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COMMENT

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Comment on Enantioselective total synthesis of (−)-colchicine, (+)-demecolcinone and metacolchicine: determination of the absolute configurations of the latter two alkaloids by B. Chen, X. Liu, Y.-J. Hu, D.-M. Zhang, L. Deng, J. Lu, L. Min, W.-C. Ye and C.-C. Li, *Chem. Sci.*, 2017, 8, 4961–4966

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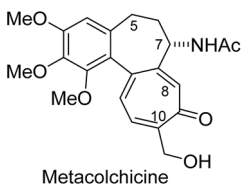
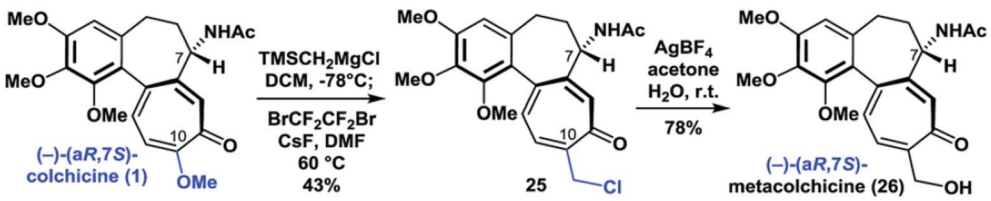
We note that some features of the NMR spectra deposited for the purported isomeric metacolchicines (*Chem. Sci.* **8**, 4961 (2017)) are not compatible with the assignment of those isomers as being atrop-diastereomers. We suggest that there are no such isomeric metacolchicines as reported. The differences in the spectra could rather be a consequence of a (precedented) monomer/dimer equilibrium of metacolchicine in solution.

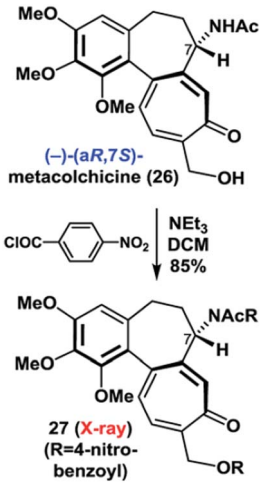
Metacolchicine has been isolated and characterized in 2011.[1] Its structure assignment rests on ^{1}H and ^{13}C NMR spectra including ^{1}H–^{1}H-COSY, HMBC und NOE investigations. The authors fully assigned the spectra.



Recently approaches to the synthesis of metacolchicine were published by Li.[2] The Li group used a complex reaction sequence to arrive at compound **26** which did not fully match the data reported for metacolchicine.

This non-identity apparently was reason to prepare the bis-4-nitrobenzoate of **26** in order to subject it to X-ray crystallographic analysis. This revealed that compound **26** possesses the structure assigned to metacolchicine.





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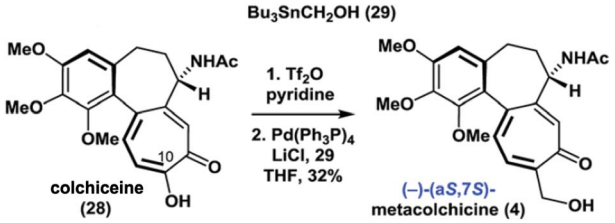
In the course of their efforts to synthesize metacolchicine the Li group explored a second route originating from colchiceine which furnished compound **4**. The spectral data of the latter were claimed to be identical to those of natural metacolchicine.[3]



These findings suggested that there are two different compounds with the constitution of metacolchicine. Li and his coauthors address these, more or less by default, as being stereoisomers, *i.e.* atrop-diastereomers, **26** = (a**R**,7S) and **4** = (a**S**,7S). Unfortunately they did not provide any evidence (such as CD-spectra *cf.*[4]) for this interpretation.

This interpretation appears daring, as the rotational barrier at the axis of colchicine and colchicine-derivatives (which should include metacolchicine) is $\leq$90 kJ mol^{-1} (ref. 5) rendering atrop-diastereomers short-lived. Unfortunately Li and coworkers do not report information on any thermal interconversion of **26** and **4**. Atrop-diastereomers can be isolated and studied, though, in the case of iso-colchicine-derivatives.[4]

In the search for features which are characteristic of individual atropisomers we noted the ^{1}H NMR signal position of H-7 in the isocolchicines:[4,6] In the (a**R**,7S)-isomer it appears at 4.6 ppm, whereas in the (a**S**,7S)-isomers it resonates at $\geq$5.0 ppm. This difference is caused by the position of H-7 over the aromatic ring in the (a**R**,7S)-isomer, whereas after rotation at the axis and concomitant inversion of the cycloheptane ring H-7 enjoys a position remote from the aromatic ring in the (a**S**,7S)-isomers. This should apply as well to colchicine-derivatives, where the same conformation-based determining factors prevail. Li and coworkers report that the signal of H-7 resonates in both compound **26** and **4** at 4.6 ppm. Hence, both compounds belong to the same (a**R**,7S)-family. This finding then renders the thesis that **26** and **4** are atrop-diastereomers untenable.

By the same token, the claim[2] that colchiceine would exist in solution as the (a**S**,7S)-atropisomer is contrasted by the chemical shift of H-7 in colchiceine which resonates at δ = 4.7 ppm.

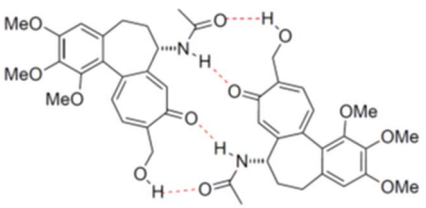
When the two isomeric metacolchicines are not atrop-diastereomers, what else are they? Any consideration along these lines has to start from the differences in the NMR spectra, which are summarized in Table 1:

Table 1 Differences in the ^{13}C- and ^{1}H NMR spectra of compounds **26** and **4**

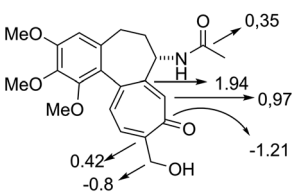
Atom	**26**	**4**	$\Delta\delta$ (ppm)
^{13}C NMR			
C-7a	153.68	151.74	1.94
C-8	135.36	134.39	0.97
C-9	185.68	186.89	−1.21
C-10	150.95	150.53	0.42
C-11	134.22	134.39	−0.17
CH_3CO	170.00	169.65	0.35
^{1}H NMR			
H-6α	1.92	1.8	0.12
H-8	7.35	6.88	0.47

The pattern of the ^{13}C NMR differences turned out to be not compatible with the assumption, that compound **4** might be an iso-colchicine type compound, that could arise by the synthetic route employed to generate **4** (Nor was this pattern in line with the differences displayed by atrop-diasteromeric iso-colchicide derivatives[7]).

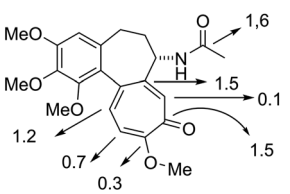
In view of the fact that the spectral differences between **26** and **4** are rather small, we found ourselves eventually confronted with the question: are they real? Could it be that the small differences in the NMR spectra are simply caused by solvent or concentration effects? This appeared the more probable, given the solvent and concentration effects reported for the ^{1}H- and ^{13}C NMR spectra of colchicine.[8] These effects are due to a monomer/hydrogen-bonded dimer equilibrium. This dimer formation should be even more facile in the case of metacolchicine, due to two additional hydrogen bonds:



Looking at the ^{13}C NMR spectra, we compared the differences recorded for **26** *vs.* **4** with the differences reported for colchicine in $CDCl_3$ (high dimer content) and DMSO-D_6 (low dimer content).



Differences in the ^{13}C-NMR signal positions between **26** and **4** (ppm)



Differences in the ^{13}C-NMR signal positions of colchicine in $CDCl_3$ and DMSO-D_6 (ppm)

It is remarkable that essentially the same atoms on the eastern side of the molecule are involved in these differences. Moreover, the (small) magnitude of the effects is very similar. Encouraged by these coincidences we examined the ^{1}H NMR spectra. In the case of **26** and **4** we noted that the signals of H-8 and H-6α are broadened compared to the other signals. This points to the involvement of H-8 and H-6α in some dynamic process. In the colchicine case[8] it is exactly the signals of H-8 and H-6α that show a conspicuous concentration dependence of their chemical shifts. These signals are the only ones in the ^{1}H NMR spectra of **26** and **4** that display recognizable differences in chemical shift, *cf*. also,[3] the direction of which points to the solution of **26** being the more highly concentrated one (the latter fact is substantiated by looking at the relative size of the solvent peak in the spectra).

We therefore conclude that a concentration-dependent monomer/dimer equilibrium of metacolchicine could explain the differences recorded for the samples **4** and **26**. This explanation would obviate the postulate that **4** and **26** represent stable atrop-diastereomers, a postulate which appears not to be tenable (see above). We should nevertheless stress, that the hypothesis of the monomer/dimer equilibrium of metacolchicine, while plausible, still lacks experimental proof which we cannot provide without authentic samples.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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3 According to the spectra deposited in the ESI[2] this holds for the ^{13}C NMR data, whereas in the ^{1}H NMR spectrum the signal of H-8 is off by 0.42 ppm.
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