ORGANIC LETTERS

2013
Vol. 15, No. 5
1004–1007

Enantioselective Total Synthesis of (+)-Colletoic Acid via Catalytic Asymmetric Intramolecular Cyclopropanation of an α-Diazo-β-keto Diphenylphosphine Oxide

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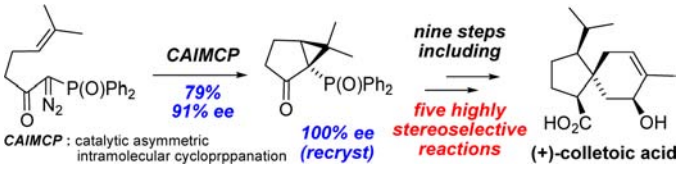
Received December 18, 2012

ABSTRACT



The enantioselective total synthesis of (+)-colletoic acid, a potent naturally occurring 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor, is described. This total synthesis features a highly enantioselective catalytic asymmetric intramolecular cyclopropanation of an α-diazo-β-keto diphenylphosphine oxide and five highly stereoselective reactions (cyclopropane opening, Diels–Alder reaction, iodolactonization, alkene formation, and reduction of α,β-unsaturated carboxylic acid).

(+)-Colletoic acid (Figure 1) was isolated from a fungus identified as *Colletotrichum gloeosporioides* SANK 21404 by a research group at Daiichi Sankyo Co., Ltd.[1] The relative stereochemistry of (+)-colletoic acid was confirmed by X-ray crystallographic analysis, and its absolute structure was elucidated by a modified Mosher's method.[1] (+)-Colletoic acid is a potent naturally occurring inhibitor of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) with an IC_{50} of 13 nM and a K_i value of 3.9 nM but exhibits almost no effect on 11β-HSD2 (IC_{50} = >10000 nM).

Although 11β-HSD1 is an NADP(H)-dependent oxidoreductase, it primarily acts as a reductase in intact cells, converting inactive cortisone to cortisol, a potent bioactive hormone in humans. Cortisol elevates blood glucose levels by increasing glucose production in the liver as well as by inhibiting uptake and disposal of glucose in muscle and adipose tissues.[2]

Consequently, it has been suggested that metabolic syndrome may be attributed to increased levels of cortisol, which may be derived from elevated 11β-HSD1 activity, and that inhibition of 11β-HSD1 may reduce cortisol. Thus, 11β-HSD1 has been a promising target for the treatment of diseases associated with metabolic syndrome.[3]

(+)-Colletoic acid is a member of the acorane-type sesquiterpenes,[4] a class of molecules featuring a spiro-[4.5]decane core, which consists of a six-membered ring containing a methallyl alcohol and a five-membered ring bearing *cis*-oriented isopropyl and carboxyl groups. The core of (+)-colletoic acid possesses four stereogenic centers, three of which are successive and incorporate the all-carbon quaternary stereogenic spiro center.

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(4) For recently reported acorane-type sesquiterpenes, see: (a) Sun, L.; Li, D.-L.; Tao, M.-H.; Dan, F.-J.; Zhang, W.-M. *Helv. Chim. Acta* **2012**, *95*, 157. (b) Song, T.-F.; Zhang, W.-D.; Xia, X.-H.; Shen, Y.-H.; Liu, C.-M.; Lin, S.; Jin, H.-z.; Li, H.-L. *Arch. Pharm. Res.* **2009**, *32*, 1233. (c) Nagashima, F.; Suzuki, M.; Takaoka, S.; Asakawa, Y. *J. Nat. Prod.* **2001**, *64*, 1309.

10.1021/ol303459x
Published on Web 02/11/2013

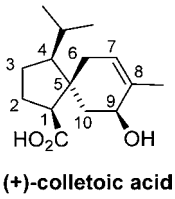


Figure 1. Structure of (+)-colletoic acid.

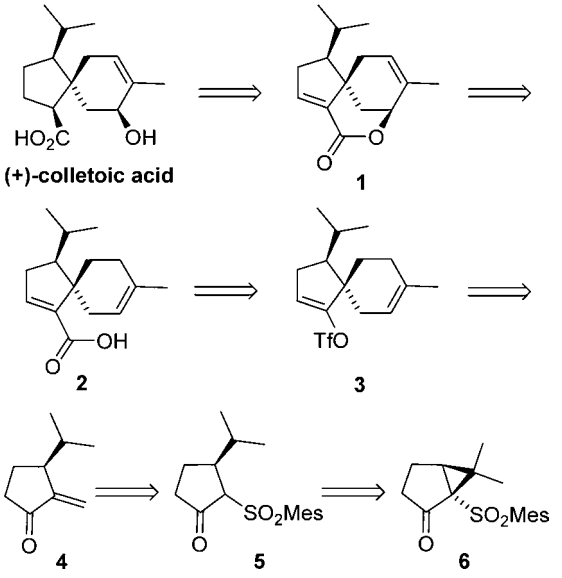
To the best of our knowledge, (+)-colletoic acid is the first acorane-type sesquiterpene with a carboxyl group at the C1 position, which has been reported to be a crucial moiety for 11β-HSD1 inhibitory activity since all other acorane-type sesquiterpenes and (+)-colletoic acid methyl ester have no 11β-HSD1 inhibitory activity.[1] The potent 11β-HSD1 inhibitory activity, unique structure, and structure–activity relationships of (+)-colletoic acid make it an attractive target. Herein, we report the first enantioselective total synthesis of (+)-colletoic acid.

We select lactone **1** (Scheme 1) as the synthetic intermediate for (+)-colletoic acid because the C1–C2 electron-deficient alkene would preferentially undergo nucleophilic reduction at the less-hindered face to afford the desired product. Lactone **1** was envisaged to be prepared from **2** via electrophile-induced lactonization and subsequent alkene formation. Carboxylic acid **2** would be obtained by palladium-catalyzed carbonylation of enol triflate **3**, which could be prepared from the corresponding ketone. Construction of the scaffold of **3** was envisioned via Diels–Alder reaction of enone **4** with isoprene because it could preferentially occur at the less-hindered side of **4**. Enone **4** was thought to be obtained by the reaction of keto sulfone **5**, which would be prepared from cyclopropane **6**.

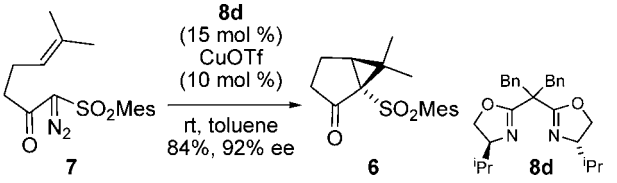
We reported the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-keto sulfone **7**, which successfully affords **6** in high yield and ee (Scheme 2).[5] Moreover, enantiopure **6** is easily available by a single recrystallization owing to its highly crystalline nature. Hence, we initially studied the total synthesis of (+)-colletoic acid starting from **6**.

The cyclopropane-opening reaction of **6** proceeded with several reducing reagents, but in most cases, both **5** and the corresponding desulfonylated product were formed. The reaction with tri-*n*-butyltin hydride in the presence of AIBN, however, provided **5** as a single isomer in 67% yield (Scheme 3). It was expected that β-keto sulfone **5** would afford compound **9** upon reaction with formaldehyde or an equivalent because the same reaction has been reported for the corresponding β-keto esters[6] and a simple

Scheme 1



Scheme 2



β-keto aryl sulfone.[7] Under the reported conditions, however, **9** was not formed. Moreover, reductive enolate formation from **5** with lithium naphthalenide or SmI_2 and subsequent reaction with formaldehyde or its equivalents[8] did not afford **10**, and the corresponding desulfonylated product was formed instead. The same results were obtained in the reaction of less bulky phenyl sulfone **5a**, and attempted Julia–Kociensky-type reactions of **5b**[9] and **5c**[10] also failed to provide the desired products.

As no promising results were obtained in the reaction of **5**, we turned our attention to β-keto phosphine oxide **11** (Scheme 3), which should undergo a Horner reaction of the β-keto phosphine oxide with an aldehyde. Compound **11** was thought to be prepared by the same method as **5**. However, to the best of our knowledge, no CAIMCP of α-diazo-β-keto diphenylphosphine oxide has been reported thus far. Hence, we decided to develop the CAIMCP of α-diazo-β-keto

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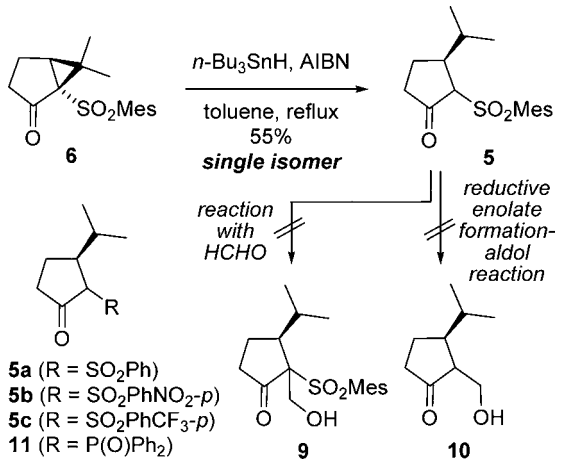
(9) Mirk, D.; Grassot, J.-M.; Zhu, J. *Synlett* **2006**, 1255.

(10) (a) Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett.* **2004**, *45*, 573. (b) Alonso, D. A.; Fuensanta, M.; Nájera, C.; Varea, M. *J. Org. Chem.* **2005**, *70*, 6404.

Scheme 3

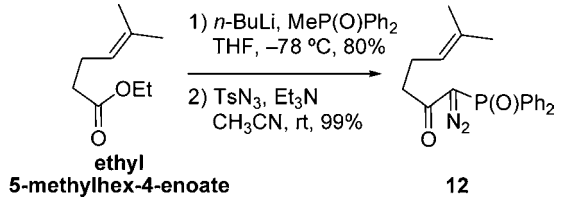


diphenylphosphine oxide because the CAIMCP of α-diazo-β-keto arylsulfones we previously developed indicated that the bulky diphenylphosphine oxide group could control the enantioselectivity of the CAIMCP.

α-Diazo-β-keto diphenylphosphine oxide **12** (Scheme 4) was prepared through the reaction of ethyl 5-methylhex-4-enoate[11] with lithiated methyl diphenylphosphine oxide and subsequent diazo-transfer.

The CAIMCP of α-diazo-β-keto sulfones developed by us revealed that the enantioselectivity could be improved by changing the structure of the bisoxazoline ligands. Hence, the CAIMCP of **12** was examined using a variety of bisoxazoline ligands **8a**–**h**[12] bearing an isopropyl group on the oxazoline and different substituents at the bisoxazoline junction (Table 1). The reactions with ligands **8a**–**c** (15 mol %) and CuOTf (10 mol %) afforded desired product **13** with ee's in the range of 63–75% (entries 1–3). Better results were obtained from the reactions with ligands **8d**–**h** and CuOTf (entries 4–8). Finally, **13** (91% ee) was obtained by the reaction with ligand **8d** (15 mol %) and $CuBF_4$ (10 mol %) in 79% yield (entry 9).

Scheme 4



Compound **13** was highly crystalline, and 58% of enantiopure **13** was obtained by a single recrystallization. Its absolute configuration was elucidated by X-ray crystallographic analysis.[13] The crystal structure indicated that

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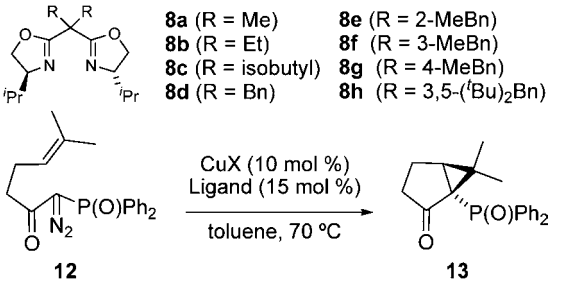
(13) See the Supporting Information.

Table 1. CAIMCP of α-Diazo-β-keto Diphenylphosphine Oxide **12**



entry	ligand	CuX	time (h)	yield[a] (%)	ee[b] (%)
1	**8a**	CuOTf[c]	1.5	43	63
2	**8b**	CuOTf[c]	16	37	73
3	**8c**	CuOTf[c]	4	90	75
4	**8d**	CuOTf[c]	4	59	86
5	**8e**	CuOTf[c]	3	51	75
6	**8f**	CuOTf[c]	19	43	81
7	**8g**	CuOTf[c]	5	44	84
8	**8h**	CuOTf[c]	30	64	84
9	**8d**	$CuBF_4$[d]	12	79	**91**

[a] Isolated yields. [b] ee determined by HPLC. For conditions, see the Supporting Information. [c] $(CuOTf)_2 \cdot$toluene was used. [d] $CuBF_4 \cdot 4MeCN$ was used.

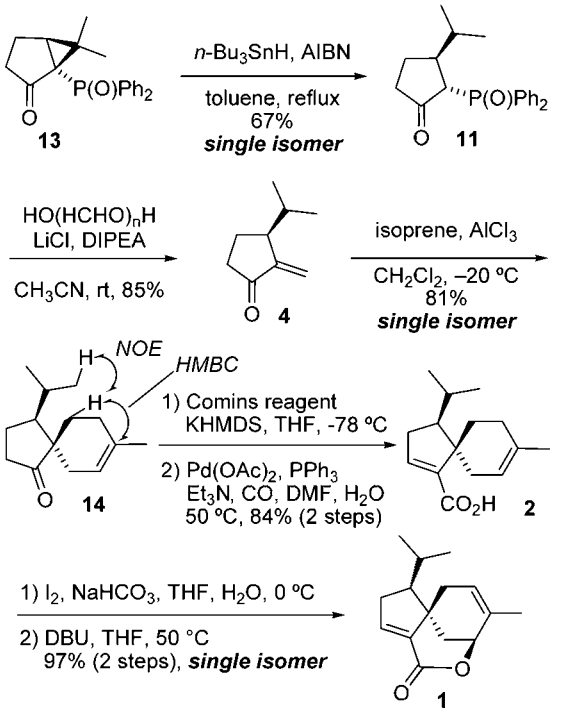
the absolute configuration of **13** was as shown in Table 1 and that sense of enantioselectivity of the CAIMCP of **12** was the same as those of α-diazo-β-keto sulfones. Therefore, the enantioselective outcome would be well explained by our proposed model.[5a]

With enantiopure **13** in hand, the total synthesis of (+)-colletoic acid was investigated. The reductive ring-opening reaction of cyclopropane **13** proceeded with tri-*n*-butyltin hydride under the same conditions used in the reaction of **6** (Scheme 5). The reaction of **11** with paraformaldehyde under Masamune conditions[14] afforded **4** in 85% yield. The Diels–Alder reaction of **4** and isoprene at elevated temperature resulted in decomposition of **4**. However, we found that the reaction in the presence of aluminum chloride as a Lewis acid proceeded at −20 °C to afford **14** as a single product. The structure of **14** was elucidated by NMR studies as shown in Scheme 5. Ketone **14** was then converted to the enol triflate and subsequent palladium-catalyzed carbonylation afforded **2**. The reaction of **2** with iodine and $NaHCO_3$ in aqueous THF induced iodolactonization of the carboxylic acid to afford the iodolactone as a single product, which underwent regioselective alkene formation to afford **1** as a single product upon treatment with DBU in THF at 50 °C.

With **1** in hand, the chemo- and stereoselective reduction of the C1–C2 alkene was examined. Several reducing reagents for 1,4-reduction were surveyed, and L-Selectride was found to effectively reduce **1** to afford the product as a single isomer, which was subjected to hydrolysis under

(14) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

Scheme 5

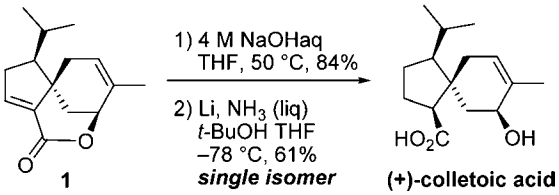


basic conditions to afford the final product. However, the ^{1}H NMR spectrum of the synthesized product differed from the reported data of (+)-colletoic acid, which suggested the formation of C1-*epi*-(+)-colletoic acid.[15]

We speculated that the conformation of the δ-lactone in **1** would be restricted by the tricyclic ring system, resulting in formation of the thermodynamically more stable undesired C1-epimer. Consequently, we examined the reduction of the C1−C2 double bond of the hydroxy carboxylic acid derived from **1** (Scheme 6). As a result, Birch reduction of the hydroxy carboxylic acid successfully afforded the single isomer. The final product proved to be identical

(15) C1-*epi*-(+)-Colletoic acid was unstable and spontanously converted to the corresponding lactone in part during isolation probably because the carboxyl group is close to the hydroxyl group.

Scheme 6



to (+)-colletoic acid in all respects (^{1}H and ^{13}C NMR, IR, MS, and $[\alpha]_D$), thus confirming the enantioselective total synthesis of (+)-colletoic acid.

In summary, the first enantioselective total synthesis of (+)-colletoic acid has been achieved. The total synthesis relies on an approach via the highly enantioselective CAIMCP of α-diazo-β-keto diphenylphosphine oxide, which has been developed in this study. Further elaboration from the CAIMCP product to (+)-colletoic acid features highly controlled reactions: regioselective cyclopropane-opening reaction of the CAIMCP product, stereoselective Diels−Alder reaction to construct the spiro[4.5]-decane core, regioselective iodolactonization and subsequent alkene formation by DBU treatment, and chemo- and stereoselective Birch reduction of the C1−C2 double bond to yield (+)-colletoic acid. It is noteworthy that all the above reactions afforded a single isomer and no protecting groups were used in this total synthesis.

Acknowledgment. We thank Daiichi Sankyo RD Novare Co., Ltd. for kindly donating (+)-colletoic acid. This work was financially supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances" (No. 2105).

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

The authors declare no competing financial interest.