Asymmetric Diels–Alder reaction *via* enzymatic kinetic resolution using ethoxyvinyl methyl fumarate

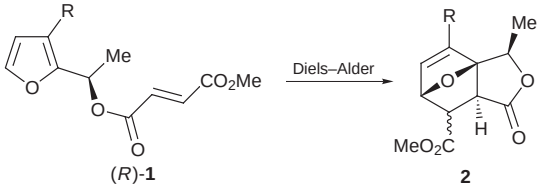
Yasuyuki Kita,*† Tadaatsu Naka, Masashi Imanishi, Shuji Akai, Yasushi Takebe and Masato Matsugi

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565 Japan

A domino-type asymmetric [4 + 2] cycloaddition reaction following enzymatic kinetic resolution using ethoxyvinyl methyl fumarate is described.

We have already reported that ethoxyvinyl esters are better acylating reagents for enzymatic kinetic resolution of alcohols than the generally used vinyl esters.[1] One of the remarkable features of these acylating reagents is the facile preparation of esters bearing various acyl moieties.[2] Therefore, we planned a novel reaction system based on the idea that the acyl moiety inserted by enzymatic kinetic resolution is used in the subsequent reaction stage. Here we report a convenient asymmetric one-pot [4 + 2] cycloaddition reaction following an enzymatic kinetic resolution using readily-prepared ethoxyvinyl methyl fumarate.

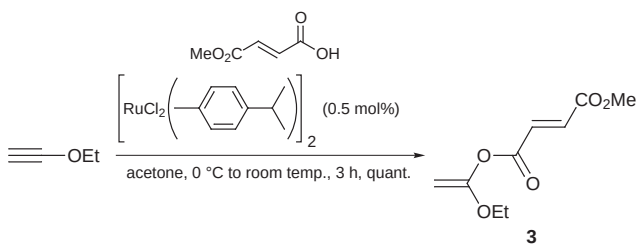
The enatiomerically pure 7-oxabicyclo[2.2.1]heptene derivative **2** is a useful compound in the syntheses of many natural products.[3] Many synthetic approaches to **2** have been reported to date,[4] and the intramolecular Diels–Alder reaction of the enantiomerically pure furfuryl fumarate derivative **1** is one of the most effective methods (Scheme 1).[5]



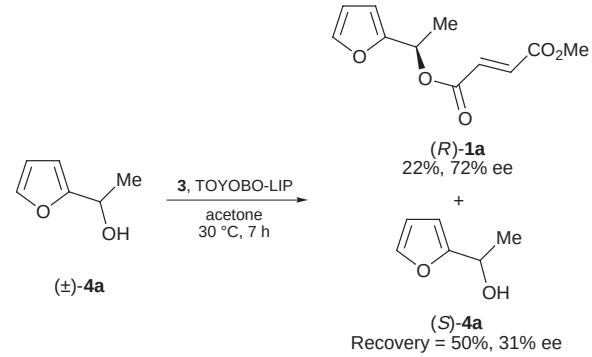
Scheme 1

We anticipated an easy and highly stereoselective synthesis of optically active **2** *via* the enzymatic acylation of (±)-furfuryl alcohol **4** using ethoxyvinyl methyl fumarate **3**, followed by rapid intramolecular Diels–Alder reaction between the inserted fumarate moiety and the diene moiety on the furan ring. In the reactions related to the kinetic resolution by enzymatic acylation, use of the acylating reagent not only as an acyl donor but also as a component of the next reaction stage has rarely been reported.‡ The unknown ethoxyvinyl methyl fumarate **3** was prepared by the reported[6] method shown in Scheme 2 and used as an acetone solution without further purification.§

First, we examined which enzyme was suitable for kinetic resolution of (±)-**4a** using **3** as the acylating reagent. We checked the optical purity of the acylated product **1a** prior to the



Scheme 2

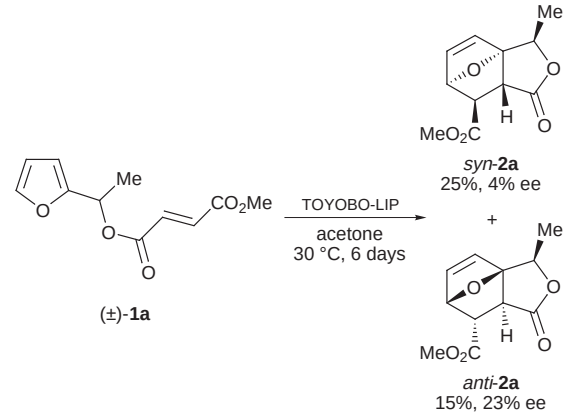


Scheme 3

formation of cycloadduct **2**. After screening a number of enzymes (amano AK, AY, PS, PPL, PLE, A-6, meito-MY, OF, chirazyme L3, TOYOBO-LIP)¶ we found that only TOYOBO-LIP gave an optically active furfuryl methyl fumarate (*R*)-**1a** (22% yield, 72% ee) (Scheme 3). The absolute configuration of the product **1a** was determined by converting the unreacted **4a** to the known nitrobenzoate derivative.[7]

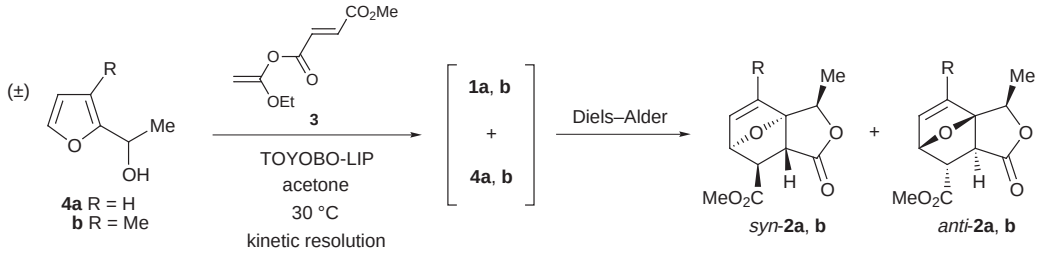
Next, we studied the influence of enzyme TOYOBO-LIP on the intramolecular Diels–Alder reaction of (±)-**1a**.[8] Consequently, we found that the cycloadduct product, *syn*-**2a** (4% ee), was obtained with 24% de in preference to *anti*-**2a** (23% ee).‖ Thus it is apparent that enzyme TOYOBO-LIP played an important role in the diastereo- and enantio-facial selectivity of this intramolecular cycloaddition process (Scheme 4).[9]

Although it can be assumed that the enzymatic hydrolysis, which utilizes the small amount of water in the solvent, depends on the asymmetric environment produced by TOYOBO-LIP,[10] how the enzyme participates in the face-selectivity of the cycloaddition remains to be elucidated at the present time. This result suggests that the possibility exists of increasing the enantioselectivity observed at the enzymatic kinetic resolution stage (72% ee) by carrying out the cycloaddition reaction in the same pot. In practice, we succeeded in the highly stereoselective



Scheme 4

Table 1 Asymmetric Diels–Alder reaction following kinetic resolution using enzyme



Entry	Substrate	Solvent	*t*/days	Total yield of **2** (%) (% de)[a]	Ee (%)[b] *syn*-**2**	Ee (%)[b] *anti*-**2**	Recovery of **1** (%)	Recovery of **4** (%) (absolute config. of major **4**)
1	**4a**	Acetone	6	18 (26)	86	93	21	56 (*S*)
2	**4a**	Acetone	8	32 (24)	79	81	20	18 (*S*)
3	**4a**	THF	8	28 (24)	81	48	5	38 (*S*)
4	**4b**	Acetone	1	43 (100)	84	N.D.[c]	N.D.[d]	39 (*S*)
5	**4b**	THF	1	37 (100)	84	N.D.[c]	N.D.[d]	33 (*S*)

[a] Diastereomeric excess was determined *via* ^{1}H NMR analysis of the crude product. [b] Enantiomeric excess was determined by HPLC (Chiralcel OJ). [c] *anti*-**2b** was not detected *via* ^{1}H NMR analysis. [d] **1b** was not detected by thin layer chromatography.

synthesis of **2** (*syn*-**2**: 84–86% ee, *anti*-**2a**: 93% ee) as a result of carrying out the enzymatic kinetic resolution and cycloaddition in one pot in acetone (Table 1, entry 1). The success of this one-pot reaction is mainly due to the acylating reagent **3**, which could be used without a work-up procedure, since compound **3** is not stable and cannot usually be isolated.

In conclusion, we developed a novel methodology such that the acyl moiety inserted during an enzymatic kinetic resolution was used as part of the constituent structure during the next reaction stage.** In this one-pot reaction, an interesting phenomenon was observed, *i.e.* the optical purity of the enzymatic acylated product was increased during the cycloaddition stage. Consequently, we achieved the convenient synthesis of optically active **2**. This one-pot asymmetric synthesis might be applied to the syntheses of other useful biologically-active compounds, and other applications are now being developed.

Notes and References

† E-mail: kita@em.phs.osaka-u.ac.jp

‡ Only one example of an enzymatically acrylated product being utilized in the synthesis of chiral polymers has been reported; A. Ghogana and S. Kumar, *J. Chem. Soc., Chem. Commun.*, 1990, 134.

§ Ethoxyvinyl methyl fumarate was used as an acetone solution, since it could not be purified due to its instability. Although the solution contained a catalytic amount of the ruthenium complex, it has already been confirmed that enzymatic kinetic resolution of various alcohols is not affected by the ruthenium complex. Details of these results will be reported in the near future.

¶ LIP is *Pseudomonas aeruginosa* on Hyflo Super-Cel and is commercially available from TOYOBO.

‖ In the absence of an enzyme, the diastereomeric excess was 10% de in this cycloaddition reaction using (*R*)-**1**; B. Thomas and S. Jürgen, *Tetrahedron: Asymmetry*, 1997, **8**, 703.

** *Typical procedure*: a mixture of (±)-furfuryl alcohol **4a** (0.5 mmol), LIP (100 mg) and ethoxyvinyl methyl fumarate (0.5 mmol) (see footnote §) was stirred at 30 °C. After 6 days, the reaction mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over silica (hexane–EtOAc) to give cycloadduct **2a** (40 mg, 18%), furfuryl methyl fumarate (*R*)-**1a** (46 mg, 21%) and furfuryl alcohol (*S*)-**4a** (73 mg, 56%).

1 Y. Kita, Y. Takebe, K. Murata, T. Naka and S. Akai, *Tetrahedron Lett.*, 1996, **37**, 7369; S. Akai, T. Naka, Y. Takebe and Y. Kita, *Tetrahedron Lett.*, 1997, **38**, 4243.
2 N. Shibata, M. Matsugi, S. Fukui, C. Fujimori, K. Gotanda, K. Murata and Y. Kita, *Tetrahedron: Asymmetry*, 1997, **8**, 703; Y. Kita, Y. Takeda, M. Matsugi, K. Iio, K. Gotanda, K. Murata and S. Akai, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1529.
3 R. H. Schlessinger, X. H. Wu and T. R. Pettus, *Synlett*, 1995, 536; M. E. Jung and V. C. True, *Tetrahedron Lett.*, 1988, **29**, 6059; L. M. Harwood, T. Ishikawa, H. Phillips and D. J. Watkin, *J. Chem. Soc., Chem. Commun.*, 1990, 605.
4 Y. N. Yamakoshi, W.-Y. Ge, K. Okayama, T. Takahashi and T. Koizumi, *Heterocycles*, 1996, **42**, 129; R. H. Schlessinger, T. R. R. Pettus, J. P. Springer and K. Hoogsteen, *J. Org. Chem.*, 1994, **59**, 3246; E. J. Corey and T.-P. Loh, *Tetrahedron Lett.*, 1993, **34**, 2979.
5 J. Zylber, A. Tubul and P. Brun, *Tetrahedron: Asymmetry*, 1995, **6**, 377.
6 Y. Kita, H. Maeda, K. Omori, T. Okuno and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2999.
7 J. Kamiñska, I. Górnicka, M. Sikora and J. Góra, *Tetrahedron: Asymmetry*, 1996, **7**, 907.
8 H. Oikawa, K. Katayama, Y. Suzuki and A. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1995, 1321.
9 S. Laschat, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 289.
10 T. S. Cload, R. D. Liu, M. R. Pastor and G. P. Schultz, *J. Am. Chem. Soc.*, 1996, **118**, 1787; 1996, **118**, 1789.

Received in Cambridge, UK, 23rd February 1998; 8/01496E