Enantioselective preparation of (+)- and (–)-Z-2-hydroxyethyl-1-methylcyclopropan-1-ol

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Dedicated to Professor Oleg Kulinkovich on the occasion of his 60th birthday


Abstract
Both (+)- and (–)-**1** have been prepared in gram quantities starting from ethyl L-lactate. The primary alcohol in the side chain of these chiral building blocks allows subsequent elaboration. Ring opening reactions of the resulting trans-dialkylcyclopropanols are expected to provide new approaches to suitably substituted tetrahydropyrans.

Keywords: Cyclopropanol, cyclopropanation, allylation, building blocks, asymmetric synthesis


Introduction

In connection with our research program involving ring-opening reactions of cyclopropanols,[1] we required easy access to both antipodes of a functionalized cyclopropanol **1**.[2] The primary alcohol in the side chain provides a convenient handle for subsequent elaboration. For example, either **2** or **3** should be readily available by means of a reliable asymmetric allylation reaction.[3] Of particular significance is the lack of a stereoselective route to the (*S,R,R*)-stereoisomers typified by **2**, whereas the hydroxycyclopropanation of homoallylic alcohols gives convenient access to the alternate trans-dialkyl stereochemistry present in **3**.[4,5] Thus, chiral building blocks (+)- and (–)-**1** promises to be of considerable utility in providing an expedient method for stereoselectively preparing **2** and its derivatives, as well as **3**. We report herein an enantioselective preparation of (+)- and (–)-**1** starting from an inexpensive lactate derivative.
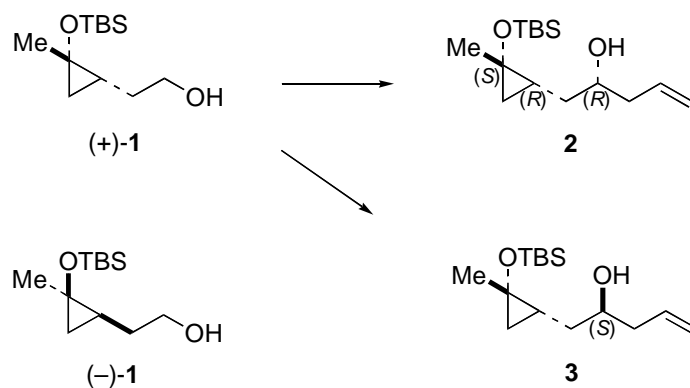
Results and Discussion

Our synthesis began with the known alcohol **4**, which was prepared in multi-gram quantities from ethyl lactate by the literature procedure (Scheme 1).[6] The hydroxyl-directed cyclopropanation of **4** with ethyl acetate afforded a ~1.2:1 ratio of **6** and **7** in 59% yield.
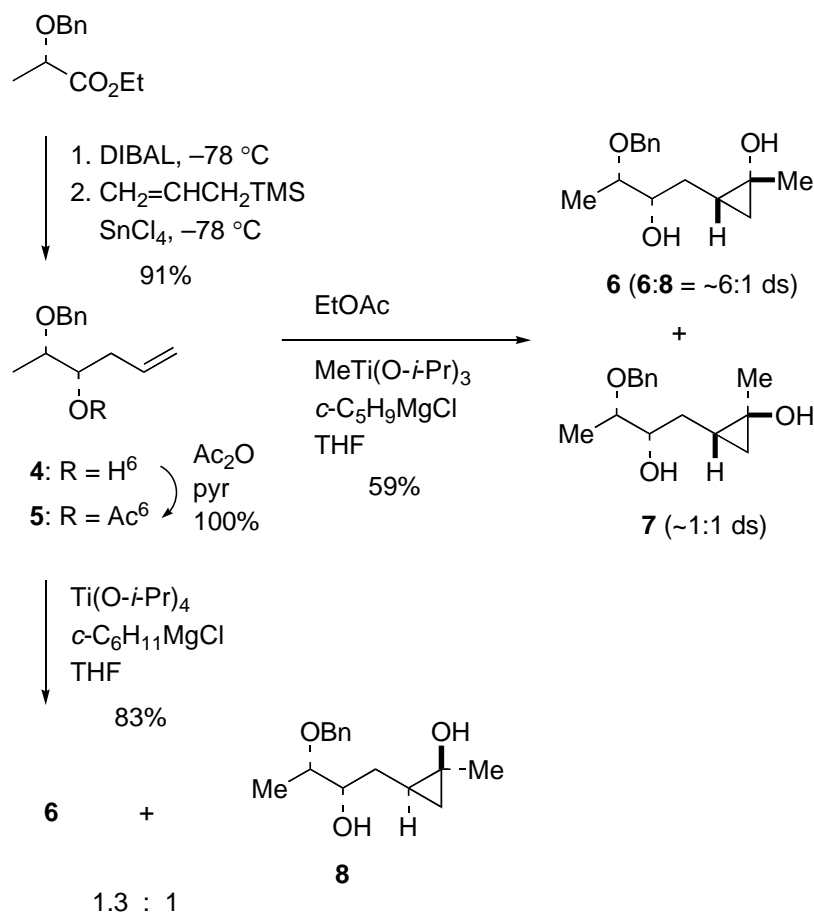
Scheme 1. Low-Valent Titanium-mediated Cyclopropanation of **4** and **5**.

The stereochemistry of **6** and **7** was assigned on the basis of ^{1}H NMR analysis and also by analogy to related examples.[4] Formation of the cis-dialkyl isomer **7** in surprisingly significant amounts was attributed to the presence of the benzyloxy moiety.[7] In order to preclude the undesirable formation of **7**, we opted to rely on an intramolecular cyclopropanation of **5**. The intramolecular cyclopropanation reactions of esters of homoallylic alcohols were shown by us, along with other laboratories, to proceed in excellent yields to give trans-dialkyl cyclopropanols, albeit with low 1,3-diastereoselectivity.[4,8] Indeed, the hydroxyl-directed cyclopropanation of **5** afforded both trans-dialkyl isomers **6** and **8** in good (83%) yield. Following separation by column chromatography, the nonselective formation of **6** and **8** was taken advantage of to develop an enantiodivergent route to both antipodes of **1** by straightforward elaboration of the side chain functionalities (vide infra).

Treatment of **6** with TBSCl and imidazole resulted in selective silylation to afford **9** in 67% yield, along with recovered **6** in 18% yield (Scheme 2). The Dess-Martin oxidation of **9** proceeded cleanly to give ketone **10** (89%). The Baeyer-Villiger oxidation of **10** with m-CPBA and subsequent treatment of the resulting ester **11** with DIBAL furnished (–)-**1** in 72% overall yield. Next, (+)-**1** was also secured in comparable yields by applying the identical sequence to **8**.
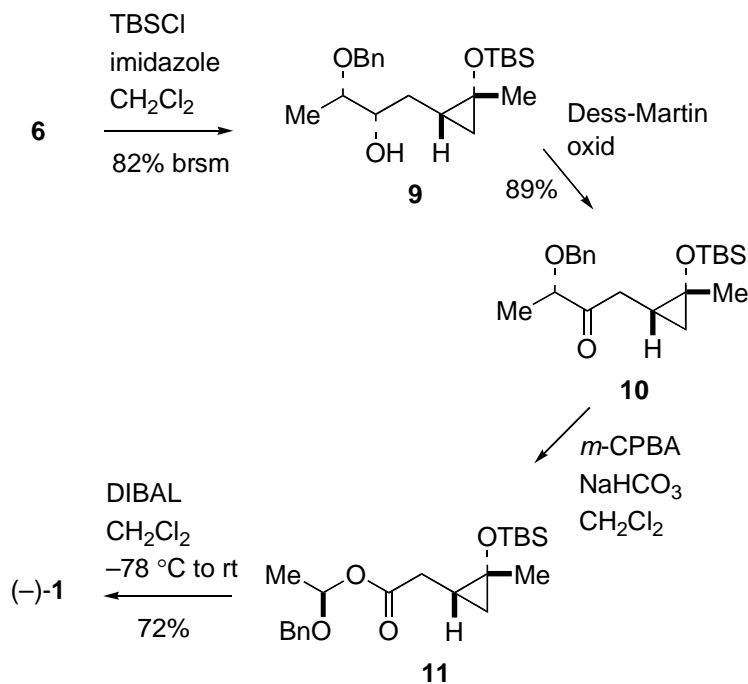
Scheme 2. Elaboration of **6** and **8** to (-)-**1** and (+)-**1**.

Finally, Swern oxidation of (+)-**1** and subsequent allylation by the method of Leighton[9] delivered **2** in 86% yield. The stereoselective conversion of **2** to a tetrahydropyran derivative

serves to not only showcase the synthetic utility of these chiral building blocks, but also confirm the indicated stereochemistry of the cyclopropanols.[2b,10]

Conclusions

A convenient preparation of enantiomerically pure (+)- and (–)-**1**, valuable building blocks, has been achieved starting from an inexpensive lactate derivative. A strategic advantage of this method is ready access to (+)- and (–)-**2**, which are not easily available by other methods. Enantiomerically pure cyclopropanols such as **1** and **2** are versatile intermediates for the preparation of suitably functionalized tetrahydropyrans and skipped polyols. Synthetic applications of (+)- and (–)-**1** in natural product synthesis will be reported in due course.

Experimental Section

(2*S*,3*S*)-2-Benzyloxy-5-hexen-3-yl Acetate (5). The spectral data for **5** are in accord with those in the literature:[6d] $[\alpha]_D$ = 20.2 (*c* 1.0, CHCl$_3$) {lit.[6d] $[\alpha]_D$ = 12.8 (*c* 1.0, CHCl$_3$)}; IR (neat) 1738 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.33 (m, 4H), 7.29 (m, 1H), 5.71 (m, 1H), 5.1–4.97 (m, 3H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 3.62 (dq, *J* = 6.5, 4.1 Hz, 1H), 2.48–2.30 (m, 2H), 2.06 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.7, 138.4, 133.8, 128.3, 127.7, 127.6, 117.6, 74.9, 74.3, 71.1, 34.5, 21.1, 15.4.

Cyclopropanation of (+)-5
To a solution of (+)-**5** (10 g, 40.3 mmol) and Ti(O-*i*-Pr)$_4$ (13 mL, 44.3 mmol) in THF (300 mL) was added over 1 h (syringe pump) a 2 M solution of cyclohexylmagnesium chloride (81 mL) in THF. The reaction mixture was stirred for an additional 30 min and quenched by addition of water (40 mL) at 0 °C. The reaction mixture was stirred for an additional 1 h at rt, dried over anhydrous Na$_2$SO$_4$ and filtered. The filter cake was washed with CH$_2$Cl$_2$ (50 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the crude mixture (6/8 = ~1.3) by column chromatography on silica gel (eluting with 15 % EtOAc/hexanes) afforded 3.2 g (32 %) of **6**, 2.8 g (28 %) of **8**, and fractions (2.36 g, 23 %) containing both **6** and **8**. The latter was separated by another column chromatography.
Data for 6. $[\alpha]_D$ = 47.1 (*c* 1.0, CH$_2$Cl$_2$); IR (neat) 3384 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 7.16–7.01 (m, 5H), 4.33 (d, *J* = 11.9 Hz, 1H), 4.06 (d, *J* = 11.9 Hz, 1H), 3.84 (br s, 1H), 3.44 (dt, *J* = 8.2, 4.0 Hz, 1H), 3.31 (dq, *J* = 8.2, 6.1 Hz 1H), 3.00 (br s, 1H), 1.77 (dt, *J* = 15.0, 4.0 Hz, 1H), 1.63 (m, 1H), 1.32 (s, 3H), 0.87 (d, *J* = 6.1 Hz, 3H), 0.53–0.47 (m, 2H), 0.38 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.8, 128.7, 128.3, 127.9, 77.2, 74.8, 70.7, 53.7, 31.0, 26.3, 21.0, 20.5, 14.9; MS (ESI) m/z 251 (M+H)+, 257 (M+Li)+, 273 (M+Na)+, 289 (M+K)+; HRMS m/z calcd for C$_{15}$H$_{20}$O$_2$ (M–H$_2$O)+ 232.1463, found 232.1461.

Data for 8. $[\alpha]_D$ = 52.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3385 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.18–7.05 (m, 5H), 4.32 (d, *J* = 11.9 Hz, 1H), 4.06 (d, *J* = 11.9 Hz, 1H), 3.82 (br s, 1H), 3.39 (m, 1H), 3.02 (br s, 1H), 3.01 (dq, *J* = 7.3, 6.1 Hz, 1H), 1.82 (m, 1H), 1.46 (s, 3H), 1.29 (m, 1H), 0.87 (d, *J* = 6.1 Hz, 3H), 0.60–0.49 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.0, 128.6, 128.3, 127.9, 79.1, 75.9, 71.0, 54.0, 32.0, 26.5, 23.5, 20.4, 15.3; MS (ESI) m/z 251 (M+H)+, 257 (M+Li)+, 273 (M+Na)+, 289 (M+K)+; HRMS m/z calcd for $C_{15}H_{20}O_2$ (M–H_2O)+ 232.1463, found 232.1467.

(1'*S*,2'*R*,2*S*,3*S*)-3-Benzyloxy-1-[2'-(*tert*-butyldimethylsiloxy)-2'-methylcyclopropyl]butan-2-ol (9). To a solution of diol **6** (3.0 g, 12.0 mmol) and imidazole (8.2 g, 120 mmol) in CH_2Cl_2 (60 mL) was added TBSCl (1.99 g, 13.2 mmol) at 0 ^{o}C. The reaction mixture was slowly allowed to warm to rt and stirred overnight. The mixture was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluting with 5 % EtOAc/hexanes) to give 2.93 g (67 %) of **9** as a colorless oil, along with recovered **6** (0.54 g, 18 %): $[\alpha]_D$ = –9.5 (*c* 1.0, CH_2Cl_2); IR (neat) 3473 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.24–7.21 (m, 2H), 7.17–7.12 (m, 2H), 7.09 (m, 1H), 4.45 (d, *J* = 12.2 Hz, 1H), 4.23 (d, *J* = 12.2 Hz, 1H), 3.74 (m, 1H), 3.34 (dq, *J* = 6.5, 6.4 Hz, 1H), 2.70 (d, *J* = 3.3 Hz, 1H), 1.81 (ddd, *J* = 14.6, 8.1, 4.9 Hz, 1H), 1.65 (ddd, *J* = 14.6, 8.9, 3.2 Hz, 1H), 1.29 (s, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 0.94 (m, 1H), 0.93 (s, 9H), 0.49 (dd, *J* = 9.7, 5.7 Hz, 1H), 0.34 (apparent t, *J* = 5.7 Hz, 1H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.2, 128.4, 127.7, 127.5, 78.8, 75.3, 70.9, 56.4, 32.6, 26.5, 25.8, 21.0, 20.1, 18.0, 15.8, –3.3, –3.7.

(1'*R*,2'*R*,3*S*)-3-Benzyloxy-1-[2'-(*tert*-butyldimethylsiloxy)-2'-methylcyclopropyl]butan-2-one (10). To a solution of alcohol **9** (2.8 g, 7.68 mmol) in CH_2Cl_2 (77 mL) was added Dess-Martin periodinane (4.89 g, 11.5 mmol) at 0 ^{o}C. After the reaction mixture had been stirred for 5 h at rt, it was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluting with 5 % EtOAc/hexanes) to provide 2.48 g (89 %) of **10** as a colorless oil: $[\alpha]_D$ = –20.1 (*c* 1.0, CH_2Cl_2); IR (neat) 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H), 7.30 (m, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.99 (q, *J* = 6.5 Hz, 1H), 2.76 (dd, *J* = 18.6, 7.3 Hz, 1H), 2.68 (dd, *J* = 18.6, 6.5 Hz, 1H), 1.40 (s, 3H), 1.35 (d, *J* = 6.5 Hz, 3H), 0.88 (m, 1H), 0.85 (s, 9H), 0.70 (dd, *J* = 9.7, 5.7 Hz, 1H), 0.32 (apparent t, *J* = 5.7 Hz, 1H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 137.7, 128.4, 127.7, 127.6, 80.3, 71.7, 55.6, 37.2, 26.0, 25.7, 19.8, 18.5, 17.9, 17.4, –3.3, –3.8.

(1'*S*,2'*R*)-2-[2'-(*tert*-Butyldimethylsiloxy)-2'-methylcyclopropyl]ethanol, (–)-1. To a solution of ketone **10** (2.3 g, 6.34 mmol) in CH_2Cl_2 (63 mL) were added sodium bicarbonate (0.8 g, 9.52 mmol) and m-CPBA (77 %; 1.85 g, 8.25 mmol) at 0 ^{o}C. The reaction mixture was stirred for 2 h at rt. Excess m-CPBA was quenched by addition of saturated aqueous $Na_2S_2O_3$ and the resulting mixture was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was directly used without further purification for next step.

The crude ester was dissolved in CH_2Cl_2 (63 mL) and cooled to −78 °C. A 1 M solution (15.8 mL) of DIBAL in hexane was added dropwise at −78 °C. The mixture was stirred for an additional 10 min at −78 °C, allowed to warm to room temperature, and then quenched by addition of methanol and water at 0 °C. After the reaction mixture had been diluted with ether, the resulting mixture was stirred for 2 h at rt, dried over anhydrous Na_2SO_4, and filtered. The filter cake was washed with ether, and the combined filtrates were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 5 % EtOAc/hexanes) to afford 1.05 g (72 %) of (−)-**1** as a colorless oil: $[\alpha]_D$ = −31.7 (*c* 1.0, CH_2Cl_2); IR (neat) 3356 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.74 (apparent dt, *J* = 10.4, 4.3 Hz, 1H), 3.62 (apparent dt, *J* = 10.4, 3.1 Hz, 1H), 3.00 (br s, 1H), 2.00 (ddd, *J* = 14.7, 8.0, 3.1 Hz, 1H), 1.48 (ddd, *J* = 14.7, 10.4, 4.3 Hz, 1H), 1.39 (s, 3H), 0.89 (s, 9H), 0.69 (dd, *J* = 9.5, 5.2 Hz, 1H), 0.63 (m, 1H), 0.39 (dd, *J* = 5.5, 5.2 Hz, 1H), 0.17 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 62.8, 56.6, 31.7, 26.2, 25.6, 22.8, 20.1, 17.8, −3.4, −3.7; MS (ESI) m/z 231 (M+H)+, 253 (M+Na)+, 269 (M+K)+; HRMS m/z calcd for $C_{12}H_{26}O_2Si$ (M+) 230.1702, found 230.1706.

Data for (+)-1. $[\alpha]_D$ = 30.7 (c 1.0, CH_2Cl_2); MS (ESI) m/z 231 (M+H)+, 253 (M+Na)+, 269 (M+K)+; HRMS m/z calcd for $C_{12}H_{26}O_2Si$ (M+) 230.1702, found 230.1705.

Acknowledgements

References and Notes

1. For reviews, see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (b) Gibson, D. H.; DePuy, C. H. *Chem. Rev*. **1974**, *74*, 605. (c) Ryu, I.; Murai, S. *Houben-Weyl Methods of Organic Chemistry*; Thieme: Stuttgart, 1997; Vol. E17c, pp 1985-2040.
2. (a) Epstein, O. L.; Lee, S.; Cha. J. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 4988. (b) Lee, H. G.; Lysenko, I. L.; Cha. J. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 3326.
3. For reviews, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000, pp 299-402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000, pp 403-490. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732.
4. Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2160.
5. For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (c) Kulinkovich, O. G. *Eur. J.*

Org. Chem. **2004**, 4517. (d) García, P.; Díez, D.; Antón, A. B.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G. *Mini-Rev. Org. Chem.* **2006**, *3*, 291.

6. (a) Heathcock, C. H.; Kiyooka, S.-I.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (b) Stojanovic, A.; Renaud, P.; Schenk, K. *Helv. Chim. Acta* **1998**, *81*, 268. (c) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905. (d) McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, 322.

7. Quan, L. G.; Lysenko, I. L.; Cha, J. K. Unpublished results.

8. (a) Racouchot, S.; Ollivier, J.; Salaün, J. *Synlett* **2000**, 1729. (b) Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160. (c) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079.

9. Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920.

10. Lysenko, I. L.; Lee, H. G.; Cha, J. K. Unpublished results.