Facile Construction of the Colchicine Skeleton By a Rhodium-Catalyzed Cyclization/Cycloaddition Cascade**

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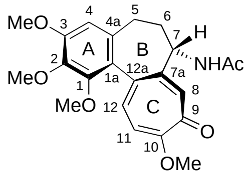
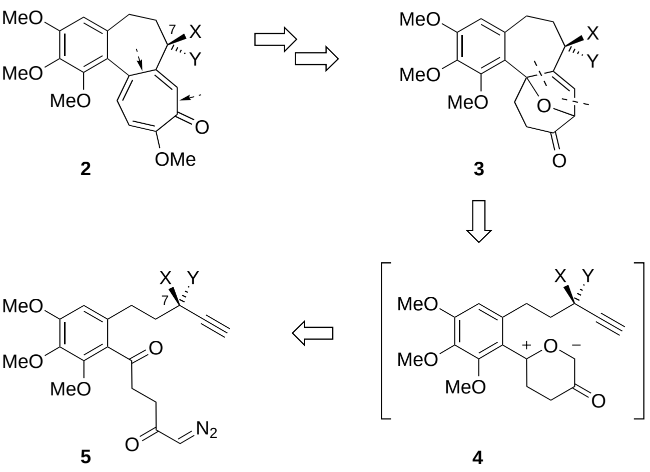
Colchicine (**1**), the major alkaloid of the meadow saffron (*colchicum autumnale*), has long been known for its remarkable antimitotic activity. It is an established drug in the treatment of acute gout and familial mediterranean fever and, moreover, it is currently being tested against a broad variety of other diseases.[1] The biological activity of **1** mainly depends on its selective binding to tubulin which leads to an inhibition of microtubule formation.[2] Structural analogues of the natural product are also of great interest, in particular as potential antitumor agents.[3]



1: (a*R*,7*S*)-colchicine

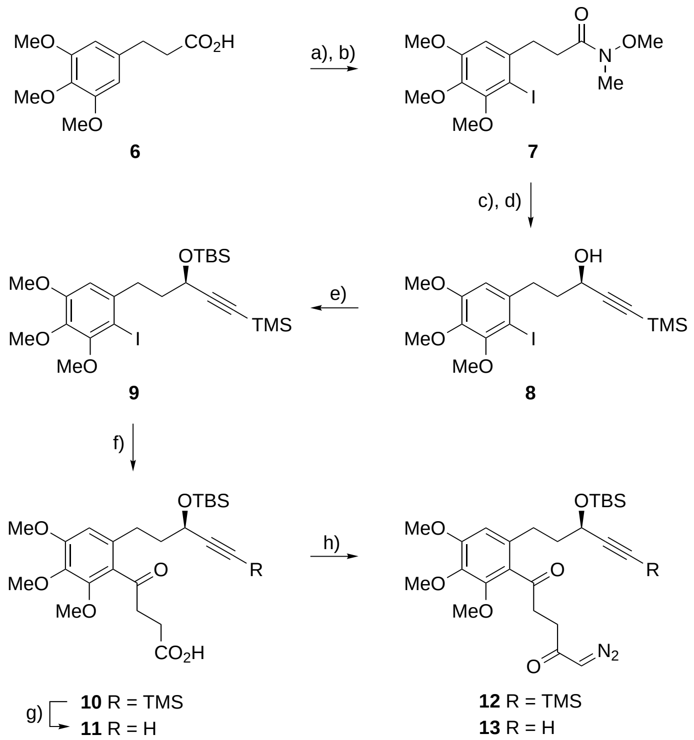
Owing to its biological importance and unique chemical structure, colchicine (**1**) has received considerable attention from synthetic chemists, and several total syntheses of **1** have been elaborated.[4] During this work, it became apparent that the major difficulty lies in the construction of the tropolone ring C, which is condensed to a second seven-membered ring (B). Still, the search for general and practicable synthetic routes towards **1** and structurally related compounds remains an important challenge. We here disclose an unprecedented short and efficient entry to the fully elaborated colchicine carbon skeleton which exploits the synthetic power of a metal-catalyzed domino reaction as the key step.[5, 6]

Our retrosynthetic analysis (Scheme 1) was guided by the consideration that it would be, for general strategic (topological) reasons, very attractive to build up the rings B and C simultaneously by an intramolecular cycloaddition (A → ABC approach).[7, 8] According to the methodology for the synthesis of benzotropolones and heteroanalogues published previously,[9] it seemed feasible that a tropolone of type **2**[10] could be generated from a precursor of type **3**,[11] which in turn would be the product of an intramolecular [3+2] cycloaddition of a carbonyl ylide (**4**) formed in situ by rhodium-catalyzed decomposition of an α-diazoketone of type **5**.[9, 12] The intramolecular mode of the cycloaddition step could even permit the use of an *unactivated* acetylene and thus allow prior installation of the stereocenter at position 7.



Scheme 1. Retrosynthetic analysis (X = H, Y = NHR; or X = OR, Y = H).

As a precondition for the investigation of the envisioned key transformation, a synthesis of cyclization precursors of type **5** was developed (Scheme 2). Starting from the commer-



Scheme 2. Synthesis of cyclization precursors: a) $(COCl)_2$ (1.2 equiv), CH_2Cl_2, 0 °C to RT, 12 h, removal of all volatiles, then NHMeOMe · HCl (1.1 equiv), Py (2.2 equiv), CH_2Cl_2, 0 °C, 1 h; b) $Ag(CF_3CO_2)$ (1.05 equiv), I_2 (1 equiv), $CHCl_3$, RT, 4 h, 92 % (over two steps); c) DIBAH (1 M in THF, 2.5 equiv), THF, −78 °C, 45 min, then CH_3COCH_3, −78 to −20 °C, workup with 0.5 M aqueous tartaric acid; d) $Cl_2CeC{\equiv}CTMS$ (2 equiv), THF, −78 °C to RT, 16 h, 98 % (over two steps); e) TBSCl, imidazole, DMF, RT, 15 h, 93 %; f) *i*PrMgBr (1.7 equiv), THF, −25 °C, 4.5 h, then succinic anhydride (2 equiv), THF, 0 °C, 30 min, 52 %; g) K_2CO_3, MeOH, RT, 3 h, 99 %; h) *i*BuOCOCl (1 equiv), NEt_3 (1 equiv), THF:Et_2O (1:1), −20 °C to −15 °C, then CH_2N_2 (5 equiv), Et_2O, −5 °C, 16 h, 66 % (*rac*-**12**), 70 % (*rac*-**13**). DIBAH = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

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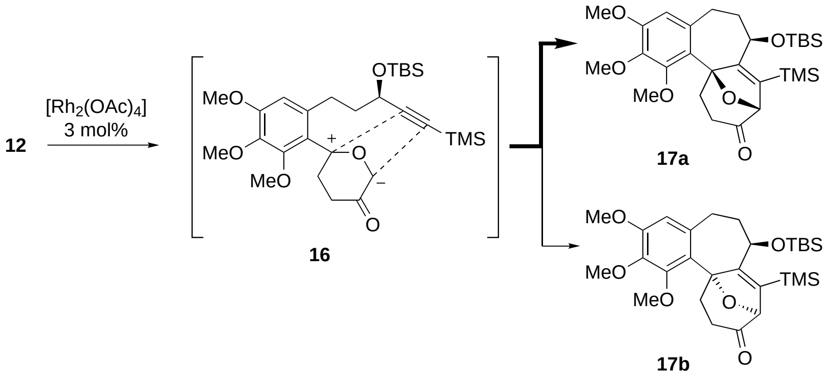
cially readily available acid **6**, the bifunctional compound **7** was prepared by converting the acid functionality (via the acid chloride) into the Weinreb amide[13] and subsequent aromatic iodination using iodine in the presence of silver trifluoroacetate.[14] To elaborate the "upper" carbon chain, the Weinreb amide was reduced with DIBAH, and the resulting aldehyde was alkynylated by using the reagent prepared from lithiated trimethylsilylacetylene and cerium(III) chloride in THF. The obtained propargylic alcohol *rac*-**8** was then converted into its *tert*-butyldimethylsilyl-protected derivative *rac*-**9** under standard conditions. Following this straightforward five-step sequence, the iodide *rac*-**9** was obtained in 84 % overall yield starting from **6**.

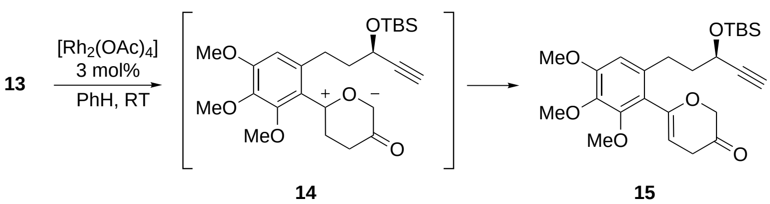


Scheme 4. Successful cyclization of **12**: a) benzene, reflux, slow addition of *rac*-**12** over 3.5 h, 30 min, 25 %; b) toluene, reflux, slow addition of *rac*-**12** over 3.5 h, 30 min, 62 % (*rac*-**17a**:*rac*-**17b** = 14:1).

To attach the "lower" 1,4-dicarbonyl chain, the iodide *rac*-**9** was first converted into the corresponding Grignard compound by treatment with isopropylmagnesium bromide at low temperatures.[15] Addition of the resulting solution to succinic anhydride in THF at 0 °C directly afforded the desired 4-ketocarboxylic acid *rac*-**10** in 52 % yield. This was transformed into the α-diazoketone *rac*-**12** by reacting the in situ prepared mixed anhydride with an excess of diazomethane.[12d, 16] Alternatively, the acid *rac*-**11** (obtained from *rac*-**10** by selective desilylation using K_2CO_3 in MeOH) was transformed into *rac*-**13**. The two α-diazoketones *rac*-**12** and *rac*-**13** were obtained as yellow oils after flash chromatographic purification (SiO_2, EtOAc:cyclohexane = 1:1) and directly employed in the cyclization experiments.

When *rac*-**13** was subjected to standard conditions for the Rh-catalyzed generation of carbonyl ylides (3 mol% $[Rh_2(OAc)_4]$, benzene, room temperature)[12] not even traces of the desired cycloadduct (of type **3**) could be detected in the product mixture. Instead, the enolether *rac*-**15**, arising from simple proton transfer (1,4-H shift) within the intermediate *rac*-**14**, was isolated as the only product in 76 % yield (Scheme 3).[17]

To avoid a possible participation of the relatively acidic alkynyl hydrogen atom in the undesired proton transfer and to promote the cycloaddition step, the silylated α-diazoketone *rac*-**12** was subjected to the same Rh catalyst, but at elevated reaction temperatures. Indeed, when a solution of *rac*-**12** was slowly added to a refluxing solution of 3 mol% of $[Rh_2(OAc)_4]$ in benzene, the cycloadduct *rac*-**17** was formed in 25 % yield, and in refluxing toluene an even greatly improved yield of 62 % was obtained (Scheme 4). In both cases, the diastereomers *rac*-**17a** and *rac*-**17b** were formed in a 14:1 ratio together with significant ammounts of the corresponding enolether. Evidently, the initially generated ylide *rac*-**16** had now undergone the crucial intramolecular cycloaddition reaction.



Scheme 3. Unsuccessful attempt at the cyclization of **13**.

Notably, in contrast to earlier reports,[12b] this demonstrates that the Rh-catalyzed cyclization/cycloaddition methodology can efficiently be used for the construction of ring systems containing two fused seven-membered rings, but only if higher temperatures are employed, which had not been considered as beneficial for such reactions so far.[12] The relative configuration of the main diastereoisomer *rac*-**17a** was initially secured by NMR-NOE experiments and later confirmed by X-ray crystallography (Figure 1).[18]

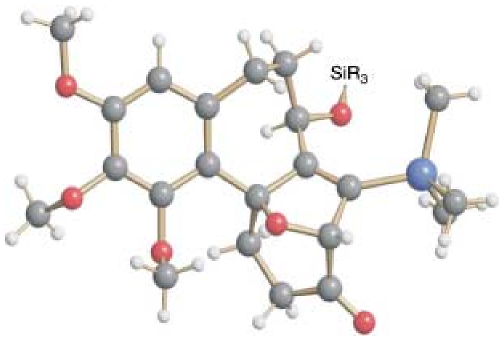


Figure 1. Structure of *rac*-**17a** in the crystalline state. The atoms of the large TBS group are not shown for reasons of clarity.

In conclusion, the advanced colchicine intermediate *rac*-**17** was prepared in only eight steps (18 % overall yield) starting from simple and readily available building blocks. The high efficiency of the sequence is based both on a powerful domino reaction and on an economical use of functional groups during the assembly of the cyclization precursor. We are currently focussing on the completion of the synthesis of colchicine (also in the non-racemic series) and on the exploitation of the chosen strategy in the synthesis of new colchicine analogues.

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[17] Products of this kind had been observed before in (related) intermolecular reactions when unactivated dipolarophiles were employed[12a] but also in attempts to prepare ring systems with two fused seven-membered rings by intramolecular cycloaddition.[12b]

[18] For crystal data of *rac*-**17a** see Supporting information. CCDC-177454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Aromatic Boranes with Planar-Tetracoordinate Boron Atoms and Very Short B–B Distances[**]

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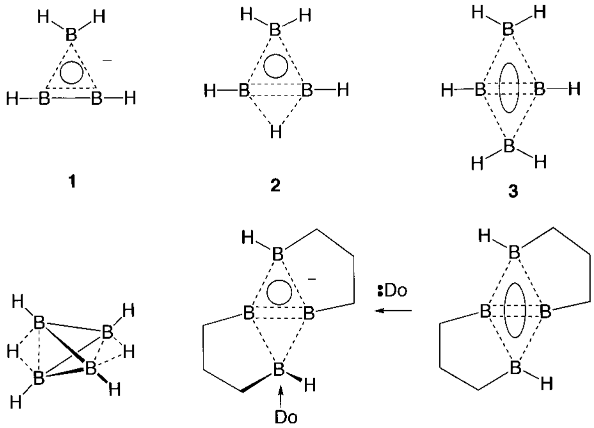
Dedicated to Professor Anton Meller on the occasion of his 70th birthday

Boranes with planar-tetracoordinate boron atoms have until now only been studied by computations.[1–3] The prototype of such compounds is anion **1** (Scheme 1), whose planar-tetracoordinate boron atom forms a three-center, two-electron (3c2e) σ bond as well as a 3c2e π bond with the two other boron atoms.[2] Thus **1** is one of the simplest double aromatics.[4] Upon protonation the classical B–B bond in **1** is transformed into a 3c2e B-H-B bond in **2**. However, the double aromatic electronic structure of **1** is retained in **2**. In tetraborane(6) **3**[5] the hydrogen bond in **2** is replaced by a planar BH_2 bridge.[6, 7] Known tetraboranes(6) are derivatives of the distorted tetrahedral isomer **4**, which according to computations at the MP2/6-31G* level is 9.2 kcal mol^{-1} lower in energy than **3**.[5] Here we present **5a** and **6a** (Scheme 2), the first derivatives of the prototypes **5u** and **6u**; both represent



Scheme 1. Borane prototypes **1**–**3**, **5u**, and **6u** with planar-tetracoordinate boron atoms. Solid lines symbolize 2c2e bonds, triangles drawn with dashed lines 3c2e σ bonds, circles 3c2e π bonds, and ellipsoids 4c2e π bonds. In the distorted tetrahedral **4** the four connecting lines between the boron atoms are drawn to indicate the spatial relationships. In **4** there are ten electrons available to connect the boron atoms. In contrast, in the isomer **3** as well as in **5u** and **6u** there are only six electrons each.

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