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An Efficient Method for Synthesis of Succinate-Based MMP Inhibitors

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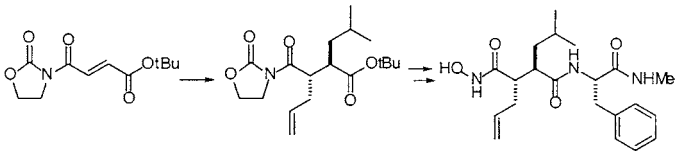
ABSTRACT

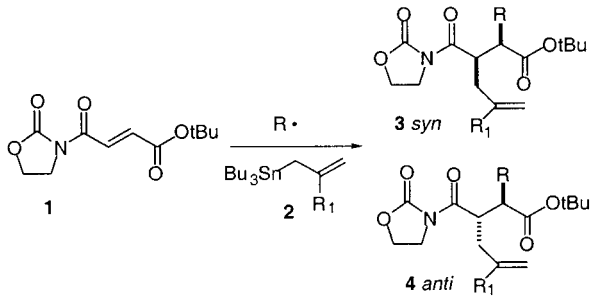


A differentially protected fumarate undergoes radical addition followed by allylstannane trapping to provide disubstituted succinates in good yields and high anti diastereoselectivity. The conversion of the succinate to a known MMP inhibitor has been accomplished.

Matrix metalloproteinases, a family of zinc-containing proteases, play a key role in tissue degradation and have been implicated in diseases such as arthritis and cancer.[1] In the past several years, succinates with substituents on the carbon backbone have received attention because of their potential use in the development of potent matrix metalloproteinase (MMP) inhibitors.[2] In this regard, a differentially protected succinate is an extremely useful synthon for ready functionalization of the carbon backbone. We have recently shown that the intermediate radical formed from conjugate radical addition to simple enoates can be efficiently trapped with allyl stannane.[3] These reactions proceed with high diastereo- and enantioselectivity. In an effort to expand the utility of this chemistry to the synthesis of MMP inhibitors, we have undertaken the regio- and stereocontrolled radical additions to differentially protected fumarate **1** and trapped the intermediate radical with a variety of allylstannanes to provide products **3** or **4** (Scheme 1). Furthermore, the application of the radical methodology to the synthesis of BB-1101, a compound of some promise in the MMP inhibitor arena, is illustrated.[4]

Our experiments began with finding optimal reaction conditions for the addition/trapping process using fumarate **1** (eq 1) as the substrate. We[5e] and others[5] have previously shown that the regioselectivity in radical addition to desymmetrized fumarates can be controlled either by Lewis acids or other factors. Initial experiments were designed to evaluate different Lewis acids for the addition of *i*-BuI to **1**[6] followed by trapping with allylstannane using triethylborane/oxygen as a radical initiator (Table 1). Reaction even in the absence of a Lewis acid was possible, suggesting that the fumarate is a highly reactive substrate (entry 1). Magnesium Lewis acids were only marginally effective, and the chemical efficiency was dependent on the counterion, with magnesium perchlorate performing the best (compare entry 2 and 4 with

Scheme 1



(1) (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305. (b) Michaelides, M. R.; Curtin, M. L. *Curr. Pharm. Des.* **1999**, *5*, 787. (c) Foda, H. D.; Zucker, S. *Drug Discovery Today* **2001**, *6*, 478.

(2) For a recent review article, see: Whittaker, M.; Floyd, C. D.; Brown, P.; Geraing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735 and references therein.

(3) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.

(4) Crimmin, M. J.; Beckett, P. R.; Davis, M. H. British Bio-Technology Ltd.; WO 94 21,625; *Chem. Abstr.* **1995**, *122*, 188173y.

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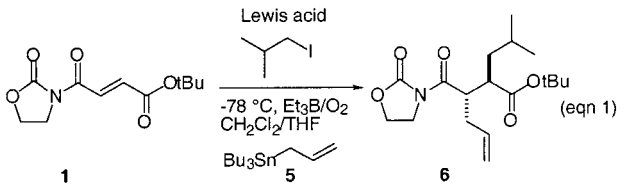
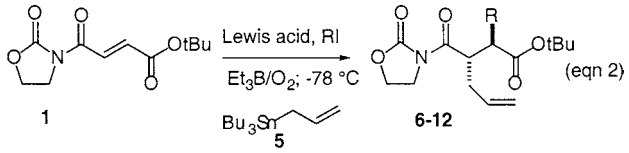
Table 1. Effect of Lewis Acid on Radical Addition/Trapping



entry	Lewis acid	time (h)	yield (%)[b]	dr[c]
1		4	44	≥99:1
2	MgI_2	6	26	≥99:1
3	$Mg(ClO_4)_2$	4	70	≥99:1
4	$Mg(OTf)_2$	2	58	≥99:1
5	$Al(OTf)_3$	4	41	≥99:1
6	$In(OTf)_3$	4	43	≥99:1
7	$Sc(OTf)_3$	4	56	≥99:1
8	$Y(OTf)_3$	2	91	≥99:1
9	$Sm(OTf)_3$	2	85	≥99:1
10	$Yb(OTf)_3$	4	67	≥99:1

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Diastereomer ratio determined by ^{1}H NMR (500 MHz).

Table 2. Addition/Trapping Experiments with Different Radicals



		Y(OTf)$_3$		Sm(OTf)$_3$	
entry	product	yield (%)[a]	dr[b]	yield (%)[a]	dr[b]
1	**7** R = Et	85	≥99:1	87	≥99:1
2	**8** R = $(CH_2)_3CH{=}CH_2$	66	≥99:1	63	≥99:1
3	**9** R = $(CH_2)_3Ph$	72	≥99:1	74	≥99:1
4	**6** R = *i*-Bu	91	≥99:1	85	≥99:1
5	**10** R = *i*-Pr	80	≥99:1	82	≥99:1
6	**11** R = *t*-Bu	62	≥99:1	64	≥99:1
7	**12** R = adamantyl	15	≥99:1	22	≥99:1

[a] Isolated yield. [b] Diastereomer ratio determined by ^{1}H NMR (500 MHz).

3).[7] Aluminum and indium Lewis acids were less effective (entries 5 and 6). In contrast, prelanthanide and lanthanide triflates gave better yields (entries 7−10). Of these, yttrium and samarium triflates showed the best reaction characteristics (entry 8 and 9).[8] The selectivity in all of these reactions was very high. The stereochemistry of the major diastereomer was established as anti[9] by converting **6** to a known compound.[10] The high anti selectivity is noteworthy since this stereochemistry is required for the preparation of MMP inhibitors with high bioactivity (vide infra).

Having established the feasibility of the addition/trapping reactions, we then examined the efficacy of different nucleophilic radicals using both yttrium and samarium triflates as the Lewis acid (eq 2). Results from these studies are tabulated in Table 2. Addition of a variety of primary radicals proceeded in moderate to good yields but with high diastereoselectivity (entries 1−4).[11] Of the two Lewis acids examined, yttrium triflate gave slightly better results. Addition of a secondary radical was also very effective, providing **10** (entry 5). Even the bulky tertiary radical derived from *t*-BuI gave the addition/trapping product **11** with good chemical yield as a single diastereomer (entry 6). However, addition of adamantyl radical was not efficient (entry 7). A large amount of **7** (33%), the ethyl addition byproduct, was obtained in this reaction. These results show that a variety of disubstituted succinates can be prepared in moderate to high chemical yield with very high anti diastereoselectivity.

Three different allyl stannanes were investigated as trapping agents in the tandem reaction (eq 3). The addition of isobutyl radical to **1** using yttrium triflate as the Lewis acid was used to evaluate the trapping reagents (Table 3). The reaction with parent allyl stannane is shown in entry 1 for comparison. Trapping experiments with the more reactive methallylstannane **13** was also very efficient, and the product (**15**) was produced as a single isomer (entry 2).[12] In contrast, reaction with 2-acetoxymethylallylstannae (**14**) gave only a modest yield of the product (**16**) but as a single isomer (entry 3). Thus different allyl stannanes can be employed as trapping reagents to produce functionalized succinates.

A variety of methodologies have been developed to prepare disubstituted succinates to access MMP inhibitors.[13] Generally, the establishment of the required anti stereochemistry for the substituents in these approaches has been problematic. To demonstrate the utility of our stereoselective methodology we undertook the synthesis of BB-1101, a representative succinate-based MMP inhibitor (Scheme 2).[4] Selective cleavage of the *tert*-butyl ester in **6** using TFA gave the mono functionalized succinate **17** in high yield. The

(5) For work on radical addition to fumarates using imides derived from Kemps triacid, see: (a) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. For examination of selectivity in radical addition to fumarates and related systems, see: (b) Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664. (c) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741. (d) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311. (e) Sibi, M. P.; Liu, P.; Ji, J.; Chen. J. *J. Org. Chem.* **2002**, *67*, 1738.

(6) See Supporting Information for the synthesis of **1**.

(7) For an excellent recent review, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. Also see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. (c) Sibi, M. P.; Ji, J.; Sausker J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517. (d) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(8) Varying amounts (1−20%) of the ethyl radical addition/trapping product was also observed depending on the Lewis acid.

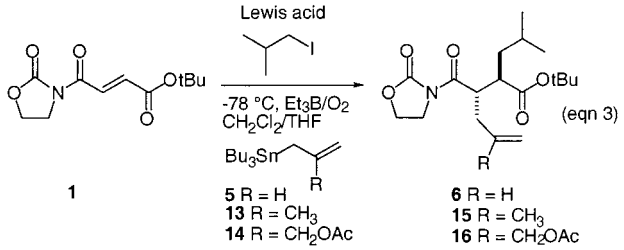
(9) For a discussion on the origins of the high anti selectivity observed in the addition/trapping experiments, see ref 3.

(10) The oxazolidinone functionality in compound **6** was selectively hydrolyzed to a known acid. Pratt, L. M.; Bowles, S. A.; Courtney, S. F.; Hidden, C.; Lewis, C. N.; Martin, F. M.; Todd, R. S. *Synlett* **1998**, 531. See Supporting Information for details.

(11) The amount of ethyl addition byproduct in entries 2−6, Table 2, varied from 1% to 10%. This is an indirect reflection of radical chain length.

(12) The anti stereochemistry for the product was assigned on the basis of analogy.

Table 3. Addition/Trapping Experiments with Different Allylstannanes

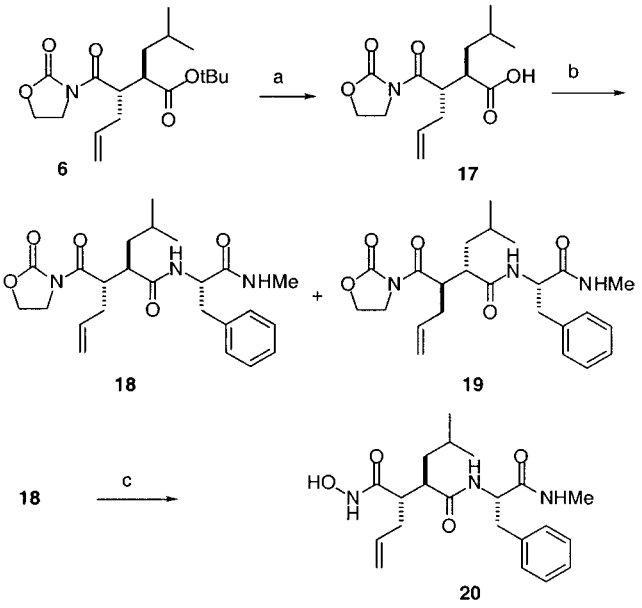


entry	allyl stannane	product	yield (%)[a]	dr[b]
1	**5**	**6** R = H	91	≥99:1
2	**13**	**15** R = CH_3	77	≥99:1
3	**14**	**16** R = CH_2OAc	28	≥99:1

[a] Isolated yield. [b] Diastereomer ratio determined by ^1H NMR (500 MHz).

racemic acid **17** was coupled with enantiomerically pure phenylalanine-*N*-methylamide using EDCI as a coupling agent to produce a diastereomeric mixture of amides **18** and **19** in 63% yield. The diastereomers were cleanly separated using column chromatography. We have recently developed a very convenient methodology for the conversion of oxazolidinones to hydroxamic acids.[14] A variety of nucleophiles were evaluated for the conversion of **18** to BB-1101 using the previously established conditions with little success ($Sm(OTf)_3$/amine/rt or heat).[15] Reaction with THP-protected hydroxylamine proved to be very efficient. Thus, treatment of **18** with $THPONH_2$ and $Sm(OTf)_3$ gave the protected hydroxamic acid product, which was treated with acid

Scheme 2[a]



[a] Key: (a) TFA, CH_2Cl_2, 98%. (b) EDCI/HOBT/amino acid/DMF 63% yield (36% of **18** and 27% of **19**). (c) (i) $THPONH_2$/$Sm(OTf)_3$/THF, (ii) dilute HCl workup, 75% over two steps.

without purification to produce BB-1101 (**20**) in excellent yield in four steps starting from **1**. Thus the methodology developed in this work is a convenient way to prepare biologically active targets efficiently.

In conclusion, we have developed an efficient protocol for the preparation of a variety of disubstituted succinates with excellent control of relative stereochemistry. The application of the methodology in an efficient synthesis of a MMP inhibitor was also accomplished. Experiments are underway to carry out the addition/trapping sequence enantioselectively.

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Supporting Information Available: Characterization data for compounds **1**−**20** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026331T

(13) For some selected examples of the synthesis of succinate-based MMP inhibitors, see: (a) Hilpert, H. *Tetrahedron* **2001**, *57*, 7675. (b) Yamamoto, M.; Tsujishita, H.; Hori, N.; Ohishi, Y.; Inoue, S.; Ikeda, S.; Okada, Y. *J. Med. Chem.* **1998**, *41*, 1209. (c) Levy, D. E.; Lapierre, F.; Liang, W.; Ye, W.; Lange, C. W.; Li, X.; Grobelny, D.; Casabonne, M.; Tyrrell, D.; Holme, K.; Nadzan, A.; Galardy, R. E. *J. Med. Chem.* **1998**, *41*, 199. (d) Fray, M. J.; Burslem, M. F.; Dickinson, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 567. (e) Fray, M. J.; Dickinson, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 571. (f) McClure, K. F.; Axt, M. Z. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 143. (g) Steinman, D. H.; Curtin, M. L.; Garland, R. B.; Davidsen, S. K.; Heyman, H. R.; Holms, J. H.; Albert, D. H.; Magoc, T. J.; Nagy, I. B.; Marcotte, P. A.; Li, J.; Morgan, D. W.; Hutchins, C.; Summers, J. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2087. (h) Pratt, L. M.; Beckett, P.; Bellamy, C. L.; Corkill, D. J.; Cosins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.; Drummond, A. H.; Helfrich, K.; Lewis, C. N. Mangan, M.; Martin, F. M.; Miller, K.; Nayee, P.; Ricketts, M. L.; Thomas, W.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1359.

(14) Sibi, M. P.; Hasegawa, H.; Ghorpade, S. *Org. Lett.* **2002**, *4*, 3343.

(15) Reaction with $BnONH_2$ was effective (68%). However, the benzyl group could not be cleaved selectively without affecting the alkene. Reaction with NH_2OH, $TMSONH_2$, or TMSONHTMS gave low yields of BB-1101.