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α-Chloro-β,γ-ethylenic Esters: Enantiocontrolled Synthesis and Substitutions

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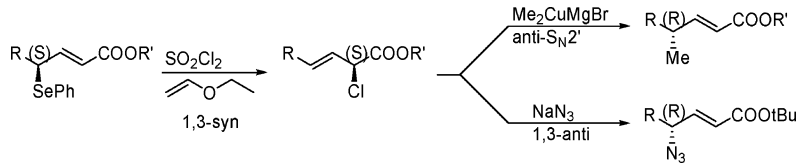
ABSTRACT



Chiral nonracemic γ-seleno-α,β-ethylenic esters, when treated with sulfuryl chloride and ethyl vinyl ether in hexanes, produced α-chloro-β,γ-ethylenic esters in 65−75% yields, with ee values of 95−97%, and with 1,3-syn transfer of chirality. Reaction of these allylic chloride electrophiles with methylcuprate and with sodium azide nucleophiles afforded exclusively γ-substituted-α,β-ethylenic esters with faithful anti-transfer of chirality on multigram scale.

Current literature records considerable interest in enantiomerically pure secondary allylic chlorides[1,2] and secondary α-chloro esters.[3] These useful chirons have been employed in a variety of organic reactions including the following: inter- and intramolecular S_N2 and S_N2' reactions,[4] Pd cross couplings,[5] Friedel−Crafts alkylations,[6] radical reactions,[7] and a wide variety of organometallic reactions (e.g., Grignard).[8] We describe here asymmetric, organocatalytic synthesis of γ-seleno-α,β-ethylenic esters[9,10,11] and, for the first time, their enantiocontrolled conversion, in one step, into diverse α-chloro-β,γ-ethylenic esters **2**. These highly enantioenriched electrophilic secondary allylic chlorides **2**, which are also α-chloro esters, undergo highly stereocontrolled substitution reactions with carbon and nitrogen nucleophiles yielding γ-methyl-α,β-ethylenic esters **3** and γ-amino-α,β-ethylenic *tert*-butyl esters **5** in good yields and high ee values (Scheme 1).

Previous reports described reactions of some racemic γ-seleno-α,β-ethylenic esters with sulfuryl chloride to form putative selenium dichloride intermediates followed in situ by spontaneous allylic transpositions to produce α-chloro-β,γ-ethylenic esters as mixtures of di- and trisubstituted olefin geometric isomers.[12] We show now for the first time that

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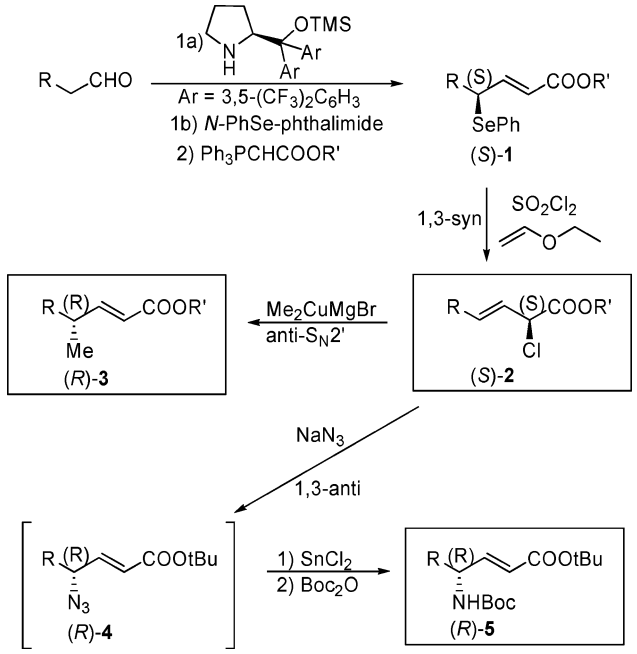
Scheme 1



this protocol, when applied to chiral nonracemic γ-seleno-α,β-ethylenic esters **1**, proceeded with faithful 1,3-syn transfer of chirality to form diverse α-chloro-β,γ-ethylenic chlorides **2** in good yields, with exclusive (*E*)-olefin geometry, and, especially significant, in at least 95% ee as determined by chiral HPLC (Scheme 1, Table 1). The

Table 1. Selenide **1** to Chloride **2** Transformations

product	R	R′	yield of **1** (%)	yield of **2** (%)	ee of **2** (%)
a	$PhCH_2$	*t*-Bu	91	75	97
b	$PhCH_2$	Me	72	75	95
c	$PhCH_2$	Et	79	72	95
d	$PhCH_2$	$PhCH_2$	80	78	95
e	$CH_3(CH_2)_4$	Me	75	71	97
f	$CH_2{=}CH(CH_2)_7$	*t*-Bu	54	69	97
g	cyclohexyl	*t*-Bu	75	65	96
h	$PhCH_2O(CH_2)_4$	*t*-Bu	72	68	97

important role of ethyl vinyl ether is likely to trap any PhSeCl produced during the conversions of allylic selenides **1** into allylic chlorides **2**. This protocol tolerated a diverse range of R and R′ groups. X-ray crystallographic analysis of the diol **6**, the major diol diastereomer formed via osmium tetroxide catalyzed syn-dihydroxylation of allylic chloride **2a** (Scheme 2), led to the unambiguous assignment of the three contiguous stereocenters as 2*S*, 3*S*, 4*R*. Therefore, the conversion of allylic selenide **1** into allylically transposed chloride **2** proceeded reliably with syn stereochemistry.[2] The chemically and stereochemically rich diol **6** is itself a synthetically versatile chiron.[13] Secondary allylic chlorides

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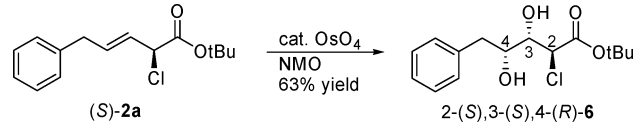
Scheme 2



2 were chemically and stereochemically stable for at least 3 days at room temperature when dissolved in methanol, tetrahydrofuran, acetonitrile, chloroform, acetone, or hexanes; however, after only a few hours at room temperature in *N*,*N*-dimethylformamide, considerable racemization was observed by chiral HPLC analysis. Disappointingly, the corresponding α-chloro-β,γ-ethylenic nitriles, produced in good yields and high ee values, partially racemized in such solvents as chloroform, tetrahydrofuran, and especially acetonitrile at 40 °C for 48 h. We report here successful use of carbon and nitrogen nucleophiles to effect substitutions of the chloride in allylic chlorides **2**.

Asymmetric organocopper S_N2' substitution reactions on α-hydroxy-β,γ-ethylenic esters in which the hydroxy group has been esterified into a phosphate leaving group have been reported.[14] However, asymmetric organocopper substitution reactions on α-chloro-β,γ-ethylenic esters have not been reported probably due to the previous inaccessibility of these chirons. Pursuing our long interest in organocopper chemistry,[15] we treated allylic chlorides **2a**,**d**−**f**,**h** with $Me_2CuMgBr$ (derived from 1 equiv of CuCN and 2 equiv of MeMgBr) in THF (Scheme 1, Table 2) to yield γ-methyl-

Table 2. Methylations of Allylic Chlorides **2**

product	R	R′	yield of **3** (%)	ee of **3** (%)
3a	$PhCH_2$	*t*-Bu	88	95
3d	$PhCH_2$	$PhCH_2$	57	93
3e	$CH_3(CH_2)_4$	Me	70	96
3f	$CH_2{=}CH(CH_2)_7$	*t*-Bu	57	97
3h	$PhCH_2O(CH_2)_4$	*t*-Bu	80	96

α,β-ethylenic esters **3** via an S_N2' mechanism in good yields and with faithful transfer of chirality from the starting allylic chloride. Since both syn and anti S_N2' pathways are possible during organocopper allylic substitutions,[16] the anti-S_N2' pathway of this transformation was established by stereochemical correlation of ester **3e** with the same intermediate reported in a total synthesis of the mealworm sex pheromone (*R*)-4-methyl-1-nonanol (**7**) (Scheme 3). This new 4-step synthesis of alcohol **7**, in 22% overall yield and in 97% ee,

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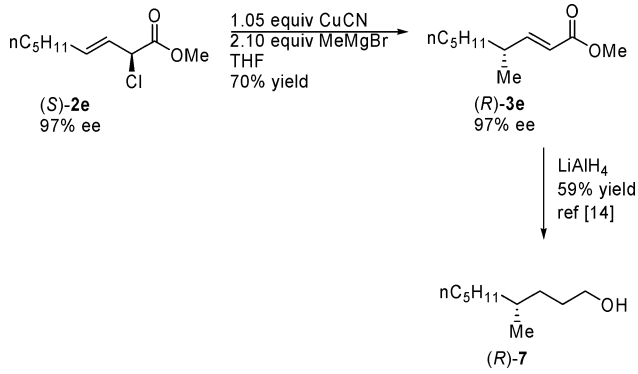
Scheme 3



has distinct advantages over previously reported asymmetric syntheses of this pheromone in terms of stereochemical purity,[14] number of steps, and total yield.[17] Furthermore, the chiral γ-methyl-α,β-enoate structural unit is present in many natural products, including steroids,[18] macrolides,[19] and squalestatins.[20] The scalability of this short protocol was confirmed when 2.8 g of γ-methyl ester **3a** was synthesized in 60% overall yield and 95% ee starting with commercial 3-phenylpropanal.[21] Lithium dimethylcuprate (Me_2CuLi) also gave exclusive S_N2' methylation but in much lower yield than the magnesiocuprate used in Table 2. Attempts to synthesize other γ-alkyl-α,β-ethylenic esters with this magnesiocuprate allylic substitution procedure yielded mixtures of inseparable α- and γ-substitution products. We do not yet understand fully the critical factors that determine α- vs γ-substitution.

Syntheses of non-natural γ-amino-α,β-ethylenic esters (vinylogous α-amino esters)[22] **5** (Scheme 1) are appealing due to these amino esters having diverse chemical properties ranging from induction of a non-natural secondary structure in polypeptides[23] to inhibition of enzyme function.[24] To this end, we treated allylic chlorides **2** with sodium azide, followed by in situ stannous chloride reduction to the amine, which was then treated with di-*tert*-butyl dicarbonate affording the *N*-Boc-γ-amino-α,β-ethylenic *tert*-butyl esters **5** (Scheme 1, Table 3) in good yields and with faithful 1,3-anti-transfer of chirality. Anti-S_N2' substitutions with nitrogen nucleophiles are well documented.[25] The stereochemical course of this transformation was confirmed to be 1,3-anti by comparing the $[\alpha]_D$ +14.4 optical rotation of the Fmoc-γ-amino-α,β-ethylenic *tert*-butyl ester **5a** (Fmoc) with that of the known standard.[26] We cannot rule out the possibility that this substitution proceeded via an initial direct S_N2 mechanism with stereochemical inversion followed by a spontaneous syn-3,3-sigmatropic rearrangement of the initial allylic azide **4**α to the thermodynamically favored[27] conjugated ester azide **4**γ; subsequent azide reduction and protection yielded the known[26] γ-amino conjugated ester **5a**(Fmoc) in 60% yield (Scheme 4).

Table 3. Synthesis of Vinylogous *N*-Boc α-Amino Esters **5**

product	R	yield of **5** (%)	ee of **5** (%)
5a	$PhCH_2$	76	95
5f	$CH_2{=}CH(CH_2)_7$	51	93
5h	$PhCH_2O(CH_2)_4$	52	97

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(21) **Experimental Details for γ-Seleno-α,β-ethylenic Ester (*S*)-1a.** To a 500 mL round-bottomed flask with stirbar under argon was added 3-phenylpropanal (2.68 g, 20.00 mmol, 1.00 equiv) in toluene (50 mL). (*S*)-α,α-Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (2.39 g, 4.00 mmol, 0.20 equiv) was added and the reaction was allowed to cool to −20°C and stirred for 5 min at that temperature. *N*-(Phenylseleno)phthalimide (7.85 g, 26.00 mmol, 1.30 equiv) was added in one portion and the reaction was allowed to stir for 2 h at −20°C. At this time TLC analysis indicated complete reaction, and the flask was further cooled to −40 °C and anhydrous THF (150 mL) was added dropwise via pressure equalizing addition funnel. A solution of (*tert*-butoxycarbonylmethylene)triphenylphosphorane (10.15 g, 27.00 mmol, 1.35 equiv) in anhydrous THF (100 mL) was added dropwise via pressure equalizing addition funnel. After addition was completed the reaction was warmed to −20°C and the reaction was allowed to stir overnight. At this time TLC analysis indicated complete reaction. The reaction was quenched with sat. NH_4Cl solution, then the aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified via column chromatography (1% EtOAc in hexanes) to yield the desired ester **1a** (7.00 g, 18.00 mmol) as a pale yellow oil in 91% yield. **Experimental Details for α-Chloro-β,γ-ethylenic Ester (*S*)-2a.** To a 500 mL round-bottomed flask with a stirbar under argon was added ester **1a** (7.0 g, 18.0 mmol, 1.0 equiv) in hexanes (67 mL). Ethyl vinyl ether (21.0 mL, 220.0 mmol, 12.0 equiv) was added followed by the dropwise addition of a solution of sulfuryl chloride (2.9 mL, 36.0 mmol, 2.0 equiv) in hexanes (140 mL) via pressure equalizing addition funnel. After 10 min TLC analysis indicated complete reaction. The volatiles were removed by rotary evaporation and the resulting crude oil was immediately purified via column chromatography (1% EtOAc in hexanes). The chloride **2a** was isolated as a yellow oil (3.5 g, 13.0 mmol) in 75% yield and 97% ee as determined by chiral HPLC. **Experimental Details for γ-Methyl-α,β-ethylenic Ester (*R*)-3a.** To a 250 mL three-necked round-bottomed flask with a stir bar under argon was added CuCN (1.24 g, 13.80 mmol, 1.05 equiv) in anhydrous THF (85 mL). The suspension was cooled to −78 °C and a solution of 3 M MeMgBr in Et2O (9.20 mL, 27.60 mmol, 2.10 equiv) was added dropwise via syringe over 5 min and the resulting solution was allowed to stir for 30 min at −78 °C. At this time a solution of chloride **2a** (3.50 g, 13.15 mmol, 1.00 equiv) in anhydrous THF (50 mL) was added dropwise via pressure equalizing addition funnel over 15 min. After addition was completed the reaction was allowed to stir for an additional 30 min after which TLC analysis indicated complete reaction. The reaction was quenched with sat. NH_4Cl. The aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were dried over anhydrous $MgSO_4$, the solids were filtered, and the filtrate was concentrated in vacuo. The resulting crude oil was purified via column chromatography to yield the ester **3a** (2.80 g, 11.30 mmol) as a colorless oil in 88% yield and in 95% ee as determined by chiral HPLC.

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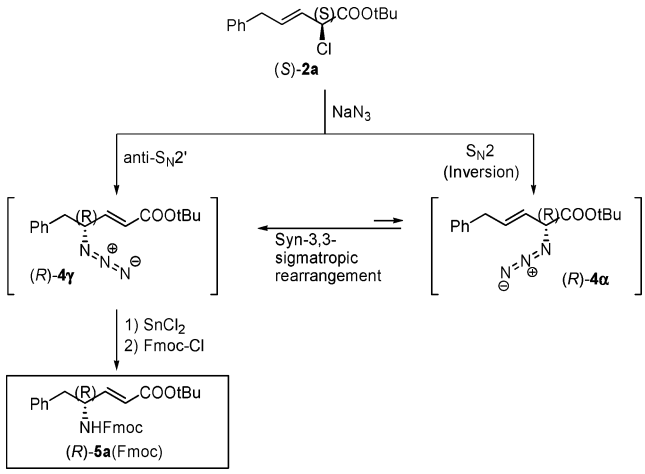
Scheme 4



In conclusion, starting from simple achiral aldehydes, α-chloro-β,γ-ethylenic esters **2a**−**h** were synthesized for the first time in good yields and with ee values greater than or equal to 95% via 1,3-syn allylic replacements of selenide by chloride (Scheme 1, **1** → **2**). These secondary allylic chlorides **2** were converted via organocopper 1,3-anti substitutions into highly enantioenriched γ-methyl-α,β-ethylenic esters **3** (Scheme 1, **2** → **3**), with **3e** being a known precursor to the natural pheromone (*R*)-4-methyl-1-nonanol (**7**). Additionally, we report here enantiocontrolled syntheses of functionality-rich non-natural vinylogous α-amino esters **5** via 1,3-anti allylic substitutions (Scheme 1, **2** → **4** → **5**). The chiral, nonracemic allylic chlorides **2** are versatile and stereochemically stable electrophilic chirons which are expected to undergo various other useful nucleophilic substitution reactions as well as olefin addition reactions with excellent control of chirality.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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