Lipase-catalyzed domino kinetic resolution of α-hydroxynitrones/intramolecular 1,3-dipolar cycloaddition: a concise asymmetric total synthesis of (−)-rosmarinecine†

Shuji Akai, Kouichi Tanimoto, Yukiko Kanao, Sohei Omura and Yasuyuki Kita*

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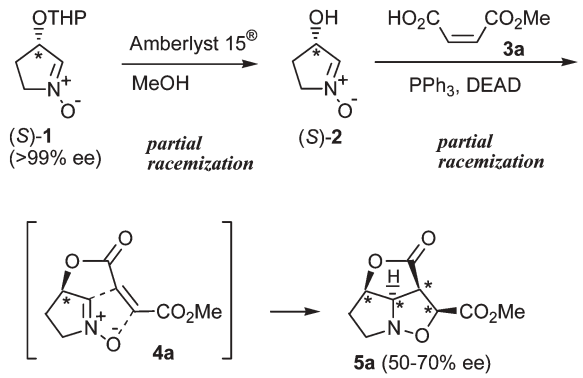
The title domino reactions were developed to directly provide tetrahydrofuro[3,4-*c*]isoxazole derivatives (5 and 9) in ⩾90% ee from racemic α-hydroxynitrones (2 and 6), which were used in the concise asymmetric total synthesis of (−)-rosmarinecine 10.

The 1,3-dipolar cycloaddition reaction of optically active nitrones to olefins is a powerful and versatile method for preparing polysubstituted isoxazolidines and has been extensively employed as a key step in the asymmetric total syntheses of a variety of biologically important compounds such as alkaloids and amino sugars.[1–4] Among these reactions, the intramolecular cyclizations of nitrones connected to olefin moieties by tethers usually give rise to excellent regioselectivities and diastereofacial (*i.e.*, *endo* and *exo*) selectivities, and the stereogenic centres in the tethers play a critical role in the induction of stereogenic carbon centres in the products.[1,3]

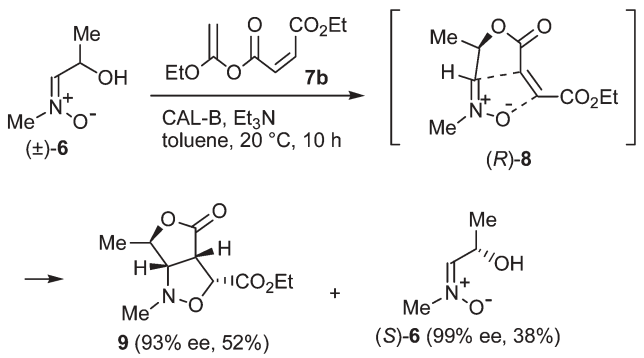
Optically active nitrones have been generally prepared from optically active precursors, the so-called chiral pool including amino acid derivatives,[3a] hydroxycarboxylic acid derivatives,[3b,4] and sugars.[3c] However, during transformation of these precursors into nitrones, some of them suffered racemization of their pivotal stereogenic carbon centres.[3a] Scheme 1 shows an example, in which partial racemization took place during both the deprotection of the THP ether (*S*)-**1** to (*S*)-**2** and its Mitsunobu reaction.[4,5] If optically active **4a** or **5a** could be directly and catalytically prepared from a racemic nitrone **2**, such a method should provide an alternative approach to the cycloadducts, free from the racemization.[6] This protocol would also be advantageous in terms of the ready availability of racemic substrates and the shortening of the transformation steps. However, no example of this idea has been reported to date.



Scheme 1

Recently, we have developed the first domino synthesis, in which the lipase-catalyzed kinetic resolutions of racemic dienols with ethoxyvinyl esters having dienophilic acyl moieties were successively followed by the intramolecular Diels–Alder reactions of the resulting optically active esters. Tricyclic compounds bearing multi-stereogenic carbon centres were directly obtained in high yields.[7] In this communication, the application of this domino protocol to the acyclic, (±)-**6**, and the cyclic α-hydroxynitrones, (±)-**2**, to achieve the one-pot preparation of the optically active tetrahydrofuro[3,4-*c*]isoxazole derivatives (**9** and **5**), is reported. Particularly, the domino reaction of (±)-**2** proceeded with dynamic kinetic resolution, and thereby the first catalytic asymmetric total synthesis of optically pure (−)-rosmarinecine **10** was achieved in 6 steps from commercially available racemic 3-hydroxypyrrolidine **11**.

To the best of our knowledge, there has been no precedent for the hydrolase-catalyzed kinetic resolution of hydroxynitrones. Therefore, our studies started with the domino reaction of a simple acyclic nitrone (±)-**6**[8] with a functionalized acyl donor **7b**.[7b] After intensive screening of commercial lipases and ordinary organic solvents, we discovered that *Candida antarctica* lipase, fraction B (CAL-B)[9] effectively catalyzed the kinetic resolution of (±)-**6** in toluene at 20 °C. The subsequent intramolecular dipolar cycloaddition of thus generated ester (*R*)-**8** was so fast that the cycloadduct **9** (93% ee, 52% yield) was directly obtained as a single diastereomer along with the recovery of (*S*)-**6** (99% ee, 38% yield) (Scheme 2).



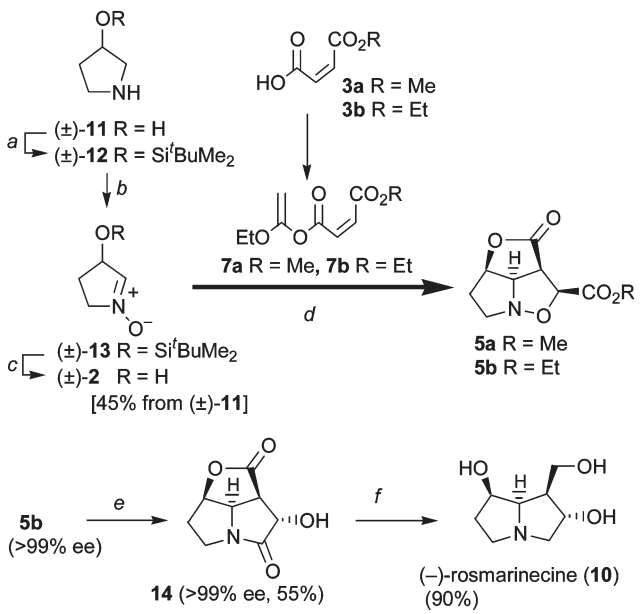
Scheme 2

† Electronic supplementary information (ESI) available: determination of the optical purity and absolute structure of (*S*)-**2**, **5a**,**b**, (*S*)-**6**, **9** and **14** and typical procedures for the lipase-catalyzed domino reaction (Table 1, entry 5) and the one-pot synthesis of **5b** (entry 7). See http://www.rsc.org/suppdata/cc/b4/b419426h/

*kita@phs.osaka-u.ac.jp

With these successful results in hand, our next attention focused on the domino reaction of the cyclic nitrone (±)-**2** with the acyl donors **7a**,**b** aimed at the effective asymmetric total synthesis of (−)-rosmarinecine **10**, a typical necine-base-portion of some natural alkaloids such as rosmarinine (Scheme 3).[10] In contrast to the case of **6**, the reaction of (±)-**2** was somewhat problematic. First, although a similar reaction of (±)-**2** with **7a** in toluene, as well as other solvents such as THF and $^{i}Pr_2O$, at 30 °C gave the expected cycloadduct **5a** as a single diastereomer, the enantioselectivity was low (up to 60% ee). Second, the decomposition of **2** was observed, probably *via* its competitive intermolecular dipolar cycloaddition to **7a**. These problems were solved using MeCN at 0 °C. Thus, the enantioselectivity was improved (Table 1, entry 1) and the side reactions were sufficiently depressed at 0 °C to give **5a** (92% ee, 53% yield) and the recovered (*S*)-**2** (entry 2). In a similar manner, the reaction of (±)-**2** with the ethyl ester **7b** afforded **5b** with a slightly better enantioselectivity (94% ee, 49% yield) (entry 3).

To our surprise, partial racemization of the remaining (*S*)-**2** was observed during these reactions. Thus, the optical purity of (*S*)-**2** should be almost the same as that of the products **5** at about 50% conversion; however, it was always lower (entries 2 and 3). Among the intensive studies to achieve the domino reaction with a dynamic kinetic resolution by changing the temperature, the amount of the lipase, and some additives, the reaction using CAL-B (300 wt%) at 10 °C for 17 h afforded **5b** (86% ee, 69% yield) (entry 4) and that at 5 °C for 12 h gave **5b** (91% ee, 60% yield) (entry 5). Similar to the above-mentioned studies using pure **7a**,**b**, the more convenient one-pot procedure, including the preparation of **7b** from **3b** and the enzymatic domino reaction of (±)-**2**, gave **5b** with the same optical and chemical yields (entry 6). This method was scarcely affected by the reaction scale and was suitable for multigram synthesis of chiral products. For instance, under identical reaction conditions using the same ratio of (±)-**2**, **3b**, CAL-B, and the solvent, the reactions of (±)-**2** (40 mg and 1.0 g) afforded similar results (entries 6 and 7).



Scheme 3 *Reagents and conditions:* a, $Me_2{}^{t}BuSiCl$, imidazole, MeCN; b, Na_2WO_4, H_2O_2, Et_4NCl, CH_2Cl_2–H_2O; c, CsF, MeOH; d, i) ethoxyacetylene, $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%), acetone; ii) CAL-B, MeCN; e, $Pd(OH)_2$, H_2, MeOH; f, Red-Al, THF.

Table 1 Lipase-catalyzed domino reactions of (±)-**2** and **7a**,**b** in MeCN

Entry	7	Amount of CAL-B[a]	Conditions	5	(*S*)-2
1[b]	**7a**	150 wt%	30 °C, 12 h	**5a** 89% ee, 27%	trace
2[b]	**7a**	150 wt%	0 °C, 12 h	**5a** 92% ee, 53%	73% ee, 43%[c]
3[b]	**7b**	150 wt%	0 °C, 8 h	**5b** 94% ee, 49%	77% ee, 33%[c]
4[b]	**7b**	300 wt%	10 °C, 17 h	**5b** 86% ee, 69%	trace
5[b]	**7b**	300 wt%	5 °C, 12 h	**5b** 91% ee, 60%	96% ee, 28%
6[d]	**7b**	300 wt%	5 °C, 11 h	**5b** 90% ee, 60%	99% ee, 30%
7[d]	**7b**	300 wt%	5 °C, 11 h	**5b** 92% ee, 58%	95% ee, 23%[c]

[a] Weight% of commercial CAL-B to (±)-**2**. [b] Carried out using purified **7** (1.5 equiv.). Substrate amount was 50 mg. [c] ^{1}H NMR yield. [d] Carried out by the one-pot procedure; for details, see ESI. Substrate amount was 40 mg for entry 6 and 1.0 g for entry 7.

Finally, the asymmetric total synthesis of (−)-rosmarinecine **10** was attained as follows: a recrystallization of **5b** (92% ee) from a mixture of hexanes and EtOAc afforded the optically pure **5b** [43% yield from (±)-**2**]. Hydrogenolysis of **5b** gave **14** (>99% ee based on chiral HPLC analysis using Daicel Chiralpak AD-H), $[\alpha]_D^{23}$ +89.4 (*c* = 0.36, abs. EtOH) [lit.[4a] $[\alpha]_D^{27}$ +94.2 (*c* = 0.31, abs. EtOH)]. The Red-Al reduction of **14** (>99% ee), according to Goti's paper,[4a] afforded (−)-rosmarinecine **10** in 90% yield. The physical properties and the ^{1}H and ^{13}C NMR data of the synthesized **10** showed good agreement with those of the natural compound: mp 167–170 °C, $[\alpha]_D^{24}$ −117.7 (*c* = 0.98, EtOH) [lit.[10] mp 168–170 °C, $[\alpha]_D^{21}$ −119.8 (*c* = 1.01, EtOH)]. Because we prepared (±)-**2** from commercially available (±)-**11** (45% overall yield) in 3 steps,[11] the total synthesis of (−)-**10** was achieved in 6 steps with a 9.6% overall yield from (±)-**11** (Scheme 3).

Although the asymmetric total synthesis of (−)-**10** had already been reported by three groups, all of them used optically active substrates as either the starting material or as a chiral auxiliary.[4,10,12] Our method features the first catalytic asymmetric total synthesis of (−)-**10** starting from the commercially available racemic material (±)-**11**, the fewest steps, and the highest overall yield. The acceleration of the racemization of the alcohol (*S*)-**2** to attain more effective dynamic kinetic resolution is now under investigation in our laboratory.[13]

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Shuji Akai, Kouichi Tanimoto, Yukiko Kanao, Sohei Omura and Yasuyuki Kita*
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail: kita@phs.osaka-u.ac.jp; Fax: (+81) 6-6879-8229

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