ORGANIC LETTERS

2011
Vol. 13, No. 4
800–803

Fast and Flexible Synthesis of Pantothenic Acid and CJ-15,801

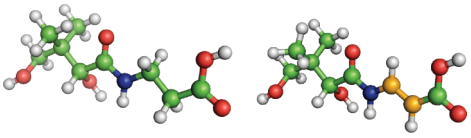
Alan L. Sewell,[†] Mathew V. J. Villa,[†] Mhairi Matheson,[†] William G. Whittingham,[‡] and Rodolfo Marquez*[,†,§]

WestCHEM, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom, and Syngenta, Jealott's Hill Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom

r.marquez@chem.gla.ac.uk

Received December 23, 2010

ABSTRACT



The fast and efficient syntheses of pantothenic acid and the antiparasitic agent CJ-15,801 have been achieved starting from a common imide unit through the selective manipulation of enamide intermediates.

Pantothenic acid (**1**), otherwise known as vitamin B_5, is a water-soluble vitamin whose name is derived from the Greek *pantothen* meaning "from everywhere". It gets this name from the fact that small quantities of pantothenic acid are found in nearly every natural food source. Although no specific role has been determined, pantothenic acid deficiencies can result in fatigue, allergies, nausea, and abdominal pain.[1] Pantothenic acid supplements, however, have also shown a measurable benefit on patients suffering from diabetes.[2] The dextrorotatory D-(−) enantiomer of pantothenic acid is the biologically active isomer (Figure 1).

Although pantothenic acid can be found in numerous foods, no RDA has been proposed. However, it is possible to find vit B_5 in many dietary supplements (as calcium-D-pantothenate), and a number of beverage companies

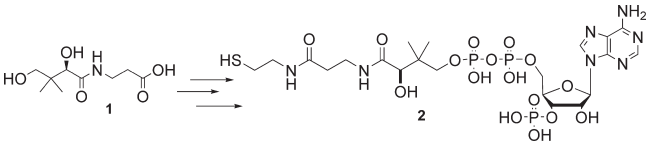


Figure 1. Pantothenic acid (**1**) and CoA (**2**).

are now adding pantothenic acid to their products. Studies have also shown that pantothenic acid has a positive effect on the treatment of acne, and the cosmetic industry routinely adds pantothenic acid to various cosmetic products, including shampoo, and continuously advertises pantothenic acid additives.[3] Hence it is not surprising that the increased industrial demand for

[†] University of Glasgow.
[‡] Syngenta.
[§] Ian Sword Reader of Organic Chemistry and EPSRC Leadership Fellow.

(1) Sweetman, L. In *Encyclopedia of Dietary Supplements*; Marcel Dekker: New York, NY, 2005; Vol. 1, p 517.
(2) (a) Abdelatif, M.; Yakoot, M.; Etmaan, M. *J. Wound Care* **2008**, *17*, 108. (b) Weimann, B. J.; Hermann, D. *Int. J. Vitam. Nutr. Res.* **1999**, *69*, 113.
(3) (a) Leung, L. H. *Med. Hypotheses* **1995**, *44*, 490. (b) Leung, L. H. *J. Orthomol. Med.* **1997**, *12*, 99.
(4) (a) Vandamme, E. J. *Biotechnology of Vitamins, Pigments, and Growth Factors*; Elsevier: New York, NY, 1989; p 209. (b) Shimizu, S.; Kataoka, M.; Chung, M. C.; Yamada, H. *J. Biol. Chem.* **1988**, *263*, 12077.

10.1021/ol103114w
Published on Web 01/20/2011

pantothenic acid has resulted in the development of a number of synthetic and biochemical routes for its production.[4]

Biologically, pantothenic acid is the starting substrate in the biosynthesis of coenzyme A (**2**, CoA), an enzyme cofactor necessary for a number of metabolic processes including the citric acid cycle.[5] Coenzyme A plays a major role in the biosynthesis of many important metabolites such as fatty acids, cholesterol, and acetylcholine.[6]

Numerous studies have shown that a range of parasites are unable to synthesize pantothenate and are therefore dependent on the uptake of pantothenic acid from their environment for the synthesis of CoA.[7−9] This dependence is exhibited in the malarial parasite *P. falciparum*.[10] Blood cells infected by plasmodia utilize new permeability pathways to bring in small molecules such as pantothenate, whereas uninfected cells do not exhibit these molecule permeability pathways.[10]

CJ-15,801 (**3**) is a pantothenic acid analogue isolated from *Seimatosporum* sp. CL28611.[11] Structurally, CJ-15,801 differs from pantothenate only in the fact that it has a double bond in the β-alanine moiety. Biologically, CJ-15,801 has shown selective activity against *P. falciparum* and multidrug-resistant *S. aureus* with MIC values between 30 and 230 μM without affecting mammalian cell lines.[11] This makes CJ-15,801 **3** an interesting lead for the generation of potential new antiparasitic therapies (Figure 2).

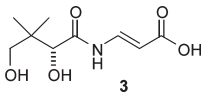


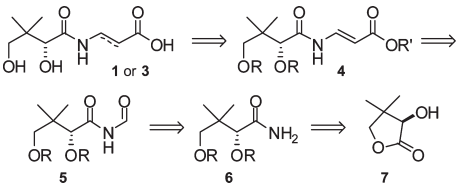
Figure 2. Antiplasmodial agent CJ-15,801 (**3**).

The combination of its promising biological profile, coupled with its interesting enamide unit, has made CJ-15,801 an attractive synthetic target, with a total synthesis reported by Porco[12] and a formal synthesis reported by Nicolaou.[13]

We would like to report our efficient and divergent synthesis of both pantothenic acid (**1**) and CJ-15,801 (**3**) taking advantage of the imide olefination methodology developed recently in our group.[14,15]

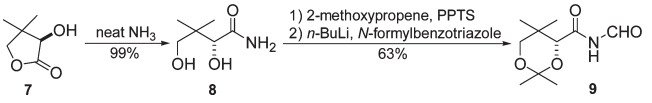
Retrosynthetically, we envisioned both pantothenic acid and CJ-15,801 as originating from a common enamide intermediate **4**, which could be generated through the olefination of imide **5**. Imide **5** could in turn originate from the *N*-formylation of amide **6**. Amide **6** could be obtained efficiently from the ammonia mediated opening of pantolactone **7** (Scheme 1).

Scheme 1



Synthetically, treatment of D-pantolactone **7** with neat liquid ammonia generated the desired amide **8**, which was then protected as the corresponding acetonide. *N*-Formylation of the amide intermediate then afforded the key *N*-formyl imide intermediate **9** in good yield over the 3-step sequence (Scheme 2).

Scheme 2



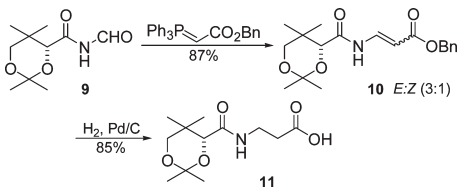
Synthesis of Pantothenate. The key imide intermediate **9** having been accessed, the choice of enamide unit to be generated was considered carefully. It was rationalized that by employing the correct choice of ester derivative it might be possible to simultaneously reduce the enamide unit and liberate the carboxylic acid unit.

Olefination of imide **9** with benzyltriphenylphosphoranylidene acetate gave the desired benzyl ester **10** in good yield and as a 3:1 mixture of *E*:*Z* isomers. With the desired enamide **10** at hand, the tandem hydrogenation−hydrogenolysis sequence was attempted. Gratifyingly, treatment of (*Z*)-enamide **10*Z*** with 10% palladium on carbon under a hydrogen atmosphere cleanly gave the reduced carboxylic acid **11** in excellent yield (Scheme 3).

Having successfully shown the feasibility of the reduction-deprotection sequence, the decision was taken to carry out this transformation as the final stage of the synthesis for ease of compound handling. Thus, enamide **10*E*** was treated with $BiCl_3$ to generate the free diol **12** in good yield. Treatment of enamide **12** under the same hydrogenation−hydrogenolysis conditions used previously

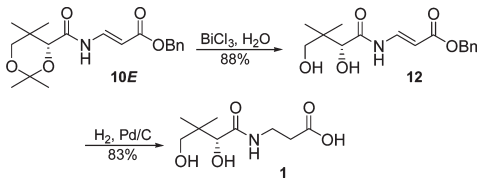
(5) Daugherty, M.; Polanuyer, B.; Farrell, M.; Scholle, M.; Lykidis, A.; de Crécy-Lagard, V.; Osterman, A. *J. Biol. Chem.* **2002**, *277*, 21431.
(6) Russell, D. W. *Cardiovas. Drugs Ther.* **1992**, *6*, 103.
(7) Spry, C.; Kirk, K.; Saliba, K. J. *FEMS Microbiol. Rev.* **2008**, *32*, 56.
(8) Saliba, K. J.; Horner, A. H.; Kirk, K. *J. Biol. Chem.* **1998**, *273*, 10190.
(9) Saliba, K. J.; Kirk, K. *J. Biol. Chem.* **2001**, *276*, 18115.
(10) Saliba, K. J.; Ferru, I.; Kirk, K. *Antimicrob. Agents Chemother.* **2005**, *49*, 632.
(11) Saliba, K. J.; Kirk, K. *Mol. Biochem. Parasitol.* **2005**, *141*, 129.
(12) Han, C.; Shen, R.; Su, S.; Porco, J. A. *Org. Lett.* **2004**, *6*, 27.
(13) Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992.
(14) Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R. *Org. Biomol. Chem.* **2009**, *7*, 2170.
(15) Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. *Org. Lett.* **2007**, *9*, 1631.

Scheme 3



afforded pantothenic acid **1** as the free acid in good overall yield (Scheme 4).

Scheme 4



Although the reactions and yields are shown only for the *E* isomer, similar yields were obtained when a mixture of the (*E*)- and (*Z*)-benzyl esters were subjected to the same conditions to generate D-(−)-pantothenic acid, **1**.

Total Synthesis of CJ-15,801. The synthesis of CJ-15,801 (**3**) posed a different challenge as the unmasking of the carboxylate group was to be achieved without affecting the enamide double bond. Porco and Nicolaou resorted to the use of allyl esters in their respective syntheses, which required an elaborate procedure to generate the free acid.[12,13]

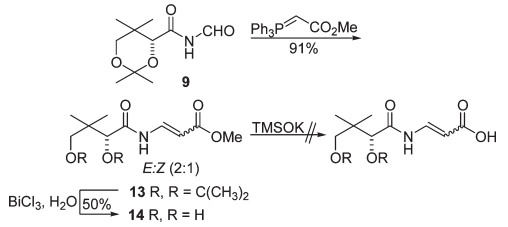
Our initial studies toward the synthesis of CJ-15,801 focused on the selective hydrogenolysis of the previously obtained benzyl ester unit without affecting the enamide double bond by taking advantage of hydrogen transfer conditions.

Unfortunately, despite extensive experimentation with a variety of hydrogen transfer reagents and metal catalysts, the hydrogenolysis could not be achieved selectively either on the ketal protected **10*E*** or free diol **12**. Careful monitoring of the reaction showed that in all cases, hydrogenation of the enamide double bond was more rapid than the desired hydrogenolysis. Attempts to convert the benzyl ester into a more labile silyl ester using palladium mediated silylation were also unsuccessful under all the conditions attempted.

In a modified approach, imide **9** was treated with methyltriphenylphosphoranylidene acetate to generate the desired methyl ester **13** as a 2:1 ratio of *E*:*Z* isomers (Scheme 5).

Unfortunately, TMSOK treatment of both the acetonide and free diol methyl ester enamides **13** and **14** failed

Scheme 5

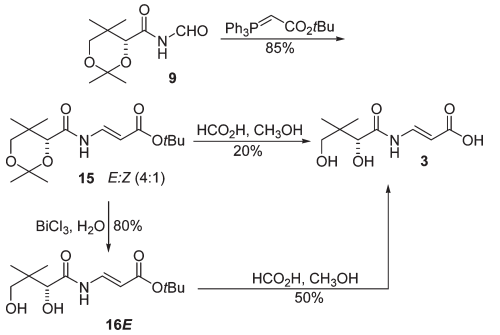


to generate the desired carboxylic acids, affording instead unreacted starting materials in both cases.

Faced with the difficult unmasking of the carboxylic acid, a modified protecting group strategy was envisioned. Thus, treatment of imide **9** with *tert*-butyl triphenylphosphoranylidene acetate cleanly generated the desired *tert*-butyl ester enamide **15** as a separable 4:1 *E*:*Z* mixture of double bond isomers.

With the clean (*E*)-enamide **15*E*** in hand, the key double deprotection sequence was attempted. As expected, treatment of enamide **15*E*** with $BiCl_3$ cleanly removed the acetonide unit in good yield to afford diol **16*E***. Gratifyingly, the key removal of the *tert*-butyl ester unit was also successfully carried out using formic acid to afford CJ-15,801 in good yield (Scheme 6).

Scheme 6



The fact that the enamide unit was stable to the mildly acidic conditions used to unmask the carboxylic acid unit made us consider the possibility that the removal of both the acetonide and *tert*-butyl ester protecting groups could be achieved simultaneously. Indeed, treatment of ester **15*E*** with formic acid in methanol at room temperature yielded CJ-15,801 in a single step, albeit in lower yield than the two-step sequence.

The structure of synthetic CJ-15,801 obtained by both methods was corroborated by comparison with the spectral data and optical rotation published in the literature.

However, despite having completed the total synthesis of CJ-15,801 (**3**) via two different end game approaches, we were still interested in developing a synthetic route

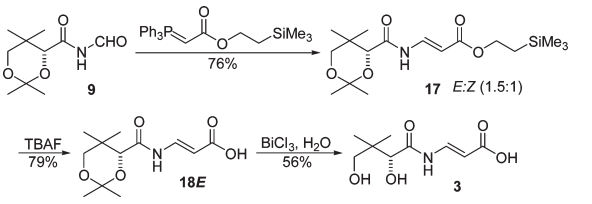
which would allow us to unmask the carboxylic acid unit while retaining the acetonide protecting group in place. Such a route would not only provide a potentially higher yielding end game sequence but would also provide us with a key free acid intermediate that could prove invaluable in the divergent and efficient generation of novel enamide bearing CJ-15,801 analogues.

Our modified approach started from the key *N*-formyl imide **9**, which was olefinated with trimethylsilylethylphosphoranylidene acetate[16] to generate the TMSE protected ester **17** as a separable 1.5:1.0 *E*:*Z* mixture of double bond isomers in excellent yield (Scheme 7). Gratifyingly, the major **17*E*** isomer could be selectively TMSE deprotected to generate the desired key free carboxylic acid **18*E*** in high yield and as a single double bond isomer. Significantly, acetonide removal using $BiCl_3$ proceeded cleanly to afford CJ-15,801 in an improved higher overall yield.

In conclusion, we have completed the divergent synthesis of both pantothenic acid (**1**) and CJ-15,801 (**3**). Our approach is fast and flexible, compares favorably with other approaches published to date in terms of efficiency and cost, and is amenable for the rapid and efficient synthesis of CJ-15,801 and pantothenic acid analogues. Furthermore, this work opens up the possibility to develop CJ-15,801 as a viable antiparasitic drug lead.

(16) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387.

Scheme 7



Acknowledgment. We would like to thank the Lord Kelvin-Smith programme, the School of Chemistry, and Syngenta for postgraduate support (M.M., A.L.S., and M.V.J.V., respectively). The authors also thank Dr. Ian Sword and the EPSRC for funding.

Note Added after ASAP Publication. There were errors throughout the version of this paper and the Supporting Information published on January 12, 2011. The correct version published January 28, 2011.

Supporting Information Available. Experimental procedures and characterization data of the described compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.