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Efficient Preparation of [2-^{13}C]- and [3-^{13}C]-3-Cyano-4-methyl-3-pyrrolin-2-one

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[2-^{13}C]- and [3-^{13}C]-3-cyano-4-methyl-3-pyrrolin-2-one have been prepared by a new synthetic route. α,α-Dimethoxy ketones react with bifunctional molecules in an extended Knoevenagel reaction. The products of this reaction are converted in a few steps and in high yields into the biologically important 3-pyrrolin-2-ones. This new approach also allows simple stable isotope incorporation at many sites of the ring system.

Introduction

Plants detect the quality of the light in their environment using chromoproteins called phytochromes.[1,2] Phytochromes exist in two forms known as Pr (phytochrome red, λ_{max} = 665 nm) and Pfr (phytochrome far-red, λ_{max} = 730 nm). Phytochrome is a water-soluble biliprotein of 124 KDa.[3] The chromophore is phytochromobilin.[4] Its structure, numbering and linkage to the apoprotein are given in Figure 1.

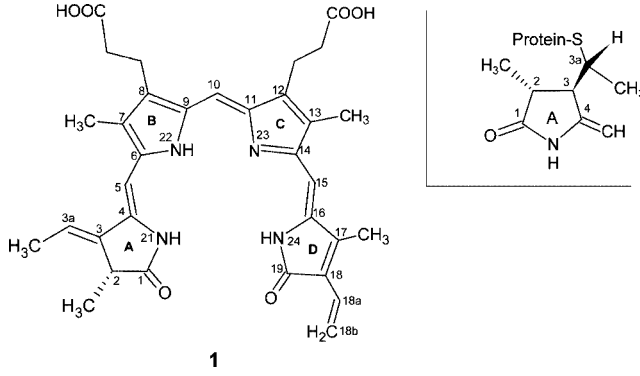

Figure 1. Structure and numbering of (2*R*)-phytochromobilin. In the Pr and Pfr forms it is linked through a thioether bond at C-3a attached to ring A, leading to the structure depicted in the insert. In the Pr form, the chromophore has the (15*Z*) structure, as indicated in this Figure, whereas the Pfr form has the (15*E*) structure.

Pr and Pfr are interconvertible in the presence of light. The two forms differ in the configuration at the 15–16 double bond of the chromophore: the Pr form has a (*Z*) configuration, as depicted in Figure 1, whereas Pfr has a (15*E*) configuration.[5] The λ_{max} value of Pr and Pfr differ; as a result of these differences, the spectral composition of light in the red and the far-red regions is translated into differences in the photostationary states of Pr and Pfr in this spectral region. Pr and Pfr are the messengers that trigger the biological action in living plants that forms the basis of photomorphogenesis, such as seed germination, switching between vegetative growth or reproductive development, induction of flowering and senescence.

In view of the importance of the photochemistry of phytochromes in the development of plants and of photomorphogenesis in agriculture, knowledge of the structural and functional role of Pr and its photoproducts at the atomic level without perturbation of the chromophores is essential. To obtain this type of information we will study Pr and its photoproducts with site-directed stable isotope incorporation (^{2}H, ^{13}C, ^{15}N) in the chromophore using isotope-sensitive noninvasive techniques such as resonance Raman spectroscopy, FTIR difference spectroscopy and ^{13}C and ^{15}N NMR spectroscopy. This approach has been used by us in collaboration with others earlier to study rhodopsin photochemistry[6] and to identify the atomic interactions that lead to the colour of α-crustacyanin, the blue pigment of lobster carapaces.[7]

In this paper we will describe the preparation of 3-cyano-4-methyl-3-pyrrolin-2-one isotopically labelled at positions 2 and 3 (see Scheme 1). This system is the basis of ring D of phytochromobilin. We started with ring D because the (15*Z*) and (15*E*) bonds in Pr and Pfr and their photoproducts link ring D directly to the rest of the chromophore. Besides the role of 3-pyrrolin-2-ones as synthons in the preparation of bile pigments they and their derivatives are of great importance owing to their wide range of biological activities. They are very useful in the field of crop protection.[8] 4-Substituted 1,5-diphenylpyrrolin-2-ones show antimicrobial and antineoplastic activities.[9] 3-Acyl-3-pyrrolin-2-ones bearing long-chain alkoxy substituents possess useful neurotogenic properties and are members of a class of chemotherapeutics used to treat neuroblastoma tu-

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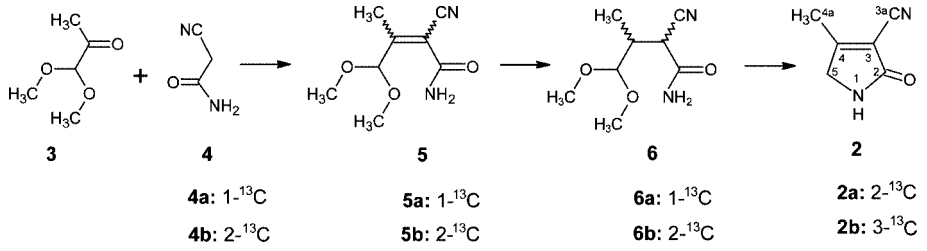


Scheme 1. The preparation of 3-cyano-4-methyl-3-pyrrolin-2-one (**2**) starting from 1,1-dimethoxyacetone (**3**) and 2-cyanoacetamide (**4**).

mours.[10] 1,3,4-Trialkyl-3-pyrrolin-2-ones act as selective and potent cyclooxygenase-2 inhibitors[11] and 5-substituted 3-pyrrolin-2-ones show selective inhibitory activity against cathepsin B.[12] Moreover 3-pyrrolin-2-ones have been employed as useful intermediates in the synthesis of (+)-lactacysytin,[13] (–)-rolipram[14] and bile pigments.[15] Recently new synthetic procedures for their preparation have gained interest in organic synthesis.[16–27] By studying these previous synthetic protocols we have concluded that none of them allows the easy preparation of 3-pyrrolin-2-ones with site-directed ^{13}C and ^{15}N incorporation at any position or combinations of positions. We have therefore derived a novel synthetic strategy (Scheme 1) that can lead to 3-cyano-4-methyl-3-pyrrolin-2-one in a few steps. This strategy was first optimized by using 1,1-dimethoxyacetone (**3**) and 2-cyanoacetamide (**4**) with natural abundance isotope incorporation. These synthons have not been prepared in a highly stable isotope-enriched form before. In this paper we describe how we have prepared [2-^{13}C]- and [3-^{13}C]-3-cyano-4-methyl-3-pyrrolin-2-one from [1-^{13}C]- and [2-^{13}C]-2-cyanoacetamide, respectively, by a simple route. We feel that this approach has a wide scope such that these biologically important 3-pyrrolin-2-ones can easily be prepared in the right stable isotopically enriched forms, such that metabolic products of these biologically important materials can be studied in fine detail, as in the cases of β-carotene and vitamin A.[28]

Results and Discussion

Scheme 1 shows how commercially available 1,1-dimethoxyacetone (**3**) and 2-cyanoacetamide (**4**) can be converted in three steps into the target pyrrolinone **2**. The conversions in Scheme 1 were first optimized through reactions with synthons in non-enriched forms. 1,1-Dimethoxyacetone (**3**) (6.20 g, 52 mmol) and 2-cyanoacetamide (**4**) (4.04 g, 50 mmol) were condensed together in toluene (250 mL) for 2 h at 130–135 °C in the presence of ammonium acetate (1.00 g) and acetic acid (5 mL) under Knoevenagel conditions.[29,30] This gave an 87% yield of 4,4-dimethoxy-3-methyl-2-cyanobut-2-enamide (**5**) as a (*Z*,*E*) mixture. We call this as an extended Knoevenagel reaction because as far as we know in all Knoevenagel reactions reported thus far only ketones or aldehydes without a protected carbonyl function directly attached to the free reactive carbonyl function have been used. This extended Knoevenagel reaction has a protected carbonyl moiety linked directly to the reactive free carbonyl function that is involved in forming the double bond with another substrate to form the condensed product.

The starting material **3** and product **5**, respectively, survive the acidic reaction conditions. This may be related to the fact that owing to the presence of a carbonyl in **3** and a double bond with two electron-accepting groups in the product **5**, which induce sufficient stability towards acids of the acetal function in **3** and **5** under the reaction conditions, the protection survives intact. This unexpected stability towards acidic conditions allows the Knoevenagel reaction to be extended to ketones and aldehydes with an adjacent protected carbonyl function.

The double bond in product **5** can be easily reduced by sodium borohydride in methanol to form stereoisomers of 2-cyano-4,4-dimethoxy-3-methylbutanamide (**6**). A similar simple borohydride reduction of the double bond in 2-cyano-3-methylbut-2-enenitrile has been reported previously.[31] Treatment of the isomeric mixture of **6** with acetic acid leads in one pot to the expected product **2**. In **6** the protected aldehyde function is no longer linked to the electron-poor double bond. Now acidic deprotection should be very efficient. Proton-induced removal of one methoxy group in **6** will give an intermediate carbenium ion. This electrophilic carbon atom is attacked by the amide function to form a new C–N bond resulting in a five-membered ring. Proton-induced removal of the other methoxy group and a subsequent shift of the resulting double bond as a result of stabilization by conjugation with the two electron-withdrawing groups (cyano and carbonyl) lead to an efficient preparation of novel **2**. We obtained 2.39 g (20 mmol) of **2** in 40% overall yield based on **4**. We feel that this process can be easily scaled up. This three-step high-yield procedure has wide scope and many important 3-pyrrolin-2-ones are easily accessible. Through this new method stable isotopes can also be easily incorporated into the system.

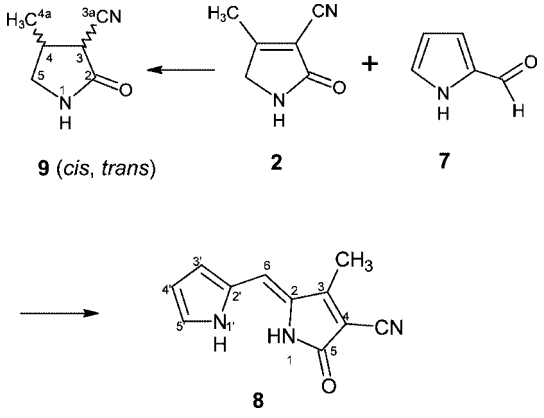
To incorporate ^{13}C isotopes into **2** we selected positions 2 and 3 in the pyrrolinone ring of **2**. First, incorporation of a ^{13}C label at position 2 in pyrrolinone **2** (ring D) corresponds to a ^{13}C label at atom 19 in phytochromobilin (**1**). This will allow us to probe the lactam function in the Pr and Pfr photoproducts. In a similar way, incorporation of a ^{13}C label at position 3 in pyrrolinone **2** will allow us to probe the carbon atom 18 in phytochromobilin (**1**) to which the vinyl function is attached. 2-Cyanoacetamides labelled at these positions are not commercially available. The com-

mercially available [1-^{13}C]bromoacetic acid and [2-^{13}C]bromoacetic acid were treated with KCN in ethanol to yield the corresponding cyanoacetic acids which were further converted into the corresponding 2-cyanoacetyl chlorides with oxalyl chloride or PCl_5. Treatment of these 2-cyanoacetyl chlorides with dry ammonia in THF yielded the corresponding 2-cyanoacetamides **4a** and **4b** in high yield. [2-^{13}C]- (**2a**) and [3-^{13}C]-3-Cyano-4-methyl-3-pyrrolin-2-one (**2b**) were obtained according to the reactions in Scheme 1. The *m*/*z* value of the parent peak of **2** is 122.0485, which agrees very well with the calculated value of 122.048013 for the formula $^{12}C_6{}^{1}H_6{}^{14}N_2{}^{16}O$. The *m*/*z* values for **2a** and **2b** are in agreement with the calculated values for $^{12}C_5{}^{13}C_1{}^{1}H_6{}^{14}N_2{}^{16}O$. The quality of the spectra is very good such that very high ^{13}C incorporation in **2a** and **2b** can be observed (≈99%). Besides the parent peak, the characteristic peaks at *m*/*z* = 107, 67, 52 for **2**, *m*/*z* = 108, 67, 52 for **2a** and *m*/*z* = 108, 68, 53 for **2b** are observed due to loss of NH, C–C=O and CH_3. The ^{1}H NMR chemical shifts of **2a** and **2b** were compared with the natural abundance chemical shifts of **2**. Doublets arising from the methyl group [^3J(C,H) = 5 Hz] at the 4 position and the methylene group ($^3J_{C,H}$ = 3 Hz) at the 5 position in product **2b** were observed as a result of the ^{13}C-enriched carbon atom at the 3 position. Similarly, the ^{13}C NMR chemical shifts of **2a** and **2b** were compared with the natural abundance chemical shifts of **2**. The greater downfield shift (δ = 174 ppm) of C-4 relative to the carbonyl carbon of the lactam at δ = 167 ppm is noticeable and results from the extended conjugation with the electron-withdrawing group at the double bond in **2**. The intense peaks arising from C-2 at δ = 167.7 ppm in **2a** and C-3 at δ = 108.2 ppm in **2b** reveal high ^{13}C incorporation at the expected positions without any ^{13}C scrambling.

3-Cyano-4-methyl-3-pyrrolin-2-one is a new system. In order to unambiguously establish its structure and ^{1}H and ^{13}C shift values a 2D ^{13}C-^{13}C INADEQUATE spectrum was needed to establish C–C connectivities. Owing to its poor solubility in NMR solvents this did not work for **2** itself which has a double bond bound to the electron acceptor. Sodium borohydride reduction of **2** in methanol led to a mixture of *trans* and *cis* isomers of 3-cyano-4-methyl-2-oxopyrrolidine in a ratio of 2:1 (Scheme 2). The 2D INADEQUATE ^{13}C-^{13}C NMR spectrum of the *trans* isomer in $CDCl_3$ confirmed that the carbonyl carbon atom is linked to C-3, which has a CN substituent, and which is also linked to C-4 bearing a methyl group and finally C-4 is linked to the methylene C-5 atom bound to NH. This unambiguously establishes the structure of the *trans* reduction product of **2** and by implication the structure of **2** itself, its C–C connectivity and the assignment of ^{13}C and ^{1}H NMR signals of **2**. The ^{1}H and ^{13}C NMR spectra of **2a** and **2b** fully agree with this assignment.

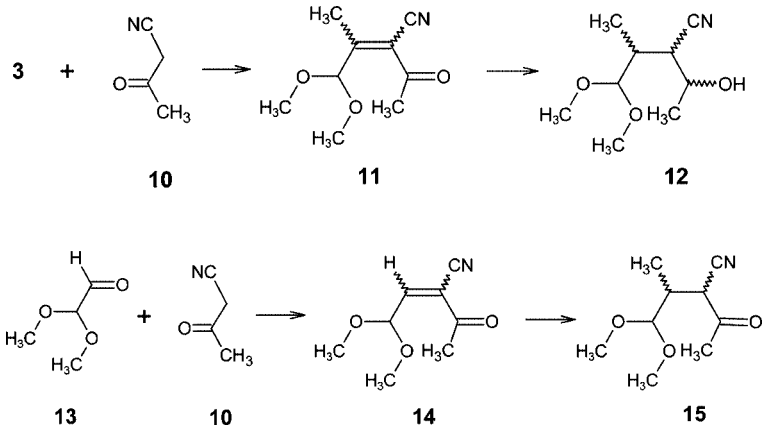
3-Cyano-4-methyl-3-pyrrolin-2-one is now accessible in high yield from simple starting materials, 1,1-dimethoxyacetone and 2-cyanoacetamide. Two of the possible isotopomers **2a** and **2b** have been prepared according to Scheme 1. There are no difficulties in preparing all the possible ^{13}C and ^{15}N isotopomers. The three possible isotopomers of bromoacetic acid are commercially available, the same is true of the cyanide ion and ammonia. Our present strategy to prepare 2-cyanoacetamide started with the acid chloride of cyanoacetic acid, which would lead in the case using $^{15}NH_3$ to a loss of 1 equiv. of precious $^{15}NH_3$. Simply using the mixed anhydride of cyanoacetic acid with ethyl chloroformate is expected to give [^{15}N]-2-cyanoacetamide. At the moment no strategies have been reported for the preparation of all the possible isotopomers of 1,1-dimethoxyacetone (**3**). However, for this small molecule, their access should not be a problem which means there should be no difficulty in accessing of all possible isotopomers of **2**.

3-Cyano-4-methyl-3-pyrrolin-2-one has the required functionality to form the structure of ring D of phytochromobilin **1** except that the nitrile group has to be converted into a vinyl function in the final product. For this conversion there are now three strategic choices. Either effect the conversion in the 3-pyrrolin-2-one system or secondly in the 2,2′-pyrromethen-5(1*H*)-one system forming the [C + D] unit and/or thirdly in the tetrapyrrole stage. Based on the reported instability of vinylpyrrolinone[32] we decided to postpone this conversion to later stages of the synthesis. (2*Z*)-2,2′-Pyrromethen-5(1*H*)-one can be prepared through the condensation of 3-pyrrolin-2-one with pyrrole-2-carbaldehyde under strict exclusion of air.[33,34] In order to test if 3-cyano-4-methyl-3-pyrrolin-2-one (**2**) could easily be converted into a pyrromethenone system under these conditions we condensed **2** with commercially available pyrrole-2-carbaldehyde (**7**) to yield 62% of the product **8** (Scheme 2) as a single geometric isomer. The product **8** has a (*Z*) structure, based on the strong NOE between CH_3 at the 3 position and H at the 6 position.



Scheme 2. The preparation (2*Z*)-4-cyano-3-methyl-2,2′-pyrromethen-5(1*H*)-one (**8**) starting from pyrrole-2-carbaldehyde (**7**) and 3-cyano-4-methyl-3-pyrrolin-2-one (**2**).

This exclusive formation of the (2*Z*) form of pyrromethenones has been reported before.[35] We feel that the three-step method in Scheme 1 allows the simple preparation of many more 3-pyrrolin-2-ones, which, by this method, can be easily prepared in stable isotope-labelled form.



Scheme 3. Condensation of **3** with cyanoacetone (**10**) to obtain 2-acetyl-4,4-dimethoxy-3-methylbut-2-enenitrile (**11**) and the condensation of **13** with cyanoacetone (**10**) to obtain 2-acetyl-4,4-dimethoxybut-2-enenitrile (**14**).

Before we carried out the Knoevenagel condensation reaction of 1,1-dimethoxyacetone (**3**) and 2-cyanoacetamide (**4**) we condensed **3** with cyanoacetone (**10**), which can be easily prepared from commercially available 3-aminocrotononitrile by a known procedure (Scheme 3).[36]

A mixture of (*Z*)- and (*E*)-2-acetyl-4,4-dimethoxy-3-methylbut-2-enenitrile (**11**) was obtained in high yield. Product **11** contains all the carbon atoms necessary for ring D of phytochromobilin **1**. Reduction with sodium borohydride led to 3-cyano-5,5-dimethoxy-2-hydroxy-4-methylpentane (**12**). The conditions under which the double bond in **11** could be reduced without reduction of the keto function has not been found.

After this strategy failed we next tried the following approach: compound **10** was condensed with commercially available dimethoxyacetaldehyde (**13**). 2-Acetyl-4,4-dimethoxybut-2-enenitrile (**14**) was obtained. 1,4-Addition of methylmagnesium iodide/cuprous cyanide gave the reduced **15**, the molecule that corresponds to **11** in which the double bond has been selectively reduced.

We first tried to convert **15** by an acid-catalyzed reaction in one pot into the required 4-methyl-3-pyrrolin-2-one. All the conditions we first tried led to the destruction of the starting material. A two-pot method in which we tried to convert the nitrile function into an amide did not give useful results either.

At this point we decided to identify the reactions in Scheme 1 that lead to an efficient method by which to prepare 3-cyano-4-methyl-3-pyrrolin-2-one. In order to obtain more information about the catalyst we carried out the Knoevenagel condensation reaction in the presence of β-alanine and also in the presence of piperidine.[30] In both cases almost no **5** was formed. This means that besides an amine, excess acetic acid is also essential to effect an efficient Knoevenagel condensation in those cases.

Conclusions

Conditions have been found in which α,α-dimethoxyacetone and activated methylenes with two electron-withdrawing groups can be condensed in high yield to give an alkene system with two electron-withdrawing groups on one end and a protected aldehyde on the other. These systems allow easy access to 3-pyrrolin-2-ones as well as easy stable isotope incorporation. We feel that this method will have a wide scope, allowing the preparation of many 3-pyrrolin-2-one systems with important biological properties.

Experimental Section

General: Reactions were monitored by thin-layer chromatography [TLC, on Merck F254 silica gel 60 aluminium sheets, 0.2 mm: spots were visualized by treatment with an oxidizing spray (2 g of $KMnO_4$ and 4 g of $NaHCO_3$ in 100 mL of water)]. Column chromatography was performed on Merck silica gel 60. ^{1}H NMR spectra were recorded with a Bruker WM-300 spectrometer with tetramethylsilane (TMS: δ = 0.00 ppm) as internal standard. ^{1}H noise-decoupled ^{13}C NMR spectra were recorded with a Bruker AM-600 spectrometer at 150 MHz. For the ^{13}C-enriched materials the signal of the enriched position is indicated by the word intense. Mass spectra were recorded with a Finnigan MAT 900 spectrometer equipped with a direct insertion probe (DIP) or with a Finnigan MAT 700-TSQ spectrometer equipped with a custom-made electron-spray interface (ESI). A Perkin-Elmer Paragon 1000 FTIR spectrometer and Varian cary 50 series UV spectrophotometer were used for IR and UV measurements, respectively. The experimental conditions are given for the unlabelled compounds. For labelled compounds, only the changes relative to the corresponding unlabelled compounds are given. [1-^{13}C]Bromoacetic acid and [2-^{13}C]-bromoacetic acid were purchased from Cambridge Isotope Laboratories Inc., USA. All other chemicals were purchased from Aldrich Fluka or Acros Chimica.

[1-^{13}C]-2-Cyanoacetamide (4a): [1-^{13}C]Bromoacetic acid (6.99 g, 50 mmol) was dissolved in H_2O (50 mL). A solution of Na_2CO_3 (5.30 g in 25 mL H_2O) was added to it until pH 8. Then a solution of KCN (3.25 g, 50 mmol) in H_2O (50 mL) was added to the solution. The mixture was heated at 80–85 °C for 2 h and further stirred at room temperature for 24 h. Then it was acidified with 12% HCl to make pH 5–6. The solvent was evaporated and the residue was extracted with ethanol (6 × 100 mL) to yield [1-^{13}C]cyanoacetic acid (3.80 g, 88%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.08 (d, $^2J_{C,H}$ = 6.5 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO):

δ = 27.11 (d, $^1J_{C,C}$ = 46.6 Hz, CH_2), 118.9 (CN), 164.8 (C=O, ^{13}C-labelled, intense peak) ppm.

A solution of oxalyl chloride (6.35 g, 50 mmol) in CH_2Cl_2 (25 mL) was added to a suspension of [1-^{13}C]cyanoacetic acid (3.80 g, 44 mmol) in CH_2Cl_2 (200 mL) at room temp. The mixture was refluxed for 30 min and the solvent was evaporated in vacuo. The colourless residue was dissolved in THF (200 mL) and NH_3 gas was bubbled through it for 10 min. The yellow suspension was stirred for 1 h at room temp. and filtered, the residue was washed with THF (3 × 50 mL), the filtrates were collected and the solvent evaporated in vacuo to yield a light-yellow solid of [1-^{13}C]-2-cyanoacetamide (**4a**) (2.24 g, 60%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.56 (d, $^2J_{C,H}$ = 6.6 Hz, 2 H, CH_2), 7.69, 7.92 (br., NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 25.32 (d, $^1J_{C,C}$ = 47.5 Hz, CH_2), 116.3 (CN), 164.1 (C=O, ^{13}C-labelled, intense peak) ppm.

[2-^{13}C]-2-Cyanoacetamide (4b): Similarly, [2-^{13}C]bromoacetic acid (6.99 g, 50 mmol) yielded [2-^{13}C]cyanoacetic acid (3.95 g, 93%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.13 (d, $^1J_{C,H}$ = 134.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 27.02 (CH_2, ^{13}C-labelled, intense peak), 118.7 (d, $^1J_{C,C}$ = 57.3 Hz, CN), 165.5 (d, $^1J_{C,C}$ = 47.6 Hz, C=O) ppm.

Similarly, [2-^{13}C]cyanoacetic acid (3.85 g, 45 mmol) yielded a light-yellow solid of [2-^{13}C]-2-cyanoacetamide (**4b**) (2.82 g, 74%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.55 (d, $^1J_{C,H}$ = 135.4 Hz, 2 H, CH_2), 7.31, 7.62 (br., NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 25.28 (CH_2, ^{13}C-labelled, intense peak), 116.2 (d, $^1J_{C,C}$ = 60.8 Hz, CN), 163.9 (d, $^1J_{C,C}$ = 47.8 Hz, C=O) ppm.

Mixture of (2*Z*)- and (2*E*)-2-Cyano-4,4-dimethoxy-3-methylbut-2-enamide (5): To a mixture of 1,1-dimethoxyacetone (**3**) (6.20 g, 52 mmol) and 2-cyanoacetamide (**4**) (4.04 g, 50 mmol) in toluene (250 mL) was added ammonium acetate (1.00 g) and acetic acid (5 mL). The mixture was refluxed for 2 h at 130–135 °C using a Dean–Stark water separator. The organic solution was washed with a half-saturated NaCl solution. The aqueous phase was again extracted with CH_2Cl_2 (3 × 50 mL). The extracted organic solvents were combined together and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield a red-yellow oil of **5** (8.01 g, 87%). The product was purified by column chromatography (silica gel 60, ethyl acetate/hexane, 8:2) to yield a light-yellow oil of **5** (5.89 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E*, 1:1): δ = 2.19, 2.25 (CH_3), 3.31, 3.33, 3.41, 3.43 (OCH_3), 5.09, 5.84 (CH), 6.54, 6.63 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.27, 17.48 (CH_3), 55.47, 55.61 (OCH_3), 99.90, 104.8 (CH), 107.2, 108.8 (NC-*C*=), 115.3, 115.6 (CN), 162.3, 162.8 (C=O), 165.50, 166.2 (CH_3-*C*=) ppm.

Mixture of (2*Z*)- and (2*E*)-[1-^{13}C]-2-Cyano-4,4-dimethoxy-3-methylbut-2-enamide (5a): Similarly, [1-^{13}C]-2-cyanoacetamide (**4a**) (2.12 g, 25 mmol) was condensed with **3** (3.54 g, 30 mmol) in toluene (150 mL) in the presence of ammonium acetate (0.50 g) and acetic acid (2.5 mL) to yield (3.25 g, 67%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E*, 1:1): δ = 2.12, 2.20 (CH_3), 3.33, 3.31, 3.49, 3.46 (OCH_3), 5.10, 5.87 (CH), 6.63, 6.54 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.33, 17.48 (CH_3), 53.24, 55.70 (OCH_3), 99.85, 104.8 (CH), 107.1, 108.7 (d, $^1J_{C,C}$ = 57.7 Hz, NC-*C*=), 115.4, 115.6 (CN), 162.1, 162.3 (C=O, ^{13}C-labelled, intense peak), 165.8, 166.6 (CH_3-*C*=) ppm.

Mixture of (2*Z*)- and (2*E*)-[2-^{13}C]-2-Cyano-4,4-dimethoxy-3-methylbut-2-enamide (5b): Similarly, [2-^{13}C]-2-cyanoacetamide (**4b**) (2.12 g, 25 mmol) was condensed with **3** (3.54 g, 30 mmol) in toluene (150 mL) in the presence of ammonium acetate (0.50 g) and acetic acid (2.5 mL) to yield (3.30 g, 71%) a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E*, 1:1): δ = 2.21 (d, $^3J_{C,H}$ = 6.3 Hz, CH_3), 2.26 (d, $^3J_{C,H}$ = 5.6 Hz, CH_3), 3.41, 3.43 (OCH_3), 5.09 (d, $^3J_{C,H}$ = 3.2 Hz, CH), 5.85 (d, $^3J_{C,H}$ = 1.5 Hz, CH), 6.54, 6.39 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.31, 17.56 (CH_3), 55.52, 55.66 (OCH_3), 104.9, 106.7 (NC-*C*=, ^{13}C-labelled, intense peak), 115.1 (d, $^1J_{C,C}$ = 23.1 Hz), 116.1 (d, $^1J_{C,C}$ = 23.2 Hz, CN), 161.9 (d, $^1J_{C,C}$ = 33.1 Hz), 162.8 (d, $^1J_{C,C}$ = 32.8 Hz, C=O), 165.5 (d, $^1J_{C,C}$ = 57.5 Hz), 166.5 (d, $^1J_{C,C}$ = 58.9 Hz, CH_3-*C*=) ppm.

2-Cyano-4,4-dimethoxy-3-methylbutanamide (6): $NaBH_4$ (1.32 g, 35 mmol) was added to a cooled (0 °C), stirred solution of **5** (5.89 g, 32 mmol) in MeOH (150 mL). After stirring it for 15 min at 0 °C, the solution was poured into a mixture of ice-cold water (50 mL) and CH_2Cl_2 (150 mL). 5% HCl (50 mL) was added to this solution. The product was extracted with CH_2Cl_2 (3 × 150 mL) and dried with $MgSO_4$. Evaporation of the solvent in vacuo yielded **6** (4.61 g, 78%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of stereoisomers: δ = 1.12 (d, $^3J_{H,H}$ = 6.8 Hz), 1.16 (d, $^3J_{H,H}$ = 7.0 Hz, CH_3), 2.60 (m, CH-CH_3), 3.49 (d, $^3J_{H,H}$ = 4.2 Hz), 3.78 (d, $^3J_{H,H}$ = 4.2 Hz, NC-CH), 3.37, 3.42 (OCH_3), 4.26 (d, $^3J_{H,H}$ = 7.1 Hz), 4.39 (d, $^3J_{H,H}$ = 6.8 Hz, CH), 6.22, 6.34 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.86, 13.42 (CH_3), 36.52, 36.91 (*C*H-CH_3), 39.74, 40.76 (C*H*-CN), 53.51, 55.05, 53.51, 55.32 (OCH_3), 105.7, 105.8 (CH), 116.9, 117.3, (CN), 166.4, 166.5 (C=O) ppm.

[1-^{13}C]-2-Cyano-4,4-dimethoxy-3-methylbutanamide (6a): Similarly, $NaBH_4$ (0.56 g, 15 mmol) was added to a cooled (0 °C), stirred solution of **5a** (2.00 g, 11 mmol) in MeOH (50 mL) and worked up as before to yield **6a** (1.26 g, 62%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two stereoisomers: δ = 1.12 (d, $^3J_{H,H}$ = 6.9 Hz), 1.16 (d, $^3J_{H,H}$ = 7.1 Hz, CH_3), 2.62 (m, CH-CH_3), 3.47, 3.43 (OCH_3), 3.76 (d, $^2J_{C,H}$ = 3.6 Hz), 3.79 (d, $^2J_{C,H}$ = 3.6 Hz, NC-CH), 4.26 (d, $^3J_{H,H}$ = 7.2 Hz), 4.40 (d, $^3J_{H,H}$ = 7.0 Hz, CH), 6.00, 6.29 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.89, 13.54 (CH_3), 36.90, 37.37 (*C*H-CH_3), 39.38, 40.04 (d, $^1J_{C,C}$ = 49.7 Hz, NC-*C*H), 53.74, 55.01 (OCH_3), 105.65, 105.8 (CH), 116.98, 117.28 (CN), 166.2 (C=O, ^{13}C-labelled, intense peak) ppm.

[2-^{13}C]-2-Cyano-4,4-dimethoxy-3-methylbutanamide (6b): Similarly, $NaBH_4$ (0.75 g, 20 mmol) was added to a cooled (0 °C), stirred solution of **5b** (3.00 g, 16 mmol) in MeOH (75 mL) and worked up as before to yield **6b** (1.82 g, 61%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two stereoisomers: δ = 1.11, 1.15 (m, CH_3), 2.62 (m, CH-CH_3), 3.42, 3.45 (OCH_3), 3.48 (dd, $^1J_{C,H}$ = 137.1 Hz, $^3J_{H,H}$ = 4.0 Hz), 3.77 (dd, $^1J_{C,H}$ = 136.8 Hz, $^3J_{H,H}$ = 3.6 Hz, NC-CH), 4.26 (dd, $^3J_{C,H}$ = 2.0 Hz, $^3J_{H,H}$ = 7.1 Hz), 4.39 (dd, $^3J_{C,H}$ = 1.4 Hz, $^3J_{H,H}$ = 6.9 Hz, CH), 6.03, 6.29 (br., NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.09, 13.40 (CH_3), 37.39, 38.48 (CH_3-*C*H), 39.78, 40.82 (NC-*C*H, ^{13}C-labelled, intense peak), 54.62, 55.50 (OCH_3), 105.6, 105.8 (CH), 116.8 (d, $^1J_{C,C}$ = 57.3 Hz), 117.2 (d, $^1J_{C,C}$ = 53.7 Hz, CN), 166.4 (d, $^1J_{C,C}$ = 52.9 Hz), 166.6 (d, $^1J_{C,C}$ = 49.5 Hz, C=O) ppm.

3-Cyano-4-methyl-3-pyrrolin-2-one (2): A solution of **6** (4.61 g, 25 mmol) was refluxed in acetic acid (50 mL) for 6 h under N_2. It was then stirred overnight under N_2. Ethyl acetate/hexane (8:2, 50 mL) was added to the mixture and solvent evaporated under vacuo to yield a red-brown solid. The residue was stirred and washed with ethyl acetate/hexane (8:2) (2 × 25 mL), filtered and the residue dried to give a yellow solid **2** (2.39 g, 78%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.25 (s, CH_3), 4.14 (s, CH_2), 8.56 (br., NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 16.87 (CH_3), 52.31 (CH_2), 109.4 (NC-*C*=), 114.1 (CN), 169.0 (C=O), 175.5 (CH_3-*C*=) ppm. IR: $\tilde{\nu}$ = 3181, 3074, 2235, 1711, 1698 cm^{-1}. MS:

calcd. for $^{12}C_6{}^1H_6{}^{14}N_2{}^{16}O$ 122.048013; found 122.0485; MS (EI$^+$): *m*/*z* = 122, 107, 67, 52.

[2-^{13}C]-3-Cyano-4-methyl-3-pyrrolin-2-one (2a): Similarly, 1.26 g (6.73 mmol) of **6a** yielded **2a** (0.51 g, 62%) as a yellow powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.23 (s, CH$_3$), 4.12 (s, CH$_2$), 8.52 (br., NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.7 (C=O, ^{13}C-labelled, intense peak) ppm. IR: $\tilde{\nu}$ = 3182, 3074, 2239, 1713, 1698 cm^{-1}. MS: calcd. for $^{12}C_5{}^{13}C_1{}^1H_6{}^{14}N_2{}^{16}O$ 123.051363; found 122.0514; MS (EI$^+$): *m*/*z* = 123, 108, 67, 52.

[3-^{13}C]-3-Cyano-4-methyl-3-pyrrolin-2-one (2b): Similarly, 1.82 g (9.72 mmol) of **6b** yielded **2b** (0.80 g, 67%) as a yellow powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.23 (d, $^3J_{C,H}$ = 5.5 Hz, CH$_3$), 4.12 (d, $^3J_{C,H}$ = 3.0 Hz, CH$_2$), 8.53 (br., $^3J_{C,NH}$ = 6.0 Hz, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 15.61 (CH$_3$), 51.06 (CH$_2$), 108.2 (NC-*C*=, ^{13}C-labelled, intense peak), 112.7 (d, $^1J_{C,C}$ = 69.0 Hz, CN), 167.8 (d, $^1J_{C,C}$ = 66.6 Hz, C=O), 174.2 (d, $^1J_{C,C}$ = 71.4 Hz, CH$_3$-*C*=) ppm. IR: $\tilde{\nu}$ = 3181, 3074, 2235, 1712, 1699 cm^{-1}. MS: calcd. for $^{12}C_5{}^{13}C_1{}^1H_6{}^{14}N_2{}^{16}O$ 123.051363; found 123.0519; MS (EI$^+$): *m*/*z* = 123, 108, 68, 53.

(2*Z*)-4-Cyano-3-methyl-2,2′-pyrromethen-5(1*H*)-one (8): A mixture of **2** (0.16 g, 1.31 mmol), pyrrole-2-carbaldehyde (**7**) (0.16 g, 1.68 mmol), sodium acetate (0.18 g) and acetic acid (20 mL) was refluxed for 3 h under N$_2$. The mixture was stirred overnight, added to ethyl acetate/hexane (1:3, 50 mL) and cooled to 0 °C and solid precipitated out as violet blue solid. The solid was dissolved in methanol/CH_2Cl_2 (1:2, 75 mL), washed with 5% $NaHCO_3$ and the aqueous phase was again extracted with CH_2Cl_2 (3 × 50 mL). The organic solutions were combined, dried with $MgSO_4$ and the solvent evaporated to yield 0.16 g (62%) as a yellowish orange solid. ^{1}H NMR (600 MHz, [D$_6$]DMSO + D$_2$O): δ = 2.33 (s, CH$_3$), 6.30 (ddd, $^3J_{4'H,3'H}$ = 3.8 Hz, $^3J_{4'H,5'H}$ = 2.5 Hz, $^5J_{4'H,6H}$ = 0.6 Hz, 4′-CH), 6.62 (s, 6-CH), 7.03 (ddd, $^3J_{3'H,4'H}$ = 3.8 Hz, $^3J_{3'H,5'H}$ = 1.2 Hz, $^4J_{3'H,6H}$ = 0.5 Hz, 3′-CH), 7.17 (dd,$^3J_{5'H,4'H}$ = 2.5 Hz, $^4J_{5'H,3'H}$ = 1.3 Hz, 5′-CH) ppm. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.31 (NH), 11.43 (NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 11.73 (CH$_3$), 101.0 (=*C*-CN), 108.7 (=CH), 111.8 (=CH), 113.8 (CN), 116.2 (=CH), 124.8 (=CH), 126.6 (=C), 128.9 (=C), 158.7 (=*C*-CH$_3$), 166.5 (C=O) ppm. IR: $\tilde{\nu}$ = 3282, 2225, 1710, 1638, 1592 cm^{-1}. UV (MeOH): λ_{max} (ε) = 436 (64000), 286 (5900 M^{-1} cm^{-1}) nm. MS: calcd. For $^{12}C_{11}{}^1H_9{}^{14}N_3{}^{16}O$ 199.074562; found 199.0747; MS (EI$^+$): *m*/*z* = 199, 170, 162, 122, 105, 77, 43, 17.

3-Cyano-4-methylpyrrolidin-2-one (*cis*/*trans*-9, 1:2): $NaBH_4$ (0.75 g, 20 mmol) was added to a cooled (0 °C), stirred solution of **2** (1.83 g, 15 mmol) in MeOH (50 mL). After stirring for 15 min at 0 °C, the solution was poured into a mixture of ice-cold water (50 mL) and CH_2Cl_2 (150 mL). 5% HCl (15 mL) was added to this solution. The product was extracted with CH_2Cl_2 (3 × 100 mL) and dried with $MgSO_4$. Evaporation of the solvent in vacuo yielded **9** (1.48 g, 79%) as a light-yellow oil. The ^{1}H and ^{13}C NMR spectra of *cis*- and *trans*-**9** were obtained via the *cis*/*trans* mixture of **9**. The ^{1}H NMR assignments were checked by ^{1}H-^{13}C correlation and ^{1}H COSY spectra. The ^{13}C–^{13}C connectivities were determined from ^{13}C-^{13}C INADEQUATE spectra.

***trans*-9:** ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.31 (d, $^3J_{H,H}$ = 7.0 Hz, 4a-CH$_3$), 2.80 (m, 4-CH), 3.05 (t, $^3J_{H,H}$ = 9.6 Hz, 1 H, 5-CH$_2$), 3.16 (d, $^3J_{H,H}$ = 10.7 Hz, 3-CH-CN, *trans*), 3.59 (t, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-CH$_2$), 7.39 (br., NH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.08 (CH$_3$), 36.42 (*C*H-CH$_3$), 40.94 (*C*H-CN), 48.02 (CH$_2$), 116.4 (CN), 169.8 (C=O) ppm.

***cis*-9:** ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.33 (d, $^3J_{H,H}$ = 7.0 Hz, 4a-CH$_3$), 2.80 (m, 4-CH), 3.15 (dd, $^3J_{H,H}$ = 10.8, $^4J_{H,H}$ = 4.2 Hz, 1 H, 5-CH$_2$), 3.64 (d, $^3J_{H,H}$ = 7.8 Hz, 3-CH-CN, *cis*), 3.65 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, 5-CH$_2$), 7.39 (br., NH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 16.29 (CH$_3$), 31.74 (*C*H-CH$_3$), 39.59 (*C*H-CN), 47.81 (CH$_2$), 114.9 (CN), 169.7 (C=O) ppm.

2-Acetyl-4,4-dimethoxy-3-methylbut-2-enenitrile (11): A solution of **3** (5.90 g, 50 mmol), 1-cyanopropan-2-one (**10**) (3.74 g, 45 mmol), ammonium acetate (0.90 g) and acetic acid (5 mL) in toluene (200 mL) was refluxed for 2 h at 80–85 °C in toluene (200 mL). The toluene layer was separated after washing with a half-saturated NaCl solution, dried with $MgSO_4$ and the solvents evaporated in vacuo to yield a light-yellow oil (7.45 g, 91%). ^{1}H NMR (300 MHz, CDCl$_3$/TMS) mixture of *Z* and *E*: δ = 2.19, 2.21 (CH$_3$), 2.49, 2.51 (CH$_3$), 3.41 (OCH$_3$), 3.42 (OCH$_3$), 5.11 (CH), 5.65 (CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$/TMS): δ = 14.55, 17.42, 30.19 (CH$_3$), 55.60, 55.81 (OCH$_3$), 99.87, 104.9 (CH), 112.3, 114.2 (=*C*-CN), 115.8, 116.0 (CN), 166.7, 167.3 (=*C*-CH$_3$), 192.4, 192.6 (C=O) ppm.

2-(1-Hydroxyethyl)-4,4-dimethoxy-3-methylbutanenitrile (12): $NaBH_4$ (1.02 g, 27 mmol) was added to a cooled (0 °C), stirred solution of **11** (3.66 g, 20 mmol) in MeOH (150 mL). After stirring for 15 min at 0 °C, the solution was poured into a separator containing ice-cold water (50 mL) and CH_2Cl_2 (100 mL). 5% HCl (20 mL) was added to this solution. The CH_2Cl_2 phase was separated and the aqueous phase further extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were collected and dried with $MgSO_4$. Evaporation of the solvent in vacuo yielded a light-yellow oil (2.90 g, 77%). ^{1}H NMR (300 MHz, CDCl$_3$/TMS) (mixtures of isomers): δ = 1.06–1.19 (m, CH$_3$), 1.30–1.44 (m, CH$_3$), 2.04–2.48 (m, CH), 2.50–3.0 (m, CH), 3.36–3.49 (m, OCH$_3$), 4.07 (d), 4.21 (d), 4.37 (dd, CH) ppm ^{13}C NMR (75 MHz, CDCl$_3$/TMS) (main peaks): δ = 11.30 (CH$_3$), 22.17 (CH$_3$), 33.67 (CH), 40.98 (CH), 53.46 (OCH$_3$), 65.61 (CHOH), 105.3 (CH), 118.9 (CN) ppm.

2-Acetyl-4,4-dimethoxybut-2-enenitrile (14): A solution of 1,1-dimethoxyacetaldehyde (60%) (**13**) (8.67 g, 50 mmol), **10** (3.74 g, 45 mmol), ammonium acetate (0.90 g) and acetic acid (5 mL) in toluene (200 mL) was refluxed for 1 h at 80–85 °C in toluene (200 mL). The toluene layer was separated after washing with a half-saturated NaCl solution, dried with $MgSO_4$ and the solvents evaporated in vacuo to yield a light-yellow oil (3.72 g, 46%). ^{1}H NMR (300 MHz, CDCl$_3$/TMS): δ = 2.38 (CH$_3$), 3.50 (OCH$_3$), 3.52 (OCH$_3$), 4.41 (d, CH), 4.63 (d, CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$/TMS): δ = 30.84 (CH$_3$), 55.29 (OCH$_3$), 105.1 (CH), 114.2 (=*C*-CN), 119.5 (CN), 154.6 (=CH), 196.8 (C=O) ppm.

The first reactions to convert **14** into **15** did not give good yields and this line of work was terminated in favour of the reactions in Scheme 1.

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