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A Practical Approach for Enantio- and Diastereocontrol in the Synthesis of 2,3-Disubstituted Succinic Acid Esters: Synthesis of the pan-Notch Inhibitor BMS-906024

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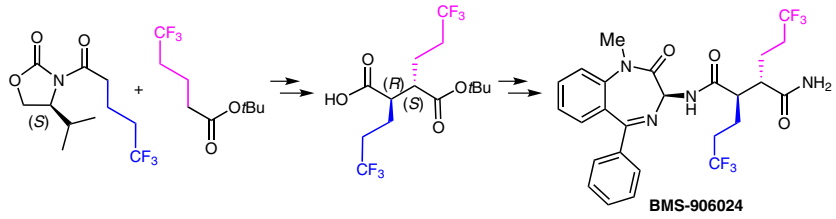

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Abstract An oxidative intermolecular enolate heterocoupling reaction was employed for the synthesis of *anti*-2,3-disubstituted succinic acid mono- and differentially protected diesters. Tactical approaches to access all the diastereomers are discussed. The method was applied to the synthesis of a potent anticancer agent, BMS-906024.

Key words oxidative enolate coupling, chiral succinic acid, pan-Notch Inhibitor BMS-906024

2,3-Disubstituted succinic acids and derivatives are found in many drugs and drug candidates and as a substructure of natural products.[1,2] In recent work aimed at the discovery of novel anticancer agents, BMS-654 (Figure 1) was identified as a potent pan-Notch inhibitor.[3] Development of further structure–activity relationships (SAR) required rapid access to either mono-protected or orthogonally di-protected succinic acid esters with anti-configuration in the succinamide portion of the molecule as shown in BMS-654.

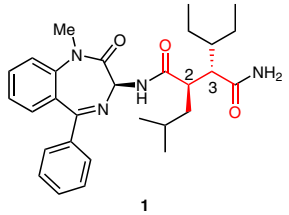

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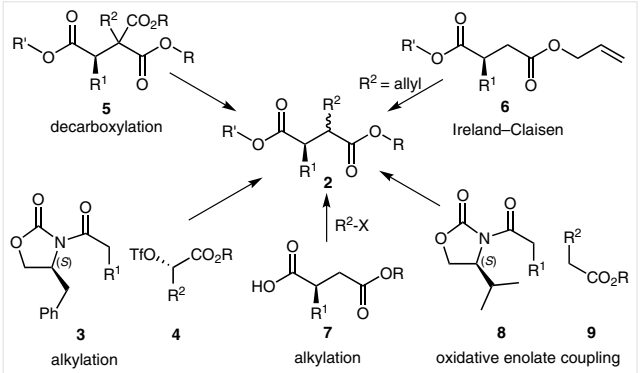
Figure 1 BMS-654 (Notch1/2/3/4 IC_{50} = 2/1/3/2 nM)

Although several methods are known to give disubstituted succinic acids, few exhibited the desired broad scope and diastereoselectivity. For example, Deccico[4] showed that either *syn* or *anti* selectivity may be obtained depending on the choice of chiral oxazolidinone **3** and chiral secondary triflate **4** (Scheme 1). However, low yields of the desired *anti*-succinate precluded the application of this method for our needs. McClure[5a] and others[5b] showed that *anti*-selective products can be obtained through decarboxylation of **5**, but the generality of this method has not been established. Martin[6] showed that an Ireland–Claisen route (**6** to **2**) can provide *anti*-selective products, but this method is limited to functionalities that can be derived from an allyl group. Crimmin[7] showed that only *syn*-selective products could be obtained upon alkylation of ester **7**. Recently, Baran[8a] reported an efficient method for generation of 2,3-disubstituted succinic acids via a copper-mediated oxidative eno-

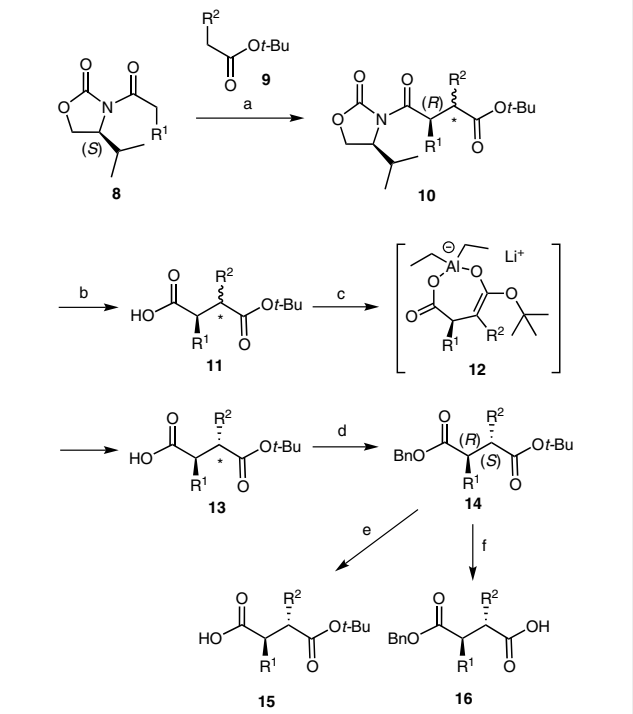


Scheme 1 Strategies to synthesize 2,3-disubstituted succinic acids

late coupling (e.g., **8** + **9** to **2**). It is the aim of this Letter to expand the scope of the oxidative enolate coupling reaction and the strategy for separation of the resulting diastereomers for rapid access to enantio- and diastereomerically pure 2,3-disubstituted succinic acid mono- and differentially diprotected esters. The method was optimized for the synthesis of BMS-906024, a highly potent pan-Notch inhibitor currently undergoing phase 1 clinical evaluation.[3]

Scheme 2 depicts the oxidative intermolecular enolate heterocoupling route employed for the synthesis of 2,3-disubstituted succinic acid esters. The efficiency of the copper(II) 2-ethylhexanoate mediated heterocoupling process was optimized by employing a modest excess (1.75 equiv) of the ester coupling partner **9** and by carrying out enolate formations in separate reaction vessels. A detailed procedure for a representative enolate coupling reaction (Table 1, entry 2) is provided.[9] As illustrated in Table 1, a variety of lipophilic moieties were tolerated in this reaction. Lower yields for the coupling reaction with trifluorobutyl amide (Table 1, entry 8) may be attributed to the reduced reactivity of the corresponding enolate. As noted before,[8] there was complete stereocontrol at the oxazolidinone α-carbon and modest diastereoselectivities were observed in favor of the desired anti diastereomer at the carbon atom situated β to the oxazolidinone moiety. Chemoselective removal of the chiral auxiliary with lithium peroxide[10] provided the corresponding succinic acid monoester **11** in excellent yield while retaining the diastereomeric ratio as determined by ^{1}H NMR spectroscopy.

Epimerization[11] at the β-carbon (bearing the R^2 group) was carried out by subsequent treatment with LDA and diethylaluminum chloride followed by kinetic quench with methanol to afford **13** as a mixture enriched, in many instances significantly, in the desired *anti* diastereomer. A representative example of the exact procedure followed for the epimerization is given.[12] Several factors may influence the outcome of this transformation. One potentially key factor driving the selectivity is the kinetic quench of a postulated seven-membered aluminum enolate **12**. Molecular modelling suggests that the R^1 group and one of the ethyl groups on the aluminum assume a pseudo-axial conformation, thereby partially blocking one face of the enolate during the transfer of the proton, resulting in the addition of the proton from the more open face. Additionally, comparing models of aluminum enolates for Table 1, entries 2 and 12, it also appears that the extra bulk of the R^2 group in entry 12 (Table 1) may cause a rotation of the *t*-Bu group such that one of the methyl groups of the *t*-Bu may now encroach upon the open face. This may explain the observed reduction in diastereoselectivity (Table 1, entries 11 and



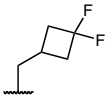
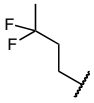
Scheme 2 Oxidative enolate coupling route to 2,3-disubstituted succinic acid esters. * Indicates a mixture of isomers at this center. *Reagents and conditions*: (a) (1) **8**, LDA, toluene, THF, –78 °C to 0 °C to –78 °C; (2) **9**, LDA, toluene, THF, –78°C; (3) Cu(2-ethylhexanoate)$_2$, –78 °C to 40 °C; (b) LiOH, H_2O, H_2O_2, 0 °C; (c) LDA, THF, Et_2AlCl, hexane, –78 °C to 0 °C; (d) BnBr, K_2CO_3, DMF; (e) H_2, 10% Pd/C, EtOAc; (f) TFA, CH_2Cl_2, r.t.

12). The selectivity may also be dependent on the efficiency of formation and equilibration of the aluminum enolate. For sterically encumbered enolates (e.g. Table 1, entries 11 and 12), additional amounts of LDA (3.4 equiv) and Et_2AlCl (3.5 equiv) provided a marginal improvement in diastereoselectivity while the use of the standard procedure (ref. 12) resulted in no enrichment.

At this stage, the mixture of the two diastereomers could be carried forward and subsequent products separated by chiral chromatography. Alternatively, **13** was converted into the corresponding benzyl ester under standard conditions and the desired *anti* diester **14** was separated by silica gel column chromatography.[13] Selective ester deprotection conditions provided enantio- and diastereomerically pure *anti*-monoesters **15** and **16** in excellent yields.

Following the initial lead BMS-654 (**1**, Figure 1), availability of these 2,3-disubstituted succinic acid monoesters greatly aided in rapid generation of SAR for pan-Notch inhibitors culminating in the identification of **18** (BMS-906024) as the clinical candidate.[3] Table 2 highlights the

Table 1 Synthesis of 2,3-Dialkyl Succinic Acid Esters

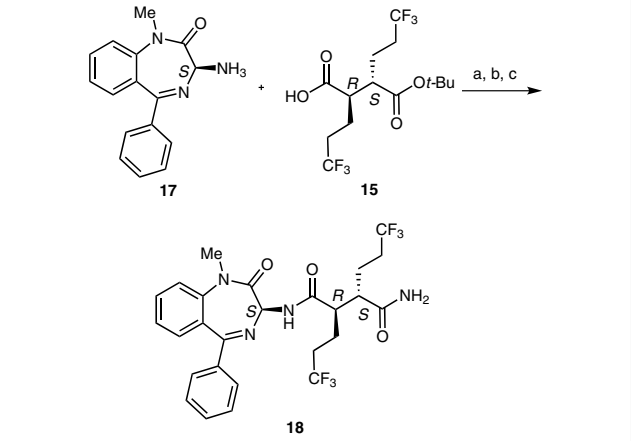
Entry	R^1	R^2	Yield (%),[a] dr[b]			
			10	**11**	**12**	**13**
1	*n*-Pr	$CF_3(CH_2)_2$	48 (1.5:1.0)	47	99 (7.6:1.0)	81
2	$CF_3(CH_2)_2$	$CF_3(CH_2)_2$	66 (1.6:1.0)	91	96 (9.0:1.0)	67
3	$CF_3(CH_2)_2$		31 (1.5:1.0)	80	87 (2.5:1.0)	53
4		$CF_3(CH_2)_2$	63 (1.2:1.0)	96	99 (14.0:1.0)	56
5	$CF_3(CH_2)_2$		47 (1.4:1.0)	97	99 (12.3:1.0)	65
6	Me_2CHCH_2	$CF_3(CH_2)_2$	50 (1.3:1.0)	88	>99 (9.9:1.0)	–[c]
7	Me_3CCH_2	$CF_3(CH_2)_2$	60 (1.2:1.0)	17	–[d]	
8	CF_3CH_2	$CF_3(CH_2)_2$	28 (1.0:1.0)	76	97 (4.6:1.0)	–[c]
9	$CF_3(CH_2)_2$	CF_3CH_2	49 (1.2:1.0)	64	83 (1.4:1.0)	–[c]
10	$CF_3(CH_2)_2$		51 (nd)[e]	>99	91 (9.0:1.0)	–[c]
11	$CF_3(CH_2)_2$		31 (2.1:1.0)	55	97[f] (3.3:1.0)	53
12	$CF_3(CH_2)_2$		54 (1.3:1.0)	49	95[f] (2.2:1.0)	–[c]
13	$CF_3(CH_2)_3$		27 (1.5:1.0)	37	–[d]	–[c]

[a] Isolated yield.
[b] Diastereomeric ratios determined by ^1H NMR integration.
[c] Benzyl esters not prepared.
[d] Epimerization not performed.
[e] Not determined.
[f] LDA (3.4 equiv) and Et_2AlCl (3.5 equiv) were used.

importance of *S*,*R*,*S* absolute configuration in this series for achieving high level of pan-Notch potency. As illustrated in Scheme 3, (3*S*)-amino-1,4-benzodiazepin-2-one **17**[14] was coupled with **15** in the presence of TBTU and triethylamine to give the corresponding amide. Ester hydrolysis with trifluoroacetic acid was followed by amide formation with ammonium chloride under standard conditions to produce **18** in good yield. The absolute configuration of **18** was confirmed by X-ray diffraction studies.

Table 2 Effect of 2,3-Succinamide Configuration on Notch 1/3 Inhibitory Potency

Compd	Configuration	Notch IC_{50} (nM)	
		Notch 1	Notch 3
18	*S*,*R*,*S*	2	3
19	*S*,*R*,*R*	1893	1679
20	*S*,*S*,*S*	>5000	>5000
21	*S*,*S*,*R*	57	73
22	*R*,*R*,*S*	646	537
23	*R*,*R*,*R*	>5000	>5000
24	*R*,*S*,*S*	271	400
25	*R*,*S*,*R*	>5000	>5000



Scheme 3 Synthesis of BMS-906024. *Reagents and conditions*: (a) TBTU, Et_3N, DMF (89%); (b) TFA, CH_2Cl_2 (75%); (c) NH_4Cl, EDC, HOBt, Et_3N, DMF (79%).

In conclusion, the oxidative intermolecular enolate heterocoupling reaction and subsequent epimerization protocol afforded a rapid and efficient entry to enantio- and diastereomerically pure *anti*-2,3-disubstituted succinic acid esters in acceptable yields. Differential protection of these succinic acid esters provided access to each individual diastereomer. This synthetic methodology led to rapid SAR generation and the identification of BMS-906024 as a potent pan-Notch inhibitor currently undergoing phase 1 clinical evaluation for the treatment of cancer.

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References and Notes

(1) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.
(2) (a) Chukwujekwu, J. C.; de Kock, C. A.; Smith, P. J.; van Heerden, F. R.; van Staden, J. *Planta Med.* **2012**, *78*, 1857. (b) Ishihara, J.; Tokuda, O.; Shiraishi, K.; Nishino, Y.; Takahashi, K.; Hatakeyama, S. *Heterocycles* **2010**, *80*, 1067. (c) Huang, Y.-L.; Chen, C.-C.; Hsu, F.-L.; Chen, C.-F. *J. Nat. Prod.* **1998**, *61*, 1194. (d) Brown, K.; Devlin, J. A.; Robins, D. J. *Phytochemistry* **1984**, *23*, 457.
(3) Gavai, A. V.; Quesnelle, C.; Norris, D.; Han, W.-C.; Gill, P.; Shan, W.; Balog, A.; Chen, K.; Tebben, A.; Rampulla, R.; Wu, D.-R.; Zhang, Y.; Mathur, A.; White, R.; Rose, A.; Wang, H.; Yang, Z.; Ranasinghe, A.; D'Arienzo, C.; Guarino, V.; Xiao, L.; Su, C.; Everlof, G.; Arora, V.; Shen, D. R.; Cvijic, M. E.; Menard, K.; Wen, M.-L.; Meredith, J.; Trainor, G.; Lombardo, L. J.; Olson, R.; Baran, P. S.; Hunt, J. T.; Vite, G. D.; Fischer, B. S.; Westhouse, R. A.; Lee, F. Y. *ACS Med. Chem. Lett.* **2015**, *6*, 523.
(4) Decicco, C. P.; Nelson, D. J.; Corbett, R. L.; Dreabit, J. C. *J. Org. Chem.* **1995**, *60*, 4782.
(5) (a) McClure, K. F.; Axt, M. Z. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 143. (b) Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Bioorg. Med. Chem.* **2002**, *10*, 2569.
(6) Pratt, L. M.; Bowles, S. A.; Courtney, S. F.; Hidden, C.; Lewis, C. N.; Martin, F. M.; Todd, R. S. *Synlett* **1998**, 531.
(7) Beckett, R. P.; Crimmin, M. J.; Davis, M. H.; Spavold, Z. *Synlett* **1993**, 137.
(8) (a) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546. See also: (b) Csákÿ, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313. (c) Guo, F.; Clift, M. D.; Thomson, R. J. *Eur. J. Org. Chem.* **2012**, 4881.
(9) Five separate vessels, all appropriately dried, were set up as follows:
1) a flask fitted with a stir bar to be used to prepare LDA, purged with N_2;
2) a flask containing bis(2-ethylhexanoyloxy)copper, placed under vacuum for several hours to remove oxygen, then purged with N_2;
3) a flask of appropriate size (this will be the main reaction flask, the larger the better for efficient heat transfer later in the procedure was found to be ideal) equipped with a stir bar was charged with LiCl, placed under vacuum then dried with a heat gun until all traces of water were removed, then purged with N_2;
4) a flask charged with the amide starting material, purged with N_2;
5) a flask equipped with a stir bar was charged with the ester starting material, purged with N_2.

Procedure

A 0.5 M solution of LDA was prepared by the addition of a solution of 2.5 M *n*-BuLi in hexanes (14.7 mL, 36.8 mmol) to a cold (–78 °C) solution of diisopropylamine (5.3 mL, 37.2 mmol) in THF (59 mL) under N_2. The solution was stirred at 0 °C for 15 min. A solution of (*S*)-4-isopropyl-3-(5,5,5-trifluoropentanoyl)oxazolidin-2-one (2.45 g, 9.2 mmol) in toluene (15.3 mL) was added with stirring to dry LiCl (1.96 g, 46.2 mmol). The mixture was cooled to –78 °C, and the freshly prepared 0.5 M solution of LDA (21.0 mL, 10.5 mmol) was added. The reaction mixture was stirred at –78 °C for 10 min, at 0 °C for 10 min, and cooled to –78 °C. Meanwhile, the freshly prepared 0.5 M solution of LDA (37.0 mL, 18.5 mmol) was added to a cold (–78 °C) solution of *tert*-butyl 5,5,5-trifluoropentanoate (3.41 g, 16.1 mmol) in toluene (15.3 mL). After 25 min of stirring at –78 °C,

this reaction mixture was transferred via cannula into the cold (–78 °C) LiCl/enolate solution. After an additional 5 min of stirring at –78 °C, solid powdered bis(2-ethylhexanoyloxy)copper (9.02 g, 25.8 mmol) was rapidly added to the reaction vessel through a funnel, and the flask was rapidly recapped with a septum. The vessel was immediately removed from the cold bath and immersed into a warm (40 °C) water bath with rapid swirling. The reaction mixture changed from the initial turquoise to a dark green then to a brown color. After 20 min of stirring, the reaction mixture was poured into 5% aq NH_4OH (360 mL) and extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (Teledyne ISCO CombiFlash Rf, 0–60% EtOAc in hexanes, RediSep silica gel, 120 g). Concentration of appropriate fractions provided the product *tert*-butyl (2*S*,3*R*)-6,6,6-trifluoro-3-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)-2-(3,3,3-trifluoropropyl)hexanoate (2.87 g, 66%) as a pale yellow oil. ^{1}H NMR indicated that the product was a 1.6:1 mixture of diastereomers, as determined by integration of the multiplets at 2.74 and 2.84 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43–4.54 (2 H, m), 4.23–4.35 (5 H, m), 4.01 (1 H, ddd, *J* = 9.54, 6.27, 3.51 Hz), 2.84 (1 H, ddd, *J* = 9.41, 7.28, 3.64 Hz), 2.74 (1 H, ddd, *J* = 10.29, 6.27, 4.02 Hz), 2.37–2.48 (2 H, m), 2.20–2.37 (3 H, m), 1.92–2.20 (8 H, m), 1.64–1.91 (5 H, m), 1.47 (18 H, s), 0.88–0.98 (12 H, m).

(10) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(11) Xue, C.-B.; Decicco, C. P.; Cherney, R. J.; Arner, E.; Degrado, W. F.; Duan, J.; He, X.; Jacobson, I.; Magolda, R. L.; Nelson, D. WO 9851665, **1998**.

(12) To a cold (–78 °C), stirred solution of DIPA (1.7 mL, 11.9 mmol) in THF (19 mL) under nitrogen was added a 2.5 M solution of *n*-BuLi in hexanes (4.8 mL, 12.0 mmol). The reaction mixture was stirred at –78°C for 5 min, then at 0 °C for 15 min, and transferred via cannula dropwise (over 25 min) to a cold (–78 °C) solution of a 1.7:1 ratio for 3-(*tert*-butoxycarbonyl)-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoic acid (1.99 g, 5.4 mmol) in THF (18 mL). The mixture was stirred at –78 °C for 15 min, then at 24 °C for 15 min, and again at –78°C for 15 min. A 1 M solution of diethylaluminum chloride in hexanes (11.4 mL, 11.4 mmol) was added dropwise via syringe, and stirring was continued at –78 °C for 10 min, at 24 °C for 15 min, and again at –78 °C for 15 min. MeOH (25 mL) was rapidly added, and the flask was swirled vigorously while warming to room temperature. The reaction mixture was concentrated to ca. 25% of the original volume. EtOAc (100 mL), aq 1 M HCl (50 mL), and ice (75 g) were added. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organics were washed with a solution of a mixture of KF (2.85 g) in water (75 mL) and aq 1 M HCl (13 mL), then subsequently washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the product (2*R*,3*S*)-3-(*tert*-butoxycarbonyl)-6,6,6-trifluoro-2-(3,3,3-trifluoropropyl)hexanoic acid (2.13 g, >99%) as a pale yellow oil. Relative integration of the *t*-Bu peaks in ^{1}H NMR established a 9:1 ratio for the *anti*/*syn* diastereomers, respectively.

anti-Isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.64–2.76 (2 H, m), 2.04–2.35 (4 H, m), 1.88–2.00 (2 H, m), 1.71–1.83 (2 H, m), 1.48 (9 H, s).

(13) The residue was purified by flash chromatography using a Teledyne ISCO CombiFlash Rf system with an external ELS detector, and a gradient from 60–100% toluene and hexane.

(14) Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Homnick, C. F.; Veber, D. F.; Freidinger, R. M. *Tetrahedron Lett.* **1987**, *28*, 521.