ORGANIC LETTERS

2010
Vol. 12, No. 5
980−983

Total Synthesis and Determination of the Absolute Configuration of (−)-Idesolide

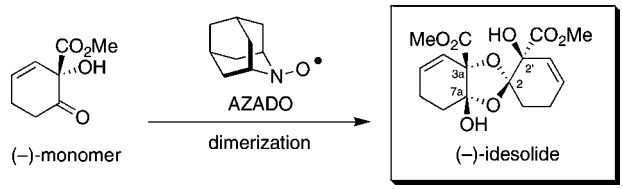
Hiroyuki Yamakoshi, Masatoshi Shibuya, Masaki Tomizawa, Yuji Osada, Naoki Kanoh, and Yoshiharu Iwabuchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

iwabuchi@mail.pharm.tohoku.ac.jp

Received December 28, 2009

ABSTRACT



The first total synthesis of (−)-idesolide was achieved via organocatalytic, enantioselective oxidative kinetic resolution (OKR) using (1*S*,4*S*)-4-Bn-1-Bu-AZADOH- and AZADO-catalyzed dimerization of (*S*)-(−)-methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate. The absolute configuration of (−)-idesolide is determined to be 2*R*,2′*S*,3a*S*,7a*R*.

Dimerization is a ubiquitous process in nature to endow molecule complexity and biological activity, and reproduction of the process often offers chemists significant challenges.[1,2] In 2005, Kim and co-workers reported the isolation of (−)-idesolide (**1**) from the fruit of *Idesia polycarpa*; this compound effectively inhibits nitric oxide (NO) production induced by lipopolysaccharide (LPS) in BV2 microglial cells (Figure 1).[3] The unprecedented structure of idesolide featuring a tetrahydrobenzodioxole was confirmed by X-ray crystallography, but the absolute configuration remained unknown.

The hemiketal/ketal functionality of idesolide leads to a straightforward analysis that the natural product may be formed from two identical molecules of an α-hydroxy ketone,[4] more specifically, optically identical methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate (**2**).[5] However, Snider and co-workers reported that they could not observe the formation of idesolide from either racemic or optically enriched **2** under a variety of conditions.[6]

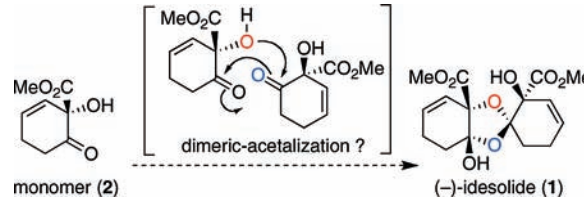


Figure 1. Possible biogenesis of idesolide.

(1) For a review, see: Vrettou, M.; Gray, A. A.; Brewer, A. R. E.; Barrett, A. G. M. *Tetrahedron* **2007**, *63*, 1487.

(2) For leading references, see: (a) Snyder, S. A.; Kontes, F. *J. Am. Chem. Soc.* **2009**, *131*, 1745. (b) Ondrus, A. E.; Movassaghi, M. *Chem. Commun.* **2009**, 4151. (c) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J *J. Am. Chem. Soc.* **2007**, *129*, 1760. (d) Shoji, M.; Hayashi, Y. *Eur. J. Org. Chem.* **2007**, 3783. (e) Porco, J. A., Jr; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. *Angew. Chem., Int. Ed* **2006**, *45*, 5790.

(3) Kim, S. H.; Sung, S. H.; Choi, S. Y.; Chung, Y. K.; Kim, J.; Kim, Y. C. *Org. Lett.* **2005**, *7*, 3275.

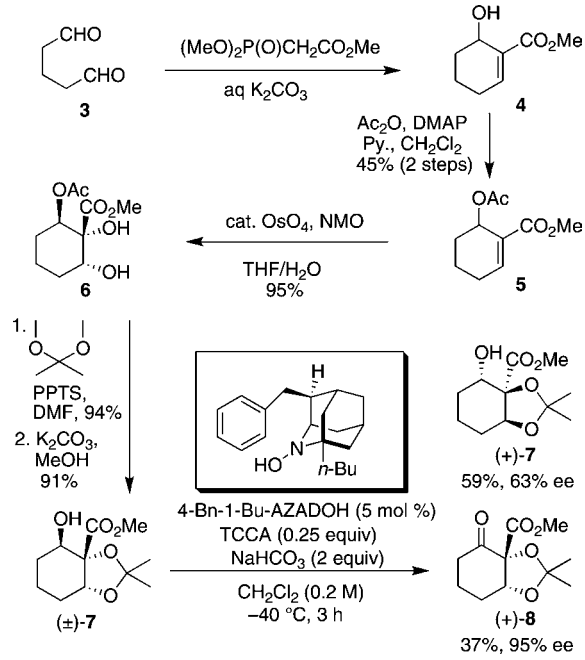
(4) Dimerization of α-hydroxy ketones: (a) Creary, X.; Rollin, A J. *J. Org. Chem.* **1977**, *42*, 4226. (b) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1977**, *42*, 4231. (c) Banks, M. R.; Gosney, I.; Grant, K. J.; Reed, D.; Hodgson, P. K. G. *Magn. Reson. Chem.* **1992**, *30*, 996. (d) Jauch, J.; Schurig, V.; Walz, L. *Zeit. Kristallograph.* **1991**, *196*, 255.

10.1021/ol9029676
Published on Web 02/05/2010

Fascinated with the exquisite structure coupled with the interesting biological activity, we also embarked on the synthetic journey to idesolide and encountered the same difficulty as Snider's team. Fortunately, an unexpected discovery led to the completion of this synthesis. We herein report the first total synthesis and determination of the absolute configuration of (−)-idesolide, featuring a highly enantioselective oxidative kinetic resolution (OKR) using a chirally modified AZADO[7] and AZADO-catalyzed dimerization of the monomer **2**.

The synthesis began with the Horner−Wadsworth−Emmons reaction of glutaraldehyde (**3**) with trimethyl phosphonoacetate to give cyclohexenol **4**.[8] The hydroxy group of **4** was protected as an acetate ester, and the resulting acetate **5** was subjected to catalytic dihydroxylation using OsO_4 and NMO to furnish diol **6** in a highly diastereoselective manner. After acetonide protection of the diol moiety followed by methanolytic removal of the acetyl group, the racemic alcohol **7** thus obtained was subjected to the OKR using a chirally modified AZADO which had recently been developed by our group (Scheme 1).[7a]

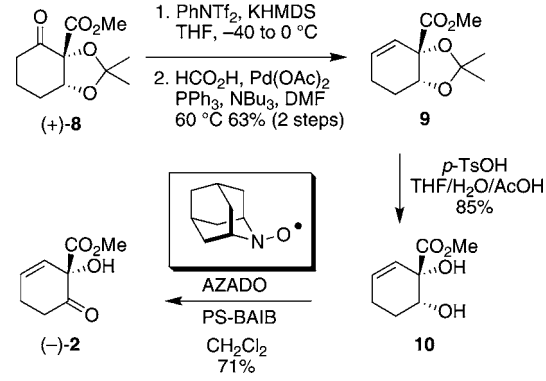
Scheme 1. Oxidative Kinetic Resolution



Upon treatment with 0.25 equiv of trichloroisocyanuric acid (TCCA)[7a,9] in CH_2Cl_2 at −40 °C for 3 h in the presence of 5 mol % of (1*S*,4*S*)-4-Bn-1-Bu-AZADOH and 2 equiv $NaHCO_3$ (solid), *rac*-**7** was resolved to give (+)-ketone **8** in 37% yield with 95% ee, and (+)-alcohol **7** was recovered in 59% yield with 63% ee[10] (k_R/k_S = 39).[11] The absolute configuration of recovered, enantiomerically enriched (+)-**7** was established to be that of the (*S*)-alcohol by comparison with the specific rotation of an authentic sample of (−)-**7**, which was independently synthesized from known (*R*)-**4**[8] (see the Supporting Information).

The highly enantiomerically enriched (+)-ketone **8** (95% ee) was converted to (−)-cyclohexene **9** via a conventional sequence consisting of enol triflate formation and the subsequent palladium-catalyzed reduction (Scheme 2). Treatment of acetonide **9** with *p*-TsOH in

Scheme 2. Synthesis of Monomer **2**



THF−H_2O−AcOH[12] at ambient temperature allowed selective hydrolysis of the acetonide to give *cis*-diol **10**. While oxidation of **10** to monomer **2** was somewhat troublesome, the goal was achieved by AZADO catalysis employing polymer-supported bis(acetoxy)iodobenzene[13] (PS-BAIB) as the bulk oxidant. Note that the use of BAIB as the bulk oxidant suffered from cleavage of the diol moiety of **10**. The spectral data for **2** were identical to those of the isolated product and reported by Snider.[6] The $[\alpha]_D$ value of our synthetic (−)-**2** of −278 (*c* 1.0, $CHCl_3$) establishes that natural (−)-monomer **2** has the *S*-configuration.[5a]

Having secured the highly enantiomerically enriched monomer, the stage was set for the crucial dimerization. We confirmed that (−)-monomer **2** does not dimerize under

(5) Isolation of methyl 1-hydroxy-6-oxo-2-cyclohexenecarboxylate: (a) Rasmussen, B.; Nkurunziza, A.-J.; Witt, M.; Oketch-Rabah, H. A.; Jaroszewski, J. W.; Stærk, D. *J. Nat. Prod* **2006**, *69*, 1300. (b) Kim, S. H.; Jang, Y. P.; Sung, S. H.; Kim, Y. C. *Planta Med.* **2007**, *73*, 167. (c) Ekabo, O. A.; Farnsworth, N. R. *J. Nat. Prod.* **1993**, *56*, 699.

(6) Richardson, A. M.; Chen, C.-H.; Snider, B. B. *J. Org. Chem.* **2007**, *72*, 8099.

(7) AZADO : (a) Tomizawa, M.; Shibuya, M.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1829. (b) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

(8) Yamane, T.; Ogasawara, K. *Synlett* **1996**, 925.

(9) (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.

(10) 99.5% ee of (+)-**7** was obtained in 44% yield after 24 h reaction under the same conditions, together with 77% ee of (+)-ketone **8** in 54% yield. Oxidation of the highly enantiomerically enriched (+)-**7** gave (−)-**8** which was converted to unnatural idesolied (+)-**1** (see the Supporting Information).

(11) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

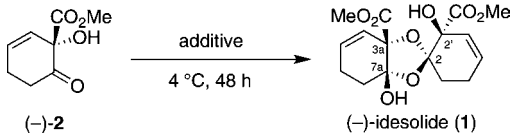
(12) Kaburagi, Y.; Osajima, H.; Shimada, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron Lett.* **2004**, *45*, 3817.

(13) Togo, H.; Nogami, G.; Yokoyama, M. *Synlett* **1998**, 534.

neutral conditions: even ultrahigh pressure condition (0.8 GPa)[14] did not give any detectable amount of the dimer. Acidic conditions (cf. *p*-TsOH or BF_3•OEt_2)[2a,6] gave methyl salicylate as the only isolable product. Basic treatment of (−)-**2** using NaH,[2a] NaOMe, or DBU led to decomposition or ring-opening of the β-ketoester moiety.[6] After several unsuccessful experiments, we eventually found that a small amount of crystalline idesolide was formed in a stock flask containing an oily, crude monomer contaminated with AZADO. This observation prompted us to examine AZADO as a possible promoter.

To our surprise, AZADO significantly promoted the dimerization (Table 1). The yield of idesolide increased

Table 1. Dimerization of (−)-Monomer **2**



(−)-**2** (−)-idesolide (**1**)

.

entry	additive (equiv)	solvent ($CDCl_3$)	yield[b] (%) idesolide	yield[b] (%) diastereomer
1	none	none	0	0
2	AZADO (1.0)	0.1 M	6	0
3	AZADO (1.0)	0.4 M	35	0
4	AZADO (1.0)	2 M	62	0
5	AZADO (1.0)	10 M	68	0
6	AZADO (1.0)	none	73	0
7	AZADO (0.1)	none	38	0
8	AZADOH (1.0)[a]	none	38	0
9	1-Me-AZADO (1.0)	none	63	0
10	TEMPO (1.0)	none	0	0
11	DMAP (1.0)	none	65	0
12	pyridine (1.0)	none	0	0
13	Et_3N (1.0)	none	65	6
14	*i*-Pr_2NEt (1.0)	none	50	12
15	DMAPO•H_2O (1.0)[a]	none	22	6
16	NMO (1.0)[a]	none	11	30

[a] Additive did not dissolve completely. [b] Calculated yield (^{1}H NMR).

as the concentration of AZADO increased (entries 1−6). Addition of 0.1 equiv of AZADO to (−)-monomer **2** yielded idesolide in 38%, indicating that AZADO acts as a catalyst in this reaction (entry 7). Note that AZADOH showed a considerably decreased productivity compared with AZADO (entry 8). Interestingly, 1-Me-AZADO showed an attenuated performance compared with AZADO, and TEMPO did not give any detectable amount of idesolide after 48 h, indicating the importance of less-hinderd nature of the *N*-oxyl group on the promotion of dimerization (entries 9 and 10). Eventually, we found that DMAP promoted the desired dimerization of which the efficiency was comparable with that AZADO (entry 11). Pyridine did not give idesolide (entry 12), implying that the sp^3-nitrogen would play an essential role in this particular dimerization process. Indeed, Et_3N as well as *i*-Pr_2NEt were confirmed to promote the dimerization and afforded idesolide (**1**) along with an unstable diastereomer (entries 13 and 14).[15−17] Interestingly, DMAPO and NMO gave similar results with attenuated efficiencies (entries 15 and 16). The catalytic property of AZADO to promote the dimerization of **2** would be attributable to the less-hindered, basic nature of the *N*-oxyl moiety.[18]

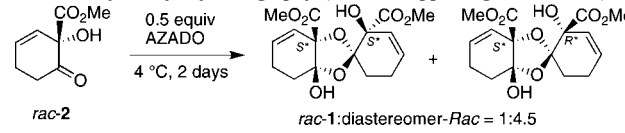
Synthetic (−)-idesolide (**1**) was isolated in 34% yield ($[\alpha]^{25}_D = -238.9$ (*c* 0.27), lit.[3] $[\alpha]^{25}_D = -230.0$ (*c* 1.0)) from the oily mixture containing AZADO and (−)-monomer **2** after a gel-filtration chromatograpy.[15] The structure of synthetic (−)-idesolide was unambiguously confirmed by X-ray crystallography, thereby establishing the absolute configuration of natural (−)-idesolide to be 2*R*,2′*S*,3a*S*,7a*R*.

In conclusion, we have achieved the first total synthesis of (−)-idesolide (**1**) that establishes the absolute configuration of the dimeric natural product. The successful enantioselective synthesis of monomer (−)-**2** highlights the power of our organocatalytic OKR methodology using chiral AZADOH. Central to the completion of this synthesis was the seren-

(14) Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* **2001**, 1027.

(15) This diastereomer dissociated to the monomer **2** during silica gel column chromatography. Although we could not isolate the diastereomer, we obtained a mixture of the diastereomer and idesolide after gel filtration chromatography. The ^{13}C NMR spectrum (see the Supporting Information) indicated that this diastereomer is the epimer at the ketal carbon.

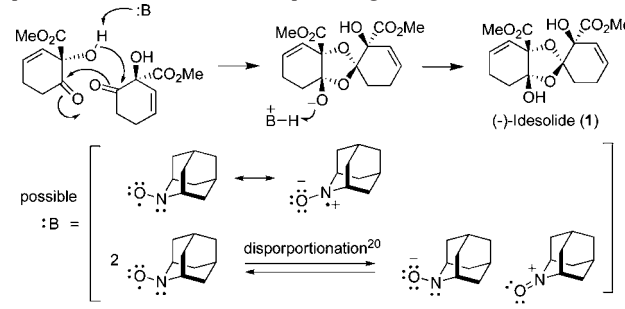
(16) AZADO-catalyzed dimerization of racemic monomer **2** gave racemic idesolide (*rac*-**1**) along with the diastereomer (diastereomer-*Rac*) consisting of (*R*)-**2** and (*S*)-**2**. The structure of this diastereomer was confirmed by X-ray crystallography (see the Supporting Information).



rac-**2** *rac*-**1**:diastereomer-*Rac* = 1:4.5

(17) We found that some chiral tertiary amines induced the dimerization of *rac*-**2** to give an optically active diasetereomer-*Rac* consisting of (*R*)-**2** and (*S*)-**2**, in which deMeQDAc[19] brought about 45% ee (see the Supporting Information).

(18) In light of the experimental results that the dimerization was promoted either by tertiary alkylamines or tertiary amine *N*-oxide, we speculate AZADO behaved as a possible general base.



For hydrogen-bonding interactions between stable nitroxyl radical and ROH, see: (a) Morishima, I.; Ishihara, K.; Tomishima, K.; Inubushi, T.; Yonezawa, T *J. Am. Chem. Soc.* **1975**, *97*, 2749. (b) Otsuka, T.; Motozaki, W.; Nishikawa, K.; Endo, K. *J. Mol. Struct.* **2002**, *615*, 147. (c) Russ, J. L.; Gu, J.; Tsai, K.-H.; Glass, T.; Duchamp, J. C.; Dorn, H. C. *J. Am. Chem. Soc.* **2007**, *129*, 7018.

(19) Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658.

(20) (a) Kinoshita, S.; Ohsaka, T.; Tokuda, K. *Electrochem. Acta* **2003**, *48*, 1589. (b) Sen, V. D.; Golubev, V. A. *J. Phys. Org. Chem.* **2009**, *22*, 138.

dipitous discovery that AZADO enables the dimerization of the monomeric α-hydroxy ketone **2**. Mechanistic studies to elucidate the precise role of AZADO as well as to expand the synthetic scope are now underway and will be reported in due course.

Acknowledgment. We thank Dr. Mikiko Sodeoka and Dr. Takeshi Shimizu (RIKEN) for the use of the ultrahigh pressure reaction apparatus and helpful discussions on the dimerization chemistry.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9029676