Tetrahedron 73 (2017) 5563–5576

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Woodward's unfinished total synthesis of colchicine, a collaborative prelude

Hans-Peter Sigg [a,†], James B. Hendrickson [b], G. Wayne Craig [c,*]

[a] Sandoz AG, CH-4104 Oberwil, Switzerland
[b] Dept. of Chemistry, Brandeis University, Waltham, MA, USA
[c] Lead Finding Research, Syncoba GmbH, CH-4144 Arlesheim, Switzerland

ARTICLE INFO

Article history:
Received 25 September 2015
Received in revised form 7 May 2016
Accepted 19 May 2016
Available online 24 May 2016

Dedicated to the memory of *Uli Schwieter* (1928–2014) and *Heinz-Günther Viehe* (1929–2010)

Keywords:
History of chemistry
Robert B. Woodward
Albert Eschenmoser
Total synthesis
Colchicine
Vitamin B_{12}

ABSTRACT

This article describes *Robert B. Woodward*'s unfinished total synthesis of colchicine and the strategy that required a brilliant new beginning in 1959.

1. Introduction

In 1959 the first total synthesis of colchicine (Fig. 1) was completed at the Eidgenössische Technische Hochschule (ETH), Zürich by a young *Albert Eschenmoser* (b. 1925). It represented a maturation in *Eschenmoser*'s already close relationship to Harvard chemist, *Robert B. Woodward* (1917–1979), who had frequently presented lectures at the ETH. *Woodward* was also on the brink of completing his own synthesis of colchicine by another route in 1959. However, synthetic chemistry can be unforgiving and *Woodward*, although a well-established expert in natural product synthesis, had to rethink his first synthesis to finally achieve a successful completion in 1963.

In this article we describe *Woodward's* 1959 unfinished synthesis, which failed to achieve colchicine (Fig. 1), and discuss it in light of his successful synthesis reported in 1963. We also discuss *Woodward's* relationship with *Eschenmoser* who successfully completed the first total synthesis of colchicine in the same year by another strategy. Their brief professional encounter in the course of this synthesis would lay the foundation for their remarkable collaboration that later fully engaged their research groups in the legendary chemistry adventure, the total synthesis of CN-cobalamin better known as vitamin B_{12} (Fig. 2).

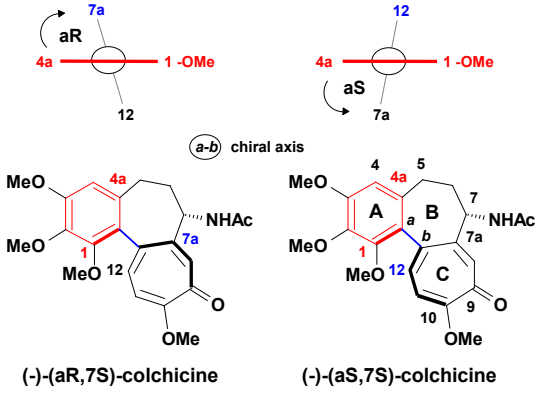

Fig. 1. *Natural colchicine* (−)-(a*R*,7*S*), atropisomer left.

* Corresponding author. E-mail address: cralion@sunrise.ch (G.W. Craig).
† Retired.

http://dx.doi.org/10.1016/j.tet.2016.05.051
0040-4020/

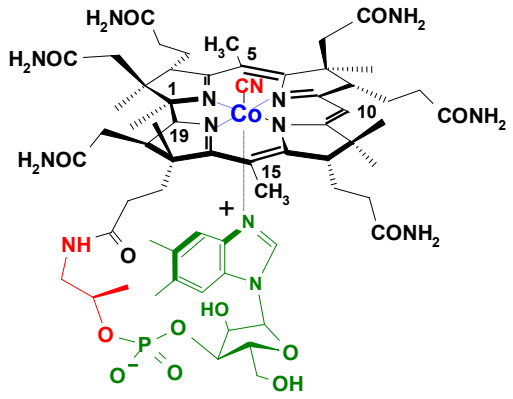

Fig. 2. *CN-cobalamin* (vitamin B_{12}).

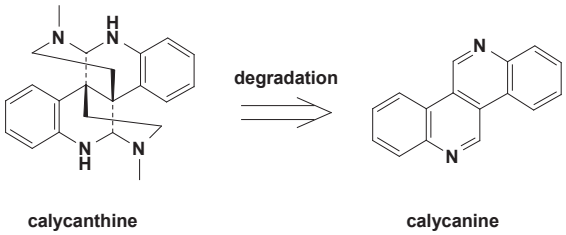

Fig. 3. Degradation of calycanthine to calycanine.

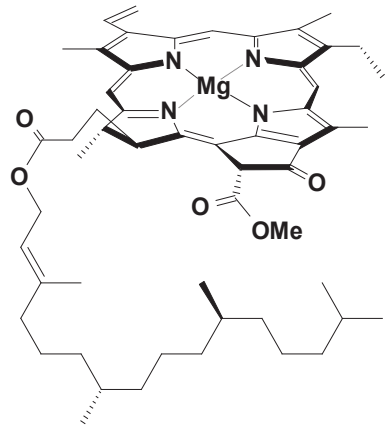

Fig. 4. Chlorophyll-*a* synthesis completed in 1960.

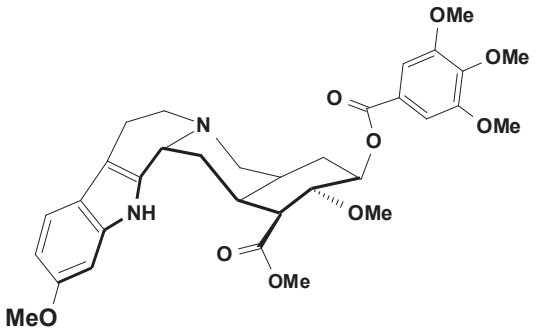

Fig. 5. Reserpine synthesis completed in 1956.

2. Woodward's successful synthesis of colchicine, 1963

A recent review by *Graening* and *Schmalz* summarized in-detail the various synthetic routes to colchicine (Fig. 1) over the last 50 years.[1] The colchicine (Fig. 1) molecule contains only one asymmetric carbon at C7, however this very unusual structure with two fused seven-membered rings, one of which is a tropolone, offers an attractive and challenging synthetic target for the creative chemist. In Nature, colchicine (Fig. 1) exists as the (−)-(a*R*, 7*S*)-atropisomer with an approximate 90° dihedral angle between (Fig. 1, view along the *a*-*b*—chiral axis) the benzene A-ring and tropolone C-ring.[2] This atropisomerism was not recognized at the time of the initial syntheses but wreaked havoc during the synthesis due to the formation of unexpected '*side products*'. From a pharmaceutical perspective, biological studies have shown that only natural (−)-(a*R*,7*S*)-colchicine inhibits cell division by interruption of tubulin protein depolymerization during cell mitosis.[1]

Woodward had designed into both of his colchicine syntheses a key tactic to use a heterocycle to mask the C7-carbonyl in the B-ring (Scheme 1, *stage* 1) and the double bond in the tropolone C-ring. After demasking the heterocyclic scaffold (*stage* 3), methylation of the equilibrium mixture of colchiceine **2a** and regioisomer **2b** (*stage* 4)[3] resulted in the desired colchicine **1a**. Before presenting the unpublished work, we first examine *Woodward's* successful isothiazole route to colchicine reported at the Harvey Lectures in 1963 (Schemes 2–5).[4]

The 1,2-thiazole (isothiazole) **4** was synthesized by 1,3-addition of the aminocrotonate **1** to thiophosgene which can eliminate HCl under basic conditions with subsequent formation of the reactive thiocarbonyl chloride **4a**. Regioselective addition of the imine-NH to the thiocarbonyl resulted in ring closure to form the desired isothiazole **4** (Scheme 2). In his lecture, *Woodward* related,

> *One aspect of our plan to base a synthesis of colchicine upon a simple isothiazole intermediate might well have given us pause. A forceful reminder of the fantastic multiformity of organic chemistry is provided by the fact that although literally millions of different organic molecules were known at the time our plan was laid down, no simple isothiazole of any kind had been prepared!*[4]

The methyl group of isothiazole **4** was photobrominated (Scheme 1, *step* 2) followed by alkylation (*step* 3) to the phosphonium salt **6**. The isothiazole ylide, prepared in situ by base treatment of **6**, reacted with trimethoxybenzaldehyde to *cis*-alkene **7** (*step* 4).

Chemoselective diimide reduction of the C—C-double bond of **7** (Scheme 3, *step* 5) to **8a** did not reduce the sensitive N—S bond of the isothiazole. Reductive-oxidative manipulation of the ester group **8a** to aldehyde **8c** allowed elongation by another *Wittig* coupling with ylide **9** (*steps* 8–9). Conversion of the *cis-trans* mixture **8d** to the all-*trans* isomer was achieved under free-radical conditions (*step* 10). The closure of the B-ring took place by a *Friedel—Crafts* 1,5-conjugate addition to **10** (*step* 11), diimide reduction of the double bond (*step* 12) and lithiation of the isothiazole and dry ice quench introduced the carboxyl group (*step* 13). Transformation to the ester **11** (*step* 14) enabled synthesis of the second seven-membered tropone C-ring **13** by *Dieckmann* condensation and decarboxylation (*steps* 15–16).

Introduction of a formyl group in **14a** (*step* 17) had a stronger activating effect compared to the ester group (not shown) and it was conveniently lost during formation of the dithioketal **14d** with the bis-thiotosylate reagent **15** (*step* 18). A mercuric acetate assisted hydrolysis of the dithioketal (*step* 19) demasked the α-diketone **16**. Acetylation (*step* 20) trapped the C9,10-double bond as the enediol diacetate **17** which was conveniently oxidized and hydrolyzed to afford the aromatic tropolone **18** (*step* 21).