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Selective reduction of stereodefined cyclopropyl substituted acrylate esters to the corresponding propionate esters

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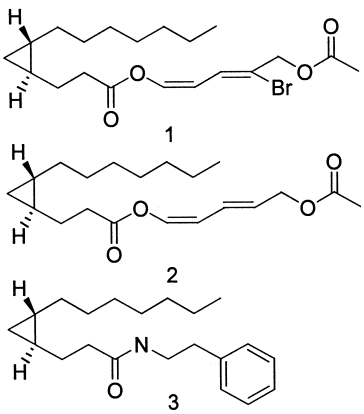
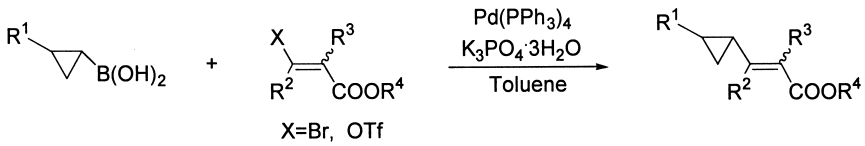
Abstract—Stereodefined cyclopropyl substituted acrylate esters were selectively reduced to the corresponding propionate esters by sodium borohydride in methanol/DMF with a catalytic amount of $CoCl_2$ without the opening of the cyclopropane ring. The configuration and chirality of the stereodefined cyclopropyl function were retained in the reaction. Combined with the cross-coupling reaction of stereodefined cyclopropylboronic acids with bromoacrylate esters or alkenyl triflates, the reaction method provides a novel route to stereodefined 3-cyclopropyl propionate ester, an important subunit existing in a wide range of natural compounds.

1. Introduction

The stereodefined 3-cyclopropyl propionate ester subunit is present in a wide range of natural compounds.[1,2] Three natural compounds (Scheme 1) containing stereodefined 3-cyclopropyl propionate ester subunit were isolated from *L. majusula* by Gerwick et al.[1] These compounds have specific bioactivities: grenadadiene (**1**) has an interesting profile of cytotoxicity in the NCl 60 cell line assay; grenadamide (**3**) exhibited modest brine shrimp toxicity (LD_{50}=5 μg/mg) and cannabinoid receptor binding activity (K_i=4.7 μM).[1] Moreover, such a unique structure has also proved to be an important synthon to construct γ-lactones.[3] Thus, developing an efficient method to construct stereodefined 3-cyclopropyl propionate unit seems significant. A reasonable method would be the selective reduction of the corresponding cyclopropyl substituted acrylate esters. However, under traditional reducing conditions, the reduction of the double bond was often accompanied with opening of the cyclopropane ring due to its ring strain[4] and reduction of the ester moiety.[5] Thus, selective reducing conditions should be found to carry out the transformation of stereodefined cyclopropyl acrylates to the corresponding cyclopropyl propionate esters. Recently, we have developed a new method for synthesis of cyclopropyl substituted acrylate esters using the cross-coupling reaction of stereodefined cyclopropylboronic acid with bromo-substituted acrylate or alkenyl triflates (Scheme 2).[6] In this paper, we report the novel synthesis of cyclopropyl substituted propionate esters.



Scheme 1.



Scheme 2.

Keywords: selective reduction; 3-cyclopropyl propionate ester; sodium borohydride; cobaltous chloride.

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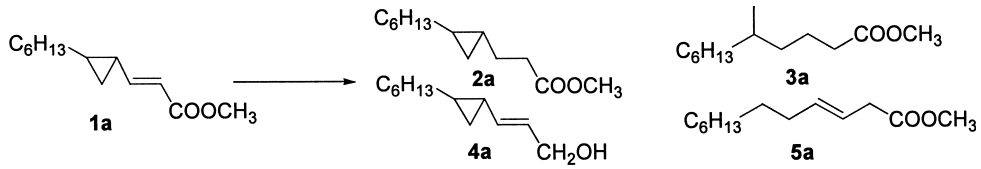
Table 1. The reduction of methyl *E*-3-(*trans*-2-hexylcyclopropyl) acrylate **1a**



Entry	Reduction system	Conversion (%)	Products	Yield %
1[a,b]	Pd/C, H_2, CH_3OH	100	**3a**	92
2[c]	$NaCNBH_3$	<5	/	Trace
3[d]	$NaBH_4$	<5	/	Trace
4[e]	DIBAL-H, toluene	100	**4a**	92
5[b,f,g]	Catechol borane, $RhCl(PPh_3)_3$	33	**2a**	30
6[b,h]	SmI_2, DMA, CH_3OH	60	**2a/5a**	49/16[i]
7[b,j]	Mg, CH_3OH	100	**2a/5a**	72/18[i]
8	$NaBH_4$, $CoCl_2$	100	**2a**	87

[a] Pd/C, 5–10%, H_2, CH_3OH, rt, 6 h.
[b] Compounds **3**–**5** were characterized by ^1H NMR.
[c] To a solution of substrate (0.5 mmol) in MeOH was added a trace of bromocresol green followed by $NaCNBH_3$ (0.5 mmol) and 4 N HCl in dioxane was added dropwise to maintain pH=4, stirred at rt, 4 h.
[d] To a cold (0–5°C), stirred slurry of 0.5 mmol $NaBH_4$ in MeOH was added 0.5 mmol substrate, then stirred at rt, 48 h.
[e] To a solution of substrate (0.5 mmol) in dry THF (2 mL), a solution of DIBAL-H in toluene (1.3 mmol) is added at −65° under N_2, 1 h.
[f] CB is catechol borane.
[g] −20°C, substrate (1 mmol) was added to $Rh(PPh_3)_3Cl$ (0.01 mmol) in THF, then CB (1.0 mmol), 12 h.
[h] To a solution of substrate (0.5 mmol) in THF and MeOH (1 mmol) was added successively a SmI_2/THF solution (0.1 mol dm^{-3}, 7.5 mL) and DMA (2.5 mL) under N_2.
[i] Ratios were determined by GC and ^1H NMR.
[j] Mg (10 equiv.)/CH_3OH, rt, 3 h.

2. Results and discussion

A review of the literature revealed that reduction systems such as Rh–DuPHOS/H_2,[7a] KOOCN=NCOOK/MeOH/AcOH,[7b] DIBAL-H/MeCu/HMPA,[7c] Pd/C/H_2,[7d–f] $NaCNBH_3$[7g] and $NaBH_4$[7h] in MeOH have been reported for selective reduction of α,β-unsaturated ester containing cyclopropyl ring. Considering the use of Rh reagents or diimide are difficult and the procedure using DIBAL-H/MeCu/HMPA was complicated, the reduction reaction of *E*-3-(*trans*-2-hexyl-cyclopropyl) acrylate **1a** was first attempted using Pd/C catalytic hydrogenation conditions.[7d–f] However, after work up, compound **3a** was obtained in high yield, which indicated reduction of the double bond accompanied with ring opening of the cyclopropane moiety (Table 1, entry 1). This was the same as Barrett's result.[8] According to the reported procedure,[7g] reduction of **1a** with sodium cyanoborohydride in methanol at pH=4 did not afford the reduction product (Table 1, entry 2). Engel et al. reported excess $NaBH_4$ in MeOH reduced methyl 3-cyclopropylacrylate to give the corresponding substituted propionate ester in 26% yield at room temperature overnight.[7h] But we found that using $NaBH_4$ alone as a reductant in MeOH or in a mixture of MeOH and DMF, the ester **1a** was virtually inert at room temperature (<5% conversion after 48 h). This was similar with Pfaltz's result.[13] Using DIBAL-H in toluene, the reaction gave 3-(*trans*-2-hexylcyclopropyl) propenol **4a** in 92% yield (entry 4).[9] Nevertheless, when Wilkinson's reagent and catechol borane were used, we were encouraged to find the formation of the desired product **2a** in 30% yield (based on 33% conversion) (entry 5).[10] Using SmI_2/DMA[11] or Mg in CH_3OH[12], we also obtained the product **2a** in 49% (based on 60% conversion) and 72% yield, respectively, together with the ring opening product **5a** as a mixture (entries 6 and 7). Pfaltz et al. reported that $NaBH_4$ and catalytic amount of chiral cobalt–semicorrin complexes could selectively reduce α,β-unsaturated esters without cyclopropyl substituent to afford the corresponding saturated esters in good yields.[13] We found that the reduction of 3-(*trans*-hexyl-cyclopropyl) acrylic acid ester by $NaBH_4$ and a catalytic amount of $CoCl_2$ without ligand did not open the cyclopropane ring and gave **2a** in 87% yield (entry 8). All the results are summarized in Table 1.

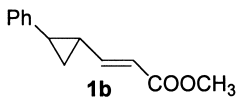
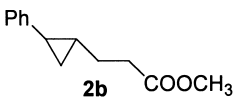
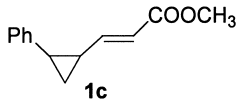
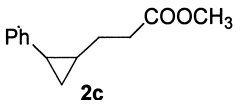
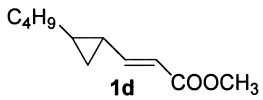
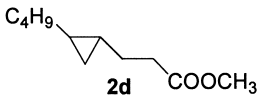
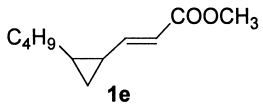
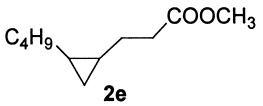
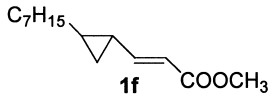
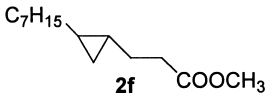
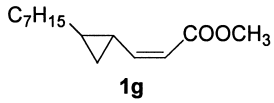
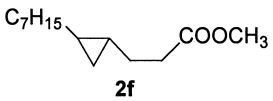
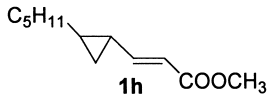
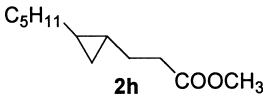
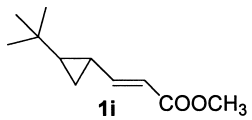
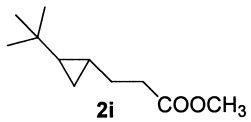
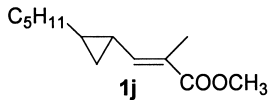
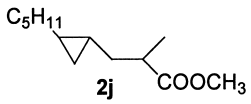
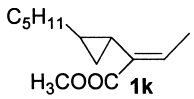
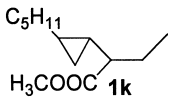
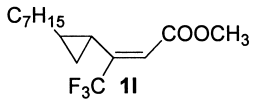
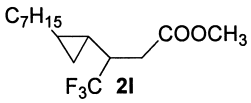
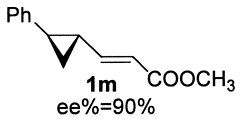
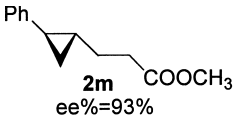
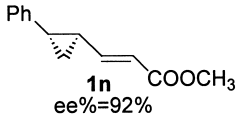
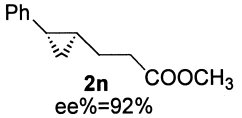
Having optimized reaction conditions in hand, we next used it in a series of stereodefined cyclopropyl substituted acrylic acid esters **1b**–**1n**. As shown in Table 2, the cyclopropane ring was not destroyed and the configuration of the cyclopropyl moiety in all the substrates was retained. Both *E*- and *Z*-cyclopropylsubstituted acrylic acid esters were readily reduced (entries 5 and 6). The substituted group on the cyclopropane has little effect on the yield. Surprisingly, the reactions with trisubstituted α,β-unsaturated esters were retarded and the position of cyclopropyl group affects the reaction results remarkably (entries 10–11).

In order to confirm that the two chiral centers of the cyclopropyl group in the starting materials would remain intact, the chiral substrates **1m**, **1n** were synthesized and reduced. As was expected, from entries 12 and 13, the ee values of the reduction products were similar to those of the corresponding α,β-unsaturated esters.

3. Conclusion

In summary, we have developed a new and convenient method for construction of stereodefined 3-cyclopropyl-propionic esters, which is an important subunit in natural

Table 2. The selective reduction of various cyclopropyl substituted acrylic esters

Entry	Cyclopropyl acrylic esters	Products	Yield (%)
1	 **1b**	 **2b**	85
2	 **1c**	 **2c**	82
3	 **1d**	 **2d**	86
4	 **1e**	 **2e**	82
5	 **1f**	 **2f**	83
6	 **1g**	 **2f**	74
7	 **1h**	 **2h**	81
8	 **1i**	 **2i**	77
9	 **1j**	 **2j**	62
10	 **1k**	 **1k**	Trace
11	 **1l**	 **2l**	Trace
12[a–c]	 **1m** ee%=90%	 **2m** ee%=93%	87
13[a–c]	 **1n** ee%=92%	 **2n** ee%=92%	89

[a] The ee values were determined by Chiral HPLC on a Chiralcel OD column.
[b] Running condition: **1m**,**1n** hex/ipa=100:4, 0.7 mL/min, λ=254 nm.
[c] **2m**,**2n** hex/ipa=100:1, 0.7 mL/min, λ=254 nm.

products. The method described has the advantage of a simple and practical procedure. The reducing reagents are also available and cheap. The application of this method in total synthesis of natural products is currently under investigation in our laboratory.

4. Experimental

4.1. Materials

Cyclopropyl-substituted α,β-unsaturated esters were prepared

according to the previous procedures via the cross-coupling reaction of cyclopropylboronic acids with bromoalkenes.[6] ^{1}H NMR spetra were measured at 300 MHz using $CDCl_3$ as the solvent and Me_4Si as the internal standard.

4.2. Typical procedure for the synthesis of methyl 3-(*trans*-2-hexylcyclopropyl) propionate 1a

A solution of **1a** (110 mg, 0.52 mmol) in MeOH (2 mL) and $CoCl_2{\cdot}6H_2O$ (25 mg, 0.1 mmol) was stirred for 30 min under N_2. Then, $NaBH_4$ (78 mg, 2.08 mmol) in DMF (1 mL) was added at room temperature and stirred for additional 0.5 h. Then the reaction was quenched by water (5 mL) and the mixture was extracted with CH_2Cl_2 (5 mL×3). The organic phase was washed with water (5 mL×3) to remove DMF, dried over $MgSO_4$ and concentrated. The residues were chromatographed on silica gel (elution with hexanes/ethyl acetate=20:1) to afford the **2a** (96 mg, 87%) as a colorless oil.

4.2.1. Methyl 3-(*trans*-2-hexylcyclopropyl) propionate (2a). Yield 87%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.38 (t, J=7.5 Hz, 2H), 1.55–1.50 (m, 1H), 1.36–1.21 (m, 11H), 0.88 (t, J=7.0 Hz, 3H), 0.47–0.38 (m, 2H), 0.22–0.17 (m, 2H) ppm; MS (m/z) 213 (M^++1, 6.48), 55 (100); IR (neat) 2925, 1744; Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.58; H, 11.32. Found: C, 73.33; H, 11.17.

4.2.2. Methyl 3-(*trans*-2-phenylcyclopropyl) propionate (2b). Yield 85%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.26–7.02 (m, 5H), 3.66 (s, 3H), 2.45 (t, J=7.45 Hz, 2H), 1.75–1.63 (m, 3H), 1.10–1.03 (m, 1H), 0.90 (td, J=8.5, 5 Hz, 1H), 0.7.9 (td, J=8.5, 5 Hz, 1H) ppm; MS (m/z) 204 (M^+, 20.87) 130 (100); IR (neat) 2928, 1739; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.54; H, 7.74.

4.2.3. Methyl 3-(*cis*-2-phenylcyclopropyl) propionate (2c). Yield 82%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.30–7.19 (m, 5H), 3.62 (s, 3H), 2.28 (t, J=7.57 Hz, 2H), 2.16 (td, J=8.5, 6 Hz, 1H), 1.52–1.36 (m, 1H), 1.32–1.15 (m, 1H), 1.09–1.04 (m, 1H), 0.97 (td, J=8, 5.2 Hz, 1H) 0.69 (q, J=5.6 Hz, 1H) ppm; MS (m/z) 204 (M^+, 47.82), 130 (100); IR (neat) 3002, 1739; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.19; H, 8.06.

4.2.4. Methyl 3-(*trans*-2-butylcyclopropyl) propionate (2d). Yield 86%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 2.38 (t, J=7.5 Hz, 2H), 1.59–1.51 (m, 1H), 1.35–1.27 (m, 7H), 0.88 (t, J=6.8 Hz, 3H), 0.47–0.38 (m, 2H), 0.22–0.17 (m, 2H) ppm; MS (m/z) 184 (M^+, 0.94), 41 (100); IR (neat) 2924, 1744; Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.91; H, 11.00.

4.2.5. Methyl 3-(*cis*-2-butylcyclopropyl) propionate (2e). Yield 82%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.41 (t, J=7.65 Hz, 2H), 1.77–1.72 (m, 1H), 1.45–1.18 (m, 7H), 0.90 (t, J=7.0 Hz, 3H); 0.72–0.68 (m, 2H), 0.62–0.56 (m, 1H), −0.26–−0.27 (m, 1H) ppm; MS (m/z) 184 (M^+, 3.88), 114 (100); IR (neat) 2928, 1744; Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 72.16; H, 10.97.

4.2.6. Methyl 3-(*trans*-2-heptylcyclopropyl) propionate (2f). Yield 83%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.38 (t, J=7.5 Hz, 2H), 1.65–1.62 (m, 1H), 1.27–1.17 (m, 13H), 0.89 (t, J=6.57 Hz, 3H), 0.40–0.34 (m, 2H), 0.22–0.14 (m, 2H) ppm; MS (m/z) 227 (M^++1, 18.38), 74 (100); IR (neat) 2928, 1744; Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.57. Found: C, 74.56; H, 11.84.

4.2.7. Methyl 3-(*trans*-2-pentylcyclopropyl) propionate (2h). Yield 81%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.38 (t, J=7.5 Hz, 2H), 1.62–1.48 (m, 1H), 1.37–1.08 (m, 9H), 0.88 (t, J=6.8 Hz, 3H), 0.47–0.38 (m, 2H), 0.22–0.17 (m, 2H) ppm; MS (m/z) 199 (M^++1, 19.05), 74 (100); IR (neat) 2926, 1744; Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found: C, 72.45; H, 11.04.

4.2.8. Methyl 3-(*trans*-2-tertbutylcyclopropyl) propionate (2i). Yield 77%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.38 (t, J=7.5 Hz, 2H), 1.68–1.59 (m, 1H), 1.45–1.36 (m, 1H), 0.80 (s, 9H), 0.63–0.5 (m, 1H), 0.37 (m, 2H), 0.08–0.07 (m, 1H) ppm; MS (m/z) 183 (M^+−1, 3.47), 83 (100); IR (neat) 2955, 1743; Anal. Calcd for $C_{11}H_{20}O_2$ C: 71.74; H, 10.87. Found: C, 71.96; H, 10.95.

4.2.9. Methyl 2-methyl-3-(*trans*-pentylcyclopropyl) propionate (2j). Yield 62%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 2.54–2.52 (m, 1H), 1.55–1.26 (m, 10H), 1.18–1.16 (m,3H), 0.88 (t, J=6.8 Hz, 3H), 0.48–0.32 (m, 2H), 0.24–0.12 (m, 2H) ppm; MS (m/z) 211 (M^+−1, 1.95), 57 (100); IR (neat) 2926, 1742; Anal. Calcd for $C_{13}H_{24}O_2$C:73.58; H, 11.32 Found: C, 73.39; H, 11.19.

4.2.10. (1*R*,2*R*)-Methyl 3-(*trans*-2-phenylcyclopropyl) acrylate (1m). ee: 90%; $[\alpha]_D^{20}$=−294 (c=1.0, $CHCl_3$).

4.2.11. (1*R*,2*R*)-Methyl 3-(*trans*-2-phenylcyclopropyl) propionate (2m). Yield 87%; ee: 93%; $[\alpha]_D^{20}$=−172.4 (c=0.84, $CHCl_3$).

4.2.12. (1*S*,2*S*)-Methyl 3-(*trans*-2-phenylcyclopropyl) acrylate (1n). ee: 92%; $[\alpha]_D^{20}$=+294 (c=1.0, $CHCl_3$).

4.2.13. (1*S*,2*S*)-Methyl 3-(*trans*-2-phenylcyclopropyl) propionate (2n). Yield 89%; ee: 92%; $[\alpha]_D^{20}$=+171 (c=0.93, $CHCl_3$).

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