and it was stirred overnight. The reaction mixture was concentrated, the residue was purified by column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 95/5) to give the expected macrocycle **25** (0.05 g, 26%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 10.72 (s, 1H, NH), 9.56 (s, 1H, H-2), 9.19 (s, 1H, H-4), 8.90 (d, 1H, *J* = 8.0 Hz, H-21), 8.46 (s, 1H, H-22), 8.32 (br s, 2H, H-15, H-20), 7.60 (d, 1H, *J* = 7.6 Hz, H-6), 7.47 (t, 1H *J* = 7.6 Hz, H-7), 7.33 (d, 1H, *J* = 7.6 Hz, H-8), 6.99 (d, 1H, *J* = 3.0 Hz, H-12), 6.89 (d, 1H *J* = 7.7 Hz, H-14), 3.77 (s, 3H, CH_3), 3.07 (br s, 2H, CH_2-10), 2.89 (br s, 2H, CH_2-11). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 160.5 (q), 156.0 (q), 153.2 (CH), 152.1 (q), 144.9 (q), 144.7 (CH), 142.1 (q), 139.9 (CH), 134.8 (CH), 134.3 (q), 133.6 (q), 132.8 (q), 131.8 (q), 129.5 (CH), 127.7 (CH), 127.4 (CH), 124.3 (q), 120.5 (CH), 119.4 (CH), 116.7 (CH), 112.5 (CH), 55.7 (CH_3), 36.6 (CH_2), 34.0 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_{24}H_{20}N_3O_2$ $[M+H]^+$: 382.1556, found 382.1151.

4-(Methoxymethoxy)-2-methyl-1-nitrobenzene (28): To a suspension of 60% sodium hydride (6.0 g, 150.0 mmol) in anhydrous DMF (200 mL), 3-methyl-4-nitrophenol (**27**, 15.1 g, 100.0 mmol) was added portionwise at 0 °C. After the mixture was stirred for 2 h, chloromethyl methyl ether (34.2 mL, 450.0 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. It was poured into water (600 mL), extracted with Et_2O (3 x 200 mL). The combined organic phases were washed with brine (150 mL), dried and concentrated. The residue was purified by column chromatography (heptane/EtOAc 9/1) to give the title product (**28**, 16.2 g, 82%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ ppm 8.05 (d, 1H, *J* = 9.0 Hz, H-6), 7.09 (d, 1H, *J* = 3.0 Hz, H-3), 7.05 (dd, 1H, *J* = 9.0 and 3.0 Hz, H-5), 5.31 (s, 2H, CH_2), 3.39 (s, 3H, *O*CH_3), 2.54 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 160.8 (q), 142.9 (q), 136.7 (q), 127.7 (CH), 119.7 (CH), 114.6 (CH), 94.2 (CH_2), 56.5 (*O*CH_3), 21.1 (CH_3). HRMS (*m/z*): (ESI) calcd for $C_9H_{12}NO_4$ $[M+H]^+$: 198.0766, found 198.0761.

5-(Methoxymethoxy)-2-nitrobenzaldehyde (30): To a suspension of 5-hydroxy-2-nitrobenzaldehyde (**29**, 50.1 g, 0.3 mol), potassium carbonate (165.8 g, 1.2 mol) in anhydrous DMF (500 mL), chloromethyl methyl ether (34.2 mL, 450.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. It was poured into water (1500 mL), after 30 min stirring the solid was filtered off, washed with water (500 mL) and dried *in vacuo* to give the expected product (59.8 g, 94%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 10.28 (s, 1H, CHO), 8.19 (d, 1H, *J* = 9.0 Hz, H-3), 7.43 (dd, 1H, *J* = 9.0 and 2.5 Hz, H-4), 7.36 (d, 1H, *J* = 2.5 Hz, H-6), 5.40 (s, 2H, CH_2), 3.41 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 190.3 (CH), 161.4 (q), 143.1 (q), 134.4 (q), 127.7 (CH), 120.5 (CH), 115.9 (CH), 94.7 (CH_2), 56.6 (CH_3).

HRMS (*m/z*): (EI) calcd for $C_9H_9NO_5$ $[M]^+$: 211.0481, found 211.0489.

5-(Methoxymethoxy)-2-nitrophenyl]methanol (31): To a solution of 5-(methoxymethoxy)-2-nitrobenzaldehyde (**30**, 59.8 g, 0.28 mol) in anhydrous MeOH (400 mL) and anhydrous THF (200 mL), sodium borohydride (13.4 g, 0.35 mol) was added portionwise at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and concentrated. The residue was dissolved in CH_2Cl_2 (1000 mL), washed with saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL). The organic phase was dried and concentrated to give the title product (59.3 g, 98%). ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 8.12 (d, 1H, *J* = 9.0 Hz, H-3), 7.45 (d, 1H, *J* = 2.5 Hz, H-6), 7.10 (dd, 1H, *J* = 9.0 and 2.5 Hz, H-4), 5.60 (s, 1H, OH), 5.33 (s, 2H, OCH_2O), 4.84 (s, 2H, CH_2), 3.40 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 161.6 (q), 142.7 (q), 140.5 (q), 127.8 (CH), 115.0 (CH), 114.7 (CH), 94.3 (CH_2), 60.6 (CH_2), 56.5 (CH_3). HRMS (*m/z*): (ESI) calcd for $C_9H_{12}NO_5$ $[M+H]^+$: 214.0715, found 214.0715.

2-(Bromomethyl)-4-(methoxymethoxy)-1-nitrobenzene (32): To a solution of 5-(methoxymethoxy)-2-nitrophenyl]methanol (**31**, 59.3 g, 0.28 mol) and CBr_4 (101.5 g, 0.31 mol) in anhydrous CH_2Cl_2 (1000 mL), triphenylphosphine (80.3 g, 0.31 mol) was added portionwise at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and concentrated. The residue was dissolved in Et_2O (1000 mL) and it was stirred for 30 min at 0 °C. The formed solid triphenylphosphine oxide (85.0 g) was filtered off. The filtrate was concentrated and the residue was purified by column chromatography (heptane/EtOAc 95/5 → 9/1) to give **32** (58.4 g, 76%). ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 8.14 (d, 1H, *J* = 9.0 Hz, H-6), 7.37 (d, 1H, *J* = 2.5 Hz, H-3), 7.20 (dd, 1H, *J* = 9.0 and 2.5 Hz, H-5), 5.34 (s, 2H, OCH_2O), 4.94 (s, 2H, CH_2Br), 3.40 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 161.0 (q), 141.7 (q), 135.9 (q), 128.7 (CH), 120.0 (CH), 116.8 (CH), 94.5 (CH_2), 56.6 (CH_3), 30.8 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_9H_{14}BrN_2O_4$ $[M+NH_4]^+$: 293.0137, found 293.0129.

Diethyl {5-(methoxymethoxy)-2-nitrophenyl]methyl}phosphonate (33): A solution of 2-(bromomethyl)-4-(methoxymethoxy)-1-nitrobenzene (**32**, 19.6 g, 71.0 mmol) and triethyl phosphite (13.4 mL, 78.2 mmol) in anhydrous toluene (300 mL) was refluxed overnight. The reaction mixture was concentrated, the residue was purified by column chromatography (heptane/EtOAc 4/1 → /EtOAc) to give **33** (17.0 g, 71%) and **34** (0.6 g, 5%) as a by-product. **33**: ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 8.03 (d, 1H, *J* = 9.0 Hz, H-3), 7.14-7.10 (m, 2H, H-4, H-6), 5.31 (s, 2H, *O*CH_2*O*), 3.96-3.89 (m, 4H, 2 x P-OCH_2), 3.75 (d, 2H, *J* = 22.5 Hz, CH_2*P*), 3.39 (s, 3H, *O*CH_3), 1.14 (t, 6H, *J* = 7.0 Hz, 2 x CH_3). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 160.3 (q), 143.3 (q), 130.6 (q), 128.1 (CH), 120.6 (CH), 115.1 (CH), 94.4 (CH_2), 62.2 (CH_2), 56.5 (CH_3), 30.3 (CH_2), 16.6 (CH_3). HRMS (*m/z*): (ESI) calcd for $C_{13}H_{21}NO_7P$ $[M+H]^+$: 334.1056, found 334.1051.

5-(Methoxymethoxy)-2,1-benzoxazole (34): ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 9.58 (d, 1H, *J* = 0.5 Hz, H-3), 7.64 (d, 1H, *J* = 9.5 Hz, H-7), 7.16 (dd, 1H, *J* = 0.5 and 9.5 Hz, H-6), 7.07 (dd, 1H, *J* = 0.5 and 9.5

Hz, H-4), 5.24 (s, 2H, *O*CH_2), 3.40 (s, 3H, *O*CH_3); ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 155.6 (CH), 154.1 (q), 152.9(q), 128.6 (CH), 118.3 (q), 116.6 (CH), 98.6 (CH), 94.5 (CH_2), 56.3 (CH_3); HRMS (*m/z*): (ESI) calcd for $C_9H_9NO_3$ $[M+H]^+$: 180.0652, found 180.0655.

2-(3-{(*E*)-2-[5-(Methoxymethoxy)-2-nitrophenyl]ethenyl}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36): To a solution of diethyl {5-(methoxymethoxy)-2-nitrophenyl]methyl}phosphonate (**33**, 20.0 g, 60.0 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**35**, 13.9 g, 60.0 mmol) in anhydrous DMF (200 mL), potassium *tert*-butoxide (20.2 g, 180.0 mmol) was added at 0 °C. The reaction mixture was allowed to attain room temperature and stirred overnight, it was poured into water (600 mL) and extracted with Et_2O (3 x 300 mL). The combined organic phases were washed with brine (2 x 150 mL), dried and concentrated. The resulting solid was suspended in EtOH (80 mL) and it was stirred for 30 min at 0 °C, then the solid was filtered off and dried *in vacuo* to give **36** (15.1 g, 61%). ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 8.06 (d, 1H, *J* = 9.1 Hz, H-3'), 7.90 (br s, 1H, H-2), 7.76 (d, 1H, *J* = 7.5 Hz, H-4), 7.63 (d, 1H, *J* = 7.5 Hz, H-6), 7.59 (d, 1H, *J* = 16.0 Hz, NO_2PhCH), 7.48 (d, 1H, *J* = 2.7 Hz, H-6'), 7.44 (t, 1H, *J* = 7.5 Hz, H-5), 7.37 (d, 1H, *J* = 16.0 Hz, BPhCH), 7.13 (dd, 1H, *J* = 9.1 and 2.7 Hz, H-4'), 5.40 (s, 2H, OCH_2O), 3.43 (s, 3H, OCH_3), 1.31 (s, 12H, CCH_3). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 160.8 (q), 141.9 (q), 136.3 (q), 135.6 (q), 135.1 (CH), 133.8 (CH), 133.7 (CH), 130.2 (CH), 129.0 (CH), 127.8 (CH), 124.4 (CH), 116.1 (CH), 115.0 (CH), 94.4 (CH_2), 84.3 (2 x q), 56.6 (CH_3), 25.2 (4 x CH_3), C-B not visible. HRMS (*m/z*): (ESI) calcd for $C_{22}H_{27}BNO_6$ $[M+H]^+$: 412.1931, found 412.1910.

4-(Methoxymethoxy)-2-{2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}aniline (37): A suspension of 2-(3-{(*E*)-2-[5-(methoxymethoxy)-2-nitrophenyl]ethenyl}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**36**, 15.0 g, 36.5 mmol) and 10% palladium on carbon (1.0 g) in a mixture of MeOH (150 mL) and THF (75 mL), was stirred under 4 bar of hydrogen for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite and concentrated to give **37** (13.9 g, 99%). ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 7.59 (t, 1H, *J* = 1.4 Hz, H-2'), 7.50 (dt, 1H, *J* = 7.5 and 1.4 Hz , H-4'), 7.42 (dt, 1H, *J* = 7.5 and 1.4 Hz, H-6'), 7.30 (t, 1H, *J* = 7.5 Hz , H-5'), 6.66 (d, 1H, *J* = 2.5 Hz, H-3), 6.61 (dd, 1H, *J* = 9.0 and 2.5 Hz, H-5), 6.56 (d, 1H, *J* = 9.0 Hz, H-6), 4.97 (s, 2H, OCH_2O), 4.58 (br s, 2H, NH_2), 3.33 (s, 3H, OCH_3), 2.83-2.78 (m, 2H, $PhCH_2$), 2.69-2.64 (m, 2H, $BPhCH_2$), 1.29 (s, 12H, CCH_3). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 148.6 (q), 141.9 (q), 141.5 (q), 135.0 (CH), 132.4 (CH), 132.2 (CH), 128.8 (q), 128.2 (CH), 126.6 (q), 118.5 (CH), 115.9 (CH), 115.7 (CH), 95.5 (CH_2), 84.0 (2 x q), 55.7 (CH_3), 34.8 (CH_2), 33.4 (CH_2), 25.2 (4 x CH_3). HRMS (*m/z*): (ESI) calcd for $C_{22}H_{31}BNO_4$ $[M+H]^+$: 384.2346, found 384.2383.

8-Bromo-1,6-naphthyridine-2-carboxylic acid (38): To a solution of ethyl 8-bromo-1,6-naphthyridine-2-carboxylate (**1**, 20.0 g, 71.1 mmol) in THF (200 mL), a solution of lithium hydroxide monohydrate (14.9 g, 355.5 mmol) in water (200 mL) was added and it was stirred for 1 h at

room temperature. The reaction mixture was concentrated, the residue was dissolved in water (100 mL), the pH was adjusted to 5 with aqueous 1 M hydrochloric acid. The precipitated solid was filtered off and dried *in vacuo* to give **38** (15.6 g, 87%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 13.97 (br s, 1H, CO_2H), 9.50 (s, 1H, H-5), 9.10 (s, 1H, H-7), 8.84 (d, 1H, *J* = 8.5 Hz, H-4), 8.32 (d, 1H, *J* = 8.5 Hz, H-3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 166.2 (q), 154.6 (q), 153.7 (CH), 149.1 (CH), 146.9 (q), 139.3 (CH), 126.0 (q), 124.0 (CH), 121.6 (q). HRMS (*m/z*): (ESI) calcd for $C_9H_6BrN_2O_2$ $[M+H]^+$: 252.9613, found 252.9607.

8-Bromo-*N*-[4-(methoxymethoxy)-2-[2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-ethyl]phenyl]-1,6-naphthyridine-2-carboxamide (39): A solution of 4-(methoxymethoxy)-2-{2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}aniline (**37**, 13.9 g, 36.3 mmol), 8-bromo-1,6-naphthyridine-2-carboxylic acid (**38**, 9.64 g, 38.1 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (14.6 g, 76.2 mmol) in anhydrous pyridine (250 mL) was stirred at room temperature overnight. The reaction mixture was concentrated, the residue was dissolved in CH_2Cl_2 (500 mL), washed with brine (150 mL), dried and concentrated. The resulting solid was suspended in Et_2O (150 mL), filtered off and dried *in vacuo* to give **39** (19.4 g, 86%). ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 10.32 (s, 1H, NH), 9.49 (s, 1H, H-5), 9.05 (s, 1H, H-7), 8.90 (d, 1H, *J* = 8.4 Hz, H-4), 8.43 (d, 1H, *J* = 8.4 Hz, H-3), 8.03 (d, 1H, *J* = 8.7 Hz, H-6'), 7.55 (br s, 1H, H-2"), 7.45 (d, 1H, *J* = 7.4 Hz, H-4"), 7.33 (d, 1H, *J* = 7.4 Hz, H-6"), 7.20 (t, 1H, *J* = 7.4 Hz, H-5"), 7.00 (d, 1H, *J* = 2.8 Hz, H-3'), 6.96 (dd, 1H, *J* = 8.7 and 2.8 Hz, H-5'), 5.18 (s, 2H, OCH_2O), 3.39 (s, 3H, OCH_3), 3.06-3.01 (m, 2H, MOMPhCH_2), 3.00-2.95 (m, 2H, BPhCH_2), 1.22 (s, 12H, CCH_3). ^{13}C-NMR (125 MHz, DMSO$_{d6}$): δ 161.0 (q), 154.6 (q), 154.4 (q), 153.7 (CH), 149.2 (CH), 145.6 (q), 140.9 (q), 140.3 (CH), 135.0 (CH), 134.6 (q), 132.6 (CH), 132.1 (CH), 129.6 (q), 128.2 (CH), 126.0 (q), 123.4 (CH), 121.6 (CH), 120.9 (q), 117.7 (CH), 114.6 (CH), 94.5 (CH_2), 84.0 (2 x q), 56.0 (CH_3), 35.4 (CH_2), 33.1 (CH_2), 25.1 (4 x CH_3), C (q) not visible. HRMS (*m/z*): (ESI) calcd for $C_{31}H_{34}BBrN_3O_5$ $[M+H]^+$: 618.1775, found 618.1775.

13-(Methoxymethoxy)-11,16-dihydro-1,18-etheno-5,9-(metheno)pyrido[4,3-*e*][1,4]benzodiaza-cyclopentadecin-17(10*H*)-one (40): In a 25 mL microwaveable vial, a mixture of **39** (0.62 g, 1.00 mmol), potassium fluoride (0.17 g, 3.00 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.07 g, 0.10 mmol) in a mixture of degassed 1,4-dioxane (15 mL) and water (3 mL) was sealed and heated in the microwave to 130 °C for 20 min. The reaction was repeated 30 times with the help of the automatic sample changer. The reaction mixtures were merged and filtered through a pad of Celite, the filtrate was concentrated, the residue was dissolved in CH_2Cl_2 (50 mL), washed with brine (10 mL), dried and concentrated. The obtained thick oil was purified by column chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 95/5) to give **40** (3.90 g, 32%) and **41** (0.73 g, 6%). **Macrocycle 40**: ^{1}H-NMR (500 MHz, DMSO$_{d6}$): δ 10.75 (s, 1H, NH), 9.57 (s, 1H, H-2), 9.20 (s, 1H, H-4), 8.92 (d, 1H, *J* = 8.0 Hz, H-21), 8.47 (s, 1H, H-22),

8.33 (d, 1H, *J* = 8.0 Hz, H-20), 8.33 (d, 1H, *J* = 8.0 Hz, H-15), 7.60 (d, 1H, *J* = 7.5 Hz, H-6), 7.48 (t, 1H, *J* = 7.5 Hz, H-7), 7.34 (d, 1H, *J* = 7.5 Hz, H-8), 7.08 (d, 1H, *J* = 2.5 Hz, H-12), 6.98 (br s, 1H, H-14), 5.20 (s, 2H, OCH_2O), 3.40 (s, 3H, CH_3), 3.08 (br s, 2H, CH_2-10), 2.90 (br s, 2H, CH_2-11). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 160.6 (q), 153.5 (q), 153.2 (CH), 152.1 (q), 144.9 (q), 144.7 (CH), 142.0 (q), 140.0 (CH), 134.9 (CH), 134.3 (q), 133.4 (q), 130.5 (q), 131.8 (q), 129.5 (CH), 127.8 (CH), 127.4 (CH), 124.4 (q), 120.5 (CH), 119.4 (CH), 119.0 (CH), 115.0 (CH), 94.6 (CH_2), 56.1 (CH_3), 36.6 (CH_2), 34.0 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_{25}H_{22}N_3O_3$ $[M+H]^+$: 412.1661, found 412.1657.

Macrocycle 41: ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 9.69 (s, 2H, *N*HC*O*), 9.18 (s, 2H, PyH), 8.73 (d, 2H, PyH), 8.36 (d, 2H, PyH), 7.75 (d, 2H, PhH), 7.74 (s, 2H, PyH), 7.21 (t, 2H, PhH), 7.21 (m, 2H, PhH), 7.12 (d, 2H, PhH), 6.94 (dd, 2H, PhH), 6.90 (m, 2H, PhH), 6.81 (t, 2H, PhH), 5.23 (s, 4H, *O*CH_2*O*), 3.42 (s, 6H, *O*CH_3), 2.75 (t, 4H, CH_2CH_2), 2.67 (t, 4H, CH_2CH_2). ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 161.4 (q), 154.7 (CH), 152.7 (CH), 146.2 (CH), 139.9 (CH), 130.6 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 124.5 (CH), 120.0 (CH), 118.0 (CH), 114.9 (CH), 94.5 (CH_2), 56.1 (CH_3), 37.3 (CH_2), 34.4 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_{50}H_{42}N_6O_6$ $[M+H]^+$: 823.3213, found 823.3211.

13-Hydroxy-11,16-dihydro-1,18-etheno-5,9-(metheno)pyrido[4,3-*e*][1,4]benzodiazacyclopentadecin-17(10*H*)-one (26, hydrogen chloride salt): To a suspension of **40** (47 mg, 0.11mmol) in a mixture of MeOH (2.0 mL) 1,4-dioxane (2.0 mL) and water (2.0 mL), hydrochloric acid (1.0 mL) was added. The reaction mixture was refluxed for 1 h and concentrated. The resulting solid was suspended in Et_2O (3 mL), filtered off and dried in *vacuo* to give the title product (40 mg, 87%). ^{1}H-NMR (500 MHz, $DMSO_{d6}$): δ 10.64 (s, 1H, NH), 9.69 (s, 1H, H-2), 9.24 (s, 1H, H-4), 8.98 (d, 1H, *J* = 8.5 Hz, H-21), 8.46 (s, 1H, H-22), 8.38 (d, 1H, *J* = 8.5 Hz, H-20), 8.19 (d, 1H, *J* = 9.0 Hz, H-15), 7.61 (d, 1H, *J* = 7.5 Hz, H-6), 7.49 (t, 1H. *J* = 7.5 Hz, H-7), 7.36 (d, 1H, *J* = 7.5 Hz, H-8), 6.80 (d, 1H, *J* = 2.0 Hz, H-12), 6.71 (dd, 1H, *J* = 9.0 and 2.0 Hz, H-14), 3.07 (br s, 2H, CH_2-10), 2.86 (br s, 2H, CH_2-11), OH not visible. ^{13}C-NMR (125 MHz, $DMSO_{d6}$): δ 160.0 (q), 154.3 (q), 153.1 (q), 152.1 (CH), 145.4 (q), 142.3 (CH), 142.2 (q), 140.5 (CH), 134.8 (CH), 133.7 (q), 133.4 (q), 132.9 (q), 129.5 (CH), 128.1 (CH), 127.9 (q), 127.6 (CH), 124.4 (q), 120.8 (CH), 119.9 (CH), 117.8 (CH), 114.0 (CH), 36.6 (CH_2), 33.8 (CH_2). HRMS (*m/z*): (ESI) calcd for $C_{23}H_{18}N_3O_2$ $[M+H]^+$: 368.1399, found 368.1395.

ACKNOWLEDGEMENTS

The authors acknowledge Barbara Balázs and Tamás Gáti for NMR spectroscopy measurements.

REFERENCES

1. T. Finkel, C. X. Deng, and R. Mostoslavsky, *Nature*, 2009, **460**, 587.
2. (a) C. B. Vu, J. E. Bemis, J. S. Disch, P. Y. Ng, J. J. Nunes, J. C. Milne, D. P. Carney, A. V. Lynch,

J. J. Smith, S. Lavu, P. D. Lambert, D. J. Gagne, M. R. Jirousek, S. Schenk, J. M. Olefsky, and R. B. Perni, *J. Med. Chem.*, 2009, **52**, 1275; (b) M. J. Kim, H. J. An, D. H. Kim, B. Lee, H. J. Lee, S. Ullah, S. J. Kim, H. O. Jeong, K. M. Moon, E. K. Lee, J. Yang, J. Akter, P. Chun, H. R. Moon, and H. Y. Chung, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 684; (c) Y. Matsuya, Y. Kobayashi, S. Uchida, Y. Itoh, H. Sawada, T. Suzuki, N. Miyata, K. Sugimoto, and N. Toyooka, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4907; (d) J. Wu, J. Li, M. H. Xu, and D. Liu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3050; (e) K. Cottet, B. Xu, P. Coric, S. Bouaziz, S. Michel, M. Vidal, M. C. Lallemand, and S. Broussy, *J. Med. Chem.*, 2016, **59**, 9560; (f) A. Mai, S. Massa, S. Lavu, R. Pezzi, S. Simeoni, R. Ragno, F. R. Mariotti, F. Chiani, G. Camilloni, and D. A. Sinclair, *J. Med. Chem.*, 2005, **48**, 7789.

3. S. Pervaiz and A. L. Holme, *Antioxid. Redox Signal*, 2009, **11**, 2851.
4. A. Mai, S. Valente, S. Meade, V. Carafa, M. Tardugno, A. Nebbioso, A. Galmozzi, N. Mitro, E. De Fabiani, L. Altucci, and A. Kazantsev, *J. Med. Chem.*, 2009, **52**, 5496.
5. (a) P. Wangtrakuldee, M. S. Byrd, C. G. Campos, M. W. Henderson, Z. Zhang, M. Clare, A. Masoudi, P. J. Myler, J. R. Horn, P. A. Cotter, and T. J. Hagen, *ACS Med. Chem. Lett.*, 2013, **4**, 699; (b) H. Jiang, J. Xing, C. Wang, H. Zhang, L. Yue, X. Wan, W. Chen, H. Ding, Y. Xie, H. Tao, Z. Chen, H. Jiang, K. Chen, S. Chen, M. Zheng, Y. Zhang, and C. Luo, *Org. Biomol. Chem.*, 2017, **15**, 9352; (c) H. Jiang, J. E. Taggart, X. Zhang, D. M. Benbrook, S. E. Lind, and W. Q. Ding, *Cancer Lett.*, 2011, **312**, 11; (d) H. Mao, Y. Du, Z. Zhang, B. Cao, J. Zhao, H. Zhou, and X. Mao, *Anticancer Drugs*, 2017, **28**, 376.
6. (a) G. Westerberg, J. A. Chiesa, C. A. Andersen, D. Diamanti, L. Magnoni, G. Pollio, B. Darpo, and M. Zhou, *Br. J. Clin. Pharmacol.*, 2015, **79**, 477; (b) A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J. F. Pons, J. Barker, W. T. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. O. Saunders, P. S. DiStefano, and R. Curtis, *J. Med. Chem.*, 2005, **48**, 8045.
7. C. B. Vu and R. L. Casaubon, WO 2010/101949 Al.
8. G. J. Hanson, R. W. Ware, T. E. Barta, and H. Huang, *U.S. Pat. Appl. Publ.*, 2006, US 20060030584 A1.
9. (a) R. Umeda, S. Morishita, and Y. Nishiyama, *Heteroat. Chem.*, 2011, **22**, 571; (b) V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin, and S. A. Shevelev, *Synthesis*, 1999, 2065; (c) X. B. Li, L. Wang, X. Q. Zhang, H. M. Gu, J. Guo, and B. L. Li, *J. Chem. Res.*, 2010, **34**, 489.
10. (a) J. A. Schreifels, P. C. Maybury, and W. E. Swartz, *J. Org. Chem.*, 1981, **46**, 1263; (b) R. B. Boar, D. W. Hawkins, J. F. McGhie, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans.1*, 1973, 654; (c) J. O. Osby and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 6413.

11. I. Kawasaki, K. Matsuda, and T. Kaneko, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 1986.
12. J. F. W. McOmie and D. E. West, *Org. Synth., Coll. Vol. V*, Wiley: New York, 1973, 412.
13. P. A. Grieco, S. Ferrino, and G. Vidari, *J. Am. Chem. Soc.*, 1980, **102**, 7586.
14. (a) K. A. Parker and J. J. Petraitis, *Tetrahedron Lett.*, 1981, **22**, 397; (b) T. T. Li and Y. L. Wu, *J. Am. Chem. Soc.*, 1981, **103**, 7007.
15. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 1978, 874.
16. (a) J. A. Dodge, M. G. Stocksdale, K. J. Fahey, and C. D. Jones, *J. Org. Chem.*, 1995, **60**, 739; (b) A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, and D. J. Mader, *J. Am. Chem. Soc.*, 1997, **119**, 6072.
17. A. M. Bernard, M. R. Ghiani, P. P. Piras, and A. Rivoldini, *Synthesis*, 1989, 287.
18. J. R. McCarthy, J. L. Moore, and R. J. Cregge, *Tetrahedron Lett.*, 1978, **19**, 5183.
19. (a) E. Brehm and R. Breinbauer, *Org. Biomol. Chem.*, 2013, **11**, 4750; (b) N. C. Kallan and R. L. Halcomb, *Org. Lett.*, 2000, **2**, 2687; (c) J. D. White, T. Tiller, Y. Ohba, W. J. Porter, R. W. Jackson, S. Wang, and R. Hanselmann, *Chem. Commun.*, 1998, 79.