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Cyclopropanation of Enantiopure Metal Alkenyl Carbenes with 2-Methoxyfuran: A Practical Route to Carboxycyclopropylglycine Precursors

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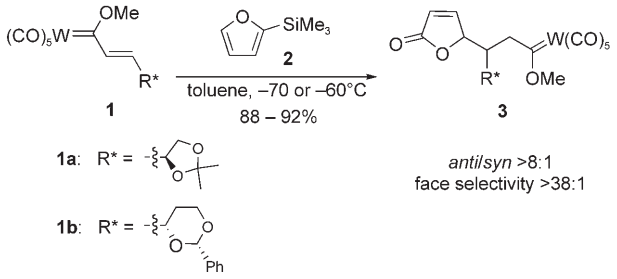
Abstract: We have examined the reactivity of enantiopure alkenyl Fischer carbene complexes **1**, readily available from the chiral pool, with 2-methoxyfuran **4**. In this reaction, polyfunctionalised cyclopropylcarbenes **5** are obtained under very mild conditions and with high selectivity, the major stereoisomer being isolated in an enantiopure form. The reaction involves the conjugate nucleophilic addition of 2-methoxyfuran **4** to the carbene complexes **1** followed by ring closure of the resulting zwitterionic intermediate species. The oxidation of the carbene **5a** results in the formation of the enantiopure cyclopropane diester **6**. Further elaboration of the cyclopropane **6** allows for an efficient enantioselective access to alcohols or diols **7–9** as well as to cyclopropanecarbaldehydes **10–12**. The protocol described herein provides a very simple entry to interesting enantiopure precursors of carboxycyclopropylglycine derivatives from readily available starting materials. In order to test this potential as carboxycyclopropylglycine precursors, the aminocyanation of the cyclopropanecarbaldehyde **10** was undertaken and the α-aminocyano derivative **13** was isolated as a single diastereosiomer.

Keywords: asymmetric synthesis · carbenes · chiral pool · cyclopropanation · diastereoselectivity

Introduction

Cyclopropane rings have emerged as an important target in modern organic synthesis. This skeleton is found as a basic structural element in a wide range of naturally occurring compounds and analogues with important biological and pharmacological applications.[1] Additionally, functionalised cyclopropanes play a prominent role as synthetic key intermediates in different processes.[2] In this sense, searching for new methods in the synthesis of enantiopure cyclopropanes[3] represents a field with increasing interest.

On the other hand, as part of our study into the synthetic potential of group 6 Fischer carbene complexes, we recently initiated the study of the potential of enantiopure Fischer carbene complexes **1a**,**b**, prepared by condensation of [pentacarbonyl methoxy(methyl)carbene]tungsten(0) complex and aldehydes readily available from the chiral pool,[4] in diastereoselective synthesis. Gratifyingly, these metal carbenes proved to be excellent acceptor substrates for the Mukaiyama–Michel addition reaction of 2-trimethylsilyloxyfuran **2** to produce new functionalised carbene complexes **3**, as summarised in Scheme 1.[5] In this case, the conjugate addition of **2** is followed by the cleavage of the O–Si bond to generate the butenolide skeleton.



Scheme 1. Stereoselective Mukaiyama–Michael addition of carbene 2-trimethylsilyloxyfuran **2** to carbene complexes **1**.

This result prompted us to investigate the behaviour of 2-methoxyfuran **4**, a reagent that lacks the labile O–Si bond, but is still reactive for conjugate addition. In this sense, isolated examples reveal that 2-methoxyfuran **4** is able to cyclopropanate highly electron-deficient alkenes and can be thus considered as a synthetic equivalent of the crotylcar-

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bene species **A** (Figure 1).[6] In such cases, the cyclopropanation involves nucleophilic addition and furan ring opening (Michael-initiated cyclopropanation reaction, MICR). On the basis of these findings, we decided to study the reaction

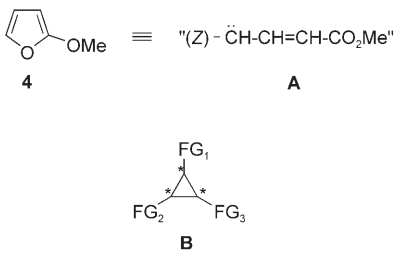
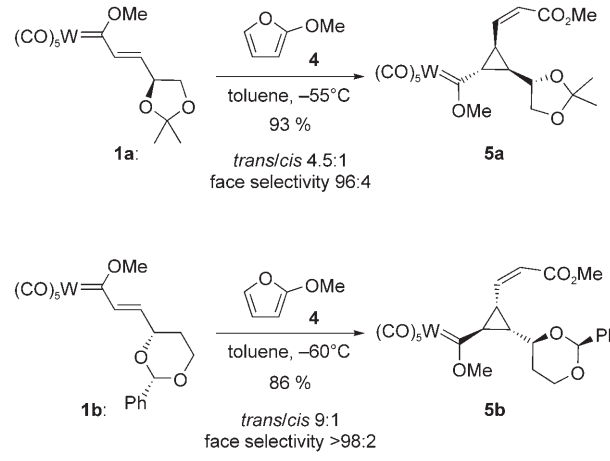


Figure 1. Schematic representations of crotylcarbene **A** and enantiopure cyclopropanes **B**. FG = functional group.

of **1** with **4** as it might provide enantiopure cyclopropanes of type **B** with very attractive structural features such as 1) three stereogenic centres, 2) a highly versatile functionalization and 3) three contiguous orthogonal functional groups attached to the cyclopropane ring. Herein, we report our results on this cyclopropanation reaction and the elaboration of the individual functionalities of the resulting cycloadduct without breaking the cyclopropane ring.[7]

Results and Discussion

Synthesis of cyclopropylcarbene complexes: The Fischer carbene complex **1a** was found to smoothly react with 2-methoxyfuran **4** (toluene, −55 °C) affording the cyclopropylcarbene complex **5a** in high yield (93 %). In terms of stereoselectivity, the *trans*/*cis* ratio was 4.5:1, while the face stereoselectivity was 96:4 (Scheme 2). Similarly, the reaction of the carbene complex **1b** with 2-methoxyfuran **4** (toluene, −60 °C) resulted in the formation of the cyclopropylcarbene **5b** in high yield (86 %) and with higher selectivity (*trans*/*cis* 9:1, face selectivity >98:2). It is noteworthy that by simply purifying the crude mixture of cyclopropylcarbenes **5a**,**b** by conventional flash column chromatography the major cycloadduct could be isolated in good yield and high purity (**5a**,**b** >98 % *de*; **5a**: 69 % yield; **5b**: 75 % yield). It should be noted that both chiral appendages lead to cycloadducts **5a** and **5b** with complementary absolute configuration at the three stereogenic centres of the cyclopropane ring. Recrystallization of cyclopropylcarbenes **5a** and **5b** from a 5:1 mixture of pentane/CH_2Cl_2 gave single crystals suitable for X-ray analysis (see Figures 2 and 3).



Scheme 2. Stereoselective cyclopropanation of carbene complexes **1** with 2-methoxyfuran **4**.

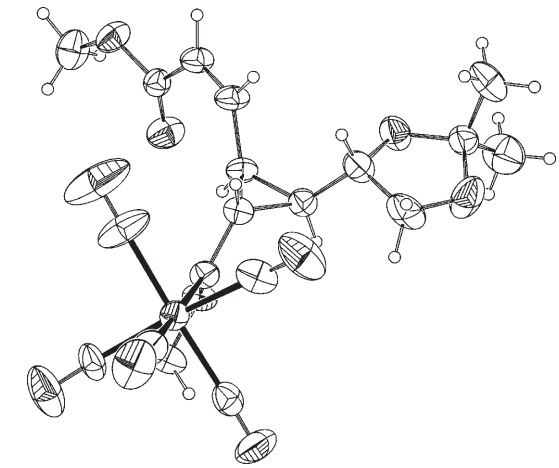


Figure 2. ORTEP view of enantiopure cyclopropylcarbene complex **5a**.

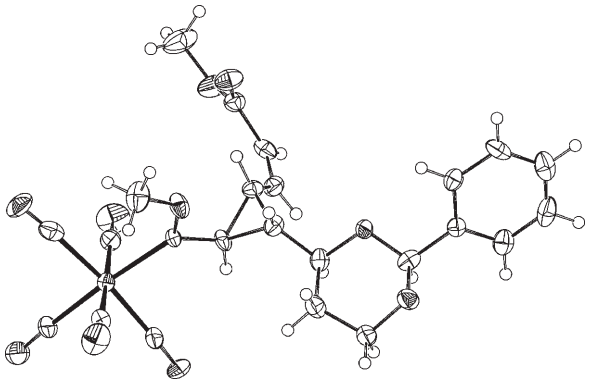
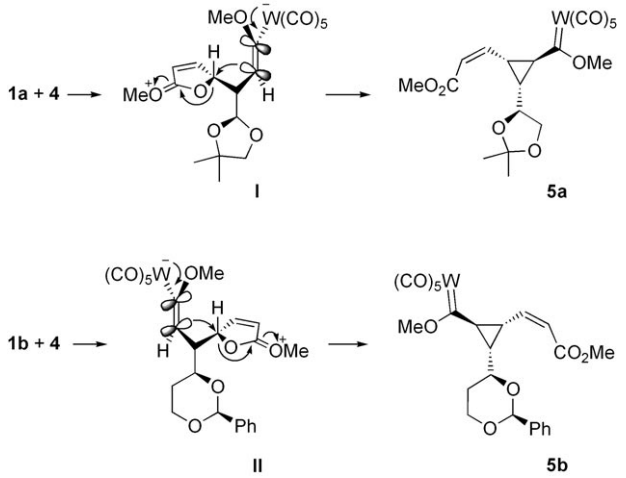


Figure 3. ORTEP view of enantiopure cyclopropylcarbene complex **5b**.

A mechanistic proposal for the formation of the cyclopropylcarbene complexes **5** is shown in Scheme 3. In a general view, the process would involve conjugate nucleophilic addition of 2-methoxyfuran to the carbene complex to generate a zwitterionic intermediate which would evolve by cyclopropane ring closure. First, the stereochemical reaction course of the attack to carbene complexes **1a** and **1b**, a process that has been previously well established in the case of the Mukaiyama–Michael addition of 2-trimethylsilyloxyfuran,[5,8] would provide intermediates **I** and **II**, respectively (Scheme 3). Therefore, this first step is common for both furan reagents, 2-trimethylsilyloxyfuran **2** and 2-methoxyfur-

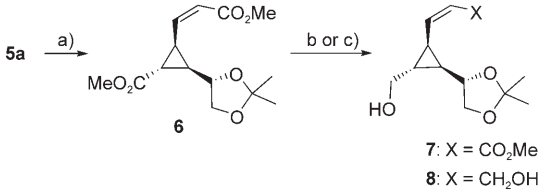


Scheme 3. Mechanistic proposal for the cyclopropylcarbene formation.

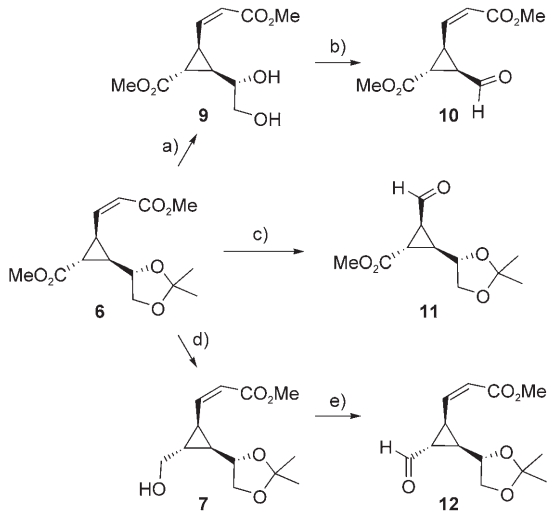
an **4**. Whereas, the intermediate resulting from the addition of silyloxyfuran evolves through the O–Si cleavage (vide supra). Furan ring opening by intramolecular nucleophilic displacement was found to be the most favourable way to follow the intermediate **I**. Thus, the nucleophilic attack from the upper face of the furan ring accounts well for the formation of the major isomer **5a** from the intermediate **I**. In the same way, ring closure of **II** permits us to rationalise the preferential formation of cyclopropane **5b**.

Elaboration of the enantiopure cyclopropyl carbene complex 5a: Once this mild and selective cyclopropanation had been set up, selective and efficient elaboration of the cyclopropane functionalities was attempted on the enantiopure adduct **5a**. Among a number of useful transformations of the metal carbene into organic moieties,[9] the oxidation to the corresponding ester **6** was found to occur in nearly quantitative yield (Scheme 4). Moreover, the reduction of the diester **6** with $LiAlH_4$ at −50 °C or at room temperature produced the monoalcohol **7** (87% yield) and the diol **8** (94% yield) which features a *cis*-allylic alcohol motif, respectively.

The potential of cyclopropane **6** was finally checked by its ready elaboration into three different cyclopropanecarbaldehydes (Scheme 5). For instance, the ketal hydrolysis provided diol **9**, which in turn was efficiently oxidised to the cyclopropanecarbaldehyde **10**, featuring two different ester functionalities. On the other hand, the oxidative cleavage of the



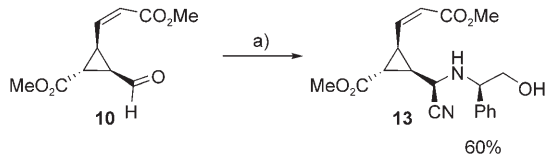
Scheme 4. Formation of cyclopropanecarboxylate **6** by oxidation of **5a** and its reduction to alcohols **7** and **8**. a) Py^+-O^-, THF, H_2O, 25 °C, 94%; b) for **7**: $LiAlH_4$, THF, −50 °C, 87%; c) for **8**: $LiAlH_4$, THF, −50 to 25 °C, 94%.



Scheme 5. Synthesis of the enantiopure cyclopropanecarbaldehydes **10**, **11** and **12**. a) HCl (6 N), THF, 25 °C, 96%; b) $NaIO_4$, CH_2Cl_2, H_2O, pH 7.2, 25 °C, 89%; c) i) O_3, CH_2Cl_2, MeOH, −78 °C, ii) SMe_2, −78 to 25 °C, 93%; d) $LiAlH_4$, THF, −50 °C, 87%; e) PCC, CH_2Cl_2, 25 °C, 91%. PCC = pyridinium chlorochromate.

alkenyl function of **6** directly afforded the cyclopropanecarbaldehyde **11** with ester and ketal motifs. Aldehyde functionalization of the third carbon of the cyclopropane to produce **12** was effected by reduction of **6** to give **7** (vide supra) followed by PCC oxidation. In terms of overall yields, the cyclopropanecarbaldehydes **10**, **11** and **12** were prepared enantiomerically pure in 57, 62 and 53% yields, respectively, from **1a** and **4**.

Taking in mind the additional interest of structures **10** and **11** as direct precursors of carboxycyclopropylglycine derivatives,[10] the Strecker reaction on compound **10** was evaluated. The use of (*R*)-(−)-2-phenylglycinol and trimethylsilyl cyanide[11] led to a reaction mixture from which the α-aminocyano adduct **13** was isolated in 60% yield as a pure stereoisomer (>98% *de*, determined by NMR spectroscopic analysis; Scheme 6). X-ray analysis of a single crystal of **13** collected from a mixture (5:1) of pentane/Et_2O enabled us to determine the absolute configuration of the new stereocentre (Figure 4).



Scheme 6. Strecker aminocyanation on aldehyde **10**. a) i) (*R*)-(−)-2-phenylglycinol, MeOH, 25 °C, ii) TMSCN, −10 °C. TMSCN = trimethylsilyl cyanide.

Conclusion

Herein we report uncatalysed, efficient and diastereoselective cyclopropanations of enantiopure electron-poor olefins

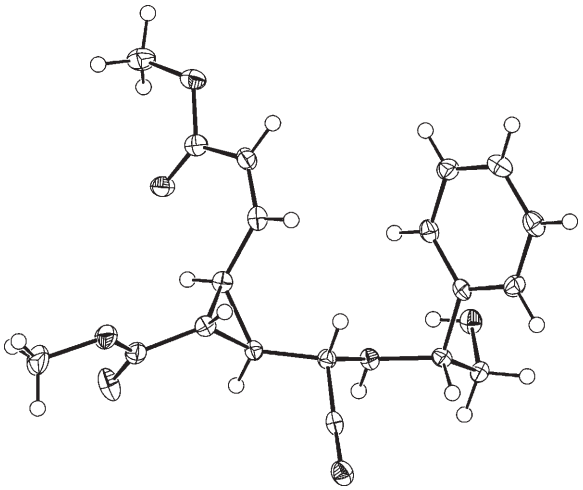


Figure 4. ORTEP view of enantiopure α-aminocyano compound **13**.

with 2-methoxyfuran which provide 1,2,3-trisubstituted, highly functionalised cyclopropanes.[12] The powerful electron-acceptor nature of the metalcarbene is responsible for this Michael-initiated cyclopropanation.[13] This protocol appears to represent a flexible and short access to a number of enantiopure cyclopropanecarbaldehydes.[14]

Experimental Section

General considerations: All operations were carried out under a nitrogen atmosphere by using conventional Schlenck techniques. All common reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Toluene, and THF were distilled from sodium benzophenone and methanol, and methylene chloride from calcium hydride, under a nitrogen atmosphere prior to use. Hexane, ethyl acetate and triethylamine were distilled before use. TLC was performed on aluminium-backed plates coated with silica gel 60, with F_{254} indicator. Flash chromatographic columns were carried out on silica gel 60, 230–240 mesh. Optical rotations were determined with a Perkin–Elmer 241 polarimeter by using a Na lamp; data are reported as follows: $[\alpha]_D^{20}$ (concentration in g per 100 mL in solvent). High-resolution mass spectra were determined on a Finnigan MAT95 spectrometer. NMR spectra were run on Bruker AV-400, NAV-400, DPX-300, AC-300 and AMX-400 spectrometers. Elemental analyses were carried out with a Perkin–Elmer 240 B microanalyser.

General procedure for the preparation of the carbenes 5: 2-Methoxyfuran **2** (0.84 mL, 5 mmol) was added to a solution of tungsten carbene complex **1a–b** (1 mmol) in toluene (90 mL) at −55 or −60 °C (Scheme 2). After stirring for 48 h at this temperature, the solvents were removed under vacuum. The residues were analysed by ^{1}H NMR spectroscopy and the major diastereoisomer was isolated by column chromatography (silica gel, hexane/ethyl acetate 5:1) to give the enantiopure carbenes **5a–b**.

Pentacarbonyl(1-{(1*R*,2*S*,3*R*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[(*Z*)-2-methoxycarbonylethenyl]cyclopropyl}-1-methoxymethylidene)-tungsten(0) (5a): Orange solid; yield: 69% (93% mixture of diastereoisomers); R_f = 0.28 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.13 (dd, J(H,H) = 11.2, 10.5 Hz, 1H), 5.93 (d, J(H,H) = 11.2 Hz, 1H), 4.56 (s, 3H), 4.16 (dd, J(H,H) = 8.2, 6.0 Hz, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 3.73 (s, 3H), 3.55 (t, J(H,H) = 4.7 Hz, 1H), 2.37 (m, 1H), 1.44 (s, 3H), 1.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 322.2 (C), 203.2 (C), 197.3 (C), 166.5 (C), 144.1 (CH), 121.3 (CH), 109.9 (C), 74.1 (CH), 69.6 (CH_3), 69.1 (CH_2), 57.5 (CH), 51.3 (CH_3), 38.2 (CH), 34.6 (CH), 26.8 (CH_3), 25.5 ppm (CH_3); HRMS (70 eV, EI): m/z: calcd for $C_{19}H_{20}O_{10}W$: 592.0560 $[M]^+$; found: 592.0557; elemental analysis calcd for $C_{19}H_{20}O_{10}W$: C 38.54, H 3.40; found: C 38.62, H 3.42.

Pentacarbonyl[1-((1*S*,2*R*,3*S*)-2-[(*Z*)-2-methoxycarbonylethenyl]-3-{(*R*)-[(2*S*,4*S*)-2-phenyl-1,3-dioxan-4-yl]}cyclopropyl)-1-methoxymethylidene]-tungsten(0) (5b): Orange solid; yield: 75% (86% mixture of diastereoisomers); R_f = 0.2 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40 (m, 5H), 6.23 (dd, J(H,H) = 11.4, 11.1 Hz, 1H), 5.88 (d, J(H,H) = 11.4 Hz, 1H), 5.47 (s, 1H), 4.56 (s, 3H), 4.29 (dd, J(H,H) = 11.4, 4.6 Hz, 1H), 3.96 (m, 3H), 3.78 (t, J(H,H) = 4.6 Hz, 1H), 3.71 (s, 3H), 2.47 (m, 1H), 1.95 (ddd, J(H,H) = 16.8, 12.2, 4.6 Hz, 1H), 1.67 ppm (d, J(H,H) = 13.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 322.9 (C), 203.4 (C), 197.3 (C), 166.6 (C), 145.1 (CH), 138.1 (C), 128.7 (CH), 128.2 (CH), 125.7 (CH), 120.6 (CH), 100.9 (CH), 74.5 (CH), 69.6 (CH_3), 66.7 (CH_2), 56.8 (CH), 51.1 (CH_3), 39.9 (CH), 35.0 (CH), 30.7 ppm (CH_2); HRMS (70 eV, EI): m/z: calcd for $C_{24}H_{22}O_{10}WNa$: 677.0645 $[M+Na]^+$; found: 677.0615; elemental analysis calcd (%) for $C_{24}H_{22}O_{10}W$: C 44.06, H 3.39; found: C 44.12, H 3.38.

(1*R*,2*S*,3*R*)-Methyl 2-[(*Z*)-2-methoxycarbonylethenyl]-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate (6): Carbene complex **5a** (296 mg, 0.5 mmol) was dissolved in a mixture of THF/water (5:1, 12 mL). Pyridine oxide (240 mg, 2.5 mmol) was added to this solution and the mixture stirred at room temperature for 15 h. At this point, the mixture was extracted with ethyl acetate (3×10 mL) and the solvents were removed under reduced pressure. Chromatographic purification of the residue (silica gel, hexane/ethyl acetate 3:1) yielded 133 mg (94%) of the enantiopure cyclopropylester **6** as white solid. $[\alpha]_D^{20}$ = +66.0 (c = 0.15 in CH_2Cl_2); R_f = 0.18 (hexane/ethyl acetate 3:1); m.p. 67–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.00 (dd, J(H,H) = 11.4, 10.2 Hz, 1H), 5.89 (d, J(H,H) = 10.2 Hz, 1H), 4.10 (dd, J(H,H) = 8.0, 5.9 Hz, 1H), 3.92 (dd, J(H,H) = 6.6, 5.9 Hz, 1H), 3.73 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.53 (dt, J(H,H) = 9.7, 5.0 Hz, 1H), 2.02 (m, 1H), 1.80 (dd, J(H,H) = 5.0, 4.9 Hz), 1.40 (s, 3H), 1.31 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.6 (C), 166.2 (C), 144.4 (CH), 121.1 (CH), 109.4 (C), 73.7 (CH), 69.0 (CH_2), 51.8 (CH_3), 50.9 (CH_3), 30.2 (CH), 26.8 (CH), 26.5 (CH_3), 25.6 (CH), 25.3 ppm (CH_3); HRMS (70 eV, EI): m/z: calcd for $C_{13}H_{17}O_6$: 269.1020 $[M-CH_3]^+$; found: 269.1026; elemental analysis calcd (%) for $C_{14}H_{20}O_6$: C 59.14, H 7.09; found: C 59.02, H 7.06.

(*Z*)-Methyl 3-{(1*R*,2*R*,3*R*)-2-(hydroxymethyl)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropyl}propenoate (7): $LiAlH_4$ (62 mg, 1.6 mmol) was added to a solution of the cyclopropane **6** (120 mg, 0.4 mmol) in THF (20 mL) at −50 °C. After stirring for 15 min at this temperature, H_2O (1 mL) was carefully added and the reaction was filtered through a plug of Celite. At this point, the mixture was extracted with diethyl ether (3× 10 mL) and the solvents were removed under reduced pressure. Chromatographic purification of the residue (silica gel, ethyl acetate) gave 89 mg (87%) of the enantiopure cyclopropane **7** as a colourless oil. $[\alpha]_D^{20}$ = −80.08 (c = 0.25 in CH_2Cl_2); R_f = 0.6 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.19 (dd, J(H,H) = 11.2, 9.1 Hz, 1H), 5.90 (dd, J(H,H) = 11.2, 1.1 Hz, 1H), 4.13 (dd, J(H,H) = 7.9, 5.9 Hz, 1H), 3.84 (ddd, J(H,H) = 9.1, 7.1, 5.9 Hz, 1H), 3.74 (m, 2H), 3.72 (s, 3H), 3.33 (dd, J(H,H) = 11.2, 8.8 Hz, 1H), 2.94 (d, J(H,H) = 5.9 Hz, 1H), 2.66 (tdd, J(H,H) = 9.1, 4.9, 1.1 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.33 (m, 1H), 1.22 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.5 (C), 147.8 (CH), 120.2 (CH), 109.3 (C), 75.2 (CH), 69.3 (CH_2), 64.8 (CH_2), 51.19 (CH_3), 29.2 (CH), 27.2 (CH), 26.8 (CH_3), 25.61 (CH_3), 22.14 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{13}H_{21}O_5$: 257.1389 $[M+H]^+$; found: 257.1397; elemental analysis calcd (%) for $C_{13}H_{20}O_5$: C 60.92, H 7.87; found: C 61.10, H 7.85.

(*Z*)-3-{(1*R*,2*R*,3*R*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxymethylcyclopropyl}prop-2-en-1-ol (8): Cyclopropane **6a** (120 mg, 0.4 mmol) was dissolved in THF (20 mL) at −50 °C. $LiAlH_4$ (31 mg, 0.8 mmol) was added to this solution and the mixture was left to reach room temperature. After stirring for 2 h at that temperature, the reaction was carefully quenched with H_2O (1 mL) and filtered though a plug of Celite. At this point, the mixture was extracted with diethyl ether (3×10 mL) and the

solvents were removed under reduced pressure. Chromatographic purification of the residue (silica gel, ethyl acetate) yielded 80 mg (92%) of the enantiopure diol **8** as a colourless oil. $[\alpha]_D^{20} = +59.7$ ($c = 0.36$ in CH_2Cl_2); $R_f = 0.13$ (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 5.75$ (dt, J(H,H) = 10.7, 7.1 Hz, 1H), 5.37 (dd, 10.6, 8.2 Hz, 1H), 4.25 (dd, J(H,H) = 12.4, 7.4 Hz, 1H), 4.14 (dd, J(H,H) = 12.6, 7.1 Hz, 1H), 4.05 (m, 1H), 3.71 (m, 2H), 3.61 (dd, J(H,H) = 11.2, 5.6 Hz, 1H), 3.36 (dd, J(H,H) = 11.3, 7.4 Hz, 1H), 1.76 (dd, J(H,H) = 13.6, 8.5 Hz, 1H), 1.40 (s, 3H), 1.29 (s, 3H), 1.11 (m, 1H), 1.00 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta = 131.2$ (CH), 130.1 (CH), 109.2 (C), 75.9 (CH), 69.3 (CH_2), 64.7 (CH_2), 58.1 (CH_2), 26.7 (CH), 26.7 (CH_3), 26.2 (CH), 25.6 (CH_3), 19.3 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{11}H_{19}O_4$: 213.1122 $[M-H]^+$; found: 213.1119; elemental analysis calcd (%) for $C_{12}H_{20}O_4$: C 63.14, H 8.83; found: C 63.16, H 8.86.

(1*R*,2*S*,3*R*)-Methyl 3-[(*S*)-1,2-dihydroxyethyl]-2-[(*Z*)-2-methoxycarbonylethenyl]cyclopropanecarboxylate (9): HCl (6N,1.5 mL) was added to a solution of **6** (134 mg, 0.5 mmol) in THF (20 mL) at room temperature. After stirring for 2 h, the mixture was extracted with ethyl acetate (3× 10 mL) and the solvents were removed under reduced pressure. A chromatographic purification of the residue (silica gel, ethyl acetate) yielded 117 mg (96%) of the enantiopure diol **9** as a colourless oil. $[\alpha]_D^{20} = +110.5$ ($c = 0.34$ in CH_2Cl_2); $R_f = 0.36$ (ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta = 6.05$ (dd, J(H,H) = 11.8, 9.0 Hz, 1H), 5.94 (d, J(H,H) = 11.8 Hz, 1H), 3.50–3.80 (m, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.37 (dt, J(H,H) = 9.5, 4.6 Hz, 1H), 2.94 (brs, 2H), 2.02 (m, 1H), 1.89 ppm (dd, J(H,H) = 5.3, 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta =$ 172.3 (C), 167.0 (C), 145.3 (CH), 121.4 (CH), 70.6 (CH), 66.0 (CH_2), 52.1 (CH_3), 51.4 (CH_3), 30.9 (CH), 27.4 (CH), 25.5 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{10}H_{13}O_5$: 213.0757 $[M-CH_3O]^+$; found: 213.0757; elemental analysis calcd (%) for $C_{11}H_{16}O_6$: C 54.09, H 6.60; found: C 54.11, H 6.56.

(1*R*,2*S*,3*R*)-Methyl 2-[(*Z*)-2-methoxycarbonylethenyl]-3-formylcyclopropanecarboxylate (10): Cyclopropane **9** (213 mg, 1 mmol) was dissolved in methylene chloride (10 mL). A buffer solution at pH 7.2 (NaH_2PO_4/Na_2HPO_4, 5 mL) and $NaIO_4$ (427 mg, 2 mmol) were added to this solution. After stirring at room temperature for 30 min, the mixture was extracted with ethyl acetate (3×10 mL) and the solvents were removed under reduced pressure. Chromatographic purification of the residue (silica gel, hexane/ethyl acetate 2:1) yielded 189 mg (89%) of the enantiopure cyclopropane **10** as a colourless oil. $[\alpha]_D^{20} = +81.9$ ($c = 0.27$ in methylene chloride); $R_f = 0.39$ (hexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 9.77$ (d, J(H,H) = 2.2 Hz, 1H), 6.08 (dd, J(H,H) = 11.5, 10.1 Hz, 1H), 5.91 (d, J(H,H) = 11.8 Hz, 1H), 3.97 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.03 (m, 1H), 2.66 ppm (t, J(H,H) = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 196.5$ (CH), 170.2 (C), 166.3 (C), 141.7 (CH), 122.4 (CH), 52.4 (CH_3), 51.4 (CH3), 36.4 (CH), 30.1 (CH), 29.9 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{10}H_{12}O_5$: 212.0679 $[M]^+$; found: 212.0675; elemental analysis calcd (%) for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.54, H 5.72.

(1*S*,2*S*,3*R*)-Methyl 2-formyl-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropanecarboxylate (11): A continuous flow of O_3 was bubbled for 20 minutes through a solution of **6** (148 mg, 0.5 mmol) in a mixture of CH_2Cl_2/MeOH (3:1, 90 mL) at −80°C. After that period, Me_2S (0.37 mL, 5 mmol) was added and the mixture was left to reach room temperature. The reaction was extracted with methylene chloride (3×20 mL) and the solvents were removed. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 2:1) to give 106 mg (93%) of the enantiopure cyclopropane **11** as a colourless oil. $[\alpha]_D^{20} = +77.2$ ($c = 0.29$ in methylene chloride); $R_f = 0.38$ (hexane/ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta = 9.72$ (d, J(H,H) = 3.0 Hz, 1H), 4.14 (dd, J(H,H) = 8.3, 6.0 Hz, 1H), 4.05 (dd, J(H,H) = 14.7, 6.0 Hz, 1H), 3.73 (m, 1H), 3.72 (s, 3H), 2.68 (m, 1H), 2.49 (dd, J(H,H) = 5.8, 5.0 Hz, 1H), 2.17 (m, 1H), 1.33 (s, 3H), 1.30 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 196.7$ (CH), 170.8 (C), 109.6 (C), 72.0 (CH), 68.8 (CH_2), 52.3 (CH_3), 34.0 (CH), 33.0 (CH), 26.7 (CH_3), 25.3 (CH_3), 24.9 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{10}H_{13}O_5$: 213.0757 $[M-CH_3]^+$; found: 213.0755; elemental analysis calcd (%) for $C_{11}H_{16}O_5$: C 57.88, H 7.07; found: C 57.65, H 7.09.

(*Z*)-Methyl 3-{(1*S*,2*R*,3*R*)-2-formyl-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropyl}propenoate (12): Pyridinium chlorochromate (215 mg, 1 mmol) was added to a room temperature solution of **7** (133 mg, 0.5 mmol) in methylene chloride (25 mL). After stirring for 2 h, the reaction was concentrated under vacuum and diethyl ether (10 mL) was added. The mixture was filtered through a plug of silica gel/Celite and the solvents were removed under reduced pressure. A chromatographic purification of the residue (silica gel, hexane/ethyl acetate 3:1) yielded 116 mg (91%) of the enantiopure diol **12** as a white solid. $[\alpha]_D^{20} = -13.11$ ($c = 0.17$ in methylene chloride); $R_f = 0.2$ (hexane/ethyl acetate 3:1); m.p. 84–86°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 9.19$ (d, J(H,H) = 4.9 Hz, 1H), 6.07 (dd, J(H,H) = 11.2, 10.0 Hz, 1H), 5.95 (d, J(H,H) = 11.2 Hz, 1H), 4.14 (dd, J(H,H) = 8.1, 5.9 Hz, 1H), 4.02 (dt, J(H,H) = 8.1, 6.4 Hz, 1H), 3.73 (s, 3H), 3.71 (m, 2H), 2.11 (m, 1H), 2.04 (dd, J(H,H) = 9.8, 4.9 Hz, 1H), 1.44 (s, 3H), 1.34 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 196.7$ (CH), 165.8 (C), 142.7 (CH), 121.1 (CH), 109.1 (C), 72.9 (CH), 68.5 (CH_2), 50.6 (CH_3), 35.5 (CH), 28.9 (CH), 26.0 (CH), 24.8 (CH_3), 24.6 ppm (CH_3); HRMS (70 eV, EI): m/z: calcd for $C_{13}H_{17}O_5$: 253.1071 $[M-H]^+$; found: 253.1071; elemental analysis calcd (%) for $C_{13}H_{18}O_5$: C 61.40, H 7.14; found: C 61.36, H 7.15.

(1*R*,2*R*,3*S*)-Methyl 3-{(*S*)-[(*R*)-2-hydroxy-1-phenylethylamino]-(cyano)-methyl}-2-[(*Z*)-2-methoxycarbonylethenyl]cyclopropanecarboxylate (13): Cyclopropane **10** (112 mg, 0.5 mmol) was dissolved in methanol (10 mL) at room temperature. (*R*)-(−)-2-Phenylglycinol (75 mg, 0.55 mmol) was added to this solution. After stirring for 2 h, the mixture was cooled down to −10°C, followed by the addition of trimethylsilyl cyanide (0.13 mL, 1 mmol). The mixture was stirred for 14 h at this temperature. At this point, the reaction was extracted with methylene chloride (3× 10 mL) and the solvents were removed under reduced pressure. Chromatographic purification of the residue (silica gel, hexane/ethyl acetate/triethylamine 1:1:1) yielded 108 mg (60%) of the enantiopure **13** as a white solid. $[\alpha]_D^{20} = +41.3$ ($c = 0.38$ in methylene chloride); $R_f = 0.6$ (hexane/ethyl acetate/triethylamine 1:1:1); m.p. 104–106°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 7.33$ (m, 2H), 5.89 (dd, J(H,H) = 11.2, 1.0 Hz, 1H), 5.45 (dd, J(H,H) = 11.2, 10.3 Hz, 1H), 4.06 (dd, J(H,H) = 9.3, 3.9 Hz, 1H), 3.77 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.61 (dd, J(H,H) = 10.8, 9.3 Hz, 1H), 3.54 (m, 2H), 3.03 (d, J(H,H) = 8.4 Hz, 1H), 2.31 (td, J(H,H) = 9.3, 5.1 Hz, 1H), 1.84 ppm (t, J(H,H) = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 171.1$ (C), 166.3 (C), 142.6 (CH), 137.8 (C), 128.9 (CH), 128.6 (CH), 127.9 (CH), 122.9 (CH), 118.5 (C), 66.9 (CH_2), 63.0 (CH), 52.4 (CH_3), 51.5 (CH_3), 47.2 (CH), 30.4 (CH), 28.0 (CH), 25.9 ppm (CH); HRMS (70 eV, EI): m/z: calcd for $C_{19}H_{24}N_2O_5$: 359.1607 $[M+H]^+$; found: 359.1618; elemental analysis calcd (%) for $C_{19}H_{23}N_2O_5$: C 63.67, H 6.19; found: C 63.69, H 6.21.

X-ray structure determination: The most relevant crystal and refinement data for **5a** are as follows: empirical formula = $C_{19}H_{20}O_{10}W$; $M_r = 592.20$; $T = 293(2)$ K; $\lambda = 1.54184$ Å; crystal system = monoclinic; space group = $P2_1$; unit cell dimensions: $a = 12.9282(2)$, $b = 9.7988(2)$, $c = 18.9921(3)$ Å; $\alpha = 90$, $\beta = 107.4210(10)$, $\gamma = 90°$; $V = 2295.58(7)$ Å^3; $Z = 4$, $\rho_{calcd} = 1.714$ Mg m^{-3}; $\mu = 9.769$ mm^{-1}; $F(000) = 1152$; crystal size = 0.35×0.12×0.05 mm; θ range for data collection = 2.44 to 67.70°; index ranges = $-15 \le h \le 14$, $-10 \le k \le 11$, $0 \le l \le 22$; reflections collected/unique = 14493/7712 ($R_{int} = 0.0606$); completeness to $\theta = 67.70$ (97.3%); absorption correction = semi-empirical from equivalents; max. and min. transmission = 1.479 and 0.707; refinement method = full-matrix least-squares on F^2; data/restraints/parameters = 7712/1/541; goodness-of-fit on $F^2 = 1.028$; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0422$, $wR_2 = 0.1067$; R indices (all data): $R_1 = 0.0435$, $wR_2 = 0.1087$; largest difference peak and hole = 2.201 and −1.257 e Å^{-3}. For **5b**: empirical formula = $C_{24}H_{22}O_{10}W$; $M_r = 654.27$; $T =$ 150(2) K; $\lambda = 1.54183$ Å; crystal system = monoclinic; space group = $P2_1$; unit cell dimensions: $a = 10.3825(3)$, $b = 6.35170(10)$, $c = 18.7192(5)$ Å; $\alpha =$ 90, $\beta = 93.631(2)$, $\gamma = 90°$; $V = 1231.99(5)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.764$ Mg m^{-3}; $\mu = 9.174$ mm^{-1}; $F(000) = 640$; crystal size = 0.17×0.10×0.05 mm; θ range for data collection = 2.37 to 68.35°; index ranges = $-12 \le h \le 12$, $-7 \le k \le$ 6, $0 \le l \le 22$; reflections collected/unique = 6644/3845 ($R_{int} = 0.0561$); completeness to $\theta = 68.35$ (99.4%); absorption correction = semi-empirical from equivalents; max. and min. transmission = 1.236 and 0.771; refinement method = full-matrix least-squares on F^2; data/restraints/parameters = 3845/1/541; goodness-of-fit on $F^2 = 1.244$; final R indices [$I > 2\sigma(I)$]:

$R_1 = 0.0329$, $wR_2 = 0.0799$; R indices (all data): $R_1 = 0.0356$, $wR_2 = 0.1005$; largest difference peak and hole = 1.035 and -1.084 e Å^{-3}. For **13**: empirical formula = $C_{19}H_{22}N_2O_5$; $M_r = 358.39$; $T = 298(2)$ K; $\lambda = 1.54178$ Å; crystal system = tetragonal; space group = $P4_1$; unit cell dimensions: $a = 9.47260(10)$, $b = 9.47260(10)$, $c = 39.7724(9)$ Å; $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 3568.78(10)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.334$ Mg m^{-3}, $F(000) = 1520$, crystal size = $0.18 \times 0.10 \times 0.05$ mm; θ range for data collection = 3.33 to 73.08°; index ranges = $-11 \le h \le 11$, $-11 \le k \le 11$, $-48 \le l \le 49$; reflections collected/unique = 16928/6309 ($R_{int} = 0.0423$); completeness to $\theta = 73.08$ (99.1 %); absorption correction = semi-empirical from equivalents; refinement method = full-matrix least-squares on F^2; data/restraints/parameters = 6309/1/490; goodness-of-fit on $F^2 = 1.032$; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0358$, $wR_2 = 0.0929$, R indices (all data): $R_1 = 0.0361$, $wR_2 = 0.0930$; largest difference peak and hole = 0.251 and -0.220 e Å^{-3}.

CCDC-615951 (**5a**), CCDC-615952 (**5b**) and -615952 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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