Diastereoselective Synthesis of Enantiomerically Pure 1,2-Disubstituted Cyclopropanols from Allylic Sulfones

D. Diez,* P. García, M. P. Pacheco, I. S. Marcos, N. M. Garrido, P. Basabe, J. G. Urones

Dpto. de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain
Fax +34(923)294574; E-mail: ddm@usal.es

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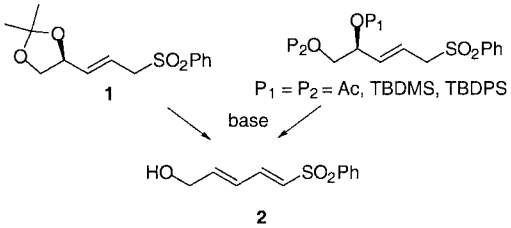
Abstract: Enantiomerically pure 1,2-disubstituted cyclopropanols have been obtained from allylic sulfones derived from (*R*)-glyceraldehyde, in good yield.

Key words: cyclopropanols, sulfones, cyclization, synthesis

There are many biologically important compounds that have a three-member carbocyclic ring,[1] so the development of an asymmetric approach to these rings is of considerable interest. The unique reactivity of cyclopropanes[2] due to the high level of strain, offers considerable utility in organic synthesis and have been widely studied during the last years.[1] Among cyclopropanes 1,2-disubstituted cyclopropanols are quite rare and its chemistry offers great potential,[3] especially vinylic ones.[4]

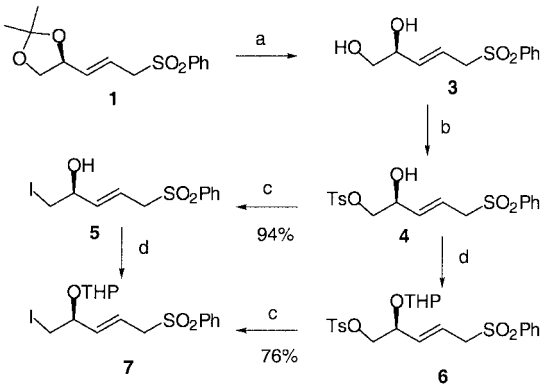
The use of enantiomerically pure olefins derived from *R* or *S*-glyceraldehyde acetonide to introduce absolute configuration into cyclopropane systems has received considerable attention in the last years,[5] but surprisingly asymmetric induction of unprotected glyceraldehyde has been little explored.

As part of our ongoing study of the reactivity[6] and synthetic applications[7] of allylic sulfones we report a new and very interesting application of these compounds. The elimination reactions of certain allyl sulfones with various protecting groups, these being the same for the primary and the secondary hydroxy group, to give 1-hydroxymethyl-4-sulfonylbutadienes, have being studied by us.[6] This kind of compound presents very interesting reactivity[8] (Scheme 1).



Scheme 1

In order to preserve and use the stereogenic center present, to obtain cyclic compounds in enantiomeric pure form instead of dienes in the above reaction, it was clearly necessary to establish differences between the hydroxyl groups. For this reason the primary alcohol was converted into a good leaving group and the secondary hydroxyl group protected with a very stable group. For the protection of the secondary alcohol the tetrahydropiranyl function was chosen, due to its stability under basic conditions.[9] Tosylation of the primary alcohol or replacement with iodide were selected due to ease of synthesis and difference in reactivity, (hardness).



Scheme 2 a) HCl 2 N, MeOH (97%); b) TsCl. Pyridine (70%); c) NaI, Acetone, 80 °C; d) DHP, *p*-TsOH, DCM (95%)

Compound **1**, previously synthesised by us[6], was deprotected with 2 N HCl in MeOH, to obtain diol **3**. This compound reacts selectively with tosyl chloride in pyridine to give **4**, which was transformed under the usual conditions into iodide **5**, thus increasing the difference in reactivity already present. Compound **4** was protected as its tetrahydropyranyl derivative to give **6** and thence transformed into iodide **7**, that could be obtained directly from **5** (Scheme 2).

Once the starting materials had been obtained, they were treated separately with LDA as base. Compound **6** gave a large number of compounds under the reaction conditions, perhaps tosylate (hard) is not displaced by the allylic anion (soft), while **7**, iodide (soft) gave in good yield a 7: 3 mixture of cyclopropanols **8** and **9** respectively[10] (Scheme 3). The same ratio was obtained using one or two equivalents of base, but better yield was obtained in the last case. When these compounds were hydrolysed with careful work up, extraction under neutral conditions, alde-

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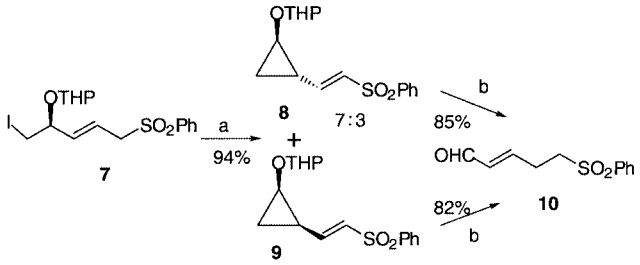
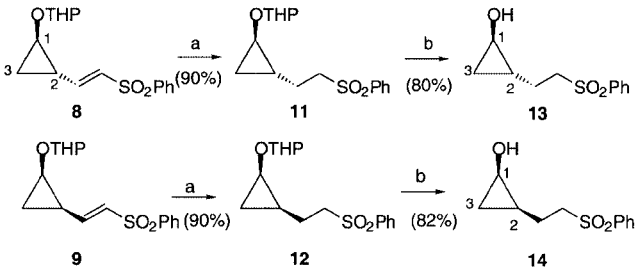
hyde **10** was obtained in both cases. This result can be understood by protonation of the double bond and opening of the cyclopropane ring to give the aldehyde function with isomerisation of the double bond to the conjugate position. The stereochemistry of the double bond was assigned by the coupling constant of hydrogen at C2 (J = 15.8 Hz).[6] The **8**/**9** ratio, has been explained in a similar system by de Meijere et al, by a deprotonation in position 2 and a chelate effect with the oxygen of the cyclopropyl group[11] (Scheme 3).



Scheme 3 a) LDA, 2 equiv THF; b) AcOH–THF–H_2O, 4:1:1

Reactivity of protected cyclopropanols has received considerable attention in the literature due to the facile and regiocontrolled ring opening.[12] So even despite of losing the stereogenic centers this methodology is a convenient procedure to obtain α,β-unsaturated aldehydes with a sulfone in δ-position (Scheme 3).

In order to stop the ring expansion, due to the double bond, this function was suppressed by hydrogenation under the usual conditions to obtain the cyclopropanes **11** and **12**. These were conveniently deprotected to give in good yield the cyclopropanols **13** and **14**,[13] which are good cyclopropane scaffolds for synthesis (Scheme 4).



Scheme 4 a) H_2, PtO_2, AcOEt; b) *p*-TsOH, MeOH

The stereochemistry of these compounds was determined by ^{1}H NMR studies of the coupling constants $J_{1,2}$ = 2.8 Hz for **13** and $J_{1,2}$ = 6.4 Hz for **14**, and extensive NOE studies.

In conclusion, we have developed a convenient method of synthesis for enantiomerically pure 1,2-disubstituted cyclopropanols that present a great synthetic potential and will be reported in due course.

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References

(1) (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589; and references cited therein. (b) Esposito, A.; Taddei, M. *J. Org. Chem.* **2000**, *65*, 9245.

(2) For leading references, see: (a) Salaün, J.; Rappoport, Z.In *The Chemistry of the Cyclopropyl Group, Rearrangements Involving the Cyclopropyl Group*; Wiley: New York, **1987**, 809. (b) *Houben-Weyl: Methods of Organic Chemistry, Carbocyclic Three and Four-membered Ring Systems*, Vol. E.17; de Meijere, A., Ed.; Thieme Verlag: Stuttgart, **1997**. (c) Sylvestre, I.; Olivier, J.; Salaün, J. *Tetrahedron Lett.* **2001**, *42*, 4991; and references cited therein. (d) Shaffer, C. L.; Morton, M. D.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2001**, *123*, 8502. (e) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; and references cited therein.

(3) For asymmetric synthesis of 1,2-disubstituted cyclopropanols in enantiomerically pure form from boronic esters, see: (a) Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977. (b) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605. (c) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986. (d) Pietruszka, J.; Witt, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, 4293. (e) Luithle, J. E. A.; Pietruszka, J.; Witt, A. *J. Chem. Soc., Chem. Commun.* **1998**, 2651. (f) Taylor, R. E.; Schmidt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601; and references cited therein. (g) Baird, M. S.; Huber, A. M.; Clegg, W. *Tetrahedron* **2001**, *57*, 9849.

(4) McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* **2001**, 3559; and references cited therein.

(5) (a) Morikawa, T.; Saski, H.; Hanai, R.; Shibuya, A.; Taguchi, T.; Muray, E. *J. Org. Chem.* **1994**, *59*, 97. (b) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503. (c) Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 388. (d) Ma, D.; Cao, Y.; Yang, Y.; Cheng, D. *Org. Lett.* **1999**, *1*, 285.

(6) (a) Urones, J. G.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Bastida, A. J.; San Feliciano, S. G.; Díez Martín, D.; Goodman, J. M. *Synlett* **1998**, 1361. (b) Díez Martín, D.; San Feliciano, S. G.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Urones, J. G. *Synthesis* **2001**, 1069.

(7) (a) Urones, J. G.; Díez Martín, D.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; San Feliciano, S. G.; Coca, R. *Synlett* **1998**, *41*, 1364. (b) Díez Martín, D.; Templo Beneitez, M.; Marcos, I. S.; Garrido, N. M.; Basabe, P.; Urones, J. G. *Synlett* **2001**, 655.

(8) (a) Carreño, M. C.; Cid, M. B.; Carcia Ruano, J. L.; Santos, M. *Tetrahedron Lett.* **1998**, *39*, 1405. (b) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739. (c) Padwa, A.; Murphree, S. S.; Ni, Z.; Watterson, S. H. *J. Org. Chem.* **1996**, *61*, 3829. (d) Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Tetrahedron* **1986**, *42*, 5321. (e) Backvall, J.-E.; Ericsson, A. M.; Juntunen, S.; Nájera, C.; Yus, M. *J. Org. Chem.* **1993**, *58*, 5221.

(9) Kociénski, P. J. *Protecting Groups*; Thieme Verlag: Stuttgart/New York, **1994**.

(10) Experimental Details for the Transformation of **7**: LDA was generated by the addition of *n*-butyllithium 1.6 M (0.25 mL, 0.38 mmol) to a solution of diisopropylamine (54 µL, 0.38 mmol) in THF (1.0 mL) at -78 ºC. After 5 minutes, the mixture was allowed to warm to room temperature, and then recooled to -78 ºC. Compound **7** (80 mg, 0.18 mmol) was then added to the reaction flask via *cannula* as a solution in THF (1 mL). The reaction mixture was left to stir for one hour at -78 ºC under argon before the addition of saturated ammonium chloride solution (1 mL). The product was extracted into ethyl acetate three times. The organic extracts were combined, washed with water and saturated brine, then dried over anhydrous sodium sulfate, filtered and removed the solvent in vacuo. The mixture was purified by flash silica column chromatography (hexane–ethyl acetate, 9:1) isolating 53 mg, 94% of a mixture 7:3 of cyclopropanes **8** and **9**. Selected data for compound **8**: $[\alpha]^{20}_D$ = +17.2º, (c = 0.79, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (1 H, m, H_β-3), 1.04 (1 H, q, *J* = 6.4 Hz, H_α-3), 1.24 (1 H, m, H-2), 1.38–1.90 (6 H, m, H-2', H-3', H-4'), 3.57 (1 H, m, H_A-5'), 3.71 (1 H, m, H-1), 3.86 (1 H, m, H_B-5'), 4.68 (1 H, m, H-1'), 6.22 and 6.30 (1 H, d, *J* = 15 Hz, CH=CH-SO_2Ph), 6.54 (1 H, dd, *J* = 15.0 and 10.0 Hz, CH=CH-SO_2Ph), 7.56 (3 H, m, -SO_2Ph), 7.86 (2 H, m, -SO_2Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0 and 17.1 (C-3), 19.3 and 19.4 (C-3'), 21.5 and 22.2 (C-2), 25.5 (C-4'), 29.9 and 30.6 (C-2'), 59.0 (C-1), 62.6 and 62.8 (C-5'), 99.1 (C-1'), 127.5 and 128.2 (CH=CH-SO_2Ph), 127.7 (C_{orto}, -SO_2Ph), 129.5 (C_{meta}, -SO_2Ph), 133.4 (C_{para}, -SO_2Ph), 141.1 (C_{ipso}, -SO_2Ph), 147.9 and 148.0 (CH=CH-SO_2Ph). EIMS *m/z* (rel. int.): 309 (M^+ + 1, 3), 279(5), 195(5), 167(10), 125,(10), 85(100). HRMS $C_{16}H_{20}O_4S$ requires 308,1082, found, 308,1082. IR (liquid film, cm^{-1}): 3063, 2942, 1620, 1447, 1308, 1146, 1086. Selected data for compound **9**: $[\alpha]^{20}_D$ = –41.7º, (c = 0.87, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (2 H, m, H-3), 1.08–1.89 (7 H, m, H-2', H-3', H-4', H-2), 3.57 (1 H, m, H_A-5'), 3.76–4.02 (2 H, m, H_B-5', H-1), 4.42 and 4.75 (1 H, m, H-1'), 6.42 (1 H, m, CH -SO_2Ph), 6.80 (1 H, m, CH=CH -SO_2Ph), 7.56 (3 H, m, -SO_2Ph), 7.88 (2 H, m, -SO_2Ph), ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8 and 17.0 (C-3), 19.3 and 19.5 (C-3'), 20.5 and 21.1 (C-2), 25.6 (C-4'), 30.3 and 30.6 (C-2'), 57.0 (C-1), 62.6 and 62.8 (C-5'), 99.3 (C-1') 127.7 (C_{orto}, -SO_2Ph), 128.6 (CH -SO_2Ph), 129.3 (C_{meta}, -SO_2Ph), 133.2 (C_{para}, -SO_2Ph), 141.4 (C_{ipso}, -SO_2Ph), 146.8 and 147.4 (CH=CH -SO_2Ph). EIMS *m/z* (rel. int.): 308 (M^+, 3), 224(5), 195(8), 125(15), 85(100). HRMS $C_{16}H_{20}O_4S$ requires 308,1082, found 308,1092. IR (film, cm^{-1}): 2945, 1618, 1447, 1317, 1144.

(11) Militzer, H.-C.; Schömenauer, S.; Otte, C.; Puls, C.; Hain, J.; Bräse, S.; de Meijere, A. *Synthesis* **1993**, 998; and references cited therein.

(12) (a) For general review see: Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147; and references cited therein.

(13) Selected data for compound **13**: $[\alpha]^{20}_D$ =–17.2º, (c = 0.40, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37 (1 H, q, *J* = 6.0 Hz, H_α-3), 0.76 (1 H, ddd, *J* = 9.2, 5.6 and 2.8 Hz, H_β-3), 0.95 (1 H, m, H-2), 1.56–1.73 (3 H, m, CH_2-CH_2 -SO_2Ph, -OH), 3.18 (2 H, m, -CH_2 -SO_2Ph), 3.25 (1 H, dt, *J* = 6.0, 2.8, 2.8 Hz, H-1), 7.58 (2 H, m, -SO_2Ph), 7.65 (1 H, m, -SO_2Ph), 7.91 (2 H, m, -SO_2Ph), ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.9 (C-3), 19.6 (C-2), 25.2 (CH_2-CH_2 -SO_2Ph), 52.8 (C-1), 56.0 (CH_2 -SO_2Ph), 128.2 (C_{orto}, -SO_2Ph), 129.5 (C_{meta}, -SO_2Ph), 133.9 (C_{para}, -SO_2Ph), 139.5 (C_{ipso}, -SO_2Ph). EIMS *m/z* (rel. int.): 226 (M^+, 5), 184(10), 143(65), 125(30), 84(85), 77(100). HRMS $C_{11}H_{14}O_3S$ requires 226.0664, found 226.0669. IR (liquid film, cm^{-1}): 3200–3600, 2926, 1447, 1304, 1142, 1086, 689. Selected data for compound **14**: $[\alpha]^{20}_D$ = –8.5º, (c = 0.46, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (1 H, m, H_α-3), 0.72 (1 H, m, H_β-3), 1.20 (1 H, m, H-2), 1.90 (2 H, m, CH_2-CH_2 -SO_2Ph), 3.25 (2 H, m, CH_2 -SO_2Ph), 3.53 (1 H, dt, *J* = 6.4, 6.4 and 3.2 Hz, H-1), 7.63 (3 H, m, -SO_2Ph), 7.92 (2 H, m, -SO_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (C-3), 16.5 (C-2), 20.4 (CH_2-CH_2 -SO_2Ph), 49.6 (C-1), 56.4 (CH_2 -SO_2Ph), 127.9 (C_{orto}, -SO_2Ph), 129.2 (C_{meta}, -SO_2Ph), 133.6 (C_{para}, -SO_2Ph), 139.7 (C_{ipso}, -SO_2Ph). EIMS *m/z* (rel. int.): 226 (M^+, 13), 184(12), 143(70), 125(30), 77(100). HRMS $C_{11}H_{14}O_3S$ requires 226.0664, found 226.0684. IR (liquid film, cm^{-1}): 3200–3600, 3063, 2926, 2855, 1447, 1304, 1144, 1086.