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Total Synthesis of (–)-Colchicine via a Rh-Triggered Cycloaddition Cascade

Timm Graening, Virginie Bette, Jörg Neudörfl, Johann Lex, and Hans-Günther Schmalz*

Universität zu Köln, Greinstrasse 4, D-50939 Köln, Germany

schmalz@uni-koeln.de

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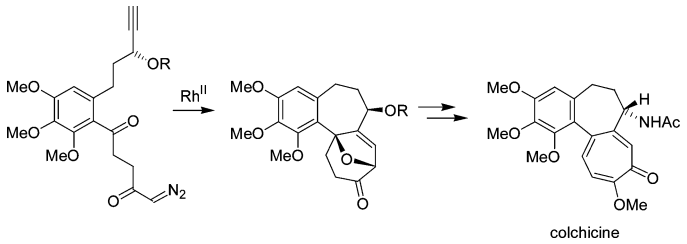
ABSTRACT



colchicine

A synthesis of the antimitotic alkaloids (–)-colchicine and (–)-isocolchicine is reported. Important steps are (a) enantioselective transfer-hydrogenation of an alkynone, (b) iodine/magnesium exchange with subsequent aromatic acylation, (c) Rh-catalyzed transformation of an α-diazoketone into an oxatetracyclic key intermediate through intramolecular [3 + 2]-cycloaddition of an in situ generated carbonyl ylide, and (d) regioselective conversion of the cycloadduct into a tropolone derivative. The new synthetic strategy opens an efficient enantioselective access to colchicine and structural analogues.

Colchicine (**1**), the major alkaloid and active principle of the meadow saffron (*Colchicum autumnale* L.), is an important antimitotic agent.[1] Like other compounds strongly binding to tubulin, colchicine and structural analogues are of interest, for instance, as vascular targeting[2] and apoptosis-inducing agents.[3]

For 50 years, colchicine has been a prominent target molecule in natural product synthesis, and a considerable number of very distinct synthetic approaches have been elaborated.[4] However, the search for efficient and general schemes also opening flexible entries to structural analogues of **1** still remains a challenging goal, especially with respect to the construction of the annulated tropolone substructure.

We have recently disclosed a new strategy for the synthesis of the colchicine skeleton based on the retrosynthetic analysis sketched in Scheme 1.[5] As a central feature, an oxatetracyclic compound of type **2** serves as a key intermediate, which can be traced back to a diazoketone of type **4**. The idea was to generate a carbonyl ylide **3**, which then undergoes an intramolecular 1,3-dipolar cycloaddition with the alkyne side chain in a domino-type process. This way, both seven-membered rings B and C are formed in one step with concomitant installation of the oxygen functions in positions C(9) and C(10). Moreover, the intramolecular mode of the cycloaddition step would permit the use of an unactivated dipolarophile and thus allow for the installation of the C(7) stereocenter prior to cyclization.

In our first communication, we have demonstrated the general feasibility of this concept by synthesizing a com-

(1) (a) Boyé, O.; Brossi, A. In *The Alkaloids*; Brossi, A., Cordell, G. A., Eds.; Academic Press: San Diego, 1992; Vol. 41, p 125. (b) Le Hello, C. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 2000; Vol. 53, Chapter 5.

(2) Soltau, J.; Drevs, J. *IDrugs* **2004**, *7*, 380.

(3) A few recent examples: (a) Cervinka, M.; Cerman, J.; Rudolf, E. *Cancer Detect. Prev.* **2004**, *28*, 214. (b) Kristensen, B.; Noer, H.; Gramsbergen, J. B.; Zimmer, J.; Noraberg, J. *Brain Res.* **2003**, *964*, 264. (c) Nakagawa-Yagi, Y.; Choi, D. K.; Ogane, N.; Shimada, S. I.; Seya, M.; Momoi, T.; Ito, T.; Sakaki, Y. *Brain Res.* **2001**, *909*, 8. (d) Zhang, S. X.; Fengs, J.; Kuo, S. C.; Brossi, A. *J. Med. Chem.* **2000**, *43*, 167.

(4) Most recent colchicine syntheses: (a) Banwell, M. G. *Pure Appl. Chem.* **1996**, *68*, 539. (b) Lee, J. C.; Jin, S.-j.; Cha, J. *J. Org. Chem.* **1998**, *63*, 2804. For a recent review on the total synthesis of colchicine, see: (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230.

(5) Graening, T.; Friedrichsen, W.; Lex, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1524. The intention to apply the same strategy for a colchicine total synthesis was put forward after our first disclosure: McMills, M.; Wright, D. L.; Weekly, R. M. *Synth. Commun.* **2002**, *32*, 2417.

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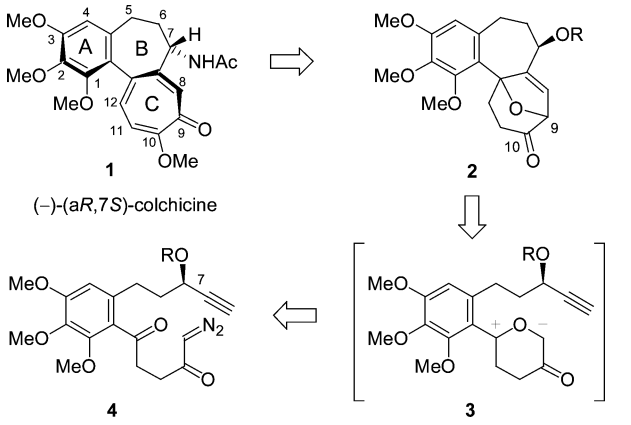
Scheme 1. Retrosynthetic Analysis

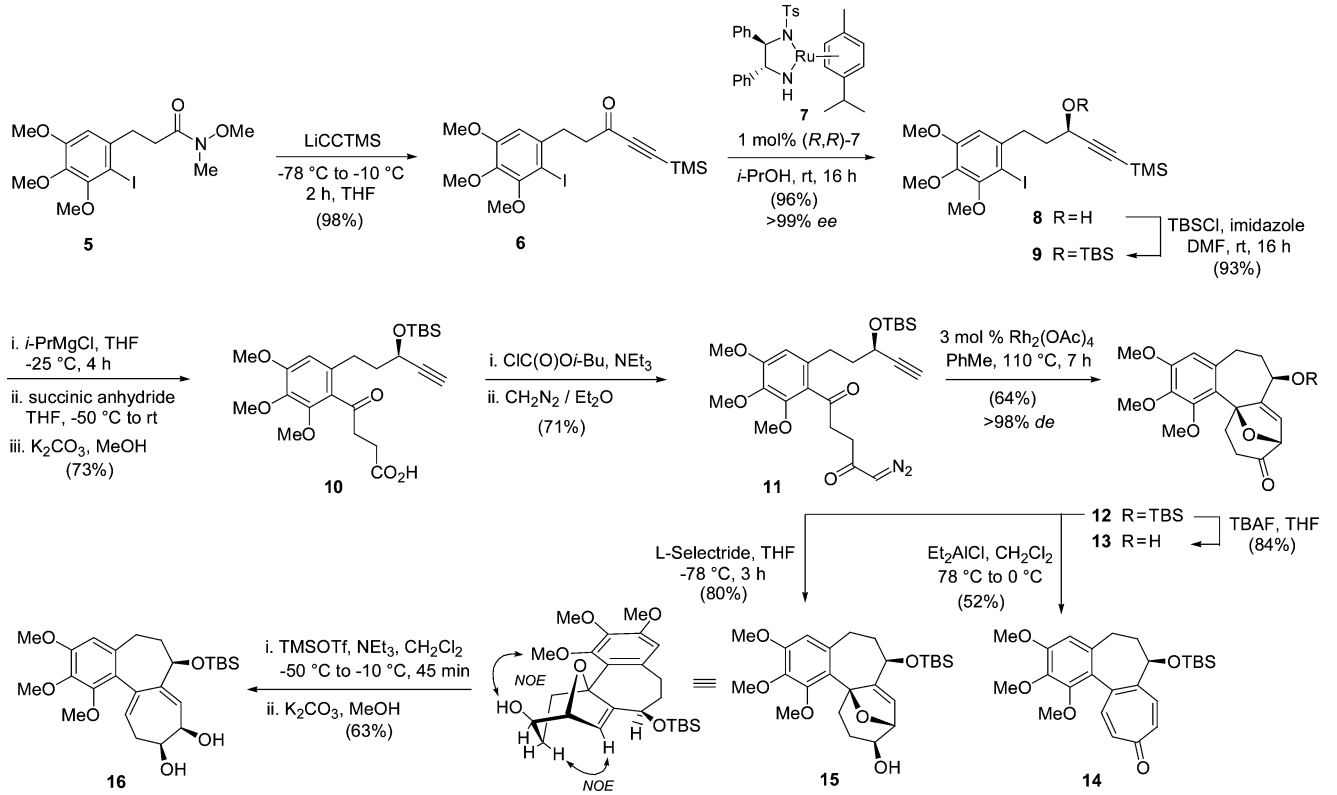


pound related to **2** in the racemic series.[5] We here disclose the completion of the synthesis of both colchicine and isocolchicine in the nonracemic series. In particular, we describe possibilities for the conversion of **2** into tropolones through selective opening of the oxa-bridge and subsequent functionalization.

An optimized sequence for the enantioselective synthesis of advanced colchicine precursors following the above-mentioned strategy is shown in Scheme 2. At first, the readily available bifunctional building block **5**[5] was reacted with lithium trimethylsilylacetylide to give the sensitive alkynone **6** in high yield. The very pure crude product was then subjected to an enantioselective transfer hydrogenation using Noyori's Ru-catalyst (*R*,*R*)-**7** in 2-propanol[6] to afford the propargylic alcohol **8** in virtually enantiopure form (>99% ee, 96% yield). The absolute configuration of **8** was confirmed by means of X-ray crystallography and is in agreement with the expected selectivity. After protection of the hydroxy group as a *tert*-butyldimethylsilyl ether (**9**), the succinoyl side chain was introduced through iodine/magnesium exchange under Knochel conditions[7,8] and subsequent addition of succinic anhydride. During workup with K_2CO_3/MeOH, the acetylenic trimethylsilyl group was cleaved off and the oxocarboxylic acid **10** was obtained in good overall yield. In situ activation of the carboxylic acid function of **10** as a pyrocarbonate followed by reaction with diazomethane afforded the α-diazoketone **11**.[9]

The key cycloaddition was then achieved by slowly adding a solution of **11** to an intensely stirred suspension of $Rh_2(OAc)_4$ (3 mol %) in refluxing toluene. Under these conditions, the key intermediate **12** was obtained in 64% yield with complete diastereoselectivity (^{1}H NMR). The relative configuration of **12** was established by NOE experiments and confirmed by X-ray crystallography, and its enantiomeric purity (99% ee) was verified by HPLC[10] using a sample of the deprotected derivative **13**. The remarkable transformation of **11** to **12** is assumed to be initiated by formation of an electrophilic Rh-carbene, which is attacked by the benzylic ketone to form a reactive carbonyl ylide **3** (Scheme 1). This 1,3-dipole is then trapped by intramolecular cycloaddition with the tethered alkyne.[11] It is noteworthy that this reaction

Scheme 2



could be successfully performed because an analogous Rh-catalyzed 7−7 cyclization of a simple (configurationally unrestrained) model system was reported to have failed.[12]

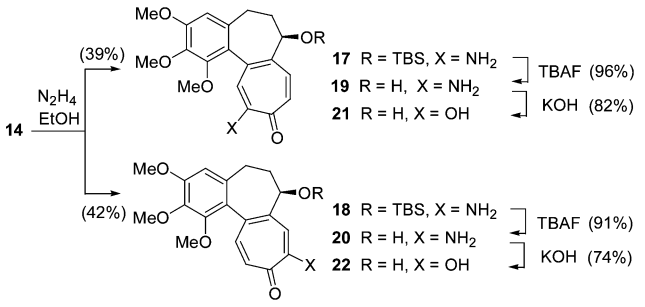
Having achieved the synthesis of **12** containing the complete carbon skeleton of colchicine, the next goal was to perform the further functionalization of ring C into the desired tropolone system. For this purpose, we envisioned that the oxa-bridge would be amenable to a regioselective cleavage in the benzylic position.[13,14]

In a first experiment carried out in the racemic series, we reacted *rac*-**12** with Et_2AlCl in dichloromethane to obtain the tropone *rac*-**14** as the only isolated product. While this represents a very convenient access to such tropone analogues of colchicine, the loss of the second oxygen substituent at ring C prompted us to search for an alternative way for the conversion of **12**. To avoid dehydratization, which obviously took place subsequently to the opening of the oxa-bridge during the formation of *rac*-**14**, we first reduced the keto functionality of **12** using L-selectride in THF. The configuration of the resulting product **15** (formed with high diastereoselectivity) and its conformation in solution were determined by NOE experiments (Scheme 2) in conjunction with an analysis of the H,H NMR coupling constants.

The selective cleavage of the oxa-bridge of **15**, which has a conformation similar to **12** in the crystalline state, was now accomplished by treatment with TMSOTf as a Lewis-acid in the presence of NEt_3. In this case, the C(10)−O bond was left unscathed. The cycloheptadienyl-bis-silyl ether, formed as the primary ring opening product, was found to easily undergo a 1,5-H shift. Therefore, the reaction product was immediately desilylated by treatment with K_2CO_3/MeOH in the cold to afford the diol **16** in 63% yield.[15]

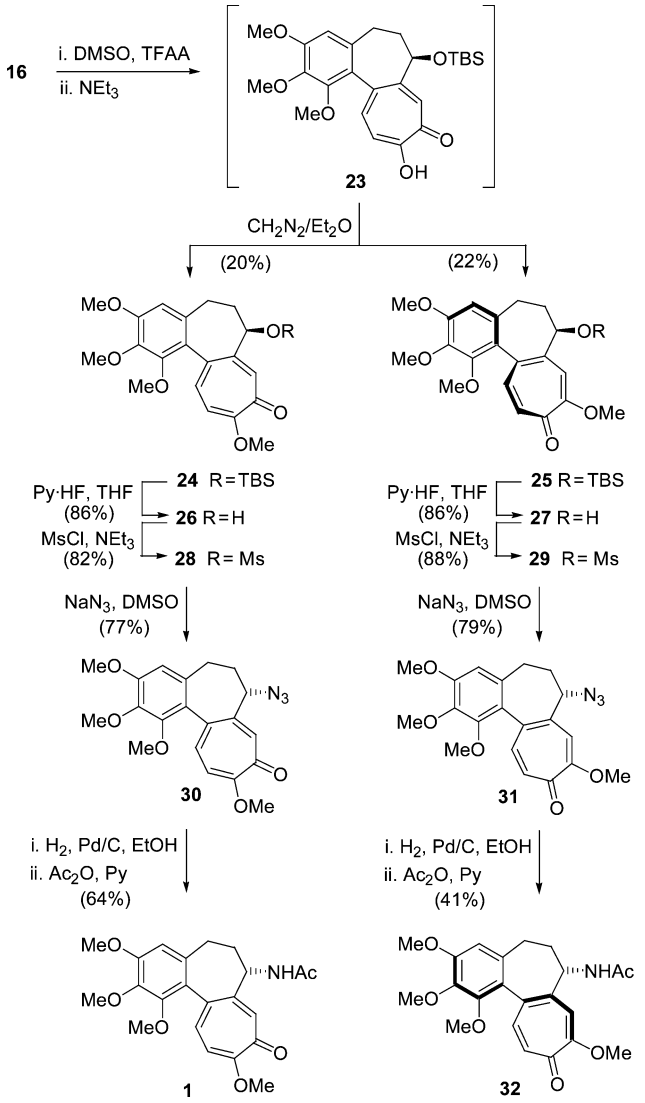
The next task was the conversion of the ring-opening products **14** or **16** into colchicinoids having a tropolone substructure. At first, we probed the possibility to transform the easily accessible compound *rac*-**14** into C(10)−C(11) oxygenated tropolones (Scheme 3). Applying the method of

Scheme 3



Nozoe for tropolone α-functionalization with hydrazine,[16] the aminotropone regioisomers *rac*-**17** and *rac*-**18** were

Scheme 4



obtained in good yields after separation (1:1 ratio). Subsequent TBS-deprotection and saponification with KOH in ethanol furnished the corresponding tropolones *rac*-**21** (a pseudocolchicine-type compound) and *rac*-**22**, respectively.

The conversion of compound **16** into the target molecules started with its oxidation using a modified Swern reagent $(CF_3CO)_2O$/DMSO[17] to give the tropolone **23** in good yield (Scheme 4). As this compound was difficult to purify, it was

(6) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285.

(7) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(8) Attempts to utilize an aryllithium species derived from **9** by treatment with BuLi failed due to deprotonation at the propargylic stereocenter (intramolecular proton transfer).

(9) Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, *48*, 8007.

(10) Diacel Chiralpak AD-H, hexane/*i*-PrOH = 9:1.

(11) (a) Padwa, A.; Fryxell, G. E.; Zhi,L. *J. Am. Chem. Soc.* **1990**, *112*, 3100. (b) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271. (c) Padwa, A.; Weingaren, M. D. *Chem. Rev.* **1996**, *96*, 223.

(12) Under the standard reaction conditions introduced by Padwa (cat. $Rh_2(OAc)_4$, PhH, rt), compound **11** only afforded a dihydropyranone side-product resulting from 1,4 H-shift of the reactive intermediate **3**. A similar side-product has been observed by Padwa in the reaction of a simple model compound. See: Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Zhang, Z. J. *J. Org. Chem.* **1992**, *57*, 5747.

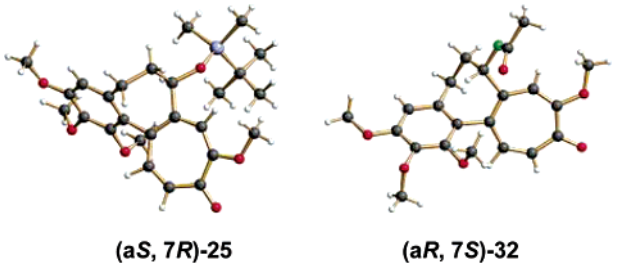


Figure 1. Structure of **25** and **2** in the crystalline state.

directly converted into the corresponding tropolonemethyl ethers by treatment with diazomethane. The products (**24** and **25**) could be separated by column chromatography. The structural assignment was confirmed by X-ray crystallography of the isocolchicine-type regioisomer **25**. Interestingly, the large OTBS residue at the *R*-configurated stereocenter C(7) in ring B is adopting a pseudoequatorial position, thus predefining an *S* configuration of the chiral biaryl axis (Figure 1).

While the conversion of **24** into colchicine (**1**) had already been performed by Banwell,[4a,18] we decided to also perform the conversion of **25** into isocolchicine (**32**). As shown in Scheme 4, the TBS protecting groups of **24** and **25** were removed with Py·HF to provide compounds **26** and **27** respectively, both in 86% yield. Mesylation and subsequent SN_2 amination using sodium azide in DMSO smoothly afforded the azides **30** and **31**. The syntheses were completed by reduction of the azides (H_2, Pd/C) and final acetylation to give colchicine (**1**) and isocolchicine (**32**). Adequate crystals of **32** were obtained from EtOAc/ether, and their crystallographic analysis showed (as expected) the 7*S* configuration and, correspondingly, the *R* configuration of the chiral axis (Figure 1). This nicely demonstrates once again the induction of the biaryl chirality by the configuration at the stereocenter C(7).[19]

In conclusion, we have completed new enantioselective total syntheses of (−)-colchicine (**1**) and (−)-isocolchicine (**32**). Furthermore, an entry to the (unnatural) pseudocolchicine series was opened. Starting from **5**, the syntheses reach the target compounds **1** and **32** in only 15 steps (overall yield ca. 1%). The success of the synthetic scheme results from a powerful metal-catalyzed domino transformation as a key step. We are optimistic that this strategy can also be applied to the synthesis of novel colchicine analogues with a modified ring B substructure.

Acknowledgment. This work was supported by the Volkswagen Foundation, the Fonds der Chemischen Industrie, and the Humboldt Foundation (fellowship to V.B.). Donations of chemicals from Bayer AG and Chemetall are gratefully acknowledged.

Supporting Information Available: Experimental procedures and characteristic data of new compounds, as well as details of the X-ray crystal structure analyses of compounds **8**, **12**, **25**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Plüg, C.; Friedrichsen, W. *Tetrahedron Lett.* **1992**, *33*, 7509. See also: (b) Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Prithard, G. J. *Org. Lett.* **1999**, *1*, 1933. For a review on ring opening reactions in oxabicyclic ring systems, see: (c) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

(14) The cleavage of the benzylic C−O bond should also be stereoelectronically assisted as the oxa-bridge is aligned with the π-system of the aromatic ring.

(15) Compound **16** also proved to be rather sensitive toward decomposition and was usually directly further oxidized to the tropolone **23** (Scheme 4).

(16) (a) Nozoe, T. *Chem. Ind.* **1955**, 66. (b) Nozoe, T. *Proc. Jpn. Acad.* **1953**, *29*, 169. (c) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425. (d) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713.

(17) (a) Baldwin, J. E.; Mayweg, A. v. W.; Pritchard, G. J.; Adlington, R. M. *Tetrahedron Lett.* **2003**, *44*, 4543. (b) Celanire, S.; Marlin, F.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron* **2005**, *61*, 3025.

(18) Banwell, M. G.; Lambert, J. N.; Mackay, M. F.; Greenwood, R. J. *J. Chem. Soc., Chem. Commun.* **1992**, 974.

(19) According to NMR spectroscopic investigations, the rates of (a*S*)−(a*R*) interconversion for colchicine-type compounds were found to be of the order of 10^{-4}−10^{-5} s^{-1} at 22 °C, which corresponds to a free activation energy of 22−24 kcal·mol^{-1}. For details, see ref 1a.