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A *trans*-vinylogous ester anion equivalent and its application to the synthesis of (+)-brefeldin A

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Abstract—A new *trans*-vinylogous ester anion equivalent which reacts with a variety of carbonyl systems has been developed. In addition, the concise total synthesis of (+)-brefeldin A utilizing facile acylation of this new variant of vinylogous acyl anion equivalent has been accomplished.

The vinylogous acyl anion has continuously attracted considerable attention from the organic and medicinal chemists due to its wide range of synthetic utilities.[1] However, its synthetic application has been limited by poor nucleophilicity, instability as well as difficulty in regiocontrol of anion generation.

Recently, we have investigated the versatile methods for γ-keto and γ-hydroxy acrylate by direct introduction of *trans*-acrylic acid to a variety of carbonyl systems as part of a program directed toward the total synthesis of (+)-brefeldin A.[2] For this efficient transformation, the *trans*-vinyl anion **2b**, generated by halogen–metal exchange of the corresponding (*E*)-1-(2-iodovinyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2a**, iodovinyl OBO orthoester[3]) was considered as the best equivalent of the requisite *trans*-vinylogous ester anion (**1**) in terms of conciseness and diversity. To the best of our knowledge, the *trans*-vinylogous ester anion equivalent and its synthetic utilization has not been reported yet although the β-alkoxy directed *cis*-vinyl anions have mainly been reported[1,4] (Fig. 1).

We herein report a novel *trans*-vinylogous ester anion equivalent (**2b**) as a variant of vinylogous acyl anion and its reaction with a variety of carbonyl systems. In addition, the total synthesis of (+)-brefeldin A achieved by employing this methodology as a key reaction is also reported.

Our initial studies on the reaction of **2b** were carried out by intensive examination of the reaction conditions for the halogen–metal exchange of halovinyl OBO orthoesters which were prepared by the modified Watt's procedure.[5] The iodo substituent of the vinyl OBO orthoester **2a** turned out to be crucial for the efficient generation of the requisite *trans*-vinyl anion **2b** since bromo or chloro-substituted vinyl substrate afforded *cis*-halovinyl anion by deprotonation rather than halogen–metal exchange.[1,4] In particular, the reverse addition of the iodoolefin **2a** to *t*-BuLi in ether provided the best results by the desired halogen–metal exchange. Table 1 summarizes the result for the reaction of the lithium anion **2b** with a series of carbonyl compounds. As anticipated, the aldehyde and ketone (entry 1–5) underwent facile addition reaction to afford the allylic alcohols in good or moderate yields. In the case of lactones (entry 6 and 7), the addition products were obtained in modest yields and the extended reaction time at −78°C and an excess amount of **2b** was necessary in order to ensure higher yield. It is noticeable that Weinreb amide (entry 8) is superior to lactone (entry 7) for acylation of the vinyl anion **2b** in terms of overall yield.

1 **2a** X = I **2b** X = Li

Figure 1.

Keywords: *trans*-vinylogous ester anion equivalent; brefeldin A; total synthesis.

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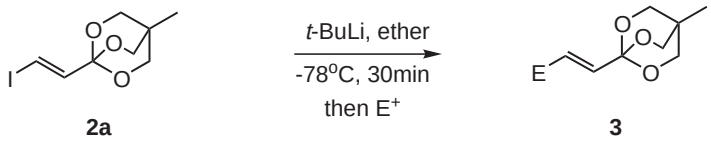
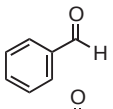
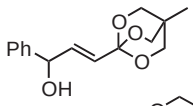
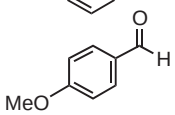
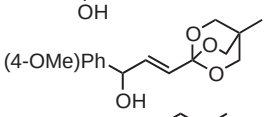
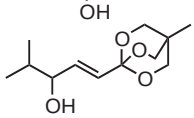
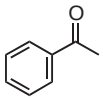
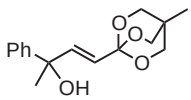
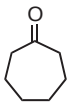
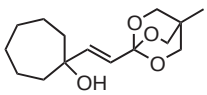
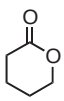
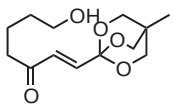
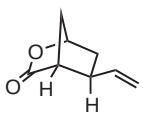
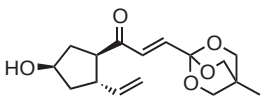
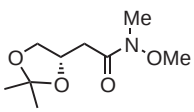
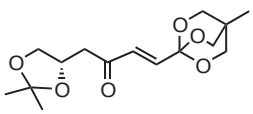
Table 1. Reaction of vinylogous acrylate anion equivalent **2b** with carbonyl compounds



2a **3**

Entry	Carbonyl compounds	Reaction conditions[a]	Products		Yield(%)[b]
1		A		**3a**	76
2		A		**3b**	61
3		A		**3c**	71
4		A		**3d**	65
5		A		**3e**	78
6		B		**3g**	61
7		B[c]		**3h**	46(72[d])
8		B		**3f**	62

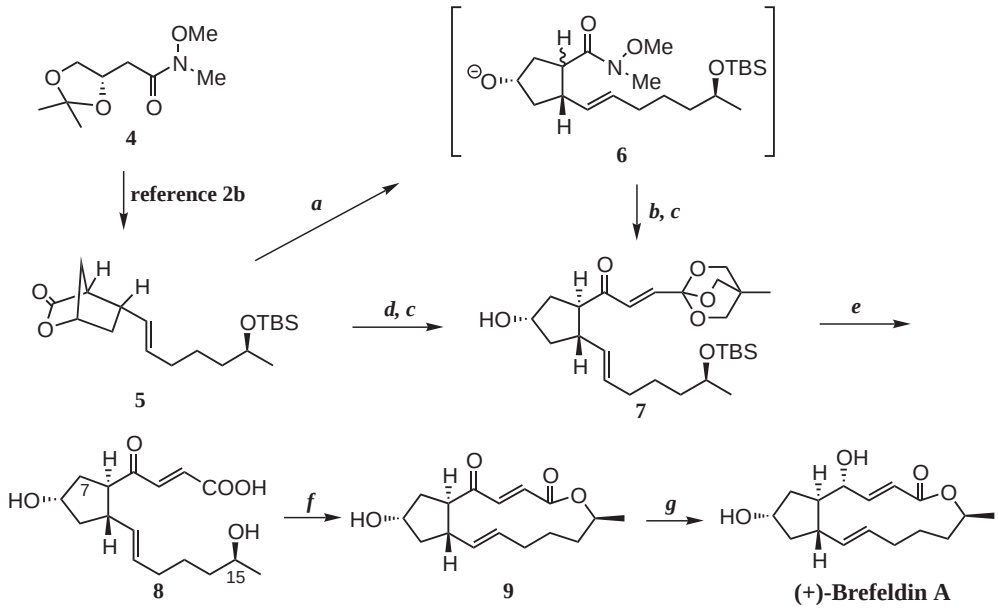
[a] Condition A : 3 equivalents of **2a** were used; Condition B : 4 equivalents of **2a** were used. [b] Isolated yields. [c] The temperature of -78°C was maintained. [d] Yield based on recovered starting material.

The facile coupling reaction of the anion **2b** as a vinylogous acyl anion equivalent with bicyclic lactone was successfully applied to the total synthesis of (+)-brefeldin A[6] (Scheme 1). Addition of **2b** to the bicyclic lactone **5**[2b], followed by DBU treatment of the resulting vinyl ketone for epimerization provided the enone intermediate **7**[7] as a single diastereomer in 51% yield. Alternatively, reaction of **2b** with the Weinreb amide **6** which was in situ generated by amidation of **5** with magnesium anion of *N*,*O*-dimethylhydroxylamine[8] afforded the enone **7** after DBU treatment. Exposure of the enone **7** to 1N HCl and then hydrolysis of the resulting hydroxy ester with LiOH afforded the dihydroxy acid **8** as an advanced precursor for macrolactonization. Macrolactonization of the hydroxy acid **8** was conducted according to the Yamaguchi procedure[9] in the presence of the free C_7-hydroxy group. The preferred macrolactonization of the C_{15}-hydroxy group is likely due to the steric and geometric advantage. Finally, stereoselective reduction[10] of the ketone **9** with $NaBH_4$ afforded (+)-brefeldin A. The synthetic brefeldin A was identical in all aspects with authentic brefeldin A.[11]

In conclusion, an efficient method for γ-keto and γ-hydroxy acrylate by the direct introduction of *trans*-acrylate moiety to the various carbonyl compounds has been developed. Moreover, the concise total synthesis of (+)-brefeldin A from the known bicyclic intermediate **5** has been accomplished by an application of the facile acylation of a new variant of *trans*-vinylogous ester anion equivalent.

Representative procedure

To a solution of *t*-BuLi (1.2 mmol, 6 equiv.) in pentane at −78°C under argon was added a solution of



Scheme 1. Reaction conditions: (a) NH(OMe)Me·HCl, *i*PrMgCl, THF, −20°C to rt; (b) **2a**, *t*-BuLi, ether, −78°C, 30 min, then **6**, −78°C to rt, 81% from **5**; (c) DBU, CH_2Cl_2, reflux, 99%; (d) **2a**, *t*-BuLi, ether, −78°C, 30 min, then **5**, −78°C, 51%; (e) 1N HCl, H_2O/THF (1/1), then LiOH, 85%; (f) 2,4,6-trichlobenzoyl chloride, Et_3N, THF, rt, 2 h , then 4-DMAP, toluene, reflux, 24 h, 51%; (g) $NaBH_4$, MeOH, −78°C, 95%.

iodovinyl OBO orthoester **2a** (169 mg, 0.60 mmol, 3 equiv.) in anhydrous ether (2 mL) using a cannula and argon pressure for the transfer. After stirring for 30 min at −78°C, a solution of benzaldehyde (20 mg, 0.20 mmol, 1 equiv.) in anhydrous ether (2 mL) was added dropwise using a cannula. The reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was quenched with H_2O (1 mL) and then diluted with ether (10 mL). The aqueous layer was extracted with ether (10 mL×2) and the combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (1 : 2) with 1% (v/v) triethylamine to afford **3a** (40 mg, 76%).

Acknowledgements

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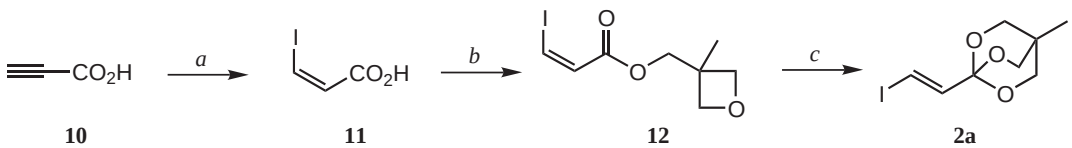
References

1. For a recent review, see: Chinchilla, R.; Nájera, C. *Chem. Rev*. **2000**, *100*, 1891.
2. (a) Suh, Y.-G.; Jung, J.-K.; Kim, S.-A.; Shin, D.-Y.; Min, K.-H. *Tetrahedron Lett*. **1997**, *38*, 3911; (b) Suh, Y.-G.; Jung, J.-K.; Suh, B.-C.; Lee, Y.-C.; Kim, S.-A. *Tetrahedron Lett*. **1998**, *39*, 5377; (c) For the recent synthesis of (+)-brefeldin A, see: Ducray, P.; Rousseau, B.; Mioskoeski, C. *J. Org. Chem*. **1999**, *64*, 3800 and other references cited therein.
3. Corey, E. J.; Raja, N. *Tetrahedron Lett*. **1983**, *24*, 5571.
4. (a) Richardson, S. K.; Jeganathan, A.; Watt, D. S. *Tetrahedron Lett*. **1987**, *28*, 2335; (b) Meyers, A. I.; Spohn, R. F. *J. Org. Chem*. **1985**, *50*, 4872; (c) For Ni(II)/Cr(II)-mediated coupling reaction of *trans*-iodoacrylate, see: Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem*. **1995**, *60*, 5386 and the references cited therein.
5. The iodovinyl OBO orthoester **2a** was conveniently prepared by regioselective hydroiodination of propiolic acid (**10**) (Scheme 2) and the procedure reported in Ref. 4a. Zoller, T.; Uguen, D. *Tetrahedron Lett*. **1998**, *39*, 6719.
6. For the indirect introduction of acrylate moiety in the synthesis of brefeldin A, see: (a) Gais, H.-J.; Lied, T. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 145; (b) Kitahara, T.; Mori, K. *Tetrahedron* **1984**, *40*, 2935.



Scheme 2. Reaction conditions: (a) 57% HI, H_2O, 85°C, 90%; (b) 3-methyl-3-hydroxymethyloxetane, DCC, DMAP, CH_2Cl_2, rt, 95%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −15°C, 73%.

7. Spectral data for **7**: $[\alpha]_D^{11}$ −29.0° (*c* 0.14, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.80 (s, 3H), 0.84 (s, 9H), 1.07 (d, 3H, $J=6.0$ Hz), 1.24–1.47 (m, 6H), 1.84 (m, 1H), 1.90 (m, 2H), 1.98 (ddd, 1H, $J=13.5$, 9.0, 6.0 Hz), 2.20 (ddd, 1H, $J=13.8$, 8.4, 5.8 Hz), 2.70 (m, 1H), 3.14 (q, 1H, $J=8.7$ Hz), 3.72 (m, 1H), 3.92 (s, 6H), 4.34 (brs, 1H), 5.35 (m, 2H), 6.45 (d, 1H, $J=16.0$ Hz), 6.50 (d, 1H, $J=16.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.7, −4.4, 14.4, 18.1, 23.7, 25.4, 25.9, 30.6, 32.3, 39.1, 39.2, 42.4, 44.3, 53.7, 68.5, 72.8, 72.9, 105.8, 130.9, 131.3, 132.7, 137.5, 201.3; IR (neat) 3852, 3441, 2927, 1651, 1384, 1055, 615, 470, 407 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{27}H_{46}O_6Si$ 494.3064, found 494.3064 (M^+).
8. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
9. Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
10. Zhu, J.-W.; Nagasawa, H.; Nagura, F.; Mohamad, S. B.; Uto, Y.; Ohkura, K.; Hori, H. *Bioorg. Med. Chem.* **2000**, *8*, 455.
11. The authentic brefeldin A was purchased from Fluka Co.