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# Synthesis of Chiral Succinates via Pd(0) Catalyzed Carbonylation / Asymmetric Hydrogenation Sequence.

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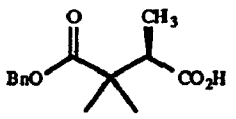
**Abstract : We report a novel 4 step synthesis of chiral trisubstituted succinic acid derivatives utilizing carbonylation of a vinyl triflate followed by catalytic asymmetric hydrogenation to yield the title compounds.**

There is considerable interest in the synthesis of chiral succinic acid derivatives due to their ability to function as amino acid isosteres in peptidomimetic molecules.[2] Incorporation of these subunits into potential enzyme inhibitors is appealing due to their increased proteolytic stability and retention of stereochemical integrity. Furthermore, they are useful starting materials for the synthesis of other chiral molecules; particularly β amino acids via Curtius Rearrangement.[3]

We recently reported the discovery of a novel series of succinate containing HIV protease inhibitors.[4] The requisite chiral succinic acid **1** is shown below. It was originally prepared via a Ireland-Claisen rearrangement starting from a chiral allylic alcohol derived from (S)-ethyl lactate.[5] Herein we report an alternative route to chiral trialkylsuccinates based on asymmetric hydrogenation of an appropriate acrylic acid (Scheme 1 ).

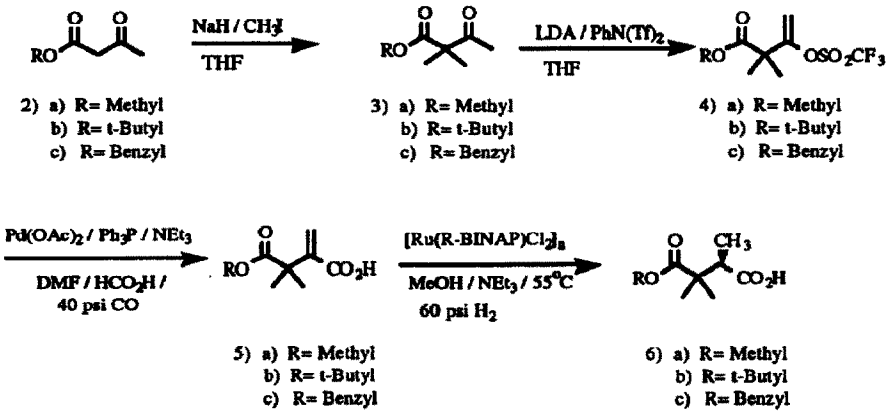



**1**

Exhaustive alkylation of readily available acetoacetate esters **2a-c** with methyl iodide proceeded uneventfully to give the dimethyl derivatives **3a-c** in good yield. Initial attempts to form the enol triflate with triflic anhydride / 2,6-di-t-butyl-4-methylpyridine[6] gave low yields of desired product accompanied by numerous

side products. However, the use of McMurray's reagent $PhN(Tf)_2$[7] gave clean conversion to the desired triflates.[8] The crude enol triflates were carbonylated without further purification.

The $Pd^0$ catalyzed carbonylation of enol triflates is well studied.[9] Typically these reactions are run in large excess of low molecular weight alcohol ( ~40eqs.) or low molecular weight amine ( ~5eqs.) to yield esters or amides respectively. We were intrigued by a report that mentioned a high yield synthesis of the acrylic acids directly from the enol triflates by use of triethylammonium formate.[10] In the absence of CO, triethylammonium formate under Pd(II) catalysis causes reduction of enol triflates to olefins.[11] Therefore we investigated whether enol triflates **4a-c** might be carbonylated to acrylic acids **5a-c** directly thus greatly simplifying product isolation.




2) a) R= Methyl
b) R= t-Butyl
c) R= Benzyl

3) a) R= Methyl
b) R= t-Butyl
c) R= Benzyl

4) a) R= Methyl
b) R= t-Butyl
c) R= Benzyl

5) a) R= Methyl
b) R= t-Butyl
c) R= Benzyl

6) a) R= Methyl
b) R= t-Butyl
c) R= Benzyl

Scheme 1

In all cases studied carbonylation occurs cleanly to yield the acrylic acids in high yield. A typical example is as follows : A 500 ml Fisher-Porter bottle was charged with 30 g (85 mmol) crude **4c**, 574 mg (2.5 mmol) $Pd^{II}(OAc)_2$, 1.34 g (5.1 mmol) $Ph_3P$, and 200 mL dry DMF. After 10 min. at 40 psi CO the reaction was vented and a solution of 24 mL (170 mmol) $NEt_3$, 6.29 g (137 mmol) 99% $HCO_2H$ in 50 mL DMF was added. The reaction was charged with 40 psi of CO and stirred at RT overnight. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and 10% aqueous $K_2CO_3$. The aqueous layer was acidified and extracted with ethyl acetate to yield 11.7 g product (52% from starting ketone **3c**).[12,13]

The formation of carboxylic acids from palladium catalyzed carbonylation of vinyl triflates is presumed to occur through the intermediacy of an unstable mixed anhydride[9a] which decomposes on workup to the observed product. Using IR or FAB-MS analysis of the DMF solution before workup we were unable to detect any evidence of an anhydride. When the carbonylation was run in the presence of $^{13}C$ labeled formic acid a

small amount (~5-10%) of label incorporation into product was observed. We were curious to see if the formic acid was necessary for product formation reasoning that one possible pathway to product could involve reductive elimination from palladium to yield a mixed anhydride derived from product acid and triflic acid. When the reaction was run in the absence of formic acid, low (5-10%) product yields resulted. Similarly, when water was substituted for formic acid, low (~15-20%) product yields were observed. Interestingly, when acetic acid is used the reaction yields are identical to the formic acid runs ( ~85-90% based on starting triflate).[10]

Asymmetric hydrogenation of prochiral olefins has emerged as a powerful tool in organic chemistry. From a historical perspective chiral bidentate phosphines bound to rhodium are the catalysts of choice.[14] Recently certain atropisomeric diphosphines, such as BINAP, bound to ruthenium have emerged as particularly versatile asymmetric catalysts.[15] Recently, one of us disclosed the preparation of a novel Ru(BINAP) catalyst ; $[Ru(R\text{-}BINAP)Cl_2]_n$.[16] This catalyst asymmetrically hydrogenated acids **5a-c** rapidly with % ee's in the 90-92 % range as determined by chiral LC.[17] The hydrogenations are run in the presence of 1 equiv of triethylamine and the ratio of substrate to catalyst was typically about 300:1. The R stereochemistry was assigned by comparison to authentic material.[5] A detailed mechanistic study of this hydrogenation is underway and will be reported shortly.

In summary, this four step sequence offers a general route to a variety of chiral trisubstituted succinates. We will be reporting on the syntheses of such succinates and their incorporation into protease inhibitors as well as the biological activity of these inhibitors in the near future.

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8. Triflates were prepared via addition of ketones **3a-c** to 1.1 equiv LDA in THF at-78° C. After 10 minutes 1.05 equiv of $PhN(Tf)_2$ was added and reactions were allowed to warm to RT overnight. Reaction workup consisted of concd *in vacuo* followed by partitioning between ethyl acetate and water. The organic phase was washed with excess aqueous base, dried and concd to an oil that was used without further purification. All triflates contained small amounts of PhNH(Tf) byproduct. The triflates are stable to dilute aqueous acid and silica gel chromatography .
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10. See Ref. 9a. After completion of this work a new approach to acrylic acids was reported by Prof. Cacchi: Cacchi, S.; Lupi, A. *Tet Lett*t., **1992**, 33, 3939.
11. Cacchi, S.; Morera, E.; Ortar, G. *Tet Lett.*, **1984**, *25*, 4821.
12. For the conversion of **3a-b** to **5a-b** yields are 70-75% for the two steps. While **5a-c** are stable, upon extended standing **5c** may polymerize. The addition of trace amounts of hydroquinone will prevent this.
13. Compound : **5a** ; mp 85-87 °C. $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.25 (s, 1H), 5.65 (s, 1H), 3.58 (s, 3H), 1.3 (s, 6H). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.71; H, 6.88. **5b** ; mp 107-109 °C. $^1$H-NMR (300MHz, $CDCl_3$): δ 6.35 (s, 1H), 5.75 (s, 1H), 1.4 (s, 9H), 1.35 (s,6H). Anal Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.27; H, 8.17. **5c** ; mp 75-77 °C. $^1$H-NMR (300MHz, $CDCl_3$): δ 7.35-7.2 (m, 5H), 6.4 (s,1H), 5.8 (s,1H), 5.1 (s, 2H), 1.4 (s,6H). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.54; H, 6.59.
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17. % ee determined for **6c** by conversion to the methyl ester (DBU / MeI) and chromatography on Daicel OB column (250mm x 4.1mm), flow rate = 0.5 ml / min, detector at 254 nM, gradient (100% hexane to 95% hexane / ethyl acetate over 60 minutes ). Retention Times ; S isomer (42.2), R isomer (45.1).

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