

**Asymmetric Synthesis of the Allocolchicinoid Natural Product  
*N*-Acetylcolchinol Methyl Ether (Suhailamine), Solid State  
and Solution Phase Conformational Analysis**

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**ABSTRACT:** An asymmetric synthesis of the allocolchicinoid *N*-acetylcolchinol methyl ether (NCME) from 3-methoxybenzaldehyde is reported. Comparison of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data obtained for this sample of NCME provide concrete evidence for the assertion that this compound is congruous with the natural product that has been dubbed suhailamine, establishing NCME as a naturally-occurring allocolchicinoid. The single crystal X-ray diffraction structure of NCME is also reported for the first time, revealing a preference for adoption of the  $(7S, R_a, Z)$  form—i.e., describing the orientation of the biaryl axis and the amide N–CO bond as well as the configuration of the stereocenic centre—in the solid state. A preference for the same form in  $\text{DMSO-}d_6$  solution is revealed upon analysis by a range of NMR spectroscopic techniques, whilst an interconverting 69:24:7 mixture of the  $(7S, R_a, Z)$ ,  $(7S, S_a, Z)$  and  $(7S, R_a, E)$  forms is observed in  $\text{CDCl}_3$ .

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*Keywords:*

Suhailamine

*N*-Acetylcolchinol Methyl Ether

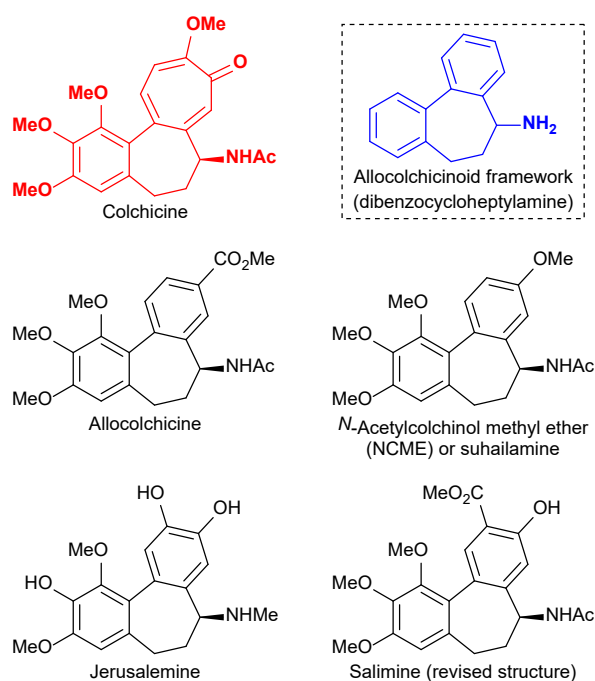
NCME

Allocolchicinoid

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## 1. Introduction

The term allocolchicinoid is applied to a number of dibenzocycloheptylamines which are often considered as analogues of the alkaloid colchicine in which the tropolone ring has been replaced with a substituted benzene ring. The structures of allocolchicine and *N*-acetylcolchinol methyl ether (NCME) are representative of this class of compound (Fig. 1). For many years, the allocolchicinoid family represented purely synthetic entities,<sup>1</sup> although they have been proposed as potential catabolites of colchicine itself (indeed, they are often prepared in the laboratory by the rearrangement or degradation of colchicine itself).<sup>1</sup> This hypothesis found some support in 1991, when Abu Zarga *et al.* reported isolation of three allocolchicinoids from *Colchicum decaisnei* Boiss., which were named as jerusalemine, salimine and suhailamine<sup>2</sup> (Fig. 1). The structures of jerusalemine and salimine were established unambiguously by the investigations of Banwell *et al.* (it should be noted that these studies involved the structural revision of salimine),<sup>3</sup> although the identification of suhailamine, which was originally proposed to have the same structure as allocolchicine but displayed distinctly different spectroscopic data, remained an unresolved issue. We recently re-evaluated the data reported for suhailamine, however, and proposed that it shared its structure with NCME, and this assertion was supported by comparison with data previously reported for this compound<sup>4</sup> (Fig. 1).

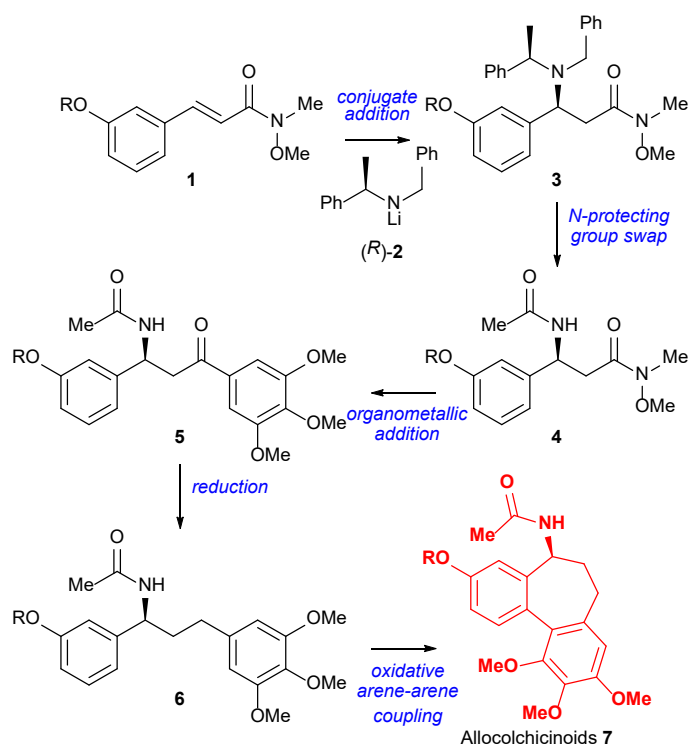


**Fig. 1.** Structures of colchicine and representative allocolchicinoids.

In order to validate our assertion, we wished to develop an independent method for the synthesis of NCME and compare its spectroscopic data to those reported for suhailamine. We herein report the results of our investigations within this area, and also present a complete solid state and solution phase conformational analysis of this alkaloid.

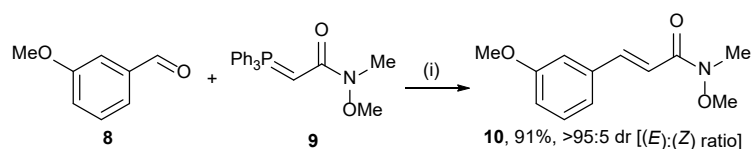
## 2. Results and Discussion

A synthesis which would potentially enable the preparation of a range of allocolchicinoids, was envisaged. In the forward sense, conjugate addition of enantiopure lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**2** to an  $\alpha,\beta$ -unsaturated Weinreb amide **1** [derived from Wittig reaction of the corresponding *O*-protected 3-hydroxybenzaldehyde derivative] would give the corresponding enantiopure  $\beta$ -amino amide **3**. An *N*-protecting group swap via hydrogenolytic removal of the *N*-benzyl and *N*- $\alpha$ -methylbenzyl substituents and acetylation would give  $\beta$ -amido amide **4**. Addition of an arylmetal reagent (derived from 5-bromo-1,2,3-trimethoxybenzene) to **4** would give the corresponding ketone **5**. Reduction of the carbonyl group to a methylene group then gives **6**, which could undergo oxidative arene-arene coupling to complete assembly of the allocolchicinoids **7**, e.g., NCME, where R = Me (Fig. 2).



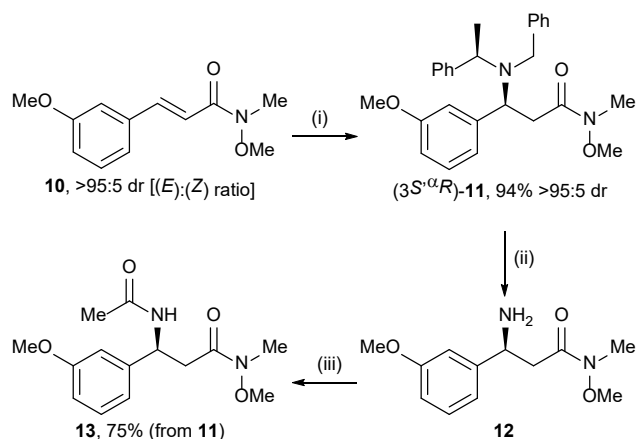
**Fig. 2.** Proposed synthesis of allocolchicinoids **7**.

In order to facilitate the synthesis of NCME, the requisite  $\alpha,\beta$ -unsaturated Weinreb amide **10** bearing an *O*-methyl substituent was prepared from the Wittig olefination of 3-methoxybenzaldehyde **8** with ylide **9** (prepared from bromoacetyl bromide).<sup>5</sup> This olefination reaction proceeded to give **10** in >95:5 dr [(*E*):(*Z*) ratio] and 91% isolated yield. The diagnostic value of the olefinic coupling constant in the <sup>1</sup>H NMR spectrum (<sup>3</sup>*J*<sub>2,3</sub> = 15.8 Hz) enabled confident assignment of the geometry of the newly formed olefin functionality (Scheme 1).



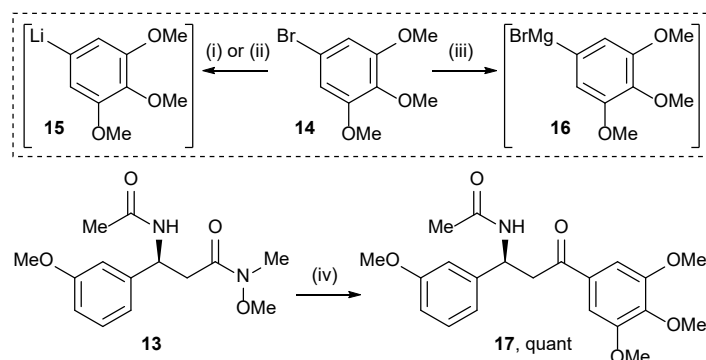
**Scheme 1.** Reagents and Conditions: (i) CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h.

Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**2** to  $\alpha,\beta$ -unsaturated Weinreb amide **10** gave the corresponding  $\beta$ -amino amide (3*S*, $\alpha$ *R*)-**11** as a single diastereoisomer (>95:5 dr), which was isolated in 94% yield. The absolute configuration at the newly formed C(3)-stereogenic center of (3*S*, $\alpha$ *R*)-**11** was assigned by reference to the transition state mnemonic that we have developed to predict the stereochemical outcome of this class of conjugate addition reaction.<sup>6</sup> A two-step *N*-protecting group swap was next effected: treatment of (3*S*, $\alpha$ *R*)-**11** with Pd(OH)<sub>2</sub>/C under a H<sub>2</sub> atmosphere resulted in removal of the *N*-benzyl and *N*- $\alpha$ -methylbenzyl groups to give the corresponding primary amine **12**, that was treated with Ac<sub>2</sub>O to furnish the corresponding  $\beta$ -amido amide **13** in 75% yield (Scheme 2).



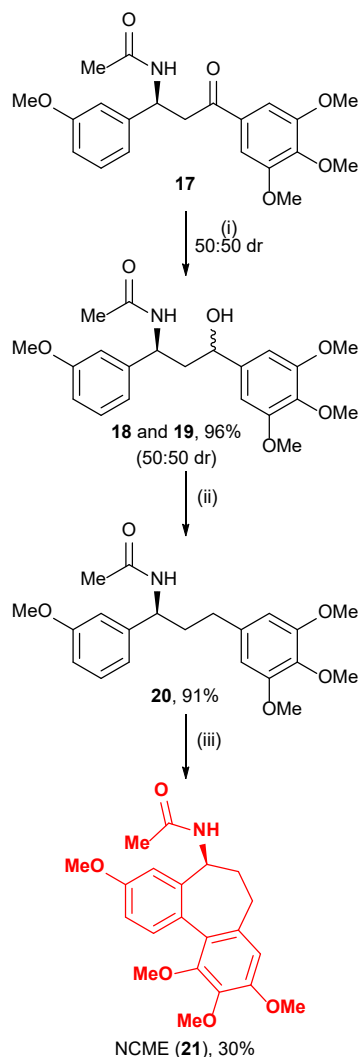
**Scheme 2.** Reagents and Conditions: (i) (*R*)-**2**, THF, −78 °C, 2 h; (ii) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt, 48 h; (iii) Ac<sub>2</sub>O, pyridine, rt, 16 h.

In order to form the corresponding ketone **17**, addition of an arylmetal reagent (derived from 5-bromo-1,2,3-trimethoxybenzene **14**) to the Weinreb amide functionality of **13** was investigated. In preliminary studies, generation of the corresponding aryllithium reagent **15** from aryl bromide **14** upon treatment with either *n*-BuLi or *t*-BuLi (following previously reported procedures)<sup>7,8</sup> followed by addition to **13** was frustrated by low conversion to ketone **17**,<sup>9</sup> although the generation and subsequent addition of the corresponding Grignard reagent **16** to Weinreb amide **13** proved more promising. Upon optimisation of this reaction, **17** was formed in quantitative yield after work-up (Scheme 3).



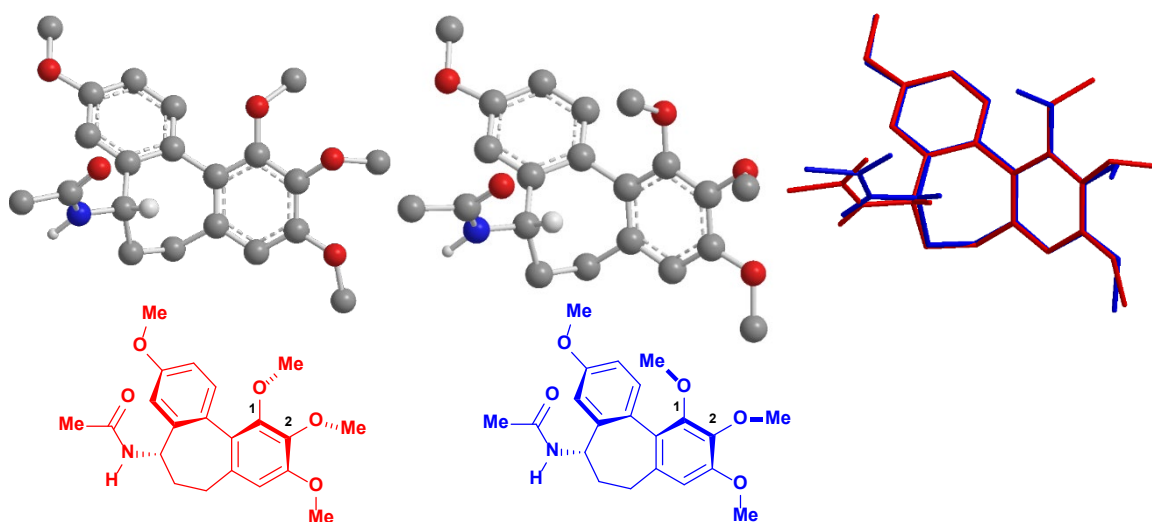
**Scheme 3.** Reagents and Conditions: (i) *n*-BuLi, THF, −78 °C, 30 min; (ii) *t*-BuLi, THF, −78 °C, 30 min; (iii) Mg, I<sub>2</sub> (cat amt), MeI (cat amt), THF, reflux, 1 h; (iv) **16**, THF, rt, 16 h.

Reduction of the ketone functionality of **17** to a methylene group was performed in two steps: treatment of **17** with NaBH<sub>4</sub> gave a near 50:50 mixture of the corresponding diastereoisomeric alcohols **18** and **19**. It was possible to separate these two species chromatographically although for ease they were isolated as a mixture on preparative scale, in 96% combined yield. Hydrogenolysis of the mixture of **18** and **19** over Pd(OH)<sub>2</sub>/C resulted in convergence to **20**, which was isolated in 91% yield. The final stage of construction of the allocolchicinoid framework required an oxidative arene-arene coupling of **20** to furnish NCME (**21**) directly. Various reagents have been employed to effect such reactions, including MnO<sub>2</sub> with BF<sub>3</sub>·OEt<sub>2</sub>,<sup>10</sup> DDQ with MeSO<sub>3</sub>H,<sup>11</sup> and PIFA with H<sub>3</sub>[PW<sub>12</sub>O<sub>40</sub>],<sup>12</sup> and MoCl<sub>5</sub> with TiCl<sub>4</sub>.<sup>13</sup> However, use of these conditions to affect the conversion of **20** to **21** all produced a complex mixture of products which were difficult to separate by column chromatography and in no case was **21** detectable by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. Use of PIFA with BF<sub>3</sub>·OEt<sub>2</sub>, TFA and TFAA—a procedure that has been used on a substrate that is structurally related to **20** to effect the synthesis of the allocolchicinoid framework<sup>14,15</sup>—some success was observed: although a relatively complex mixture of products was formed, purification by flash column chromatography gave **21** in 30% yield (Scheme 4).



**Scheme 4.** Reagents and Conditions: (i) NaBH<sub>4</sub>, MeOH, 0 °C, 3 h; (ii) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt, 48 h; (iii) TFA, TFAA, PIFA, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 h.

Crystallisation of our sample of NCME (**21**) from a mixture of  $\text{CHCl}_3$  and *n*-heptane provided single crystals suitable for X-ray diffraction analysis,<sup>15</sup> which thus unequivocally established its structure. Interestingly, two molecules were present in the asymmetric unit of the crystal structure, which can both be described as the (7*S*,*R*<sub>a</sub>,*Z*) form: in each molecule, the two biaryl rings are twisted in the (*R*<sub>a</sub>) arrangement, with a dihedral angle of approximately 50° (and the 7-membered ring adopting a twist boat conformation),<sup>16</sup> whilst the amide adopts the (*Z*) arrangement.<sup>17</sup> The two molecules in the asymmetric unit were observed to differ significantly only in the orientation of the C(1) and C(2) *O*-methyl groups (Fig. 3). This difference excepted, the gross conformation of **21** observed in the solid state is in agreement with the solid state conformation of a closely related urea reported by Brossi *et al.*<sup>18</sup>—in this case the dihedral angle between the planes defined by the two aryl rings is also approximately 50°. <sup>19</sup>



**Fig. 3.** The two molecules of the asymmetric unit observed in the X-ray crystal structure of NCME (**21**), and overlay of both (selected H atoms are omitted for clarity).

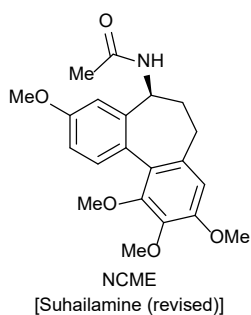
With the identity of our sample of NCME (**21**) secured, two important goals of this study remained to be addressed: (1) to establish the congruency of **21** with other samples of NCME and (2) to establish the congruency of **21** with suhailamine.

(1) It has previously noted that members of the allocolchicinoid family exist as essentially a single entity by NMR spectroscopic analysis when spectra are recorded in  $\text{MeOH-}d_4$  or  $\text{DMSO-}d_6$  although a mixture of species is observed when spectra are recorded in  $\text{CDCl}_3$ ;<sup>20</sup> generally, therefore, the NMR spectroscopic data for these alkaloids are obtained in either of the former two solvents in order to simplify the characterisation process. In the specific case of synthetic samples of NCME that have been previously reported, the accompanying  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data have generally been acquired using  $\text{DMSO-}d_6$  as the solvent.<sup>21</sup> As expected, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data recorded for the sample of NCME (**21**) prepared in this study using  $\text{DMSO-}d_6$  as the solvent matched well with these other, previously reported data. A smaller number of synthetic samples of NCME have  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data using

CDCl<sub>3</sub> as the solvent: Brecht *et al.*<sup>22</sup> reported a 71:29 ratio of species for NCME in CDCl<sub>3</sub>, whilst Takubo *et al.*<sup>23</sup> reported a 65:25:10 ratio of species. When our sample of NCME (**21**) was recorded in CDCl<sub>3</sub>, a 69:24:7 ratio of three species, **21a:21b:21c** was observed. The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data for two of these species matched with those reported by Brecht *et al.* (71:29, **21a:21b**)<sup>22</sup> and all three of those reported by Takubo *et al.* (65:25:10, **21a:21b:21c**).<sup>23</sup> The specific rotation of this sample of NCME **21** was also in good agreement with values that have been previously reported { $[\alpha]_{\text{D}}^{25}$  -66.6 (*c* 0.5 in CHCl<sub>3</sub>) *cf.* lit.<sup>22</sup>  $[\alpha]_{\text{D}}^{20}$  -65 (*c* 0.46 in CHCl<sub>3</sub>), and  $[\alpha]_{\text{D}}^{25}$  -76.5 (*c* 0.13 in MeOH) *cf.* lit.<sup>24</sup>  $[\alpha]_{\text{D}}^{20}$  -88.6 (*c* 0.67, MeOH)}.

(2) The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data of the natural allocolchicinoid that has been dubbed suhailamine were acquired using CDCl<sub>3</sub> as the solvent.<sup>2</sup> Comparison of the data sets of Brecht *et al.*<sup>22</sup> and Takubo *et al.*<sup>23</sup> for the major species of NCME provided significant support for our assertion that the natural product and NCME share the same structure. As the congruency of our sample of NCME (**21**) with those of Brecht *et al.*<sup>22</sup> and Takubo *et al.*<sup>23</sup> had been established, it was unsurprising that our sample of NCME (**21**) produced a very close match to the data reported for suhailamine:<sup>2</sup> generally  $|\Delta\delta_{\text{H}}| \leq 0.04^{25}$  and  $|\Delta\delta_{\text{C}}| \leq 0.2^{25}$ . The exceptions to this generalisation are the <sup>1</sup>H NMR chemical shift of the NH, for which  $|\Delta\delta_{\text{H}}| = 0.09^{25}$ , and the <sup>13</sup>C NMR chemical shift for C(5), for which  $|\Delta\delta_{\text{C}}| = 1.0^{25}$  (Fig. 4). In the former case, we speculated that the discrepancy is likely due to influence of difference in concentration and/or the presence of hydrogen-bond donors/acceptors (such as residual water) in the samples.<sup>4</sup> In the latter case, meanwhile, we ventured that an erroneous shift was reported for the natural product owing to the presence of colchicine as a contaminant in the sample isolated by Abu Zarga *et al.* from the natural source.<sup>4</sup> As anecdotal evidence for this hypothesis arose from analysis of the ions observed in the accompanying EI-MS data,<sup>4</sup> we next sought to investigate this assertion further. Thus, a commercial sample of colchicine and the sample of NCME (**21**) prepared in this study were subjected to analysis by EI-MS: colchicine produced a molecular ion ( $[\text{M}]^+$ ) at *m/z* 399, with relevant daughter ions being identified at *m/z* 340, 312 and 281 (and 256), whereas NCME (**21**) produced a molecular ion ( $[\text{M}]^+$ ) at *m/z* 371 with a relevant daughter ion being identified at *m/z* 312. These combined values compared well with the values originally reported by Abu Zarga *et al.*<sup>2</sup> for their sample of suhailamine: *m/z* 399, 371, 340, 312, 297, 281, 254. All these combined data support our previous assertion that NCME and suhailamine are one and the same—NCME is a naturally-occurring allocolchicinoid whilst suhailamine is a phantom natural product: in fact, an impure sample of NCME was isolated by Abu Zarga *et al.*,<sup>2</sup> with colchicine being a likely contaminant.





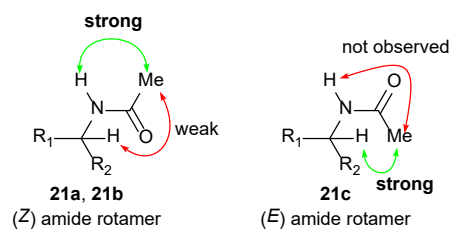
<sup>1</sup> H NMR (CDCl <sub>3</sub> )		<sup>13</sup> C NMR (CDCl <sub>3</sub> )	
Suhailamine	NCME (21)	Suhailamine	NCME (21)
1.77 (1H, m)	1.81 (1H, m)	23.3	23.5 (− 0.2)
2.05 (3H, s)	2.04 (3H, s)	29.7	30.7 (− 1.0)
2.35 (1H, m)	2.34 (1H, m)	39.8	39.7 (+0.1)
2.41 (1H, m)	2.39 (1H, m)	49.4	49.4 (− 0.0)
2.45 (1H, m)	2.44 (1H, m)	55.3	55.4 (− 0.1)
3.52 (3H, s)	3.51 (3H, s)	56.3	56.3 (− 0.0)
3.85 (3H, s)	3.85 (3H, s)	60.9	61.1 (− 0.2)
3.89 (3H, s)	3.89 (3H, s)	61.2	61.4 (− 0.2)
3.92 (3H, s)	3.92 (3H, s)	108.0	107.8 (+0.2)
4.78 (1H, m)	4.80 (1H, m)	109.2	109.3 (− 0.1)
5.71 (1H, br d)	5.82 (1H, d)	110.8	110.7 (+0.1)
6.55 (1H, s)	6.56 (1H, s)	131.4	131.5 (− 0.1)
6.80 (1H, d)	6.82 (1H, d)		
6.84 (1H, dd)	6.85 (1H, dd)		
7.42 (1H, d)	7.42 (1H, d)		

**Fig. 4.** Comparison of <sup>1</sup>H and (partial) <sup>13</sup>C NMR data for suhailamine and NCME (**21**) in CDCl<sub>3</sub>. Reference frequencies employed for the spectra of suhailamine are unknown. Reference frequencies employed for the spectra of NCME (**21**) are: CHCl<sub>3</sub>, δ<sub>H</sub> = 7.26; CDCl<sub>3</sub>, δ<sub>C</sub> = 77.16 (Refs 26 and 27). Midpoints of all multiplets are reported. Values of Δδ<sub>C</sub> are given in parentheses.

At this stage, with our investigations into the congruency of NCME and suhailamine as complete, we turned our focus to NCME itself. The non-planarity of the biaryl framework (as observed in the solid state structure of NCME) is well established within the allocolchicinoid family as a whole, and obviously leads to the possibility of the existence of atropisomers. Indeed, the observation of two species within <sup>1</sup>H and <sup>13</sup>C NMR spectra of various allocolchicinoids is usually attributed to the presence of the two possible atropisomeric forms in solution. As the axial chirality of these compounds is known to be an important feature in the tubulin-binding inhibition mode of the anti-cancer activity of these compounds (as well as that of colchicine), several investigations have appeared in which the preferred solid state and solution phase conformational preferences of this class of molecule are interrogated.<sup>28</sup> With reference to NCME itself, our own observations coupled with those of Takubo *et al.*<sup>23</sup>—that three species are present for NCME in CDCl<sub>3</sub> solution—reveals an incomplete picture of the solution phase conformational preference of this allocolchicinoid, as the atropisomerism alone cannot account for the presence of three species. We thus sought to unambiguously identify all three species **21a**, **21b** and **21c**, observed in CDCl<sub>3</sub> solution in a 69:24:7 ratio, respectively, in this study (and a 65:25:10 ratio in the study of Takubo *et al.*).<sup>23</sup>

Exchange peaks in the <sup>1</sup>H NMR EXSY spectrum could be seen between all three of the species, suggesting that they were all related as slowly-interconverting conformers on the NMR timescale. The nOe enhancements were much more intense than exchange peaks, thus the exchange between these conformers occur slow enough for analysis of nOe data to be insightful. The NOESY data indicated the presence of both (*Z*) and (*E*) amide rotamers. A strong nOe signal between NCOMe and NH could be seen in conformers **21a**

and **21b**, but no nOe signal could be seen for **21c**, suggesting that the NCOMe and NH units are close together in space for conformers **21a** and **21b** but not for **21c**. Likewise, a strong nOe signal between NCOMe and C(7)H could be seen in conformer **21c**, but only a weak nOe signal was seen for conformers **21a** and **21b**, suggesting that the NCOMe and C(7)H units are close together in space for conformer **21c** but not for **21a** and **21b**. This provides evidence that **21a** and **21b** contain the (Z) amide rotamer whilst **21c** contains the (E) amide rotamer (Fig. 5). Thus, the total (Z):(E) amide rotamer population is represented by (21a+21b):21c, i.e. 93:7 or approximately 13:1. This result is consistent with many studies in the literature that all conclude that the (Z) amide rotamer is more prevalent than the (E) amide rotamer for steric reasons.<sup>29</sup>

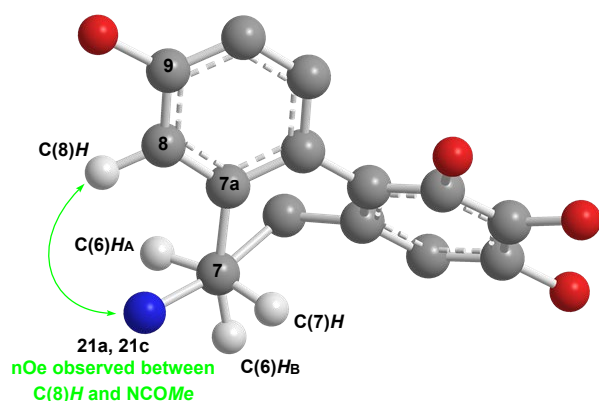


**Fig. 5.** (Z) and (E) amide rotamers, present in **21a/21b** and **21c**, respectively. Arrows signify reciprocal nOe signals.

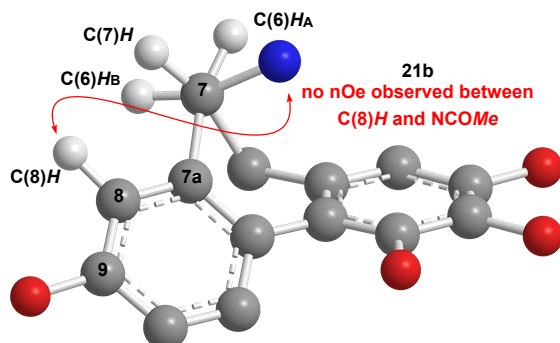
The orientation of the biaryl axis in all three conformers was next investigated. As observed in the X-ray crystal structure, the biaryl rings are twisted in the solid state with a dihedral angle of about 50°, which forces the 7-membered ring into a twist-boat structure; in fact this is directly analogous to the favoured conformation adopted by cyclohepta-1,3-diene.<sup>30,31</sup> Rotation about the biaryl axis in NCME **21**, whilst interconverting the (7*S*,*R*<sub>a</sub>) form to the (7*S*,*S*<sub>a</sub>) form, would simultaneously flip the twist-boat conformation of the 7-membered ring from one form to the other. Thus, the (7*S*,*R*<sub>a</sub>) form would have the C(7)-acetamido substituent in a pseudo-equatorial position on the twist boat [with the C(7)H proton pseudo-axial], whilst the (7*S*,*S*<sub>a</sub>) form would have the C(7)-acetamido substituent in a pseudo-axial position on the twist boat [with the C(7)H proton pseudo-equatorial]. Thus, significantly different dihedral angles would be expected between the C(7)H protons and the neighbouring C(6)H<sub>2</sub> protons. Very basic molecular modelling of the (7*S*,*R*<sub>a</sub>) atropisomeric form showed that the energy minimized (MM2 method) conformation had H–C(7)–C(6)–H dihedral angles of about 164° and 47°. These values were in excellent agreement with the values of about 165° and 47° observed in the X-ray crystal structure of **21**. Application of the same basic molecular modelling to the (7*S*,*S*<sub>a</sub>) atropisomeric form gave H–C(7)–C(6)–H dihedral angles of about 78° and 40° in the energy minimized (MM2 method) conformation. The dihedral angles associated with each of these atropisomeric forms would thus be expected to be reflected by characteristic <sup>3</sup>J<sub>6,7</sub> coupling constants observed in the <sup>1</sup>H NMR spectrum. Indeed, the multiplet associated with C(7)H within **21a** showed <sup>3</sup>J<sub>6A,7</sub> = 12.0 and <sup>3</sup>J<sub>6B,7</sub> = 6.4 Hz and, similarly, **21c** showed <sup>3</sup>J<sub>6A,7</sub> = 12.3 and <sup>3</sup>J<sub>6B,7</sub> = 6.5 Hz. The large value of the coupling constant suggests a dihedral angle close to 180° and thus indicates the (7*S*,*R*<sub>a</sub>) atropisomeric form for

**21a** and **21c**. In contrast to the other two conformers, the multiplet associated with C(7)*H* within **21b** showed  $^3J_{6A,7} \approx 0$  Hz and  $^3J_{6B,7} = 6.8$  Hz. The former value reveals a dihedral angle close to  $90^\circ$  for these protons and thus indicates the (7*S*,*S*<sub>a</sub>) atropisomeric form for **21b**. These conformational assignments are further supported by data from  $^1\text{H}$  NMR NOESY analysis: both forms **21a** and **21c** have nOe signals between C(8)*H* and the NCOMe group (albeit much weaker in the former case, and stronger in the latter) whereas conformer **21b** does not exhibit such nOe enhancements at all (Fig. 6). Thus, the total population of the twist-boat C(7)-acetamido equatorial to C(7)-acetamido axial forms is represented by (**21a**+**21c**):**21b**, i.e. 76:24 or approximately 3:1, consistent with the expected steric preference of this form.

(7*S*,*R*<sub>a</sub>) form - energy minimised



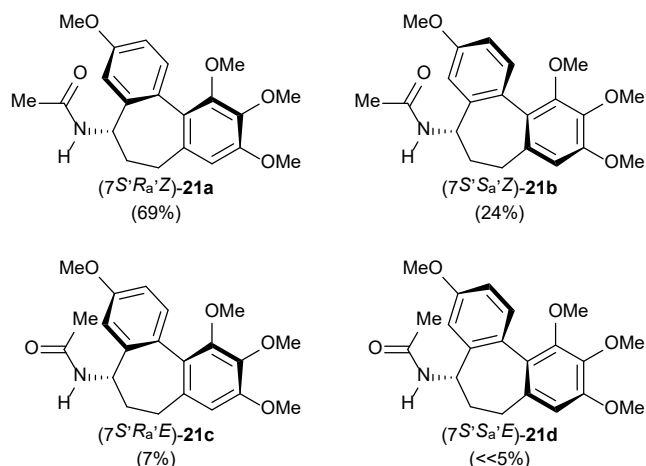
(7*S*,*S*<sub>a</sub>) form - energy minimised



**Fig. 6.** Energy minimised (7*S*,*R*<sub>a</sub>) and (7*S*,*S*<sub>a</sub>) atropisomeric forms [with the seven-membered ring viewed from C(7) along the C(7)–C(6) bond showing differences in H–C(7)–C(6)–H dihedral angles]. An nOe is observed between C(8)*H* and the NCOMe group for **21a** and **21c**, but not for **21b**. Selected atoms (including the entirety of the COMe group) are omitted for clarity.

On the basis of the above analyses, the three species present in  $\text{CDCl}_3$  solution for NCME **21** can be assigned as (7*S*,*R*<sub>a</sub>,*Z*)-**21a**, (7*S*,*S*<sub>a</sub>,*Z*)-**21b** and (7*S*,*R*<sub>a</sub>,*E*)-**21c**, arising from the hindered rotation of the biaryl axis, and the hindered rotation of the acetamide N–CO bond resulting in slow interconversion at room temperature. Whilst these two hindered rotations would lead to four theoretically possible conformers, only three conformers could be detected spectroscopically. Exchange peaks which may be attributable to the fourth form, (7*S*,*S*<sub>a</sub>,*E*)-**21d**, were observed in the EXSY although the presence of this species could not be definitively confirmed due to its low population (Fig. 7). The three conformers arising from the hindered rotation of the biaryl axis and acetamide unit suggests that the two conformers observed in the solid state

[that differ only in the conformation of the C(1) and C(2) *O*-methyl groups] are the result of crystal packing factors rather than being directly related to discrete solution-phase conformational preferences.



**Fig. 7.** The four theoretically possible rotameric/atropisomeric forms of NCME **21**, and approximate percentage populations in CDCl<sub>3</sub>.

In DMSO-*d*<sub>6</sub>, only one species was observed by <sup>1</sup>H NMR spectroscopy. A strong nOe signal was observed between NCOMe and NH, and no nOe was observed between NCOMe and C(7)H, which indicates it contains the (*Z*) amide rotamer. The <sup>1</sup>H NMR coupling constants of <sup>3</sup>*J*<sub>6,7</sub> = 12.0 and 7.8, and a strong nOe signal between the NCOMe and C(8)H units provides evidence of its (*R*<sub>a</sub>) configuration. Thus, NCME **21** exists as the (7*S*,*R*<sub>a</sub>,*Z*) form **21a** exclusively in DMSO-*d*<sub>6</sub> (also the major form in CDCl<sub>3</sub>), consistent with previous observations.<sup>21–23</sup>

### 3. Conclusion

In conclusion, a sample of enantiopure *N*-acetylcolchinol methyl ether (NCME) has been prepared from 3-methoxybenzaldehyde and its structure established unambiguously by single crystal X-ray diffraction analysis. The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data for this sample establish its congruity with other previously reported synthetic samples of this allocolchicinoid, as well as with the phantom natural product that has been dubbed suhailamine. The solution phase conformational preferences of NCME in both CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> have been investigated, with an interconverting 69:24:7 mixture of the (7*S*,*R*<sub>a</sub>,*Z*), (7*S*,*S*<sub>a</sub>,*Z*) and (7*S*,*R*<sub>a</sub>,*E*) forms being present in CDCl<sub>3</sub>, whereas the (7*S*,*R*<sub>a</sub>,*Z*) form is favoured exclusively in DMSO-*d*<sub>6</sub>.

## 4. Experimental

### 4.1. General Experimental Details

Melting points are uncorrected. Specific rotations are reported in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup> and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in

cm<sup>-1</sup>. NMR spectra were recorded in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub>, as stated. Reference frequencies employed were: CHCl<sub>3</sub>,  $\delta_{\text{H}}$  = 7.26; CDCl<sub>3</sub>,  $\delta_{\text{C}}$  = 77.16; CD<sub>3</sub>S(O)CD<sub>2</sub>H,  $\delta_{\text{H}}$  = 2.50; (CD<sub>3</sub>)<sub>2</sub>SO,  $\delta_{\text{C}}$  = 39.52.<sup>26,27</sup> <sup>1</sup>H-<sup>1</sup>H COSY and <sup>1</sup>H-<sup>13</sup>C HSQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine. Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and allowed to cool under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.<sup>57</sup> Organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> or MgSO<sub>4</sub>. Flash column chromatography was performed on Kieselgel 60 silica.

#### 4.2. *N*-Methoxy-*N*-methyl triphenylphosphoranylideneacetamide **9**.

Bromoacetyl bromide (23.0 mL, 114 mmol) was added dropwise to a stirred solution of K<sub>2</sub>CO<sub>3</sub> (120 g, 871 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (17.0 g, 174 mmol) in MeCN (400 mL) at rt and the resultant suspension was stirred at rt for 1 h then concentrated in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and H<sub>2</sub>O (300 mL) and the organic layer was dried and concentrated in vacuo. The residue was dissolved in EtOAc (300 mL), PPh<sub>3</sub> (26.2 g, 100 mmol) was added and the resultant solution was stirred at rt for 16 h, during which time a precipitate formed. The precipitate was collected by suction filtration and the filter cake was washed with Et<sub>2</sub>O (150 mL). The solid residue was then partitioned between CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and 2.0 M aq NaOH (160 mL) and the organic layer was dried and concentrated in vacuo to give **9** as a pale yellow solid (33.6 g, 92%);<sup>5</sup>  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 3.08 (3H, s, *NMe*), 3.53 (1H, s, *CH*), 3.73 (3H, s, *NOMe*), 7.41–7.71 (15H, m, *Ph*).

#### 4.3. *N*-Methoxy-*N*-methyl (*E*)-3-(3'-methoxyphenyl)propenamide **10**.

3-Methoxybenzaldehyde **8** (3.58 mL, 29.4 mmol) was added to a stirred solution of **9** (11.0 g, 30.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 3:2) gave **10** as a colourless oil (5.94 g, 91%, >95:5 dr [(*E*):(*Z*) ratio]);<sup>32,33</sup>  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 3.31 (3H, s, *NMe*), 3.76 (3H, s, C(3')*OMe*), 3.84 (3H, s, *NOMe*), 6.91 (1H, dd, *J* 8.2, 2.5, C(4')*H*), 7.01 (1H, d, *J* 15.8, C(2)*H*), 7.08 (1H, s, C(2')*H*), 7.17 (1H, d, *J* 7.9, C(6')*H*), 7.30 (1H, app t, *J* 7.9, C(5')*H*), 7.70 (1H, d, *J* 15.8, C(3)*H*).

#### 4.4. *N*-Methoxy-*N*-methyl (3*S*, $\alpha$ *R*)-3-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-3-(3'-methoxyphenyl)propanamide 11.

*n*-BuLi (2.5 M in hexanes, 16.5 mL, 41.3 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amine (>98% ee, 8.92 mL, 42.7 mmol) in THF (90 mL) at  $-78^{\circ}\text{C}$ . The resultant solution was stirred at  $-78^{\circ}\text{C}$  for 30 min, then a solution of **10** (5.90 g, 26.7 mmol, >95:5 dr [(*E*):(*Z*) ratio]) in THF (80 mL) at  $-78^{\circ}\text{C}$  was added dropwise *via* cannula. The resultant solution was stirred at  $-78^{\circ}\text{C}$  for 2 h, then satd aq  $\text{NH}_4\text{Cl}$  (40 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  (50 mL) and 10% aq citric acid (50 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL) and the combined organic extracts were washed sequentially with satd aq  $\text{NaHCO}_3$  (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent  $30\text{--}40^{\circ}\text{C}$  petroleum ether/EtOAc, 8:1 $\rightarrow$ 2:1) gave **11** as a yellow oil (10.8 g, 94%, >95:5 dr);  $[\alpha]_{\text{D}}^{25} +3.2$  (*c* 1.0 in  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  1656;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 1.33 (3H, d, *J* 5.8, C( $\alpha$ )Me), 2.53 (1H, dd, *J* 15.8, 3.7, C(2)*H*<sub>A</sub>), 2.85–2.89 (1H, m, C(2)*H*<sub>B</sub>), 3.01 (3H, s, NMe), 3.35 (3H, s, C(3')OMe), 3.77 (2H, app s, NCH<sub>2</sub>Ph), 3.83 (3H, s, NOME), 4.04 (1H, q, *J* 5.8, C( $\alpha$ )H), 4.59 (1H, dd, *J* 9.6, 3.7, C(3)H), 6.78 (1H, dd, *J* 8.1, 2.8, C(4')H), 7.01–7.04 (2H, m, C(2')H, C(6')H), 7.15–7.48 (11H, m, C(5')H, Ph);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 15.8 (C( $\alpha$ )Me), 32.0 (NMe), 34.8 (C(2)), 51.0 (NCH<sub>2</sub>Ph), 55.3 (NOME), 57.0 (C( $\alpha$ )), 58.9 (C(3)), 61.0 (C(3')OMe), 112.3 (C(4')), 114.2 (C(2')), 120.6 (C(6')), 126.6, 126.8 (*p*-Ph), 128.0, 128.1, 128.2, 128.2 (*o,m*-Ph), 129.2 (C(5')), 142.1, 144.4, 144.6 (C(1'), *i*-Ph), 159.6 (C(3')), 172.6 (C(1)); *m/z* (ESI<sup>+</sup>) 455 ([M+Na]<sup>+</sup>, 30%), 329 ([M-C<sub>8</sub>H<sub>8</sub>]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>27</sub>H<sub>33</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 433.2486; found 433.2489.

#### 4.5. *N*-Methoxy-*N*-methyl (*S*)-3-acetamido-3-(3'-methoxyphenyl)propanamide 13.

*Step 1.* A stirred solution of **11** (1.03 g, 2.37 mmol, >95:5 dr) in MeOH (11 mL) was purged with nitrogen for 10 min. After this time, Pd(OH)<sub>2</sub>/C (515 mg, 50% w/w) was added, and the resultant suspension was purged for a further 5 min before being placed under H<sub>2</sub> (5 atm) and stirred at rt for 48 h. After this time, the suspension was filtered through Celite (eluent MeOH, 250 mL) and the filtrate was concentrated *in vacuo* to give **12** as a yellow oil (688 mg);  $[\alpha]_{\text{D}}^{25} -27.6$  (*c* 1.0 in  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  3368, 1650;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 2.74 (2H, app s, C(2)*H*<sub>2</sub>), 3.19 (3H, s, NMe), 3.63 (3H, s, NOME), 3.82 (3H, s, C(3')OMe), 4.47 (1H, dd, *J* 8.0, 5.3, C(3)H), 6.81 (1H, ddd, *J* 8.2, 2.6, 1.1, C(4')H), 6.95–7.02 (2H, m, C(2')H, C(6')H), 7.26 (1H, t, *J* 8.2, C(5')H);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 32.2 (NMe), 41.9 (C(2)), 52.3 (C(3)), 55.4 (C(3')OMe), 61.3 (NOME), 112.0 (C(2')), 112.8 (C(4')), 118.8 (C(6')), 129.7 (C(5')), 147.1 (C(1')), 159.9 (C(3')), 172.9 (C(1)); HRMS (ESI<sup>+</sup>) C<sub>12</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 239.1390; found 239.1389.

*Step 2.* Ac<sub>2</sub>O (0.78 mL, 8.2 mmol) was added to a stirred solution of the residue of **12** from the previous step (688 mg) in pyridine (1.6 mL) at 0 °C. The resultant solution was allowed to warm to rt, then stirred at rt for 16 h. 1.0 M aq. HCl (20 mL) was then added and the resultant solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic extracts were washed sequentially with satd aq NaHCO<sub>3</sub> (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl<sub>3</sub>/MeOH, 80:1→40:1) gave **13** as a yellow solid (606 mg, 75% from **11**); mp 93–95 °C;  $[\alpha]_{\text{D}}^{25}$  –35.0 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3349, 1669, 1631;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 2.03 (3H, s, NCOMe), 2.08 (1H, dd, *J* 15.5, 5.4, C(2)*H*<sub>A</sub>), 3.11 (3H, s, NMe), 3.15 (1H, dd, *J* 15.5, 5.4, C(2)*H*<sub>B</sub>), 3.50 (3H, s, NOME), 3.78 (3H, s, C(3')OMe), 5.39 (1H, app dt, *J* 8.4, 5.4, C(3)*H*), 6.77 (1H, ddd, *J* 8.0, 2.6, 0.8, C(4')*H*), 6.85 (1H, app t, *J* 2.1, C(2')*H*), 6.89 (1H, ddd, *J* 8.0, 1.7, 0.8, C(6')*H*), 7.22 (1H, app t, *J* 8.0, C(5')*H*), 7.32 (1H, d, *J* 8.4, NH);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.6 (NCOMe), 32.0 (NMe), 36.8 (C(2)), 49.8 (C(3)), 55.3 (C(3')OMe), 61.4 (NOME), 112.4 (C(2')), 112.6 (C(4')), 118.6 (C(6')), 129.7 (C(5')), 143.2 (C(1')), 159.9 (C(3')), 169.5 (NCOMe), 172.1 (C(1)); *m/z* (ESI<sup>+</sup>) 303 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 281.1496; found 281.1496.

#### 4.6. (*S*)-3-Acetamido-3-(3'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)propan-1-one **17**.

A solution of **14** (3.12 g, 12.6 mmol) in THF (6.0 mL) was added dropwise to a stirred suspension of Mg turnings (307 mg, 12.6 mmol) and an iodine bead in THF (1.0 mL) at rt under nitrogen. The reaction was heated at 50 °C and a catalytic amount of MeI was added. Upon a colour change, the heating was removed and the resultant mixture was allowed to cool to rt and stirred for 1 h. A solution of **13** (442 mg, 1.58 mmol) in THF (3.5 mL) was then added dropwise and the resultant mixture was stirred at rt for 16 h. Satd aq NH<sub>4</sub>Cl was added (6.0 mL) and the resultant mixture was partitioned between EtOAc (50 mL) and H<sub>2</sub>O (50 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl<sub>3</sub>/MeOH 100:1→60:1) gave **17** as a yellow oil (653 mg, quant);  $[\alpha]_{\text{D}}^{25}$  –6.0 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3293, 1674, 1652;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 2.04 (3H, s, NCOMe), 3.34 (1H, dd, *J* 16.1, 6.8, C(2)*H*<sub>A</sub>), 3.75 (1H, dd, *J* 16.1, 4.6, C(2)*H*<sub>B</sub>), 3.77 (3H, s, C(3')OMe), 3.89 (6H, s, C(3'')OMe, C(5'')OMe), 3.91 (3H, s, C(4'')OMe), 5.50 (1H, app td, *J* 6.8, 4.6, C(3)*H*), 6.58 (1H, d, *J* 8.0, NH), 6.78 (1H, dd, *J* 7.9, 2.6, C(6')*H*), 6.86 (1H, app t, *J* 2.2, C(2')*H*), 6.90 (1H, app d, *J* 7.9, C(4')*H*), 7.17 (2H, s, C(2'')*H*, C(6'')*H*), 7.23 (1H, app t, *J* 7.9, C(5')*H*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.6 (NCOMe), 43.3 (C(2)), 50.6 (C(3)), 55.4 (C(3')OMe), 56.5 (C(3'')OMe, C(5'')OMe), 61.1 (C(4'')OMe), 105.9 (C(2''), C(6'')), 112.7 (C(6')), 113.0 (C(2')), 118.8 (C(4')), 129.9 (C(5')), 131.9 (C(1'), C(1'')), 142.5 (C(4'')), 153.2 (C(3''), C(5'')), 160.0 ((C(3')),

169.7 (NCOMe), 197.4 (C(1));  $m/z$  (ESI<sup>+</sup>) 410 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>21</sub>H<sub>26</sub>NO<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 388.1755; found 388.1750.

**4.7. (1R\*,3S)-3-Acetamido-3-(3'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)propan-1-ol 18 and (1S\*,3S)-3-acetamido-3-(3'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)propan-1-ol 19.**

NaBH<sub>4</sub> (989 mg, 7.18 mmol) was added a stirred solution of **17** (2.78 g, 7.18 mmol) in MeOH (190 mL) at 0 °C and the resultant suspension was stirred at 0 °C for 3 h. The resultant mixture was then allowed to warm to rt and partitioned between satd aq NaHCO<sub>3</sub> (150 mL) and CH<sub>2</sub>Cl<sub>2</sub> (150 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The combined organics were washed with brine (250 mL), dried, and concentrated *in vacuo*. Filtration through a plug of silica gel (eluent CHCl<sub>3</sub>/MeOH, 40:1) gave an ~50:50 mixture of **18** and **19** as a yellow oil (2.69 g, 96%). Purification of an aliquot *via* flash column chromatography (eluent CHCl<sub>3</sub>/MeOH, 80:1→40:1) gave **18** (>95:5 dr) as a colourless oil and **19** (>95:5 dr) as a colourless oil.

Data for **18**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -133 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\max}$  3287, 1647;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 2.07 (3H, s, NCOMe), 2.01–2.17 (2H, m, C(2)H<sub>2</sub>), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.84 (6H, s, C(3'')OMe, C(5'')OMe), 4.28 (1H, d, *J* 3.5, OH), 4.60 (1H, dt, *J* 10.2, 3.5, C(1)H), 5.26 (1H, ddd, *J* 9.7, 8.3, 3.7, C(3)H), 6.26 (1H, d, *J* 8.3, NH), 6.56 (2H, s, C(2'')H, C(6'')H), 6.83 (1H, ddd, *J* 7.9, 2.6, 0.8, C(4')H), 6.85 (1H, app t, *J* 2.1, C(2')H), 6.90 (1H, ddd, *J* 7.9, 1.5, 0.8, C(6')H), 7.27 (1H, app t, *J* 7.9, C(5')H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.5 (NCOMe), 46.0 (C(2)), 51.4 (C(3)), 55.4, 56.2 (C(3')OMe, C(4'')OMe), 60.9 (C(3'')OMe, C(5'')OMe), 70.7 (C(1)), 102.9 (C(2''), C(6'')), 113.0 (C(2'), C(4')), 118.9 (C(6')), 130.2 (C(5')), 137.2 (C(1'')), 139.7 (C(1')), 142.8 (C(4'')), 153.4 (C(3''), C(5'')), 160.1 ((C(3')), 171.0 (NCOMe);  $m/z$  (ESI<sup>+</sup>) 412 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>21</sub>H<sub>27</sub>NNaO<sub>6</sub><sup>+</sup> ([M+Na]<sup>+</sup>) requires 412.1731; found 412.1728.

Data for **19**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -29.8 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\max}$  3294, 1650;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.95 (3H, s, NCOMe), 2.11 (1H, ddd, *J* 14.2, 6.2, 4.2, C(2)H<sub>A</sub>), 2.29 (1H, app dt, *J* 14.2, 8.4, C(2)H<sub>B</sub>), 2.94 (1H, s, OH), 3.79 (3H, s, OMe), 3.81 (6H, s, C(3'')OMe, C(5'')OMe), 3.83 (6H, s, OMe), 4.61 (1H, dd, *J* 8.4, 4.2, C(1)H), 5.11 (1H, app td, *J* 7.7, 6.2, C(3)H), 6.11 (1H, d, *J* 7.7, NH), 6.55 (2H, s, C(2'')H, C(6'')H), 6.81 (1H, ddd, *J* 8.2, 2.4, 1.1, C(4')H), 6.84 (1H, app t, *J* 2.4, C(2')H), 6.89 (1H, app dt, *J* 7.6, 1.1, C(6')H), 7.26 (1H, app t, *J* 8.2, 7.6, C(5')H);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.6 (NCOMe), 45.9 (C(2)), 52.3 (C(3)), 55.4, 56.3 (C(3')OMe, C(4'')OMe), 60.9 (C(3'')OMe, C(5'')OMe), 72.7 (C(1)), 102.7 (C(2''), C(6'')), 112.8, 112.9 (C(2'), C(4')), 118.9 (C(6')), 130.1 (C(5')), 137.3 (C(1'')), 140.4 (C(1')), 143.8 (C(4'')), 153.4 (C(3''), C(5'')), 160.0 ((C(3')), 169.9 (NCOMe);  $m/z$  (ESI<sup>+</sup>) 412 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>21</sub>H<sub>27</sub>NNaO<sub>6</sub><sup>+</sup> ([M+Na]<sup>+</sup>) requires 412.1731; found 412.1729.



#### 4.8. (S)-3-Acetamido-3-(3'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)propane **20**.

A stirred solution of **18** and **19** (~50:50 dr, 100 mg, 0.257 mmol) in MeOH (2.2 mL) was purged with nitrogen for 10 min. Pd(OH)<sub>2</sub>/C (50 mg, 50% w/w) was then added, and the resultant suspension was purged for a further 5 min before being placed under H<sub>2</sub> (5 atm) and stirred at rt for 48 h. After this time, the suspension was filtered through Celite<sup>®</sup> (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **20** as a yellow oil (87 mg, 91%);  $[\alpha]_{\text{D}}^{25}$  -44.9 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  3291, 1647;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.97 (3H, s, NCOMe), 2.06 (1H, app ddt, *J* 13.9, 9.4, 6.6, C(2)*H*<sub>A</sub>), 2.18 (1H, app ddt, *J* 13.9, 9.1, 6.9, C(2)*H*<sub>B</sub>), 2.47–2.62 (2H, m, C(1)*H*<sub>2</sub>), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.83 (6H, s, C(3'')OMe, C(5'')OMe), 5.00 (1H, app q, *J* 7.6, C(3)*H*), 5.68 (1H, d, *J* 7.0, NH), 6.36 (2H, s, C(2'')*H*, C(6'')*H*), 6.82 (1H, dd, *J* 6.2, 2.5, C(4')*H*), 6.83 (1H, app s, C(2')*H*), 6.88 (1H, app dt, *J* 7.5, 1.2, C(6')*H*), 7.27–7.30 (1H, m, C(5')*H*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 23.7 (NCOMe), 33.1 (C(1)), 37.6 (C(2)), 53.4 (C(3)), 55.4 (OMe), 56.2 (C(3'')OMe, C(5'')OMe), 61.0 (OMe), 105.4 (C(2''), C(6'')), 112.7, 113.0 (C(2'), C(4')), 119.0 (C(6')), 130.0 (C(5')), 136.3, 137.2 (C(1'), C(1'')), 143.6 (C(4'')), 153.3 (C(3''), C(5'')), 160.1 ((C(3')), 169.3 (NCOMe); *m/z* (ESI<sup>+</sup>) 396 ([M+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>21</sub>H<sub>28</sub>NO<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 374.1962; found 374.1956.

#### 4.9. (7S)-1,2,3,9-Tetramethoxy-7-acetamido-6,7-dihydro-5H-dibenzo[*a,c*][7]annulene [*N*-acetylcolchicol methyl ether, NCME] **21**.

TFA (18.0 mL) and TFAA (4.40 mL, 31.9 mmol) were added to a stirred solution of PIFA (967 mg, 2.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The resultant solution was cooled to -4 °C and a solution of **20** (700 mg, 1.87 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) then immediately BF<sub>3</sub>·OEt<sub>2</sub> (0.6 mL, 4.5 mmol) were added and the resultant solution was warmed to rt and stirred at rt for 5 h. The resultant mixture was quenched with satd aq NaHCO<sub>3</sub> (100 mL) at 0 °C, then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL) and the combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl<sub>3</sub>/MeOH 100:1) then recrystallization (CHCl<sub>3</sub>/heptane) gave **21** as a white solid (210 mg, 30%); mp 205–206 °C;  $[\alpha]_{\text{D}}^{25}$  -66.6 (*c* 0.5 in CHCl<sub>3</sub>);  $[\alpha]_{\text{D}}^{25}$  -76.5 (*c* 0.13 in MeOH);  $\nu_{\text{max}}$  3290, 1646;  $\delta_{\text{H}}$  (400 MHz, DMSO-*d*<sub>6</sub>) 1.82 (1H, app dd, *J* 12.0, 6.9, C(6)*H*<sub>A</sub>), 1.86 (3H, s, NCOMe), 1.97–2.19 (2H, m, C(6)*H*<sub>B</sub>, C(5)*H*<sub>A</sub>), 2.46 (1H, app d, *J* 5.6, C(5)*H*<sub>B</sub>), 3.45 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 4.50 (1H, app dt, *J* 12.0, 7.8, C(7)*H*), 6.75 (1H, s, C(4)*H*), 6.86 (1H, dd, *J* 8.3, 2.7, C(10)*H*), 6.89 (1H, d, *J* 2.7, C(8)*H*), 7.23 (1H, d, *J* 8.3, C(11)*H*), 8.36 (1H, d, *J* 8.6, NH);  $\delta_{\text{C}}$  (400 MHz, DMSO-*d*<sub>6</sub>) 22.9 (NCOMe), 30.4 (C(5)), 38.7 (C(6)), 48.5 (C(7)), 55.3 (C(9)OMe), 56.1 (C(3)OMe), 60.8, 60.9 (C(1)OMe, C(2)OMe), 108.4 (C(4)), 109.7 (C(8)), 111.1 (C(10)), 124.5 (C(11b)), 126.4 (C(11a)), 130.9

(C(11)), 135.1 (C(4a)), 140.8 (C(7a)), 142.0 (C(2)), 150.6 (C(1)), 152.4 (C(3)), 158.7 (C(9)), 169.2 (NCOMe);  $m/z$  (EI<sup>+</sup>) 371 ([M]<sup>+</sup>, 100%), 312 (25%);  $m/z$  (ESI<sup>+</sup>) 394 ([M+Na]<sup>+</sup>, 77%), 372 ([M+H]<sup>+</sup>, 18%), 313 (100%), 282 (22%); HRMS (ESI<sup>+</sup>) C<sub>21</sub>H<sub>26</sub>NO<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 372.1805; found 372.1799.

<sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analyses using CDCl<sub>3</sub> as the solvent revealed three conformers, **21a:21b:21c** (in the ratio 69:24:7, respectively, observed in the <sup>1</sup>H NMR spectrum). Data for **21a**:  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.74–1.88 (1H, m, C(6)H<sub>A</sub>), 2.04 (3H, s, NCOMe), 2.28–2.39 (1H, m, C(5)H<sub>A</sub>), 2.34–2.43 (1H, m, C(6)H<sub>B</sub>), 2.40–2.48 (1H, m, C(5)H<sub>B</sub>), 3.51 (3H, s, C(1)OMe), 3.85 (3H, s, C(9)OMe), 3.89 (3H, s, C(3)OMe), 3.92 (3H, s, C(2)OMe), 4.80 (1H, ddd,  $J$  14.4, 7.4, 4.2, C(7)H), 5.82 (1H, d,  $J$  7.4, NH), 6.56 (1H, s, C(4)H), 6.82 (1H, d,  $J$  2.7, C(8)H), 6.85 (1H, dd,  $J$  7.9, 2.7, C(10)H), 7.42 (1H, d,  $J$  7.9, C(11)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 23.5 (NCOMe), 30.7 (C(5)), 39.7 (C(6)), 49.4 (C(7)), 55.4 (C(9)OMe), 56.3 (C(3)OMe), 61.1 (C(1)OMe), 61.4 (C(2)OMe), 107.8 (C(4)), 109.3 (C(8)), 110.7 (C(10)), 125.0 (C(11b)), 126.9 (C(11a)), 131.5 (C(11)), 134.8 (C(4a)), 140.8 (C(7a)), 141.5 (C(2)), 151.4 (C(1)), 152.5 (C(3)), 159.0 (C(9)), 169.2 (NCOMe).

Data for **21b**:  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.58 (3H, s, NCOMe), 2.08–2.21 (2H, m, C(5)H<sub>2</sub>), 2.47–2.61 (2H, m, C(6)H<sub>2</sub>), 3.58 (3H, s, C(1)OMe), 3.85 (3H, s, C(9)OMe), 3.89 (3H, s, C(3)OMe), 3.92 (3H, s, C(2)OMe), 5.10 (1H, app dd,  $J$  8.9, 7.2, C(7)H), 5.29 (1H, d,  $J$  8.9, NH), 6.65 (1H, s, C(4)H), 6.88–6.92 (2H, m, C(8)H, C(10)H), 7.42 (1H, d,  $J$  7.9, C(11)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 23.5 (NCOMe), 31.0 (C(5)), 40.9 (C(6)), 52.9 (C(7)), 55.4 (C(9)OMe), 56.2 (C(3)OMe), 60.6 (C(1)OMe), 61.4 (C(2)OMe), 108.1 (C(4)), 113.0 (C(8)), 114.4 (C(10)), 125.9 (C(11b)), 126.5 (C(11a)), 132.6 (C(11)), 136.0 (C(4a)), 140.7 (C(7a)), 141.6 (C(2)), 151.1 (C(1)), 152.8 (C(3)), 158.8 (C(9)), 168.1 (NCOMe).

Data for **21c**:  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 1.69 (3H, s, NCOMe), 1.80–2.60 (4H, m, C(5)H<sub>2</sub>, C(6)H<sub>2</sub>), 3.54 (3H, s, C(1)OMe), 3.85 (3H, s, C(9)OMe), 3.89 (3H, s, C(3)OMe), 3.92 (3H, s, C(2)OMe), 4.30 (1H, ddd,  $J$  12.1, 7.7, 6.9, C(7)H), 5.70 (1H, d,  $J$  7.7, NH), 6.60 (1H, s, C(4)H), 6.96 (1H, d,  $J$  2.6, C(8)H), 6.88–6.93 (1H, m, C(10)H), 7.44 (1H, d,  $J$  10.5, C(11)H);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 20.6 (NCOMe), 30.6 (C(5)), 40.4 (C(6)), 53.5 (C(7)), 55.4 (C(9)OMe), 56.2 (C(3)OMe), 60.5 (C(1)OMe), 61.2 (C(2)OMe), 107.8 (C(4)), 108.8 (C(8)), 112.4 (C(10)), 125.3 (C(11b)), 126.3 (C(11a)), 131.7 (C(11)), 134.8 (C(4a)), 140.5 (C(7a)), 141.7 (C(2)), 151.1 (C(1)), 152.7 (C(3)), 159.4 (C(9)), 173.2 (NCOMe).

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