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Addition of Cl_2C: to (−)-*O*-Menthyl Acrylate under Sonication−Phase-Transfer Catalysis. Efficient Synthesis of (+)- and (−)-(2-Chlorocyclopropyl)methanol

Makoto N. Masuno, Douglas M. Young, Alexander C. Hoepker, Colin K. Skepper, and Tadeusz F. Molinski*

Department of Chemistry, University of California, Davis, California 95616

tfmolinski@ucdavis.edu

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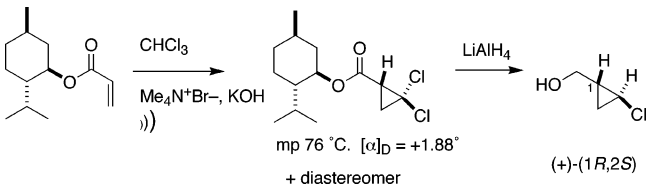

Dichlorocyclopropanation of (−)-*O*-menthyl acrylate under conditions of phase-transfer catalysis ($CHCl_3$, KOH, tetramethylammonium bromide), with sonication, gives excellent yields (85−94%) of the corresponding dichlorocyclopropanecarboxylate ester compared to thermal conditions (90 °C, 56%). No diastereoselectivity was observed, but one isomer was isolated pure by fractional crystallization. The measured kinetic isotope effect (initial rate ($CHCl_3$)/rate ($CDCl_3$) ∼1.7) suggests deprotonation of $CHCl_3$ as the rate-limiting step.

The use of phase-transfer catalysis in organic synthesis results in dramatic improvement in yield for many reactions, including alkylation of alcohols (Williamson ether synthesis), conjugate additions, and dihalocarbene addition. For example, the preparation of 2,2-dichlorocyclopropanecarboxylate esters has been achieved[1] by PTC-catalyzed heterogeneous reactions of chloroform solutions of *O*-acrylate esters in the presence of strong aqueous alkali (NaOH) (Figure 1). The reaction was reported to be highly sensitive to the structure and lipophilicity of the PT catalyst. Heating *O-tert*-butyl acrylate (**1**) in the presence of $CHCl_3$, aqueous NaOH (50% w/v) and $Me_4N^+Br^-$ (2 mol %, 45−50 °C, 8 h) gave a modest yield of the corresponding (±)-*O-tert*-butyl 2,2-dichlorocyclopropylcarboxylate ester (**2**, ∼57%).[1] Use of longer chain *N*-tetraalkylammonium salts (e.g., n-Bu_4N^+-HSO_4^-) under the same conditions gave product mixtures, predominately the Michael adduct of the CCl_3 anion to **1** and compounds that arise from subsequent side reactions.

To fulfill a need for both optically pure enantiomers of *trans*-(2-chlorocyclopropyl)methanol (**4**) we investigated the addition of Cl_2C: to (−)-*O*-menthyl acrylate [(−)**5**].[2] Under the PTC conditions used for dichlorocyclopropanation of **1** ($CHCl_3$, 2 mol % Me_4NBr, NaOH aq),[1] we found no reaction with (−)-**5**. Under more forcing conditions (90−120 °C, sealed bomb, 36 h), disappointing yields of the diastereomeric dichlorocyclopropanecarboxylate esters **6a** and **6b** were obtained (∼56%, 1:1 dr), but only after 24−36 h.[3] Presumably, slower addition of Cl_2C: to the bulkier menthyl acrylate ester allowed competition by undesirable side reactions of both product and starting material. Subsequently, we found these side-products could be bypassed through the use of PTC under conditions of insonation propagated by ultrasound acoustics [sonication,)))]. This report describes a rapid and high-yielding dichlorocyclopropanation of (−)-**5** under mild sonication conditions to provide **6** in up to 94% yield, followed by a facile separation of the crystalline diastereomer, (+)-**6a**, and its subsequent transformation into (+)-**4a**. This study also revealed insights into the mechanism of PTC-catalyzed addition of Cl_2C: from measurements of initial reaction rates. Our observation of a significant deuterium isotope effect during the latter reaction suggests that the rate-limiting step involves deprotonation of $CHCl_3$, probably within the bulk organic phase.

The use of ultrasound in promotion of PTC reactions has met with success in some reactions.[4] Only one report describes the use of ultrasound for promotion of dihalocyclopropanation of styrenes and terminal olefins with heterogeneous haloform−trihalomethane mixtures under thermal PTC conditions,[5] but to the best of our knowledge there are no accounts of ultrasound-promoted dichlorocyclopropanation of electrophilic alkenes.

Sonication of chloroform solutions of (−)-**5** in the presence of alkali metal hydroxides at ambient temperatures (25 °C) gave efficient conversion to the dichlorocarbene adducts **6a**,**b** (73−94%) within 90 min. A survey of PTC catalytic addition of Cl_2C: to (−)-**5** with ultrasound (Table 1) revealed that the yields of dichlorocyclopropanation of (−)-**5** were highly dependent upon the structure of the PTC, in consonance with the findings of Jonczyk and co-workers with *tert*-butyl acrylate esters.[1] The best catalysts appear to be TMAB and dibenzo-18-crown-6. Catalyst loading was important: high catalyst concentration (20 mol %) seemed to suppress the reaction, but loadings as low as 2% were effective. No detectable product was formed when catalyst was absent or when Triton B (*N*-benzyltrimethylammonium hydroxide, 40% w/v in MeOH) or $Ba(OH)_2$ was substituted for alkali metal hydroxide. Yields were significantly higher when *solid* sodium or potassium hydroxide was used instead of 50% w/v aqueous solutions. The best yield of **6a**,**b** (94%, entry 7) was obtained with $Me_4N^+Br^-$ (5 mol %) and solid KOH; however, high yields were also observed with

* To whom correspondence should be addressed. Tel: (530) 752-6358. Fax: (530) 752-8995.

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(3) *Caution! High pressure*. One trial reaction of **5** with $CHCl_3$ and 50% w/v aq NaOH contained in a heavy glass pressure vessel at elevated temperature (∼100−120 °C) led to an explosive failure of the glass vessel. We surmised the cause was either excessive solvent vapor pressure or an unidentified exotherm ("runaway" reaction).

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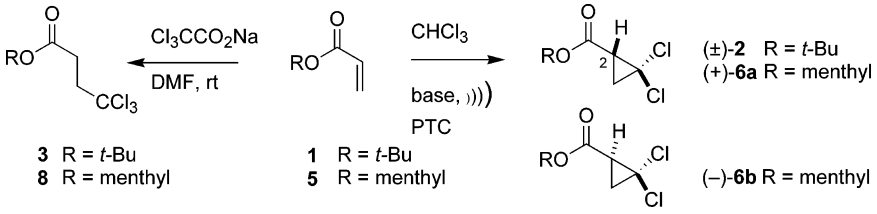

FIGURE 1. PTC-catalyzed addition of Cl_2C: to acrylate esters.

TABLE 1. Phase-Transfer Catalyst-Promoted Dichlorocarbene Additions to Acrylate Ester (−)-5 under Sonication To Give 6a,b

entry	[(−)-**5**][a] (M)	solvent	base (17 equiv)	catalyst[d]	mol %	yield[b] (%)
1	0.60	$CHCl_3$	NaOH (50% w/w)	TMAB	20	68
2	0.60	$CHCl_3$	KOH (s)	DB-18-c-6	10	43
3	0.60	$CHCl_3$	KOH (s)	DB-18-c-6	5	84
4	0.60	$CHCl_3$	NaOH (s)	cetyl-TMAB	10	17
5	0.60	$CHCl_3$	Triton B[c]		5	0
6	0.60	$CHCl_3$	NaOH (s)	TMAB	5	80
7	0.60	$CHCl_3$	KOH (s)	TMAB	5	88 (94[d])
8	0.60	$CHCl_3$	$Ba(OH)_2$ (s)	TMAB	5	0
9	0.60	$CHCl_3$	KOH (s)	18-c-6	10	0
10	0.60	$CHCl_3$	NaOH (s)	**7**	10	0
11	0.60	$CHCl_3$	KOH (s)			0
11	0.20	$CHCl_3$	KOH (s)	TMAB	5	83
12	0.05	$CHCl_3$	KOH (s)	TMAB	5	52[e]

[a] (−)-*O*-Menthyl acrylate [(−) **5**, 0.6 M, 0.6 mmol] in $CHCl_3$ solution (21 equiv of $CHCl_3$). The mixture was sonicated in a tightly sealed borosilicate glass scintillation vial (20 mL capacity) for 90 min, and products were analyzed by GCMS (DB-5MS 30 m × 320 μm i.d., 0.2 m film, He ~1 mL/min. internal standard = 1,2,4,5-tetramethylbenzene). Temperature was not controlled (ultrasound bath, T = 22−35 °C). [b] % yields were determined from GC integrations and comparison with standard **6a**,**b**. [c] Abbreviations: TMAB, tetramethylammonium bromide; DB-18-c-6, dibenzo-18-crown-6; cetyl-TMAB, *N*-cetyl-*N*-trimethylammonium bromide; Triton-B, *N*-benzyl-*N*-trimethylammonium hydroxide (40% w/v in MeOH). [d] Isolated yield, preparative run (47.5 mmol). [e] 60 min reaction.

$Me_4N^+Br^-$ (solid NaOH) and dibenzo-18-crown-6 (solid KOH). Diastereoselectivity was not observed under any of the reaction conditions, which is not surprising since ultrasound reaction conditions are highly enthalpic and predisposed to stochastic outcomes with no diastereoselection.[4] Attempts to induce asymmetric control with the chiral PT catalyst *N*-benzylcinchonidinium chloride, (**7**, entry 10) were unsuccessful.

Although the two diastereomers **6a**,**b** were difficult to separate by silica chromatography, fractional crystallization in pentane at −78 °C cleanly resolved the mixture to provide crystalline (+)-**6a** [>95% de, mp 76 °C, $[\alpha]_D$ = +1.88 (*c* 1.17, $CHCl_3$)]. Diastereomerically enriched (−)-**6b** was recovered from the supernatant [75% de, oil, $[\alpha]_D$ −89.2 (*c* 1.42, $CHCl_3$)].

The mechanism of the reaction was briefly investigated by measurement of initial rates and isotope effects. A brief kinetic investigation, carried out under "isothermal conditions" (bath temperature maintained at 24 °C) using (−)-**5** (initial c = 0.05 M) and other conditions similar to those of entry 7 (Table 1). The *initial rate* of reaction with $CHCl_3$ (Figure 2), under conditions similar to those in entry 7,[6] follows apparent zero-order kinetics in (−)-**5** (apparent initial rate = 7.5×10^{-6} mol·L^{-1}·s^{-1}). When $CDCl_3$ was substituted for $CHCl_3$, the initial rate of

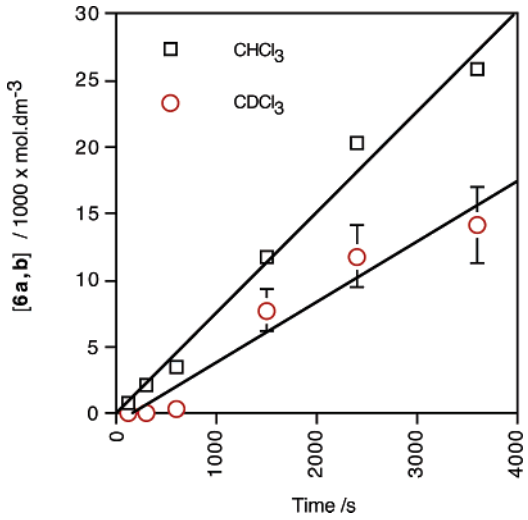

FIGURE 2. Rate of formation of **6a**,**b** from (−)-**5** (initial c= 0.05M in $CHCl_3$ or $CDCl_3$) in the presence of solid KOH and Me_4NBr (5 mol %), T = 24 °C.[8] Data were averaged from duplicate samples at each time point. Error bars are ±1 σ.

reaction was substantially slower (apparent initial rate = 4.5×10^{-6} mol·L^{-1}·s^{-1}; kinetic isotope effect, ~1.7) which suggested the rate-determining step involved deprotonation of $CHCl_3$ by HO^-.

Several possible mechanisms are consistent with the results; however, we favor the pathway shown in (Figure 3) for the following reasons. The reaction proceeds by PTC mediated-transport of HO^- into bulk $CHCl_3$ phase to produce tetralkylammonium ion pairs that rapidly attain steady-state concentration under sonication in accord with the Makosza model for PTC alkylation using tetralkylammonium salts of low lipophilicity.[7] Rate-limited deprotonation of $CHCl_3$ (possibly also at the phase interface) and ion-exchange gives a steady-state concentration of Me_4N^+ Cl_3C^- anion. Rapid decomposition of the latter by loss of Cl^- generates dichlorocarbene (Cl_2C:), which diffuses from the collapsed Me_4N^+ Cl^- ion pair and adds to the C=C double bond of the acrylate ester. The role of ultrasound, in addition to exposing reactive KOH surface through physical dispersive effects associated with cavitation,[4] may also promote the reaction by providing the energy for reorganization of the solvated tetraalkylammonium ion pairs which is necessary to allow deprotonation of $CHCl_3$ and ion-exchange. We attach important significance to the observation that high

(6) Although only initial rates were used for calculation of the isotope effect, progression of the reaction in the presence of KOH and $CDCl_3$ resulted in accumulation of DOH, HO^-, and rising concentration of $CHCl_3$ through deuteron exchange. Consequently, the apparent isotope effect (k_H/k_D ~ 1.7) may be underestimated in these experiments.

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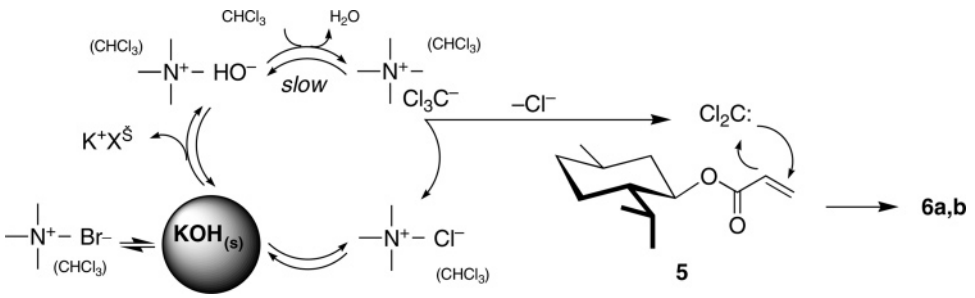
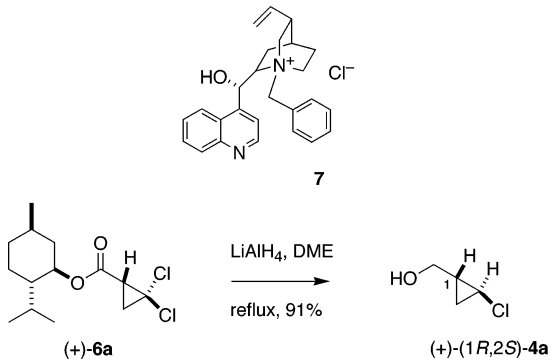


FIGURE 3. Proposed mechanism of ultrasound-promoted PTC dichlorocyclopropanation of (−)-**5**.

catalyst loading (20 mol %) suppresses the yield of the reaction, which suggests a partitioning of reaction pathways, or more likely, sequestration of Cl_3C^- anion as aggregated ion-pairs. Aggregation of tetralkylammonium ion-pairs may further stabilize Cl_3C^- anion and slow the decomposition to Cl_2C:, or possibly impede the diffusion of the carbene to the acrylate substrate. An alternate mechanism for formation of (**6a**,**b** conjugate addition of trichloromethyl anion, followed by intramolecular S_N2 displacement of chloride by the incipient tetralkylammonium enolate) is ruled out. Reaction of (−)-**5** with CCl_3^- generated independently (spontaneous decarboxylation of NaO_2CCCl_3 in anhydrous DMF)[8] gave only the conjugate addition product **8** and no detectable **6a**,**b** (NMR).

Diastereoselective reduction of (+)-**6a**, with concomitant mono-dechlorination, was effected using literature conditions ($LiAlH_4$, THF, 56 °C, 2−4 days)[9] to give the known trans alcohol, (+)-(1*R*,2*S*)-**4a**,[9b] exclusively ($[\alpha]^{24}_D$ +59 (*c* 0.57, $CHCl_3$; lit. $[\alpha]^{27}_D$ +58 (*c* 1.0, $CHCl_3$)[9b]). The latter provided proof for the configuration of (+)-**6a**. Under literature conditions, reduction was sluggish and the yields variable. Examination of the time-course of the reduction (GLC) showed that ester reduction to the corresponding 2,2-dichlorocyclopropylmethanol occurred relatively rapidly, but the reductive displacement of Cl was rate-limiting. We presume that S_N2 displacement of the Cl bond occurs by an intramolecular S_N2 mechanism through an *O*-menthoxyhydridoaluminate intermediate as the product is exclusively trans. We also surmised the slow reaction is due to the bulky menthoxyl group which impedes collinear backside attack at the C−Cl bond and that it might be possible to compensate by raising the temperature of the reduction. Indeed, when (+)-**6a** was treated with $LiAlH_4$ in refluxing DME, the reaction was complete in less than 16 h and the product (+)-**4a** was obtained cleanly (91% yield) with no erosion of stereoselectivity. Reduction of the corresponding diastereomer (−)-**6b** gave the enantiomeric alcohol (−)-**4b**.

Since both diastereomers of **6** are made accessible by the combination of PTC-promoted sonication of acrylate (−)-**5** followed by facile resolution by crystallization, the process—together with subsequent $LiAlH_4$ reduction—constitutes an efficient, scalable two-step synthesis of (+)-**4a** or (−)-**4b**. The procedure represents a marked improvement both in yield and number of steps over previous methods, which were achieved by enzymatic resolution or asymmetric transformation.[10]



In summary, an efficient dichlorocyclopropanation of (−)-menthyl acrylate (**1**) followed by reduction of the product (+)-**6a** provides an efficient two-step preparation of enantiopure (+)-**4a**. Kinetic evidence supports a mechanism of PTC-promoted dichlorocarbene addition to acrylate esters through a mechanism in which the rate-dependent step involves deprotonation of $CHCl_3$ by tetralkylammonium hydroxide, probably in bulk chloroform phase, although we cannot rule out the possibility of a reaction that is rate-limited at the solid−liquid interface.

Experimental Section

All chemicals were of reagent grade purity or better and were used without further purification. Chloroform was distilled prior to use to remove ethanol preservative (EtOH−$CHCl_3$ azeotrope)

(8) The mild conditions for generation of Cl_3C^- anion, first noted by Corey and co-workers, had been exploited for preparation of trichloromethylcarbinols by 1,2-addition of Cl_3C^- to aldehydes. Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435−3438. In our study, addition of a solution of **5** (0.21 M) in DMF to a mixture of stirred anhydrous NaO_2CCl_3 (1.5 equiv) in DMF at room temperature lead to rapid initial spontaneous evolution of CO_2 within minutes, but formation of **8** took place more slowly (∼quant, after about 12 h). These results attest to a remarkable stability of $Cl_3C^-Na^+$ at ambient temperatures under these conditions.

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(10) The Olivo preparation (ref 9b) of (+)-**4** from **1** was achieved using a four-step procedure which required two separate reduction steps in order to exploit an efficient lipase-catalyzed kinetic resolution of the primary alcohol. Paterson and co-workers prepared optically enriched **4** (98% ee) in two steps from epichlorohydrin (Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603−607). The volatile aldehyde corresponding to **4** has also been prepared by Evans (five-step procedure from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol: Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503−505) and Trost (seven-step synthesis from di-*O*-menthyl fumarate: Trost, B. M.; Gunzer, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396−10415).

and stored in the dark in a sealed amber bottle. CH_2Cl_2 and THF were dried by passage through commercial alumina solvent purification cartridges. GC analyses were performed on a capillary column instrument and GC−MS determinations on an ion-trap GC−MS instrument. Specific rotations, $[\alpha]_D$, were measured at $T = 24$ °C and concentration c expressed in g/100 mL. Assignment of ^1H and ^{13}C NMR signals was made by interpretation of gCOSY, NOESY, DEPT, and gHSQC NMR experiments and comparison with the assigned chemical shifts of (−)-menthol. The enantiomeric purity of **4a**,**b** was carried out by by GC using a Cyclodex B column (10.5% β-cyclodextrin in DB1701, 0.25 μm film × 30 m). Other procedures can be found elsewhere.[11]

(−)-Menthyl Acrylate [(−)-5]. Ester (−)-**5** was prepared by base-promoted transesterification according to a modification of a literature procedure.[2] Briefly, lithium menthoxide, prepared by addition of *n*-butyllithium in hexanes (2.8 M) to (−)-menthol in dry THF, was treated with *O*-methyl acrylate in THF (0 °C to rt). After completion of the reaction and extractive workup, (−)-**5** was obtained in 66% yield ($[\alpha]^{24}_D$ −96.4 (*c* 1.5, $CHCl_3$) [lit.[12] −85.4 (*c* 0.97, CH_2Cl_2)]. Standard esterification conditions (acryloyl chloride, (−)-menthol, pyridine, DMAP) gave inferior yields of (−)-**5** (<20%).

Preparative-Scale Dichlorocarbene Addition. Menthyl Dichlorocyclopropylcarboxylates (+)-6a and (−)-6b. A solution of (−)-**5** (10.0 g, 47.5 mmol) in $CHCl_3$ (final concentration = 0.6 M) in a 250 mL round-bottom flask was treated with TMAB (0.366 g, 2.38 mmol, 5 mol %) and powdered KOH (89 g, 1.5 mol, 33 equiv). The flask was immediately sealed with a rubber septum and the mixture sonicated by immersion in an ultrasonic cleaning bath (Fisher FS60, 40 kHz, 150 W) containing ice−water (initial temperature: 0 °C, rising to 25 °C over 3 h), with occasional venting (*Caution! Exotherm*). The mixture was cooled and diluted with 1:3 MTBE/hexane, and the filtered solution washed with aqueous sodium phosphate buffer (0.1 M, pH 7.5). After drying, the combined extracts (Na_2SO_4) were concentrated, and the crude product was purified by silica chromatography (1:5 CH_2Cl_2/*n*-hexane) to give the diastereomeric mixture **6a**,**b** (1:1, 13.1 g, 94%). The mixture was dissolved in pentane (13% w/v) and placed in a low-temperature freezer (−80 °C) for 1−3 days whereupon crystals of pure (+)-**6a** (mp 76 °C, >95% de, ^1H NMR integration) were deposited, leaving behind **6b** (∼75−88% de) in the mother liquors. **6a**: mp 76 °C; $[\alpha]_D = +1.88$ (*c* 1.17, $CHCl_3$); IR (NaCl) ν 2952, 2930, 2870, 1728, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (td, $J = 10.8$, 4.4 Hz, H1′), 2.54 (dd, 1H, $J = 10.0$, 8.0 Hz, H2), 2.07 (dd, 1H, $J = 8.0$, 7.2 Hz, H4a), 1.91 (dd, 1H, $J = -6.8$, 2.8 Hz, H7′), 1.85 (dd, 1H, $J = 10.0$, 7.2 Hz, H4b), 1.38 (m, 1H, H5′), 0.92 (d, 3H, $J = 7.0$ Hz, H10′), 0.90 (d, 3H, $J = 7.0$ Hz, H8′ or H9′), 0.76 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.6 (s, C1), 76.4 (d, C1′), 57.7 (s, C3), 47.0 (d, C2′), 41.1 (t, C6′), 33.6 (d, C2), 31.6 (d, C5′), 26.3 (d, C7′), 26.1 (t, C4), 23.5 (t, C3′), 22.1 (q, C10′), 20.9 (q, C8′ or C′9′), 16.4 (q, C9′ or C8′); HR DCIMS *m/z* 310.1350 $[M + NH_4]^+$ (calcd $C_{14}H_{26}Cl_2NO_2$ 310.1335). **6b**: oil; $[\alpha]_D = -89.2$ (*c* 1.42, $CHCl_3$); IR (NaCl) ν 2956, 2928, 2870, 1734, 1371 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (dt, 1H, dt, $J = 10.8$, 4.4 Hz, H1′), 2.55 (dd, 1H, $J = 10.0$, 8.0 Hz, H2), 2.07 (dd, 1H, $J = 8.0$, 7.2 Hz, H4a), 1.91 (hd, $J = 6.8$, 2.8 Hz, 1H, H7′), 1.83 (dd, 1H, $J = 10.0$, 7.2 Hz, H4b), 0.91 (d, 3H, $J = 6.8$ Hz, H10′), 0.90 (d, 3H, $J = 6.8$ Hz, H8′ or H9′), 0.76 (d, 3H, $J = 6.8$ Hz, H9′ or H8′); ^{13}C NMR ($CDCl_3$) δ 166.1 (s, C1), 76.0 (d, C1′), 57.4 (s, C3), 46.9 (t, C6′), 34.1 (t, C4′), 33.6 (d, C2), 31.4 (d, C5′), 26.1 (d, H7′), 26.0 (t, C4), 23.3 (t, C3′), 22.0 (q, C10′), 20.7 (q, C8′ or C9′), 16.2 (q, C9′ or C8′); HR DCIMS *m/z* 310.1329 $[M + NH_4]^+$ (calcd $C_{14}H_{26}Cl_2NO_2$ 310.1335).

Reduction of (+)-6a. (+)-Chlorocyclopropylmethanol (4a). Reduction of the menthyl ester (+)-**6a** was carried out with $LiAlH_4$ using a modification of the procedure described by Nadim and co-workers.[9a] A mixture of $LiAlH_4$ (0.64 g, 17 mmol) in dry DME (15 mL) was heated at reflux for 6 h before dropwise addition of a solution of (+)-**6a** (800 mg, 2.73 mmol) in DME (4 mL). After 12 h, the mixture was cooled in an ice−water bath and the excess hydride quenched by addition of wet ether (*Caution! Evolution of hydrogen)* followed by 4 M NaOH aq. Extractive workup of the reaction mixture with Et_2O followed by careful flash chromatography (silica, 95:5 CH_2Cl_2/Et_2O) and removal of solvent at atmospheric pressure gave essentially pure (+)-(1*R*,2*S*)-**4a** (91%). Chiral GC analysis showed the product to have >99% ee [$([\alpha]^{24}_D$ +59 (*c* 0.57, $CHCl_3$) (lit.[9b] $[\alpha]^{27}_D$ +58 (*c* 1.0, $CHCl_3$) for (+)-**4**]. ^1H and ^{13}C NMR spectral properties matched those of literature values.[9b]

Reduction of (−)-6a. (−)-Chlorocyclopropylmethanol (4b). Reduction of (−)-**6b** (88% de, GC) was carried out using $LiAlH_4$ in refluxing DME, as described for (+)-**6a**, to give (−)-**4b** ($[\alpha]^{27}_D$ −54 (*c* 0.44, $CHCl_3$)).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of (+)-**6a** and (−)-**6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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