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A synthesis of (a*R*,7*S*)-(−)-*N*-acetylcolchinol and its conjugate with a cyclic RGD peptide

Gilbert Besong [a], Denis Billen [a], Indu Dager [a], Philip Kocienski [a,*], Eric Sliwinski [a], Lik Ren Tai [a], F. Thomas Boyle [b,†]

[a] *School of Chemistry and Institute of Process Research and Development, Leeds University, Leeds LS2 9JT, UK*
[b] *AstraZeneca Pharmaceuticals, Mereside, Alderley Edge, Cheshire SK10 4TG, UK*

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Abstract

An asymmetric synthesis of (−)-*N*-acetylcolchinol is described based on a Suzuki–Miyaura coupling to generate the biaryl pharmacophore. The sole asymmetric centre was introduced by an asymmetric reduction of a dibenzosuberone derivative **24** using lithium borohydride in the presence of stoichiometric amounts of a chiral Lewis acid (TarB–NO_2). A conjugate between an $\alpha_V\beta_3$ integrin-binding cyclic peptide c[RGDfK] and colchinol (adipoyl linker) was synthesised with an aim to deliver colchinol to solid tumours selectively.
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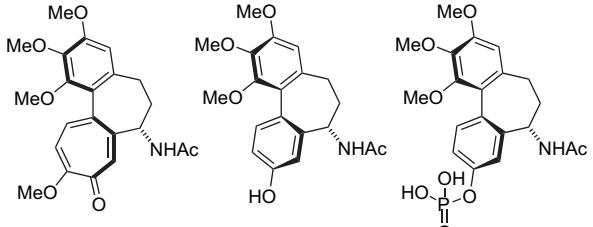
Keywords: Colchicine; Suzuki–Miyaura cross-coupling; Biaryl; Asymmetric reduction; RGD peptide

1. Introduction

The highly toxic nature of extracts of the meadow saffron (*Colchicum autumnale*) was first recorded by the Greek physician Dioscorides (A.D. 78) in his seminal *De Materia Medica*.[1] The active principle, colchicine (**1**), was isolated in pure form by Pelletier and Caventou in 1820 and the structure was finally determined in 1945 by Dewar after a protracted struggle involving many contributors.[2,9] Low doses of colchicine have been used since the 16th century for the treatment of gout but reports by Dustin (1934),[3] Lits (1934)[4] and Amoroso (1935)[4] that colchicine induces metaphase arrest in mouse tumour cells with consequent tumour regression excited much interest.[5] Unfortunately, near lethal doses of colchicine are required and subsequent efforts have focused on the search for colchicine analogues with an improved therapeutic index. One promising lead to emerge is (a*R*,7*S*)-*N*-acetylcolchinol (**2**)[6] which, in the form of its water-soluble phosphate prodrug ZD6126 (**3**), selectively induces tumour vascular damage and tumour necrosis at well-tolerated doses in animal models.[7] Like colchicine, *N*-acetylcolchinol (NAC) arrests mitosis by inhibiting tubulin polymerisation.[8]



(–)-colchicine (**1**) (–)-*N*-acetylcolchinol (**2**) ZD6126 (**3**)

Until recently, the commercial demand for NAC has been supplied by degradation of colchicine. The venerable procedure by Windaus[9] (Scheme 1), recently revived in a patent,[10] generates NAC by reaction of colchicine with sodium hypoiodite to give first *N*-acetyliodocolchinol (**4**) which is then reduced by treatment with zinc. A related oxidative ring contraction of colchiceine (**5**)[11]—itself a hydrolysis product of colchicine—with basic hydrogen peroxide at 60 °C[12] delivers NAC in 24% yield. Scheme 2 shows two further approaches.

* Corresponding author. Fax: +44 (0)113 343 6401.
E-mail address: p.j.kocienski@leeds.ac.uk (P. Kocienski).
† Deceased on 5th July, 2006.

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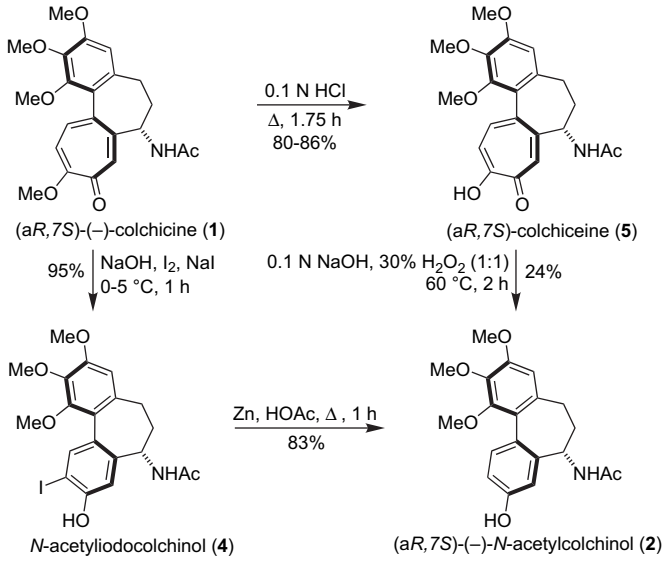
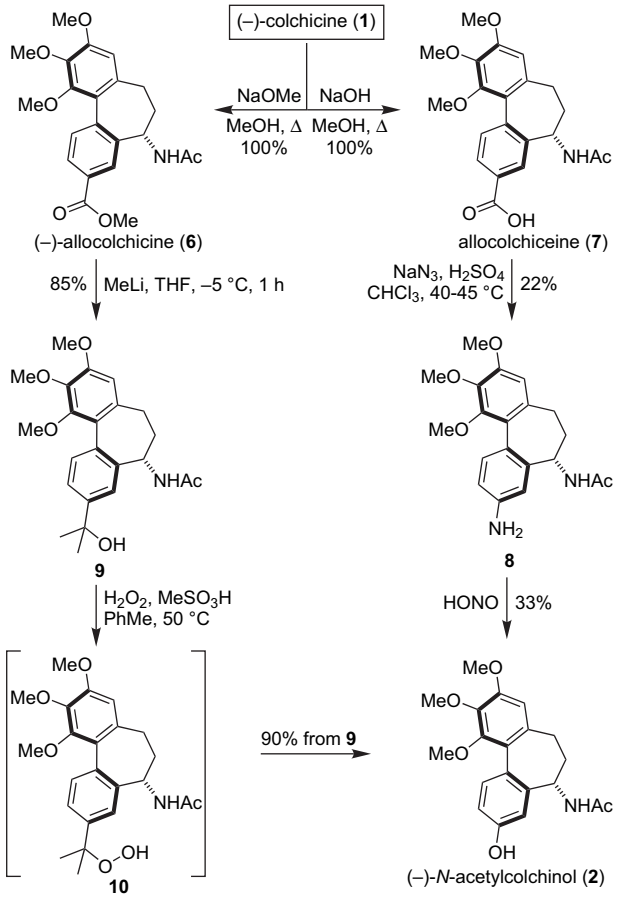


Scheme 1.

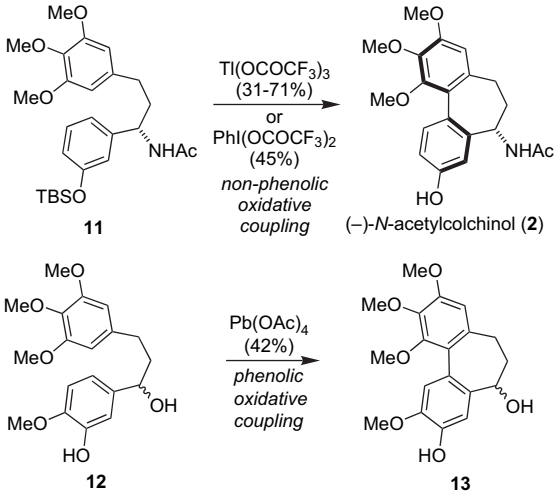
Reaction of colchicine with sodium methoxide or sodium hydroxide in refluxing methanol generates allocolchicine (**6**) and allocolchiceine (**7**), respectively,[13,14] both of which have been converted to NAC. A Schmidt reaction on allocolchiceine was used by Fernholz[14] to generate the aniline derivative **8**.



Scheme 2.

Diazotisation of **8** followed by heating then generated NAC but the yield for both steps was poor. A recent patent[15] has described a modern rendition of an old phenol synthesis as an efficient route to NAC. The tertiary alcohol **9** generated by reaction of allocolchicine with methyllithium gave the hydroperoxide intermediate **10** on treatment with hydrogen peroxide in the presence of methanesulfonic acid. The hydroperoxide rearranged under the acidic conditions to give NAC in 90% yield.

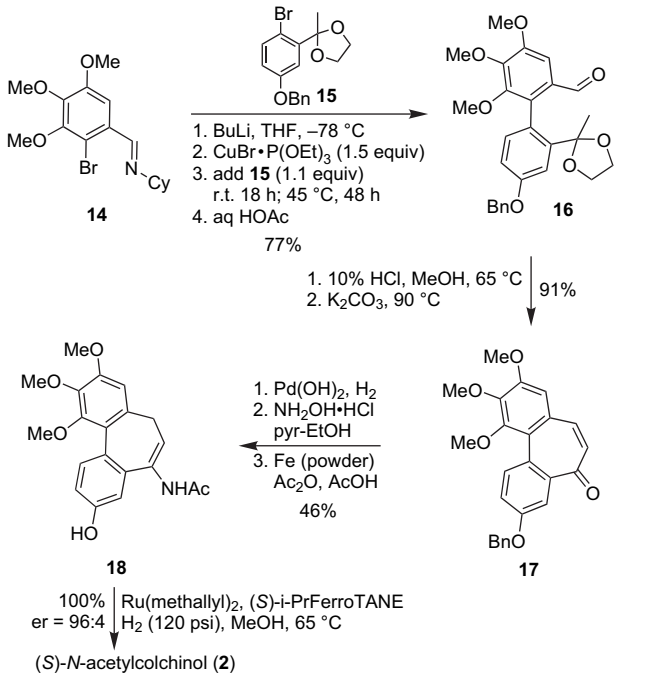
The need for more scalable and economic supplies of NAC has stimulated interest in its total synthesis. The first synthesis of (±)-NAC by Sawyer and Macdonald[16] achieved the simultaneous construction of the seven-membered B-ring and the biaryl by an intramolecular non-phenolic oxidative coupling reaction of a 1,3-diarylpropane (**11**) mediated by thallium(III) trifluoroacetate (Scheme 3). This oxidant was later used by Wu and Chong[17] in an asymmetric synthesis of (−)-NAC but the yield (53%) was lower than that reported by Sawyer and Macdonald (71%) whereas we could only muster an exiguous 31% for the identical transformation.[18] With phenyliodonium bis-(trifluoroacetate), oxidative cyclisation of **11** was accomplished reproducibly in ca. 50% yield.[19] Banwell and co-workers reported the related intramolecular phenolic oxidative coupling of **12** using lead(IV) acetate in their synthesis of colchicine.[20]



Scheme 3.

Recently a process development group at AstraZeneca described a short asymmetric synthesis of (−)-NAC (Scheme 4)[21] based on the initial construction of the biaryl pharmacophore **16** using an Ullmann coupling[22,23] followed by elaboration of the B-ring. A noteworthy feature of this approach is the concluding ruthenium-catalysed asymmetric hydrogenation of enamide **18** to install the C7 acetamide function in quantitative yield (er 96:4).[24]

We now report an asymmetric synthesis of (−)-NAC that resembles the AstraZeneca route strategically but differs substantially in tactics. We also describe the synthesis of a colchinol–RGD peptide conjugate designed for selective delivery of the drug to tumour vasculature.

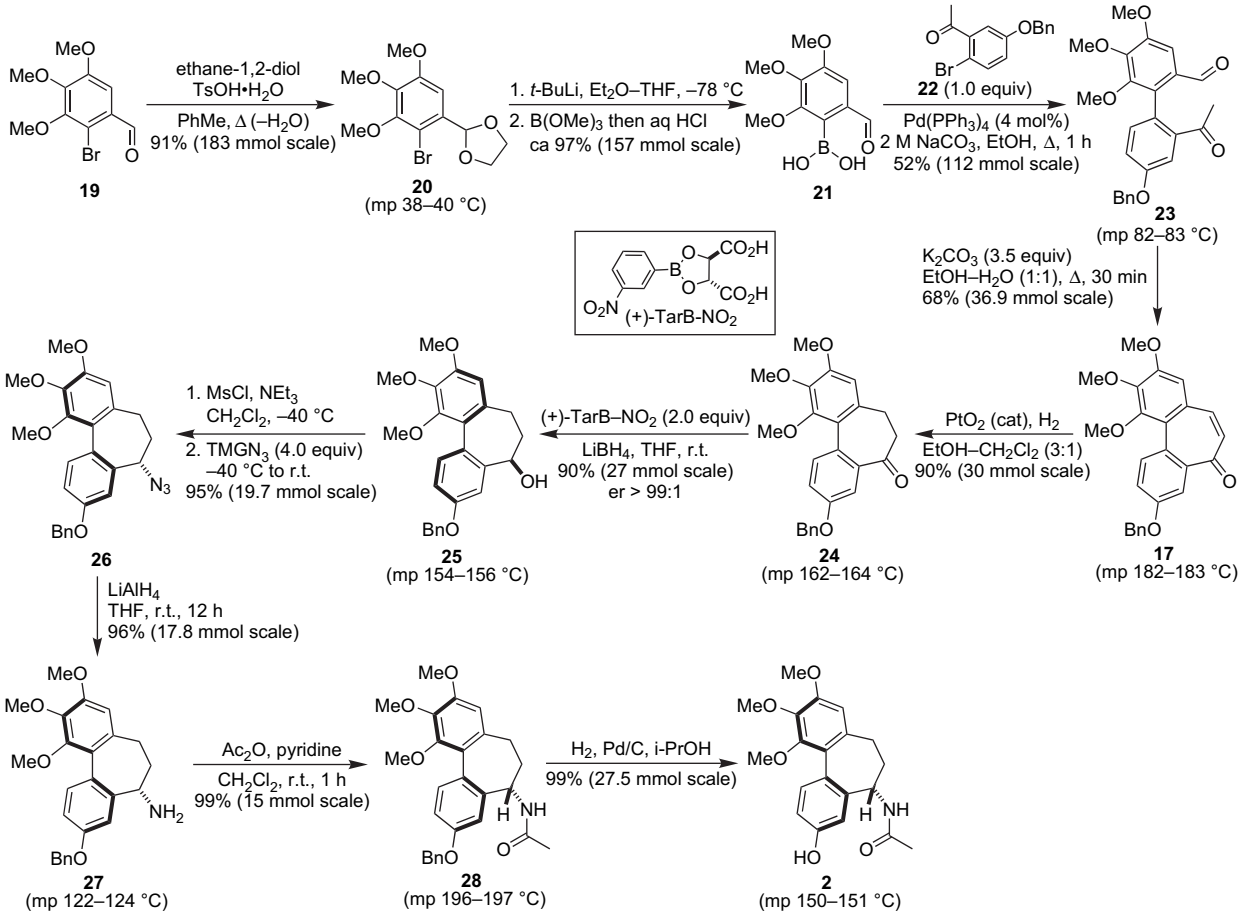


Scheme 4.

2. Results and discussion

2.1. Synthesis of (−)-N-acetylcolchinol

Our synthesis, summarised in its entirety in Scheme 5, can be divided into three phases. Phase 1, construction of the biaryl pharmacophore, began with the bromoarene **19**, prepared in 91% yield by the bromination of commercial 3,4,5-trimethoxybenzaldehyde.[25] Protection of the aldehyde as its 1,3-dioxolane derivative **20** enabled halogen−metal exchange and borylation to afford boronic acid **21** in ca. 97% yield. ^{1}H and ^{13}C NMR spectra recorded on the crude boronic acid revealed minor impurities but attempts to remove them by recrystallisation gave poor recoveries and no improvement; therefore, the crude boronic acid was used in the next step. The key Suzuki−Miyaura coupling[26] between boronic acid **21** and the bromoacetophenone derivative **22**[27] was achieved using freshly prepared $Pd(PPh_3)_4$ (4 mol %) and sodium carbonate as the base in refluxing aqueous ethanol to give the biaryl **23** in 52% yield on a 112 mmol scale (Scheme 5).[28] Other bases known to be beneficial in the case of hindered or highly oxygenated substrates such as caesium fluoride[29] and barium hydroxide[30] gave complex mixtures in our case. Attempts to use heterogeneous Pd/C as the catalyst under phosphine-free conditions were similarly fruitless.[31]



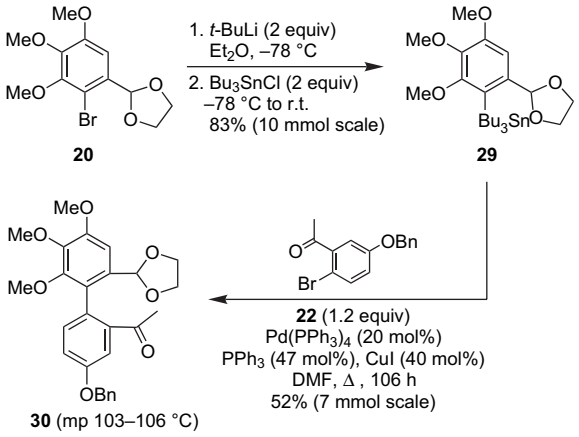
Scheme 5.

The second phase of the synthesis, construction of the seven-membered B-ring, was easily accomplished by an intramolecular aldol reaction. Treatment of the keto aldehyde **23** with potassium carbonate in refluxing ethanol consistently generated the dibenzosuberone derivative **17** in 68% yield. The reaction was complete within 30 min and prolonged heating failed to attain the 91% yield reported by the AstraZeneca group[21] for the identical transformation. Hydrogenation of the double bond in **17** without detriment to the benzyl ether group was achieved by using Adams' catalyst (PtO_2) instead of Pd/C.

The goal of the third phase of the synthesis was the introduction of the stereogenic centre at C7 by asymmetric reduction of the ketone **24**. The Noyori ruthenium-catalysed asymmetric hydrogenation[32] which had served us well in our first synthesis of NAC[19,33] gave racemic alcohol **25**. A Corey–Bakshi–Shibata reduction[34] using 5 mol % of the (*S*)-1-methyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole catalyst gave the desired (*R*)-alcohol **25** with high er (>99:1) but the yield, on a 2.5 mmol scale, was only 65%.[35,36] The best of the three methods examined involved reduction of ketone **24** with a chiral acyloxyborohydride generated in situ from lithium borohydride and 2 equiv of the cheap homochiral bifunctional Lewis acid (+)-TarB–NO_2.[37] Alcohol (*R*)-**25** was obtained in 90% yield with an er >99:1. With only 1 equiv of (+)-TarB–NO_2, the yield was comparable but the er decreased slightly to 96:4.[38,39]

To complete the synthesis of NAC the hydroxyl function in (*R*)-**25** was converted to the azide **26** in a one-pot procedure. Mesylation of **25** gave an unstable benzylic mesylate intermediate which was treated with tetramethylguanidinium azide (4 equiv) in situ at −40 °C. On gradual warming to rt, nucleophilic substitution occurred to give the desired azide in 95% yield. Chiral HPLC indicated an er >99:1 in accord with clean inversion by an S_N2 mechanism. Three methods were used to reduce the azide **26** to the amine **27** the best being lithium aluminium hydride in THF. Hydrogenolysis was complicated by competing hydrogenolysis of the benzyl ether even with palladium hydroxide as catalyst whereas zinc and ammonium chloride only gave a 78% yield and required 40 equiv of zinc. Acetylation of the amine **27** followed by hydrogenolysis of the benzyl ether **28** using the standard conditions gave (−)-*N*-acetylcolchinol in excellent yield.

The prime blemish in the forgoing route was the modest yield of the Suzuki coupling. We therefore examined a small selection of alternative Pd(0)-catalysed coupling methods in an effort at improvement. The Negishi coupling[40] gave virtually no biaryl in our hands but the Stille coupling[41] was more fruitful. The stannane **29** was prepared as shown in Scheme 6 and coupled with the *o*-bromoacetophenone **22** in 52% yield using the rather harsh conditions developed by Saá and Martorell for the synthesis of highly hindered biaryls.[42] However, the long reaction times (106 h) in refluxing DMF in the presence of 20 mol % of Pd(0) were impractical and efforts to ameliorate the conditions by using an array of ligands [e.g., P(2-furyl)$_3$ and P(^{t}Bu)$_3$] and catalysts [$PdCl_2(PhCN)_2$, $PdCl_2(MeCN)_2$, $Pd_2(dba)_3$] were to no avail. Similarly fruitless were the addition of caesium fluoride[43] or the tandem use of copper(I) iodide and caesium fluoride in the presence of $PdCl_2$–P(^{t}Bu)$_3$ as described by Baldwin and co-workers.[44] Therefore, the Suzuki coupling remains the most practical method for the synthesis of the biaryl **23**.

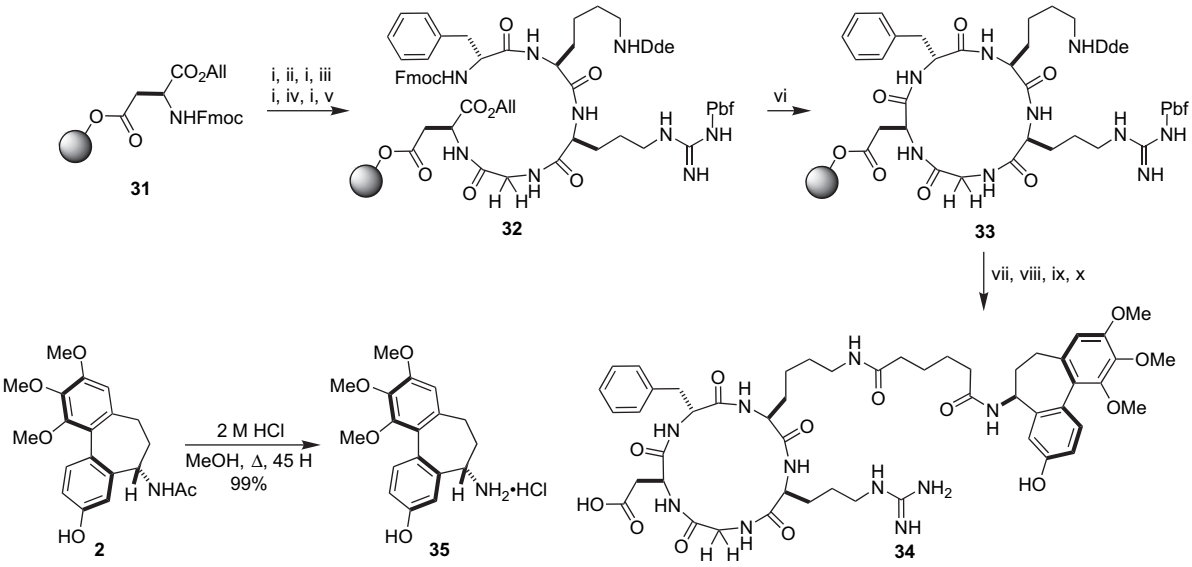


Scheme 6.

2.2. Synthesis of a colchinol–RGD peptide conjugate

NAC, as the pro-drug ZD6126 (**3**), was developed by AstraZeneca as a vascular disrupting agent for the treatment of advanced solid tumours. NAC binds to tubulin in immature proliferating endothelial cells lining the tumour blood vessels leading to blood vessel congestion with consequent tumour necrosis from hypoxia and nutrient deprivation.[45] ZD6126 showed sufficient promise to warrant phase II clinical trials. Unfortunately, vascular disrupting agents can cause acute coronary and other thrombophlebitic syndromes, alterations in blood pressure, hot flashes, neuropathy and tumour pain.[46] After adverse coronary effects were observed with ZD6126, further development ceased. We now describe a synthesis of the NAC–RGD peptide conjugate (**34**, Scheme 7) designed for selective delivery of the drug to tumour vasculature. The design of conjugate **34** was based on four principles. Firstly, previous studies had established that the acetamido group in colchicinoids is not necessary for tubulin binding and therefore its modification should not impinge on biological activity.[47] Secondly, Kessler's c[RGDfK] peptide ligand[48] binds selectively and with high affinity to $\alpha_V\beta_3$ integrin, a transmembrane adhesion receptor involved in angiogenesis and metastasis, which is overexpressed in tumour vasculature.[49] Thirdly, the terminal amino group in the lysine residue is not implicated in integrin-binding and therefore it is an ideal linkage function.[50] Fourthly, synthetic conjugates of doxorubicin and cyclic RGD peptides induce tumour regression in mice at 1/10th the dose of doxorubicin alone in accord with selective delivery of the drug to tumour vasculature and its endocytosis.[51]

The Kessler c[RGDfK] peptide was synthesised on solid phase by a modification of an earlier procedure[48,52] as shown in Scheme 7. A commercial Wang resin pre-loaded with *N*-α-Fmoc–L-Asp–OAll was first deprotected and elongated by a conventional Fmoc deprotection–amino acid condensation protocol. The resulting pentapeptide **32** was then cyclised on-resin to give **33** after allyl deprotection and removal of the last Fmoc group.



Scheme 7. Reagents and conditions: (i) piperidine–DMF (1:4), rt, 10 min (×2); (ii) *N*-α-Fmoc–Gly–OH (2 equiv), HCTU (2 equiv), DIPEA (4 equiv), DMF, rt, 2 h (×2); (iii) *N*-α-Fmoc–Arg(Pbf)–OH (2 equiv), HCTU (2 equiv), DIPEA (4 equiv), DMF, rt, 2 h (×2); (iv) *N*-α-Lys(Dde)–OH, HCTU (2 equiv), DIPEA (4 equiv), DMF, rt, 2 h (×2); (v) *N*-α-Fmoc–Phe–OH (2 equiv), HCTU (2 equiv), DIPEA (4 equiv), DMF, rt, 2 h (×2); (vi) $Pd(PPh_3)_4$ (0.3 equiv), $CHCl_3$–AcOH–*N*-methylmorpholine (37:2:1), rt, 4 h; then piperidine–DMF (1:4), rt, 10 min; then HCTU (3 equiv), DIPEA (10 equiv), DMF, rt, 24 h; (vii) H_2N–$NH_2 \cdot H_2O$, DMF, rt, 5 min (×2); (viii) adipic anhydride (10 equiv), DIPEA (12 equiv), rt, 20 h; (ix) colchinol·HCl (3 equiv), HCTU (3 equiv), HOBt (3 equiv), DIPEA (6 equiv), DMF, rt, 60 h; (x) TFA–$(i\text{-Pr})_3SiH$–H_2O (95:2.5:2.5), rt, 1 h. HCTU=2-(6-chloro-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOBt=1-hydroxybenzotriazole, Dde=2(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl, Pbf=2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl.

The colchinol was appended to the Kessler peptide **33** via an adipoyl linker. Attachment of the linker began with cleavage of the Dde protector from the lysine in **33** with hydrazine hydrate followed by N-acylation with adipic anhydride. Finally coupling of colchinol (**35**) to the peptide **33** followed by Pbf deprotection and cleavage from the resin gave the target conjugate in 16% overall yield from **31**.

3. Conclusions

An 11-step asymmetric synthesis of (a*R*,7*S*)-(−)-*N*-acetylcolchinol from commercially available 3,4,5-trimethoxybenzaldehyde was accomplished in 23% overall yield. All of the intermediates except azide **26** were either solid or crystalline. The synthesis is longer than our previous syntheses[19] (8–9 steps) but the simplicity of the present route is better suited to larger scale. The yield of the key Suzuki–Miyaura coupling step was disappointing (52%) and is substantially lower than recent syntheses of allocolchicinoids by Fagnou[53] and DeShong[54] featuring Pd-catalysed biaryl construction. Our route is capable of further abbreviation. For example, after this work was complete, we accomplished the conversion of azide **26** to NAC in one pot by hydrogenation in the presence of acetic anhydride.

4. Experimental

4.1. General

Where appropriate, solvents and reagents were dried by distillation from the usual drying agents prior to use: diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone; dichloromethane and toluene were distilled from calcium hydride; diisopropylethylamine, pyridine and triethylamine were distilled from potassium hydroxide; methanol was distilled from magnesium methoxide. All reactions were magnetically stirred and were monitored by thin layer chromatography (TLC) using SiO_2 on pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 and 366 nm) and 20% phosphomolybdic acid in ethanol w/v. Column chromatography was performed on silica gel 60 (35–70 μm). Optical rotations were recorded on an Optical Activity AA-1000 polarimeter (units in 10^{-1} deg cm^2 g^{-1}). Melting points were measured on a Griffin electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer as thin films supported on sodium chloride plates or on a Diffuse Reflectance sampling cell. Absorptions are reported as values in cm^{-1} followed by the relative intensity: s=strong, m=medium, w=weak. ^1H and ^{13}C NMR spectra were recorded on Brüker DPX300 or DRX500 Fourier Transform spectrometers using an internal deuterium lock. All spectra were obtained in 5 mm diameter tubes, and the chemical shift in parts per million is quoted relative to the residual signals of chloroform (δ_H 7.26, δ_C 77.4) or methanol (δ_H 3.34, δ_C 49.9) as the internal standard unless otherwise specified. Multiplicities in the ^1H NMR spectra are described as: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, m=multiplet, br=broad and app=apparent. Coupling constants (*J*) are reported in hertz. The numbers of protons attached to carbon in the ^{13}C NMR spectra were revealed by the DEPT spectral editing technique. Signal assignments were based on COSY, HMQC and HMBC correlations. Mass spectrometry was

carried out on a VG autospec mass spectrometer, operating at 70 eV, using electron impact ionisation (EI). Electrospray ionisation (ES) was performed on either a Micromass LCT TOF spectrometer or a Waters-Micromass ZMD spectrometer. High resolution mass spectrometry (HRMS) was obtained by peak matching using perfluorokerosene or reserpine as a standard. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units followed, in parenthesis, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by ^{1}H and ^{13}C NMR spectroscopy unless otherwise stated. High performance liquid chromatography (HPLC) was carried out on a Dionex Autosampler Model ASI-100 with the columns and eluents specified.

4.2. 2-(2′-Bromo-3′,4′,5′-trimethoxyphenyl)-[1,3]-dioxolane (**20**)

To a solution of 2-bromo-3,4,5-trimethoxybenzaldehyde (**19**)[23,25] (50.0 g, 183.2 mmol) in toluene (500 mL) were added PTSA·H_2O (2.8 g, 14.65 mmol) and ethylene glycol (113 g, 1.8 mol). The mixture was stirred under reflux for 48 h with continuous removal of water using a Dean–Stark apparatus. After cooling to rt, the reaction mixture was transferred to a separating funnel and washed with aqueous sodium bicarbonate (2×500 mL) and with brine solution (500 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a yellow oily residue which was purified by column chromatography on silica gel (4:1, hexane–Et_2O) to give the title compound as a colourless oil (42.3 g, 132.6 mmol, 91%) which slowly solidified on standing: mp 38–40 °C. ν_{max} (diamond compression system): 3096 m, 2939 s, 1570 s, 1330 s, 1172 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (1H, s, ArH), 6.04 (1H, s, C2H), 4.18–4.13 (2H, m, OCH_2), 4.10–4.05 (2H, m, OCH_2), 3.89 (3H, s, C5′OCH_3), 3.88 (6H, br s, C4′OCH_3, C3′OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3 (C3′), 151.3 (C5′), 144.3 (C1′), 132.2 (C4′), 110.0 (C6′), 106.7 (C2′H), 102.8 (C2H), 65.8 (2OCH_2), 61.45 and 61.42 (C4′OCH_3, C4′OCH_3), 56.5 (C3′OCH_3). HRMS (ES$^+$): found: 319.0175. $C_{12}H_{16}O_5{}^{79}Br$ requires: 319.0181. Found: C 45.2, H 4.75, Br 24.8. $C_{12}H_{15}BrO_5$ requires: C 45.16, H 4.74, Br 25.04%.

4.3. 6-Formyl-2,3,4-trimethoxyphenyl boronic acid (**21**)

tert-Butyllithium (203 mL of a 1.7 M solution in pentane, 345 mmol) was added to a solution of bromoarene **20** (50 g, 157 mmol) in dry Et_2O (1 L) at −78 °C. The resulting white slurry was stirred at the same temperature for 10 min before the addition of freshly distilled trimethylborate (52 mL, 48.85 g, 470 mmol) at −78 °C. The mixture was allowed to warm to rt overnight before addition of 4 M HCl (600 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×500 mL). The combined organic extracts were washed with brine solution (1 L), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was triturated with hexane to afford the title compound (36.25 g, 151.0 mmol, 97%) as a pale yellow amorphous solid which was used in the next step without further purification. ν_{max} (diamond compression system): 3436 s, 2943 s, 1682 s, 1599 s, 1455 s, 1317 s, 762 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.73 (1H, s, CHO), 7.10 (1H, s, C5H), 4.14 (2H, s, 2OH), 3.94 (6H, s, OCH_3), 3.89 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0 (CHO), 156.5 (C6), 154.2 (C4 and C3), 148.2 (C2), 134.8 (C1H), 110.0 (C5H), 61.38 and 60.95 (C3OCH_3 and C4OCH_3), 56.69 (C2OCH_3). HRMS (ES$^+$): found: 263.0703. $C_{10}H_{13}BNaO_6$ requires: 263.0697.

4.4. 2′-Acetyl-4′-benzyloxy-4,5,6-trimethoxybiphenyl-2-carbaldehyde (**23**)

Aq Na_2CO_3 (2 M, 112 mL, 224 mmol) was added to a degassed solution of 1-(5′-benzyloxy-2′-bromophenyl)-ethanone (**22**)[27] (34.2 g, 112 mmol), and $Pd(PPh_3)_4$ (5.2 g, 4.5 mmol) in DME (1.2 L). The reaction mixture was stirred for 5 min before addition of a solution of **21** (26.9 g, 112 mmol) in EtOH (224 mL) and then the mixture was heated to reflux for 1 h under nitrogen. After cooling to rt, water (400 mL) was added and aqueous layer was extracted with EtOAc (3×1.5 L) and then with CH_2Cl_2 (800 mL). The combined organic extracts were washed with brine (2.0 L), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The dark brown residue was then purified by column chromatography on silica (1:1, Et_2O–hexane) to give the title compound (24.1 g, 58.1 mmol, 52%) as a yellow solid. A sample recrystallised from MeOH gave mp 82–83 °C. ν_{max} (diamond compression system): 3363 m, 2940 s, 1692 s, 1587 s, 1452 s, 1139 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.63 (1H, s, CHO), 7.50–7.46 (2H, m, ArH), 7.44–7.42 (3H, m, ArH), 7.37 (1H, m app d, *J* 7.3, C3′H), 7.34 (1H, s, C3H), 7.14 (2H, br s, C5′H, C6′H), 5.15 (2H, s, CH_2Ph), 3.96 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.31 (3H, s, O=C–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4 (CO), 190.9 (CHO), 158.7 (C4′), 153.4 (C4), 150.8 (C6), 147.6 (C5), 141.4 (C2′), 136.5 (CH_2C_{Ph}), 134.4 (C5′H), 133.5 (C1′), 129.8 (C2), 129.0 (2$C_{Ph}H_{meta}$), 128.5 ($C_{Ph}H_{para}$), 127.9 (2$C_{Ph}H_{ortho}$), 124.4 (C1′), 117.0 (C6′H), 115.6 (C3′H), 105.7 (C3H), 70.6 (CH_2Ph), 61.3 (OCH_3), 60.9 (OCH_3), 56.3 (OCH_3), 29.0 (COCH_3). HRMS (ES$^+$): found: 443.1477. $C_{25}H_{24}NaO_6$ requires: 443.1465. Found: C 71.25, H 5.8. $C_{25}H_{24}O_6$ requires: C 71.41, H 5.75%.

4.5. 3-Benzyloxy-9,10,11-trimethoxy-dibenzo[a,c]-cyclohepten-5-one (**17**)

K_2CO_3 (17.8 g, 129.1 mmol) was added to a solution of keto aldehyde **23** (15.5 g, 36.9 mmol) in 1:1 EtOH–H_2O (900 mL) and refluxed under nitrogen for 30 min. The reaction mixture was cooled to rt and brine solution (900 mL) was added to it. The aqueous phase was then extracted with CH_2Cl_2 (3×1 L), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a yellow solid which was recrystallised from EtOAc–hexane to afford the title compound (10.1 g, 25.0 mmol, 68%) as a pale yellow crystalline solid: mp 182–183 °C. ν_{max} (diamond

compression system): 1649 s, 1598 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (1H, d, J 8.9, C1H), 7.48–7.46 (2H, m, ArH), 7.42–7.39 (3H, m, ArH, C4H), 7.36–7.33 (1H, m, ArH), 7.19 (1H, d, J 12, C7H), 7.17 (1H, dd, J_1 8.9, J_2 2.1, C2H), 6.78 (1H, s, C8H), 6.53 (1H, d, J 12, C6H), 5.17 (2H, s, CH_2Ph), 3.99 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.43 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2 (C5), 158.6 (C3), 153.1 (C9), 152.5 (C11), 144.3 (C10), 143.1 (C4a), 140.0 (C7H), 136.7 (CH_2C_{Ph}), 134.4 (C1H), 132.1 (C6H), 130.1 (C11b), 128.9 ($2C_{Ph}H_{meta}$), 128.4 ($C_{Ph}H_{para}$), 128.0 ($2C_{Ph}H_{ortho}$), 126.0 (C7a), 125.7 (C11a), 118.4 (C2H), 111.2 (C4H), 109.3 (C8H), 70.4 (CH_2Ph), 61.7 (C10OCH_3), 61.3 (C11OCH_3), 56.3 (C9OCH_3). HRMS (ES^+): found: 425.1356. $C_{25}H_{22}NaO_5$ requires: 425.1359. Found: C 74.8, H 5.75. $C_{25}H_{22}O_5$ requires: C 74.61, H 5.51%.

4.6. 3-Benzyloxy-9,10,11-trimethoxy-6,7-dihydro-dibenzo[a,c]cyclohepten-5-one (**24**)

To a solution of enone **17** (12.0 g, 29.85 mmol) in 3:1 EtOH–CH_2Cl_2 (800 mL) was added PtO_2 (0.27 g, 1.2 mmol). The reaction mixture was degassed five times with hydrogen and stirred under 1 atm of H_2 for 1 h. The reaction mixture was filtered through Celite and washed thoroughly with CH_2Cl_2 (500 mL) and concentrated in vacuo. The residual white solid was recrystallised from EtOAc–hexane to afford colourless needles of the title compound (10.85 g, 26.9 mmol, 90%): mp 162–164 °C. ν_{max} (diamond compression system): 3345 m, 2939 s, 1686 s, 1594 s, 1001 s, 863 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (1H, d, J 8.5, C1H), 7.47 (2H, d, J 7.3, ArH), 7.42–7.39 (2H, m, ArH), 7.36–7.33 (1H, t, J 7.3, ArH), 7.17 (1H, dd, J 3.0, 8.5, C2H), 7.15 (1H, d, J 3.0, C4H), 6.60 (1H, s, C8H), 5.12 (2H, s, CH_2Ph), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 3.08 (1H, t, J 13.7, C7H_AH_B), 2.99–2.83 (2H, m, C6H_AH_B), 2.64 (1H, d, J 13.7, C7H_AH_B). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9 (C5), 158.1 (C3), 153.0 (C9), 152.4 (C11), 141.8 (C4a), 140.7 (CH_2C_{Ph}), 136.8 (C7a), 136.0 (C10), 133.1 (C1H), 128.9 ($2C_{Ph}H_{meta}$), 128.4 ($C_{Ph}H_{para}$), 127.9 ($2C_{Ph}H_{ortho}$), 127.1 (C11b), 124.0 (C11a), 118.6 (C2H), 112.7 (C4H), 107.3 (C8H), 70.4 (CH_2Ph), 61.4 (C10OCH_3), 61.1 (C11OCH_3), 56.3 (C9OCH_3), 48.1 ($C6H_2$), 30.4 ($C7H_2$). HRMS (ES^+): found: 405.1691. $C_{25}H_{25}O_5$ requires: 405.1697. Found: C 74.05, H 6.05. $C_{25}H_{24}O_5$ requires: C 74.24, H 5.98%.

4.7. (5R)-(+)-3-Benzyloxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-ol (**25**)

Ketone **24** (11.0 g, 27.2 mmol) was dried in a Kugelrohr apparatus by heating at 85 °C (0.1 mmHg) for 1 h and then dissolved in a 0.4 M solution of (+)-TarB–NO_2[37] (138 mL, 54.5 mmol) in THF under N_2. This solution was stirred for 45 min and then a 2 M $LiBH_4$ solution in THF (33.0 mL, 68.1 mmol) was added over 90 min via syringe pump. After addition was complete, the reaction mixture was stirred for another 30 min and then it was poured into water (200 mL). Aq HCl (10%, 200 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3×300 mL). The combined organic extracts were washed with 10% aq NaOH (2×400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford a white solid. HPLC analysis of the crude solid (Chiralpak AS, 5% 2-propanol in hexanes, 0.5 mL min^{-1}, λ 220 nm) showed the product to have an ee of 98.43%; t_R: 64.78 min for the major enantiomer; 57.86 min for the minor enantiomer. Recrystallisation from EtOAc–hexane afforded the title compound (11.0 g, 27.0 mmol, 90%) as colourless needles: mp 154–156 °C. R_f: 0.2 (1:1, hexane–Et_2O). $[\alpha]_D$ +116.5 (c 0.84, $CHCl_3$) (99.3% ee). ν_{max} (diamond compression system): 3530 s, 3047 s, 2938 s, 1899 m, 1595 s, 1463 s, 922 m, 831 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (2H, d, J 7.7, ArH), 7.42–7.38 (3H, m, ArH, C1H), 7.35–7.32 (2H, m, ArH, C4H), 6.97 (1H, dd, J 3.0, 8.6, C2H), 6.58 (1H, s, C8H), 5.14 (2H, s, CH_2Ph), 4.63–4.59 (1H, m, C5H), 3.90 (6H, br s, C9OCH_3 and C10OCH_3), 3.62 (3H, s, C11OCH_3), 2.59–2.53 (1H, m, C6H_AH_B), 2.45–2.41 (1H, m, C7H_AH_B), 2.37–2.32 (1H, m, C7H_AH_B), 1.94–1.88 (1H, m, C6H_AH_B), 1.84 (1H, d, J 4.3, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (C3), 152.6 (C9), 151.1 (C11), 143.7 (C4a), 141.3 (CH_2C_{Ph}), 137.5 (C7a), 135.9 (C10), 131.3 (C1H), 128.9 ($2C_{Ph}H_{meta}$), 128.3 ($C_{Ph}H_{para}$), 128.0 ($2C_{Ph}H_{ortho}$), 125.8 (C11b), 124.7 (C11a), 113.1 (C2H), 109.2 (C4H), 107.8 (C8H), 75.7 (C5H), 70.3 (CH_2Ph), 61.4 (C10OCH_3), 61.2 (C11OCH_3), 56.4 (C9OCH_3), 41.7 ($C6H_2$), 30.9 ($C7H_2$). HRMS (ES^+): found: 429.1669. $C_{25}H_{26}O_5Na$ requires: 429.1672. Found: C 73.6, H 6.35. $C_{25}H_{26}O_5$ requires: C 73.87, H 6.45%.

Alternative procedure. A 25 mL flame-dried two-neck round-bottom flask, equipped with a rubber septum and magnetic stirrer, was flushed with nitrogen and charged with (*S*)-1-methyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole (122 μL of 1 M solution in toluene, 0.12 mmol) under nitrogen. A 2 M solution of $BH_3\cdot Me_2S$ (BMS) in dry THF (62.0 μL, 0.123 mmol) was added whereupon separate solutions of ketone **24** (1.0 g, 2.5 mmol) in 2.2 mL of THF and a 2 M solution of $BH_3\cdot SMe_2$ (2.2 mL) were added simultaneously via a syringe pump over 0.5 h. After addition was complete the reaction mixture was stirred for an additional 15 min before the slow addition of MeOH (9 mL), followed by 10% aq HCl (8 mL). The reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a white solid. HPLC analysis of the crude solid as above showed the product to have an ee of 99.3%. Recrystallisation from EtOAc–hexane gave colourless needles (0.65 g, 1.6 mmol, 65%).

4.8. (7S)-(−)-7-Azido-9-benzyloxy-1,2,3-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene (**26**)

A solution of alcohol **25** (8.0 g, 19.7 mmol) in dry CH_2Cl_2 (80 mL) was cooled to −40 °C. Triethylamine (4.1 mL, 29.5 mL) was added followed by the addition of methanesulfonyl chloride (1.8 mL, 23.6 mmol) at −40 °C. After stirring at −40 °C for 30 min, a solution of tetramethylguanidinium

azide (15.6 g, 98.5 mmol) in dry CH_2Cl_2 (40 mL) was added and the temperature was raised slowly to rt [Hazard].[‡] After stirring at rt for 24 h, water (100 mL) was added and mixture was transferred to a separating funnel. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The residue was then purified by column chromatography (SiO_2, 9:1, hexane–EtOAc) to give the title compound (8.05 g, 18.7 mmol, 95%) as a colourless oil. $[\alpha]_D$ −133.6 (*c* 1, $CHCl_3$). HPLC using a Chiralpak AD column (5% *i*-PrOH in hexanes, 0.5 mL min^{-1}, λ 200 nm) indicated an ee 98.7%: t_R 7.4 min for the minor enantiomer; 9.5 min for major enantiomer. ν_{max} (diamond compression system): 3366 m, 3063 s, 2940 s, 2104 s, 1595 s, 1461 s, 833 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (2H, d, *J* 7.7, ArH), 7.43–7.40 (3H, m, 2ArH and C11H), 7.36–7.34 (1H, m, ArH), 7.22 (1H, d, *J* 3.0, C8H), 6.99 (1H, dd, *J* 3.0, 8.4, C10H), 6.59 (1H, s, C4H), 5.14 (2H, s, CH_2Ph), 4.43 (1H, dd, *J* 7.1, 11.3, C7H), 3.91 (6H, s, 2OCH_3), 3.65 (3H, s, OCH_3), 2.58–2.44 (2H, m, C5$H_A$$H_B$, C6$H_A$$H_B$), 2.33 (1H, td, *J* 12.8, 7.6, C5$H_A$$H_B$), 2.01 (1H, td, *J* 7.4, 12.8, C6$H_A$$H_B$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (C9), 153.0 (C3), 151.3 (C1), 141.6 (CH_2C_{Ph}), 139.1 (C7a), 137.3 (C4a), 135.1 (C2), 131.7 (C11H), 129.0 (2C_{PhH}*meta*), 128.4 (C_{PhH}*para*), 128.0 (2C_{PhH}*ortho*), 126.7 (C11a), 124.6 (C11b), 113.6 (C10H), 110.5 (C8H), 107.9 (C4H), 70.5 (CH_2Ph), 61.5 (C2OCH_3), 61.4 (C7H), 61.2 (C1OCH_3), 56.4 (C3OCH_3), 39.3 (C6H_2), 30.8 (C5H_2). HRMS (ES^+): found: 454.1736. $C_{25}H_{25}N_3O_4Na$ requires: 454.1737.

Attempts to displace the mesylate with sodium azide in DMF were thwarted by competing elimination. A Mitsunobu reaction involving the alcohol **25** (0.15 mmol scale), $Zn(N_3)_2\cdot 2pyr$[57] (1.1 equiv), triphenylphosphine (2.0 equiv) and diisopropyl azodicarboxylate (2.0 equiv) gave a 67% yield of the azide **26** along with recovered starting material. The yield based on recovered starting material was 97%.

*4.9. (5S)-(−)-3-Benzyloxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-ylamine (**27**)*

To a stirred solution of azide **26** (7.7 g, 17.8 mmol) in THF (150 mL) under nitrogen was added dropwise a solution of $LiAlH_4$ in THF (1 M, 27 mL, 26.8 mmol) with ice bath cooling. After stirring overnight at rt, water (20 mL) was added dropwise to destroy excess hydride followed by 10% aq NaOH (200 mL). The mixture was filtered and the organic layer was separated and the aqueous layer then extracted with CH_2Cl_2 (3×200 mL). The combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The yellow oily residue was then purified by column chromatography (SiO_2, 5% Et_3N–EtOAc) to give the title compound (6.9 g, 17.1 mmol, 96%) as a white solid. A sample recrystallised from MeOH gave mp 122–124 °C. $[\alpha]_D$ −88.4 (*c* 1, $CHCl_3$). ν_{max} (diamond compression system): 3369 m, 2928 s, 1738 s, 1594 s, 1455 s, 831 s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (2H, m, ArH), 7.42–7.37 (3H, m, 2ArH and C1H), 7.35–7.32 (1H, m, ArH), 7.29 (1H, d, *J* 3.0, C4H), 6.94 (1H, dd, *J* 3.0, 8.6, C2H), 6.57 (1H, s, C8H), 5.14 (2H, s, CH_2Ph), 3.90 (6H, s, 2OCH_3), 3.82 (1H, dd, *J* 11.6, 6.4, C5H), 3.62 (3H, s, OCH_3), 2.45–2.38 (2H, m, C7H_2), 2.34–2.27 (1H, m, C6$H_A$$H_B$), 1.75–1.69 (1H, m, C6$H_A$$H_B$), 1.44 (2H, br s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (C3), 158.6, 158.4 (C9, C11), 152.7 (C10), 151.2 (C4a), 143.3 (C7a), 141.3 (CH_2C_{Ph}), 137.5 (C11b), 136.1 (C11a), 131.4 (C1H), 129.0 (2C_{PhH}*meta*), 128.9 (C_{PhH}*para*), 128.0 (2C_{PhH}*ortho*), 112.3 (C2H), 110.0 (C4H), 107.7 (C8H), 70.3 (CH_2Ph), 61.4 (C10OCH_3), 61.2 (C11OCH_3), 56.4 (C9OCH_3), 51.3 (C5H), 41.9 (C6H_2), 30.7 (C7H_2). HRMS (ES^+): found: 406.2015. $C_{25}H_{28}NO_4$ requires: 406.2013. Found: C 73.6, H 6.75, N 3.35. $C_{25}H_{27}NO_4$ requires: C 74.05, H 6.71, N 3.45%.

*4.10. (5S)-(−)-N-(3-Benzyloxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl) acetamide (**28**)*

To a solution of amine **27** (6.1 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added pyridine (4.8 mL, 60.0 mmol) followed by acetic anhydride (4.9 mL, 52.5 mmol). The resulting reaction mixture was stirred at rt for 1 h and then quenched with water (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with 10% aq HCl (100 mL) and with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the crude amide **28** (6.6 g, 14.8 mmol, 99%) as a white fluffy solid. Chiral HPLC of the crude product on a Chiralcel OD-RH column eluting with 15–25% MeCN in H_2O (1.0 mL min^{-1}) revealed an er=98:2; t_R (major)=29.8 min; t_R (minor)=27.6 min. A sample recrystallised from MeOH–H_2O gave mp 196–197 °C. $[\alpha]_D^{27}$ −86.9 (*c* 1, $CHCl_3$). ν_{max} (diamond compression system): 3259 s, 2932 s, 1635 s, 1610 s, 1375 m, 1153 m, 1100 m, 696 s cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.48 (1H, d, *J* 8.1, NH), 7.46 (2H, d, *J* 7.7, ArH), 7.39–7.30 (4H, m, 3ArH, C1H), 6.95 (1H, m, C2H), 6.94 (1H, d, *J* 2.6, C4H), 6.72 (1H, s, C8H), 5.13 (2H, AB system, J_{AB}=J_{BA}=12, CH_2Ph), 4.68–4.63 (1H, m, C5H), 3.88 (3H, s, C9OCH_3), 3.86 (3H, s, C10OCH_3), 3.49 (3H, s, C11OCH_3), 2.51 (1H, dd, *J* 12.2, 5.3, C7$H_A$$H_B$), 2.32–2.20 (2H, m, C7$H_A$$H_B$, C6$H_A$$H_B$), 1.97 (3H, s, NHAc), 1.96–1.89 (1H, m, C6$H_A$$H_B$). ^{13}C NMR (75 MHz, CD_3OD): δ 172.4 (C=O), 159.7 (C3), 153.9 (C9), 152.1 (C11), 142.5, 142.4 (C10, C4a), 138.8 (CH_2C_{Ph}), 136.6 (C7a), 132.2 (C1H), 129.5 (2C_{PhH}*meta*), 128.9 (C_{PhH}*para*), 128.6 (2C_{PhH}*ortho*), 128.3 (C11b), 126.2 (C11a), 113.4 (C2H), 110.9 (C4H), 109.2 (C8H), 71.1 (CH_2Ph), 61.6 (C10OCH_3), 61.4 (C11OCH_3), 56.6 (C9OCH_3), 50.4 (C5H), 40.0 (C6H_2), 31.5 (C7H), 22.7 (O=C–CH_3). HRMS (ES^+): found: 470.1939. $C_{27}H_{29}NNaO_5$ requires: 470.1938. Found: C 72.2, H 6.5, N 3.05. $C_{27}H_{29}NO_5$ requires: C 72.46, H 6.53, N 3.13%. ^{1}H NMR spectra recorded in $CDCl_3$ were complicated by rotamers.

[‡] HAZARD: the use of tetramethylguanidinium azide in dichloromethane is risky owing to the potential formation of explosive diazidomethane.[55] Acetonitrile has been recommended as a safer alternative.[56]

4.11. (5S)-(−)-N-(3-Hydroxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzocylohepten-5-yl)-acetamide [(aR,7S)-(−)-N-acetylcolchinol] (**2**)

A 500 mL round-bottom flask was charged with acetamide **28** (12.3 g, 27.5 mmol), 10% Pd/C (4.4 g, 4.1 mmol) and 2-propanol (300 mL). The reaction mixture was carefully degassed five times with hydrogen and stirred under 1 atm of H_2 for 2 h. The reaction mixture was then filtered through Celite and the residue thoroughly washed with methanol. The combined filtrate and washes were concentrated under reduced pressure affording a white fluffy solid. Chiral HPLC of the crude product on a Chiralcel OD-RH column eluting with 15–25% MeCN in H_2O (1.0 mL min^{-1}) revealed an er=97:3; t_R (major)=24.4 min; t_R (minor)=22.0 min. The white solid was recrystallised from EtOH–H_2O to give the title compound (9.8 g, 27.4 mmol, 99%) as white crystals: mp 152–154 °C; lit. Mp 150 °C (EtOH).[14] $[\alpha]_D^{27}$ −34.0 (*c* 1, $CHCl_3$). ν_{max} (diamond compression system): 3326 s, 2931 s, 2860 m, 1537 s, 1455 s, 1226 s, 1050 m, 826 m cm^{-1}. The ^1H and ^{13}C NMR spectroscopic data recorded at 500 and 125 MHz, respectively, were identical to those reported previously.[19]

The er of (−)-**2** is easily enhanced by crystallisation because (±)-**2** is much less soluble in MeOH and crystallises readily as colourless prisms. Thus, a sample of **2** (94% ee) was dissolved in hot MeOH. On cooling to rt, the crystals of (±)-**2** were collected by filtration leaving (−)-**2** (>99% ee) in solution. On addition of H_2O to the filtrate, the (−)-**2** then crystallised as a fine white powder. An X-ray crystal structure of (±)-**2** recrystallised from MeOH showed one tightly bound MeOH molecule for each molecule of (±)-**2** in the crystal lattice. An X-ray structure of (−)-NAC·H_2O has been determined.[58]

4.12. Tributyl-(6-[1′,3′]-dioxolan-2′-yl-2,3,4-trimethoxyphenyl)-stannane (**29**)

tert-Butylithium (13 mL of a 1.52 M solution in pentane, 20.0 mmol) was added to a solution of bromoarene **20** (3.19 g, 10.0 mmol) in dry Et_2O (50 mL) at −78 °C. The resulting black mixture was stirred at −78 °C for 55 min before the dropwise addition of tributyltin chloride (5.4 mL, 6.51 g, 20.0 mmol) at −78 °C. The mixture was allowed to warm to rt overnight and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel (3:1, hexanes–Et_2O) and distilled under reduced pressure (Kügelrohr) to afford the title compound (4.39 g, 8.3 mmol, 83%) as a colourless oil: bp 175 °C (bath), 0.15 mmHg (Kügelrohr). R_f 0.27 (3:1, hexanes–Et_2O). ν_{max} ($CHCl_3$): 2956 s, 2930 s, 2872 m, 2852 m, 1583 m, 1464 m, 1377 s, 1310 s, 1197 m, 1163 m, 1101 s, 1044 m, 733 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.03 (1H, s, C5H), 5.57 (1H, s, C2′H), 4.14 (2H, m, C4′H, C5′H), 4.02 (2H, m, C4′H, C5′H), 3.88 (3H, s, C3OCH_3), 3.86 (3H, s, C4OCH_3), 3.82 (3H, s, C2OCH_3), 1.63–1.41 (6H, m, 3C$H_2$$CH_2$Sn), 1.38–1.26 (6H, m, 3C$H_2$$CH_3$), 1.05 (6H, m, 3$CH_2$Sn), 0.88 (9H, t, *J* 7.17, 3CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3 (C2), 153.9 (C4), 140.9 (C6), 139.0 (C3), 126.3 (C1), 104.7 (C2′H), 103.8 (C5H), 65.0, 64.9 (C4′H_2, C5′H_2), 60.4 (C4OCH_3), 60.1 (C2OCH_3), 55.6 (C3OCH_3), 29.0, 28.9, 28.8 (3$CH_2$$CH_2$Sn), 27.1 (3$CH_2$$CH_3$), 13.66, 13.63 (3$CH_3$), 11.6 (3$CH_2$Sn). LRMS ($ES^+$): *m/z* 529 [$M^+$, 15%], 531 (25), 471 (65), 473 [$M^+-C_4H_7$, 90%], 475 (100). HRMS (ES^+): found: 473.1504. $C_{20}H_{35}O_5{}^{118}Sn$ requires: 473.1501.

4.13. 1-(4′-Benzyloxy-6″-[1‴,3‴]-dioxolan-2‴-yl-2″,3″,4″-trimethoxybiphenyl-2′-yl)-ethanone (**30**)

A 100 mL flame-dried round-bottomed flask, equipped with a water condenser and a nitrogen inlet, was charged with 1-(5′-benzyloxy-2′-bromophenyl)-ethanone **22** (2.13 g, 7.0 mmol), triphenylphosphine (0.865 g, 3.3 mmol), CuI (0.53 g, 2.8 mmol), $Pd(PPh_3)_4$ (1.61 g, 1.4 mmol), 2,6-di-*tert*-butyl-4-methylphenol (one small crystal), DMF (35 mL) and stannane **29** (4.44 g, 8.4 mmol). The reaction mixture was stirred for 5 min at rt and then refluxed for 106 h, before addition of water (50 mL) at rt. The layers were separated and the aqueous layer extracted with hexanes–Et_2O (1:1) mixture (4×50 mL). The combined organic extracts were washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (1:1, hexanes–Et_2O→Et_2O) to give the title compound (1.69 g, 3.63 mmol, 52%) as a white amorphous solid which was recrystallised from CH_2Cl_2–hexanes affording the title compound (1.46 g, 3.14 mmol) as colourless prisms: mp 103–106 °C ($CHCl_3$). R_f 0.09 (1:1, hexanes–Et_2O). ν_{max} ($CHCl_3$): 2940 m, 2891 m, 1690 s, 1600 s, 1563 m, 1483 s, 1463 s, 1402 s, 1335 m, 1281 m, 1233 m, 1197 m, 1150 m, 1094 s, 1040 m, 1003 m, 909 s, 732 s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49–7.48 (2H, m, ArH), 7.44–7.41 (3H, m, ArH), 7.38 (1H, m, C3′H), 7.21 (1H, d, *J* 8.1, C6′H), 7.14 (1H, dd, *J* 2.6, 8.1, C5′H), 7.01 (1H, s, C5″H), 5.37 (1H, s, C2‴H), 5.14 (2H, s, CH_2Ar), 4.07–4.01 (2H, m, C4‴H, C5‴H), 3.94 (3H, s, C4″OCH_3), 3.89 (3H, s, C3″OCH_3), 3.87–3.79 (2H, m, C4‴H, C5‴H), 3.59 (3H, s, C2″OCH_3), 2.14 (3H, s, O=C–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2 (C1), 158.3 (C4′), 153.5 (C4″), 151.2 (C2″), 143.0 (C3″), 141.6 (CH_2C), 136.8 (C2′), 133.6 (C6′H), 130.8 (C6″), 128.9 (2$C_{Ph}H_{meta}$), 128.4 (2$C_{Ph}H_{ortho}$), 128.2 (C1′), 127.9 ($C_{Ph}H_{para}$), 126.9 (C1″), 117.6 (C5′H), 114.4 (C3′H), 105.3 (C5″H), 101.5 (C2‴H), 70.4 (CH_2Ph), 65.5, 65.4 (C4‴H_2, C5‴H_2), 61.1 (C3″OCH_3), 60.9 (C2″OCH_3), 56.1 (C4″OCH_3), 29.4 (O=C–CH_3). LRMS (ES^+): *m/z* 487 [M^++Na, 100%], 488 (5), 465 [M^++H, 90%], 466 (5). HRMS (ES^+): found: 465.1923. $C_{27}H_{29}O_7$ requires: 465.1913.

A solution of biaryl **30** (107 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) was treated with 6 M HCl (6 mL). The biphasic mixture was stirred for 20 min at rt and the layers were separated. The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (3:2, hexanes–AcOEt) to give the keto aldehyde **23** (95 mg, 0.22 mmol, 98%) displaying ^1H and ^{13}C NMR spectroscopic data identical to those described above.

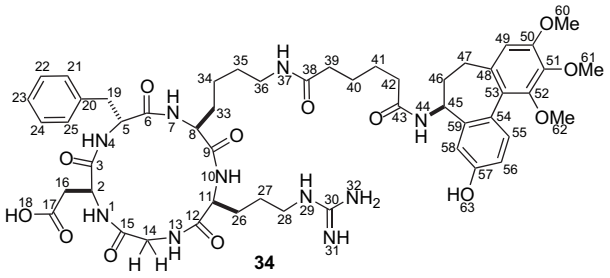
4.14. Solid phase synthesis of colchinol–RGD peptide conjugate **34**

4.14.1. Solid phase synthesis of Fmoc–D-Phe-Lys(Dde)-Arg(Pbf)-Gly-Asp–OAll (**32**)

Commercial *N*-α-Fmoc–L-Asp(Wang LL)–OAll resin (Novobiochem, 0.65 g, loading 0.35 mmol/g, 0.23 mmol) was deprotected with piperidine–DMF (1:4). Standard Fmoc protocols were then used to append in sequence *N*-α-Fmoc–Gly–OH, *N*-α-Fmoc–L-Arg(Pbf)–OH, *N*-α-Fmoc–L-Lys(Dde)–OH and *N*-α-Fmoc–D-Phe–OH. HCTU was used as coupling agent.

4.14.2. Synthesis of the resin-bound c[RGDfK] **33**

A solution of $Pd(PPh_3)_4$ in $CHCl_3$–AcOH–*N*-methylmorpholine (37:2:1, 8 mL) was added to peptide resin **32** and the resulting mixture agitated for 4 h at rt. The resin was filtered and washed consecutively with DIPEA–DMF (5:95, 3×10 mL), diethyldithiocarbamic acid sodium salt–DMF (0.5:99.5, 3×10 mL), DMF (3×10 mL) and finally CH_2Cl_2 (2×10 mL). After removal of the remaining Fmoc group with piperidine–DMF (1:4) as described above, the cyclisation was achieved by adding HCTU (3 equiv) in DMF (5 mL). After 24 h, the resin was washed with DMF (3×10 mL) and CH_2Cl_2 (3×10 mL) to give the resin-bound c[RGDfK] peptide **33**.



34

4.14.3. c[RGDfK(adipoyl-colchinol)] **34**

Removal of the Dde protecting group was accomplished by twofold treatment of **33** with hydrazine monohydrate in DMF (2:98, 5 mL) for 5 min before washing with DMF (10×1 mL). The resin was then suspended in DMF (5 mL) and adipic anhydride (290 mg, 2.3 mmol, 10.0 equiv) and DIPEA (0.5 mL, 2.8 mmol, 12.0 equiv) were added. After agitation for 20 h, the resin was washed with DMF. The resin was suspended in a solution of HCTU (285 mg, 0.7 mmol, 3.0 equiv), HOBt (106 mg, 0.7 mmol, 3.0 equiv) and DIPEA (0.24 mL, 1.4 mmol, 6.0 equiv) in DMF (3 mL). Colchinol hydrochloride (**35**, 245 mg, 0.7 mmol, 3.0 equiv) in DMF (3 mL) was added and the mixture was agitated for 60 h before exhaustive washing with DMF followed by CH_2Cl_2. Treatment of the resin with TFA–(*i*-Pr)$_3$SiH–H_2O (95:2.5:2.5, 6 mL) for 1 h was followed by washing with TFA (2×1 mL). The combined filtrate and washings were concentrated in vacuo and Et_2O (10 mL) was added to the residue. The resultant white precipitate was centrifuged and washed with more Et_2O (3×). The crude peptide was then purified by preparative reverse phase HPLC (Thermo Hypersil Keystone Hyperprep C18 column, 50–95% MeCN+0.1% TFA in water+0.1% TFA, 5 mL min^{-1}, t_R 17–18 min) and the eluent removed by freeze drying to give the target conjugate **34** (38 mg, 0.04 mmol, 16% based on the estimated peptide resin loading of 0.23 mmol/g) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.39–8.35 (1H, m, N13H), 8.27–8.19 (2H, m, N4H, N44H), 8.07–7.96 (2H, m, N1H, N7H), 7.76 (1H, t, *J* 5.5, N37H), 7.62–7.58 (1H, m, N10H), 7.53 (1H, t, *J* 5.7, N29H), 7.22–7.09 (6H, m, C21H, C25H, C22H, C23H, C24H, C55H), 7.02 (1H, s, N31H), 6.75–6.73 (1H, m, C58H), 6.72 (1H, s, C49H), 6.67 (1H, dd, *J* 8.3, 2.2, C56H), 4.62 (1H, dt, *J* 8.4, 5.9, C2H), 4.50–4.41 (2H, m, C5H, C8H), 4.16–4.11 (1H, m, C11H), 4.05–3.88 (1H, m, C14H_AH_B), 3.83–3.80 (1H, m, C45H), 3.77–3.73 (6H, m, C60H_3, C61H_3), 3.45 (3H, s, C62H_3), 3.25–3.21 (1H, dd, *J* 15.0, 4.1, C14H$_A$$H_B$), 3.08–3.02 (4H, m, C28$H_2$, C36$H_2$), 2.95–2.90 (1H, m, C19$H_AH_B$), 2.80 (1H, dd, *J* 13.2, 5.6, C19H$_A$$H_B$), 2.74–2.68 (1H, m, C16$H_AH_B$), 2.53–2.43 (4H, m, C46$H_2$, C47$H_2$), 2.37–2.34 (1H, m, C16H$_A$$H_B$), 2.20–2.02 (5H, m, C33$H_AH_B$, C39$H_2$, C42$H_2$), 1.90–1.85 (1H, m, C33H$_A$$H_B$), 1.73–1.67 (1H, m, C26$H_AH_B$), 1.52–1.10 (9H, m, C26H$_A$$H_B$, C27$H_2$, C35$H_2$, C40$H_2$, C41$H_2$), 1.03–0.99 (2H, m, C34$H_2$). ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.05 (C12), 171.92 (C9), 171.60 (C38), 171.10 (C43), 170.94 (C15), 170.57 (C17), 169.90 (C6), 169.48 (C3), 156.61 (C57), 156.41 (C30), 151.79 (C50), 150.26 (C52), 141.70 (C59), 140.50 (C51), 137.19 (C20), 134.67 (C48), 130.36 (C55H), 129.03 (C22H, C24H), 128.06 (C21H, C25H), 126.24 (C23H), 124.68 (C54), 124.38 (C53), 112.84 (C56H), 110.12 (C58H), 107.94 (C49H), 60.46 (C61H_3, C62H_3), 60.37 (C60H_3), 55.77 (C45H), 54.50 (C8H), 54.31 (C5H), 51.81 (C11H), 48.84 (C2H), 43.19 (C14H_2), 40.23 (C46H_2), 39.59 (C28H_2), 39.51 (C36H_2), 38.36 (C19H_2), 38.17 (C16H_2), 35.17 (C39H_2), 35.10 (C42H_2), 30.82 (C33H_2), 30.10 (C47H_2), 28.80 (C35H_2), 28.50 (C26H_2), 28.41 (C27H_2), 25.16 (C40H_2), 24.96 (C41H_2), 22.79 (C34H_2). LRMS (ES$^+$): *m*/*z* 1029 [M$^+$+H, 100%], 1030 (60), 731 (30). HRMS (ES$^+$): found: 1029.5044. $C_{51}H_{69}N_{10}O_{13}$ requires: 1029.5046.

4.15. Colchinol hydrochloride (**35**)

(−)-*N*-Acetylcolchinol (0.1 g, 0.3 mmol) was dissolved in 2 mL of a (1:1) mixture of 2 M aq HCl and MeOH. The solution was refluxed for 24 h before removal of the solvent in vacuo. The residue was washed several times with Et_2O and dried in vacuo affording the target molecule (0.09 mg, 0.25 mmol, 85%) as a fluffy white powder that was used without further purification in the next step: mp 192–194 °C (Et_2O). ^{1}H NMR (500 MHz, CD_3OD): δ 7.36 (1H, d, *J* 8.3, C1′H), 6.90 (1H, d, *J* 8.3, C2′H), 6.89 (1H, s, C4′H), 6.80 (1H, s, C8′H), 4.05–3.95 (1H, m, C5′H), 3.91 (3H, s, C9′OCH_3), 3.87 (3H, s, C10′OCH_3), 3.58 (3H, s, C11′OCH_3), 2.70–2.55 (2H, m, C7′H), 2.40–2.25 (1H, m, C6′H_AH_B), 2.15–2.05 (1H, m, C6′H$_A$$H_B$). ^{13}C NMR (125 MHz, CD_3OD): δ 158.8 (C3′), 154.6 (C9′), 152.5 (C11′), 143.0 (C10′), 137.0 (C4a′), 136.1 (C7a′), 133.5 (C11b′), 127.3 (C1′H), 125.8 (C11a′), 115.8 (C2′H), 110.5 (C4′H), 109.1 (C8′H), 61.9 (C10′OCH_3), 61.8 (C11′OCH_3), 57.0 (C9′OCH_3), 52.6 (C5′H), 39.3 (C6′H_2), 30.9 (C7′H_2). ν_{max} (neat): 2900 s, 1611 s, 1454 s, 1405 m,

1332 m, 1229 s, 1146 m, 1089 s, 1057 m, 1005 m, 820 m cm^{-1}. LRMS (ES^+): *m/z* 299 [M^+-NH_3Cl, 100%], 316 [M^+-Cl, 96%], 317 (25), 285 (50). HRMS (ES^+): found: 316.1555. $C_{18}H_{22}NO_4$ (M+H) requires: 316.1549.

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