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Differentiation between the ethoxycarbonyl groups in diethyl malate via their titanium-catalyzed reductive cyclopropanation with ethylmagnesium bromide and subsequent site-selective three-carbon ring cleavage

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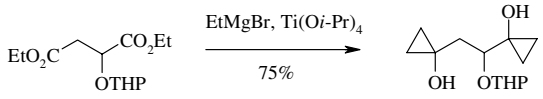
Abstract—Ethoxycarbonyl groups in *O*-THP protected racemic diethyl malate **1** were differentiated by their reductive cyclopropanation with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide and subsequent site-selective C1–C2, C2–C3 or both C1–C2 and C1–C3 ring cleavage of the cyclopropyl groups of the resulting bis-cyclopropanol **2**.

Convenient methods for the preparation of useful synthetic building blocks by transformation of functional groups in malic acid are of interest for organic synthesis because of the commercial availability of both enantiomers.[1] Esterification of malic acid,[2,3] or regioselective reduction of ester groups with hydride,[4] or transformations of reduction products of both carboxylic groups[1,5–7] are the most frequently used reactions for differentiation between carboxylic groups of malic acid. Methods for differentiation between the two sp^2-hybridized carbon atoms in malic acid derivatives via C–C bond formation are limited, at least to the best of our knowledge, to the recently published monoalkylation of protected malimides with Grignard reagents.[8] Here, we report an alternative solution by employing reductive cyclopropanation of THP-protected diethyl malate **1** with a diisopropoxytitanacyclopropane reagent[9] and subsequent selective cleavage of one of the cyclopropyl groups in the resulting bis-cyclopropanol **2**.[10]

Compound **2** was obtained in good yield upon treatment of **1** with 6 equiv of ethylmagnesium bromide in the presence of titanium(IV) isopropoxide[9] in a diethyl ether–tetrahydrofuran mixture (1:2) (Scheme 1).[11] Using



1 **2**

Scheme 1.

ether as the solvent led to the formation of abundant precipitates[12] and a substantial decrease in yield of the target product **2**.[13]

Differentiation of the tertiary hydroxyl groups in compound **2** was performed by removal of the THP group, followed by transformation of triol **3**[14] into isopropylidene acetal **4**.[15] It is worth noting that, in contrast to the analogous acetalization of (*S*)-1,2,4-butanetriol (easily available from (*S*)-malic acid) leading to the corresponding five-membered acetonide,[6,7] acetalization of triol **3** gave 1,3-dioxane derivative **4** with more than 90% selectivity. Differences in the regioselectivity of these reactions are probably determined by thermodynamic factors, such as lesser inherent strain in the spirocyclic six-membered heterocycle **4**, as compared with the corresponding five-membered derivative. Base-catalyzed C1–C2 bond cleavage in the cyclopropanol fragment[10] of compound **4** led to the smooth formation of ethyl ketone **5**,[16] while oxidation of **4** with $PhI(OAc)_2$,[17] which is accompanied by both C1–C2 and C1–C3 bond cleavage, gave ester **6**[18] in moderate yield (Scheme 2). The latter

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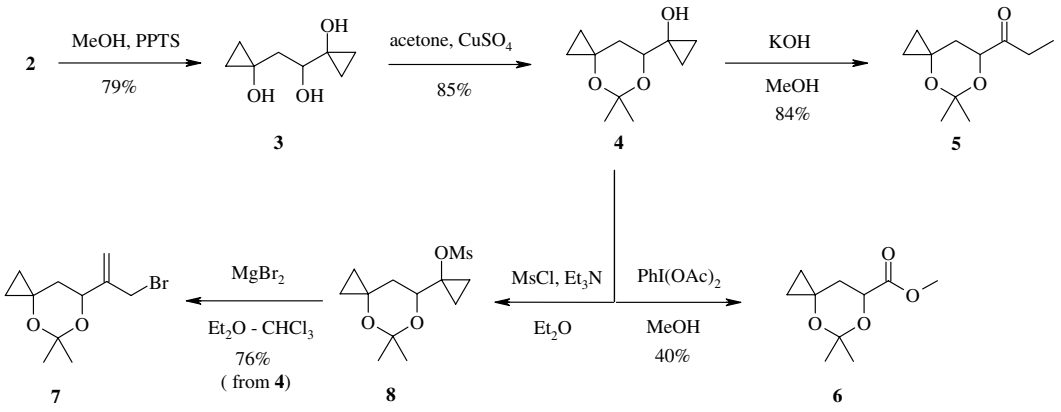
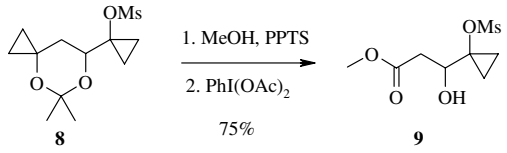


Scheme 2.



Scheme 3.

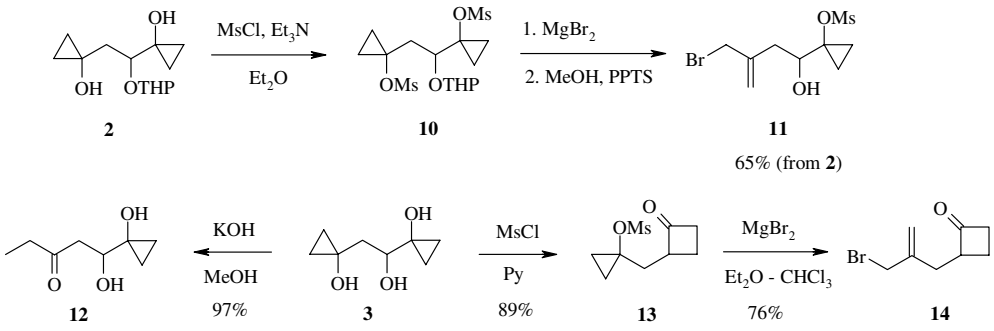
transformation demonstrates the possibility of using ester cyclopropanation and subsequent oxidative fragmentation of the resulting cyclopropanol moiety as an ester protection method. Cyclopropanol **4** was smoothly transformed into 2-substituted allyl halide **7** via magnesium halide initiated cationic cyclopropyl–allyl isomerization[12,19] of mesylate **8** (Scheme 3).[20,21]

The mesyl group in compound **8** was also successfully used for protection of the corresponding cyclopropanol fragment in the reaction with $PhI(OAc)_2$. Thus, removal of the acetonide group in mesylate **8** by acid-catalyzed methanolysis and subsequent one-pot reaction with $PhI(OAc)_2$ led to methyl ester **9**[22] in good yield (Scheme 3).

We have also found that differentiation between the cyclopropanol groups in compound **2** via a cyclopropyl–allyl isomerization reaction of the cyclopropane ring, that is further from the secondary hydroxyl group, can be performed without acetal protection of the 1,3-diol system. Thus, mesylation of bis-cyclopropanol **2** and subsequent treatment of the resulting bis-mesylate **10** with $MgBr_2$ in a diethyl ether–chloroform mixture (1:2) gave, after removal of the THP-group, *mono*-allyl bromide **11**.[23] Compound **11** was isolated by column chromatography on silica gel in 65% overall yield from bis-cyclopropanol **2** (Scheme 4). Similarly, treatment of triol **3** with KOH in methanol at room temperature led to the smooth formation of ethyl ketone **12**.[24] The high regioselectivity of the two latter reactions of compounds **2** and **3** may be due to the deactivating influence of the electron-withdrawing secondary hydroxyl group on the ring opening of the adjacent cyclopropyl ring.

On the other hand, the presence of the secondary hydroxyl group in triol **3**, makes it possible to involve the adjacent cyclopropane in the well-known cationic cyclopropylmethyl–cyclobutyl rearrangement.[25] Thus, treatment of triol **3** with methanesulfonyl chloride in pyridine[26] led to cyclobutanone **13**, which was then smoothly converted into the corresponding allyl bromide **14**[27] upon reaction with magnesium bromide in a diethyl ether–chloroform mixture (1:1).

In conclusion, titanium-catalyzed cyclopropanation of the ethoxycarbonyl groups in THP-protected diethyl malate, followed by regioselective transformation of the cyclopropanol moieties into an ethyl ketone, a 2-propenyl halide, methoxycarbonyl or cyclobutanone groups, opens up a convenient method for the preparation of trifunctional compounds **5**–**14**. Taking into account a variety of possible synthetically useful trans-



Scheme 4.

formations of the functional groups mentioned, as well as the commercial availability of both racemic and optically active malic acid, compounds **5**–**14** or their enantiomerically pure derivatives can serve as convenient intermediates in organic synthesis.[28]

Acknowledgements

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11. Our early attempts to involve the ethoxycarbonyl groups of compound **1** in regioselective reductive cyclopropanation reactions by treatment with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide were unsuccessful. Thus, the reaction of racemic ester **1** with 2.5 equiv of EtMgBr in the presence of 20 mol % of $Ti(O\textit{i}\text{-}Pr)_4$ led to a mixture of non-selective monocyclopropanation products and bis-cyclopropanol **2**.
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13. Compound **2**. IR (CCl_4) 3590, 3465, 3440, 3095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.37–0.55 (m, 3H), 0.64–0.93 (m, 5H), 1.46–1.92 (m, 6.5H), 1.70 (dd, $J = 14.7$, 3.4 Hz, 0.5H), 2.18–2.26 (m, 1H), 2.68 (br s, 0.5H), 3.44–3.71 (m, 1.5H), 3.61 (dd, $J = 9.1$, 3.6 Hz, 0.5H), 3.65 (dd, $J = 9.9$, 3.4 Hz, 0.5H), 3.92–4.08 (m, 1.5H), 4.14 (br s, 0.5H), 4.77–4.83 (m, 0.5H), 4.89–4.97 (m, 0.5H). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.73; H, 9.31.
14. Compound **3**. IR ($CICl_3$) 3550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.43–0.56 (m, 3H), 0.61–0.66 (m, 1H), 0.76–0.87 (m, 4H), 1.47 (dd, $J = 14.8$, 3.2 Hz, 1H), 2.37 (dd, $J = 14.8$, 9.6 Hz, 1H), 3.02–3.73 (br s, 3H), 3.48 (dd, $J = 9.6$, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 12.8, 13.2, 14.0, 40.4, 55.0, 58.3, 77.0. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.62; H, 8.99.
15. Compound **4**. IR (CCl_4) 3585, 3535, 3095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.35–0.64 (m, 4H), 0.69–0.90 (m, 4H), 0.93 (dd, $J = 13.2$, 2.7 Hz, 1H), 1.39 (s, 3H), 1.49 (s, 3H), 2.45 (ddd, $J = 13.2$, 11.9, 1.8 Hz, 1H), 2.77 (br s, 1H), 3.61 (dd, $J = 11.9$, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 9.8, 12.6, 14.5, 21.3, 29.7, 32.5, 53.4, 57.0, 73.3, 100.1. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.31; H, 9.08.
16. Compound **5**. IR (CCl_4) 3095, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (ddd, $J = 10.2$, 6.5, 5.5 Hz, 1H), 0.64 (ddd, $J = 10.2$, 6.5, 4.7 Hz, 1H), 0.74 (ddd, $J = 10.7$, 6.5, 5.5 Hz, 1H), 0.84 (dddd, $J = 10.7$, 6.5, 4.7, 1.8 Hz, 1H), 1.03 (t, $J = 7.3$ Hz, 3H), 1.24 (dd, $J = 13.2$, 3.1 Hz, 1H), 1.42 (s, 3H), 1.52 (s, 3H), 2.11 (ddd, $J = 13.2$, 12.1, 1.8 Hz, 1H), 2.55–2.73 (m, 2H), 4.45 (dd, $J = 12.1$, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 10.0, 14.4, 20.9, 29.6, 30.9, 33.5, 53.5, 74.1, 100.3, 211.4. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.56; H, 9.09.
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18. Compound **6**. IR (CCl_4) 3090, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.43 (ddd, $J = 10.2$, 6.5, 5.5 Hz, 1H), 0.65 (ddd, $J = 10.2$, 6.5, 4.5 Hz, 1H), 0.76 (ddd, $J = 10.7$, 6.5, 5.5 Hz, 1H), 0.85 (dddd, $J = 10.7$, 6.5, 4.5, 1.8 Hz, 1H), 1.31 (dd, $J = 13.1$, 2.9 Hz, 1H), 1.44 (s, 3H), 1.53 (s, 3H), 2.32 (ddd, $J = 13.1$, 12.1, 1.8 Hz, 1H), 3.74 (s, 3H), 4.67 (dd, $J = 12.1$, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 14.3, 20.9, 29.5, 34.1, 52.2, 53.4, 68.3, 100.7, 171.2. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.90; H, 8.02.
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20. Synthesis of compound **8**. CH_3SO_2Cl (1.44 mL, 18.6 mmol) was added over 30 min to a stirred solution of cyclopropanol **4** (2.45 g, 12.4 mmol) and Et_3N (5.18 mL, 37.2 mmol) in diethyl ether (30 mL) at 0 °C. The reaction mixture was stirred over 30 min at rt and then treated with water (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in a mixture of petroleum ether/ethyl acetate (5:1) and filtered through silica gel (10 mL) to yield compound **8** (3.39 g, 99%) as a pale yellow oil. IR (CCl_4) 3090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.43 (ddd, $J = 10.2$, 6.5, 5.5 Hz, 1H), 0.64 (ddd, $J = 10.2$, 6.5, 4.7 Hz, 1H), 0.76 (ddd, $J = 10.7$, 6.5, 5.5 Hz, 1H), 0.85 (dddd, $J = 10.7$, 6.5, 4.7, 1.8 Hz, 1H), 0.91–1.01 (m, 2H), 1.11 (dd, $J = 13.0$, 2.7 Hz, 1H), 1.18–1.27 (m, 1H), 1.37 (s, 3H), 1.39–1.47 (m, 1H), 1.52 (s, 3H), 2.19 (ddd, $J = 13.0$, 11.7, 1.8 Hz, 1H), 3.11 (s, 3H), 4.30 (dd, $J = 11.7$, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 9.5, 9.8, 14.6, 21.2, 29.6, 33.3, 39.8, 53.3, 67.8, 70.0, 100.5. Anal. Calcd for $C_{12}H_{20}O_5S$: C, 52.16; H, 7.29. Found: C, 51.97; H, 7.24.
21. Synthesis of compound **7**. A solution of $MgBr_2$, prepared from magnesium (1.09 g, 45.0 mmol) and 1,2-dibromoethane (8.45 g, 45.0 mmol) in diethyl ether (35 mL), was added in one portion to a solution of mesylate **8** (4.14 g, 15.0 mmol) in chloroform (35 mL). The reaction mixture was refluxed for 5 h under an argon atmosphere. After cooling in ice, the reaction mixture was treated with a

mixture of saturated $NaHCO_3$ solution (25 mL) and 5% Na_2CO_3 solution (25 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Compound **7** (3.02 g, 77%) was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) as a pale yellow oil. IR (CCl_4) 3090, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (ddd, $J = 10.2$, 6.5, 5.5 Hz, 1H), 0.65 (ddd, $J = 10.2$, 6.5, 4.8 Hz, 1H), 0.76 (ddd, $J = 10.7$, 6.5, 5.5 Hz, 1H), 0.86 (ddd, $J = 10.7$, 6.5, 4.8, 1.8 Hz, 1H), 1.16 (dd, $J = 13.1$, 2.7 Hz, 1H), 1.39 (s, 3H), 1.58 (s, 3H), 2.25 (ddd, $J = 13.1$, 11.7, 1.8 Hz, 1H), 3.95–4.00 (m, 1H), 4.15–4.20 (m, 1H), 4.75–4.80 (m, 1H), 5.25–5.26 (m, 1H), 5.32–5.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 14.5, 21.0, 29.8, 32.8, 36.1, 53.6, 67.8, 100.5, 115.8, 145.4. Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.35; H, 6.37.

22. Compound **9**. IR ($CHCl_3$) 3535, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (ddd, $J = 10.7$, 7.5, 6.2 Hz, 1H), 1.03 (ddd, $J = 10.7$, 7.5, 6.7 Hz, 1H), 1.21 (ddd, $J = 11.3$, 7.5, 6.2 Hz, 1H), 1.47 (ddd, $J = 11.3$, 7.5, 6.7 Hz, 1H), 2.65 (dd, $J = 16.0$, 9.0 Hz, 1H), 2.73 (dd, $J = 16.0$, 4.0 Hz, 1H), 3.08 (s, 3H), 3.45 (br s, 1H), 3.69 (s, 3H), 3.93 (dd, $J = 9.0$, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 10.5, 38.1, 39.5, 51.9, 68.2, 70.9, 172.0. Anal. Calcd for $C_8H_{14}O_6S$: C, 40.33; H, 5.92. Found: C, 40.39; H, 5.81.
23. Compound **11**. IR (CCl_4) 3540, 3090, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (ddd, $J = 10.7$, 7.6, 6.2 Hz, 1H), 1.07 (ddd, $J = 10.7$, 7.6, 6.7 Hz, 1H), 1.21 (ddd, $J = 11.2$, 7.6, 6.2 Hz, 1H), 1.56 (ddd, $J = 11.2$, 7.6, 6.7 Hz, 1H), 2.46 (ddd, $J = 14.8$, 9.8, 1.0 Hz, 1H), 2.65 (ddd, $J = 14.8$, 3.6, 1.0 Hz, 1H), 2.90 (br s, 1H), 3.11 (s, 3H), 3.60 (dd, $J = 9.8$, 3.6 Hz, 1H), 4.00–4.06 (m, 2H), 5.08–5.11 (m, 1H), 5.27–5.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 11.2, 36.8, 37.3, 39.6, 69.0, 73.5, 118.2, 141.7. Anal. Calcd for $C_9H_{15}BrO_4S$: C, 36.13; H, 5.05. Found: C, 36.42; H, 4.83.
24. Compound **12**. IR ($CHCl_3$) 3585, 3465, 3080, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.38–0.48 (m, 1H), 0.55–0.64 (m, 1H), 0.69–0.81 (m, 2H), 1.02 (t, $J = 7.3$ Hz, 3H), 2.47 (q, $J = 7.3$ Hz, 2H), 2.71 (dd, $J = 17.5$, 2.8 Hz, 1H), 2.89 (dd, $J = 17.5$, 9.3 Hz, 1H), 3.50 (dd, $J = 9.3$, 2.8 Hz, 1H), 3.97 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 10.8, 13.1, 36.8, 45.0, 57.7, 73.0, 212.8. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.85; H, 8.98.
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27. Compound **14**. IR (CCl_4) 3095, 1785, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.63–1.75 (m, 1H), 2.20–2.30 (m, 1H), 2.38 (dd, $J = 15.7$, 9.6 Hz, 1H), 2.63 (ddd, $J = 15.7$, 6.1, 0.5 Hz, 1H), 2.90–3.01 (m, 1H), 3.02–3.14 (m, 1H), 3.45–3.56 (m, 1H), 3.94–3.97 (m, 2H), 4.99–5.00 (m, 1H), 5.20–5.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 33.2, 36.3, 44.6, 58.2, 116.3, 142.6, 210.0. Anal. Calcd for $C_8H_{11}BrO$: C, 47.32; H, 5.46. Found: C, 47.47; H, 5.22.
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