Macrocyclic polyamine lactam synthesis by diphenyl ether closure of 23-, 24- and 28-membered rings

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Novel 23-, 24- and 28-membered cyclic polyamine amides (cinnamamides) have been prepared by closure of diphenyl ethers; functionalized conjugates of spermidine and spermine underwent intramolecular aromatic nucleophilic substitution to afford nitro-substituted analogues of cadabicine class (24-membered polyamine lactam) alkaloids.

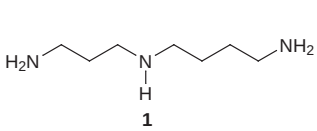
Polyamines such as triamine spermidine **1** and tetraamine spermine **2** are widely distributed in nature and display a variety of biological activities.[1] Cinnamic acid (3-phenylpropenoic acid) conjugates are commonly isolated as the corresponding *N*-substituted amides from plant sources.[2] Ferulic acid (4-hydroxy-3-methoxycinnamic acid) **3** is found as feruloylputrescine, a conjugate of 1,4-diaminobutane.[3] N^1,N^3-Di-(*E*)-feruloylspermidine **4** has been isolated from *Corylus avellana* L.[3,4] Spermidine conjugates have also been found asymmetrically substituted with both ferulic and caffeic (3,4-dihydroxycinnamic) acids **5**.[3] Maytenine,[5] from *Maytenus chuchuhuasha*, is the unsubstituted dicinnamamide of spermidine **1**. Dicinnamamides of spermine **2** include kukoamine A, a biologically active bis(dihydrocaffeoyl) conjugate.[6,7]

Cyclic polyamine amide containing cinnamamides are less common natural products whose biological activities are largely unknown.[2,8] Spermine **2** containing macrocyclic polyamine lactams include *inter alia* chaenorhine and ephedradine A.[8] Spermidine **1** containing polyamine lactams include codonocarpine **6**, from *Codonocarpus australis*,[9] and capparisinine **7**.[10] Cadabicine **8** is a diphenyl ether 24-membered ring containing spermidine **1**, from *Cadaba farinosa* Forsk. The regiochemical substitution of the diphenyl ether moiety is reversed with respect to the unsymmetrical spermidine moiety in **6** and **7**.[11] We are unaware of a synthesis[2,8] of a cadabicine **8** class alkaloid, although a regiocontrolled synthesis of the *Lunaria* diphenyl ether alkaloid codonocarpine **6** has been reported.[12]

Macrocycles containing diphenyl ethers are of chemical and biological interest as they occur in vancomycin and ristocetin antibiotic families.[13–15] Also, these substitution patterns are found in anti-cancer peptide conjugate RA-VII and ACE inhibitor K-13.[15,16] Macrocyclic polyamine lactams incorporating a diphenyl ether have been prepared using intermolecular Ullmann diaryl ether synthesis followed by lactam formation.[8,12] Herein we report the first design and synthesis of 23-, 24- and 28-membered ring polyamine lactam conjugates that are nitro-substituted analogues of cadabicine **8** class alkaloids.

The required substituted cinnamic acids were prepared from the corresponding benzaldehydes by Knoevenagel condensation.[17,18] Isoferulic acid (3-hydroxy-4-methoxycinnamic acid) **9** was prepared in good yield (92%) under standard conditions starting with malonic acid (EtOH, piperidine, pyridine, 3 h, reflux).[17] 4-Fluorobenzaldehyde was similarly converted into 4-fluorocinnamic acid **10** (85%). Nitration *ortho* to fluorine, in order to activate the final intramolecular nucleophilic substitution (S_NiAr) reaction, achieved with conc. nitric acid, afforded 4-fluoro-3-nitrocinnamic acid **11** (1 h, 0 °C, 72%).

For the 23-membered ring **12**, *N*-(3-aminopropyl)-1,3-diaminopropane was protected with trifluoroacetyl groups on the



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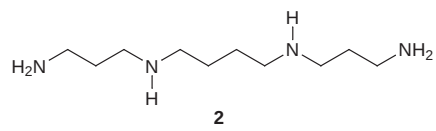

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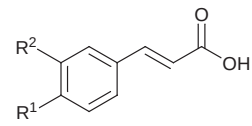
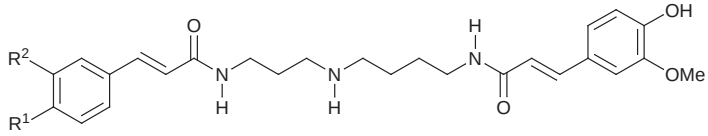
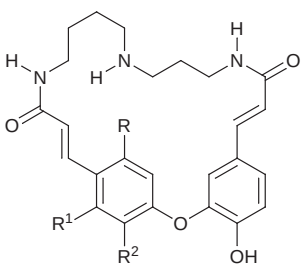


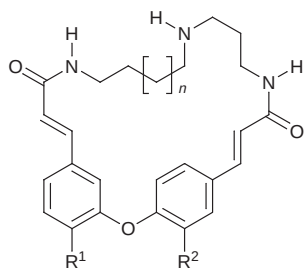
3 R^1 = OH, R^2 = OMe
9 R^1 = OMe, R^2 = OH
10 R^1 = F, R^2 = H
11 R^1 = F, R^2 = NO_2



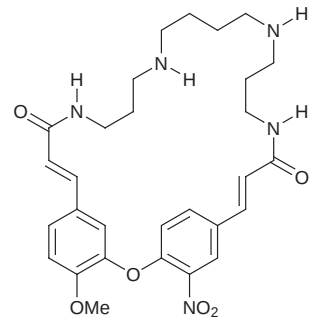
4 R^1 = OH, R^2 = OMe
5 R^1 = OH, R^2 = OH



6 R^1 = H, R^2 = OMe
7 R^1 = OMe, R^2 = H



8 *n* = 1, R^1 = OH, R^2 = H
12 *n* = 0, R^1 = OMe, R^2 = NO_2
13 *n* = 1, R^1 = OMe, R^2 = NO_2
14 *n* = 1, R^1 = OH, R^2 = NO_2



15

primary amino groups (2 equiv. CF_3CO_2Et, THF, 10 min, 25 °C).[19–21] This was followed by immediate Boc protection of the central, secondary amine (Boc_2O, THF, 18 h, 25 °C). Conc. aq. ammonia was added to the solution of tri-protected triamine until the pH was greater than 11 to remove the trifluoroacetyl protecting groups (24 h). Mono-Boc protected amine was isolated and purified by flash column chromatography (15 : 5 : 1, CH_2Cl_2–MeOH–conc. aq. NH_3, v/v/v, R_f 0.13). The cinnamic acid moieties[17,18] were coupled sequentially (first the isoferuloyl **9** then the 4-fluoro-3-nitro **11**) to the primary amines by pre-activation with 2-mercaptothiazoline (2-thiazoline-2-thiol, thiazolidine-2-thione)[5] (DCC, 0.01 equiv. DMAP, CH_2Cl_2, 1 h, 25 °C, followed by filtration to remove the urea). Mono-Boc protected triamine was added to the yellow CH_2Cl_2 solution of the *N*-acylated 2-mercaptothiazoline and the coupling was typically complete after 3 h (*ca*. 50% each acylation). Cyclisation was brought about by stirring with 5 equiv. CsF in anhydrous DMF (18 h) to give 23-membered ring polyamine lactam **12** (79% isolated yield). *O*-Arylation has occurred by intramolecular aromatic nucleophilic substitution (S_NiAr) reaction of *o*-nitro-activated fluoride by the remote phenol.

For the 24-membered ring **14**, spermidine **1** was reacted with formalin to give a hexahydropyrimidine adduct (0.95 equiv. 37% w/w aq. formaldehyde, H_2O, 1 h, 91%) as developed independently by Ganem and Hesse and their co-workers.[22,23] Isoferulic acid **9**[17,18] was coupled to the primary amine of this regioselectively protected spermidine through the 2-mercaptothiazoline activated intermediate (−78 to 25 °C, 55%). After chromatography, this hexahydropyrimidine was deprotected by heating with malonic acid and pyridine (EtOH, reflux, 2 h, 79%).[22] 4-Fluoro-3-nitrocinnamic acid **11** was coupled to the uncovered primary amine and then the secondary amine was protected by a Boc group (1.1 equiv. Boc_2O, MeOH, 18 h, 25 °C, 89%) to afford a linear precursor of cadabicine analogue **13**. Cyclisation was carried out by stirring with 3 equiv. CsF in anhydrous DMF (18 h, 71% isolated yield), final purification by RP-HPLC (5 μm C8 inertpak column eluting with 1:4 aq. TFA (0.1%)–MeOH, v/v, λ = 250 nm). TFA catalysed deprotection (1:1 TFA–CH_2Cl_2, v/v, 45 min, 0 °C, 90%) of the Boc group in diaryl ether **15** was followed by *O*-demethylation with BBr_3 (1.2 equiv., CH_2Cl_2, 3 h, −78 °C) to give 2′-nitrocadabicine **14** in 60% isolated yield.

For the 28-membered ring **15**, spermine **2** was protected in a similar fashion to *N*-(3-aminopropyl)-1,3-diaminopropane *vide supra*. Trifluoroacetyl groups were used to block the two primary amines then two Boc groups were introduced at the secondary amines. Conc. aq. ammonia was used to remove the trifluoroacetyl protecting groups and the N^2,N^3-diBoc spermine was then purified by chromatography. The two cinnamic acid moieties[17,18] were introduced in a stepwise fashion using 2-mercaptothiazoline activation to yield the cyclisation precursor. Cyclisation was carried out in anhydrous DMSO with 3 equiv. K_2CO_3 and 10 equiv. 18-crown-6, the oxygen nucleophilicity was found to be too low without the crown ether. The cyclisation reaction did not proceed to completion at 25 °C (starting material still present after 24 h). However, heating the mixture to 50 °C, in the presence of 18-crown-6, led to complete reaction after 5 h, yielding the desired macrocycle **15** (66%).

The previously proposed mechanism of cyclisation involved bringing the two sites of reaction into proximity by π-orbital stacking interactions between the electron rich guaiacol (2-methoxyphenol) ring and the electron deficient *o*-fluoronitrophenyl ring.[15] However, macrocycle formations of this type have recently been demonstrated to proceed in good yield when the aryl hydroxy group is replaced by an alkyl hydroxy group, proving that such π–π interactions are not necessary for successful cyclisation.[24] As the isolated yields are high, this practical approach by aromatic nucleophilic substitution (intramolecular S_NiAr reaction) should find ready application in the synthesis of natural products and their analogues with particular reference to cyclic spermidine and spermine alkaloids of the codonocarpine **6** and cadabicine **8** classes.

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Notes and references

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