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SYNTHESIS OF 3,4-ETHYLENEDIOXYTHIOPHENE (EDOT) FROM (*Z*)-BUT-2-ENE-1,4-DIOL OR BUT-2-YNE-1,4-DIOL

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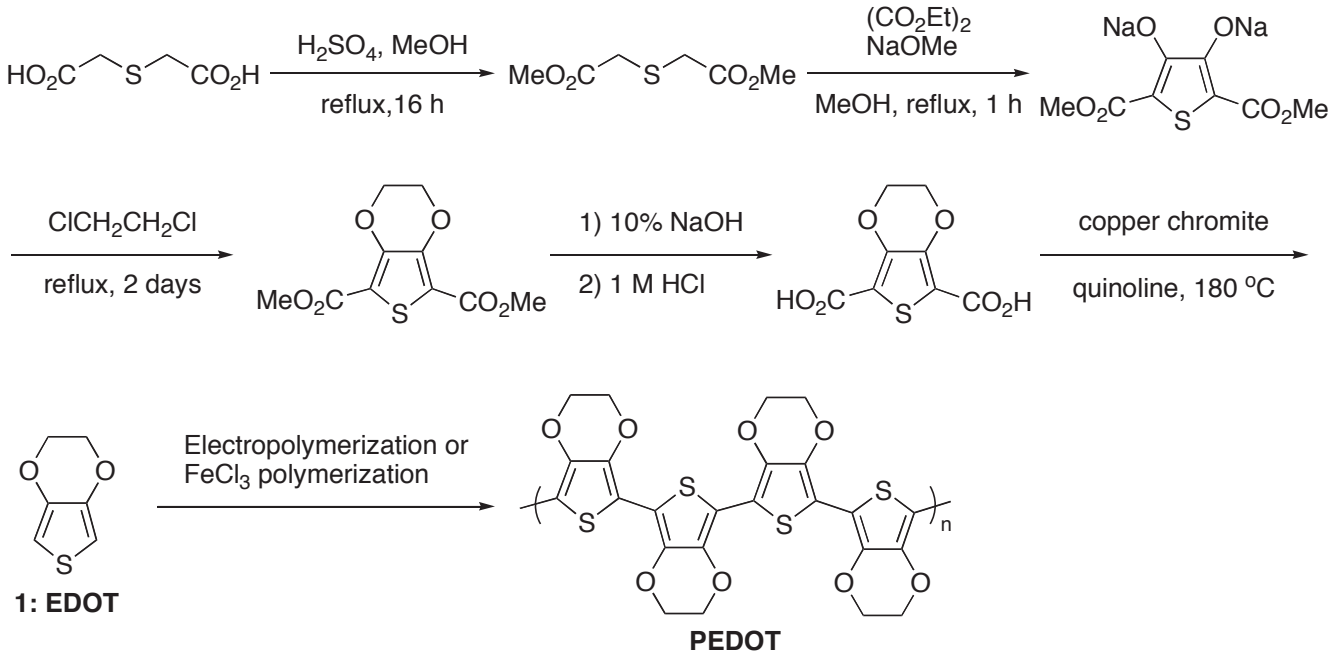
Abstract – 3,4-Ethylenedioxythiophene (EDOT) was synthesized from commercially available (*Z*)-but-2-ene-1,4-diol or but-2-yne-1,4-diol using epoxidation, etherification, and thiophene formation.

INTRODUCTION

Poly(3,4-ethylenedioxythiophene) (PEDOT) prepared by polymerization of 3,4-ethylenedioxythiophene (EDOT (**1**)) and its derivatives are one of the most successful conducting polymers and widely used as antistatic treatment of plastics and electrode materials for solid state electrolyte capacitors because they have properties such as high conductivity with excellent stability, relatively high transparency to visible light, and aqueous processability of the poly(styrene sulfonic acid)-doped form.[1] The most general synthetic route toward EDOT (**1**) is the double Williamson etherification of 3,4-dihydroxy-2,5-thiophenedicarboxylic acid esters, which are prepared from thiodiglycolic acid (Scheme 1).[2] The method has some drawbacks such as use of a carcinogenic reagent (1,2-dihaloethane), use of heavy metals (copper chromite), and high temperature (in quinoline at 180 ºC). On the other hand, Reynolds *et al*. and Bäuerle *et al*. respectively reported efficient syntheses of EDOT (**1**) and substituted EDOTs by Mitsunobu reaction of 3,4-dihydroxy-2,5-thiophenedicarboxylic acid ethyl ester with several diols as a key step.[3] However, the latter methods also used heavy metals (copper chromite or $CuCO_3/Cu(OH)_2$) in decarboxylation step. Therefore, the development of alternative methods for the synthesis of EDOT (**1**) is highly desirable.[4] Herein, we report new synthetic routes to EDOT (**1**) starting from (*Z*)-but-2-ene-1,4-diol or but-2-yne-1,4-diol.

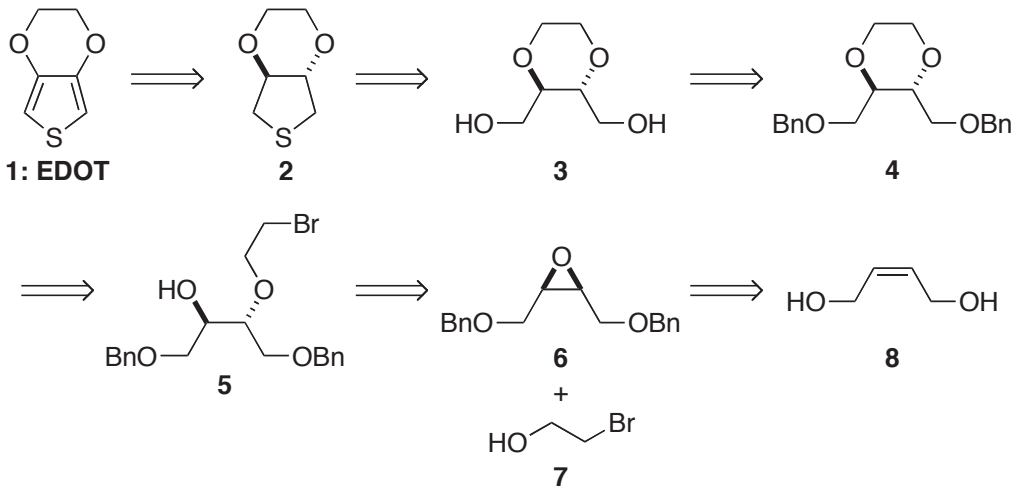
This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.



Scheme 1. Synthesis of EDOT (**1**) and PEDOT

RESULTS AND DISCUSSION

Scheme 2 shows our synthetic plan for EDOT (**1**): EDOT (**1**) could be obtained by dehydrogenation of tetrahydrothiophene (**2**), tetrahydrothiophene (**2**) from 1,4-diol (**3**), 1,4-dioxane ring by ring-opening of oxirane (**6**) with 2-bromoethanol (**7**) followed by intramolecular etherification, and the oxirane (**6**) from commercially available (*Z*)-but-2-ene-1,4-diol (**8**).

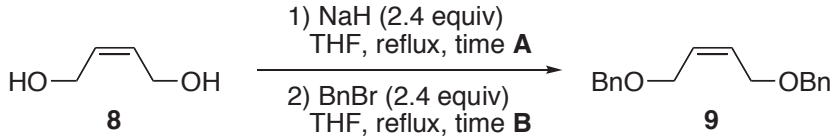


Scheme 2. Retro-synthetic Analysis of EDOT (**1**)

First, benzylation of (*Z*)-but-2-ene-1,4-diol (**8**) was carried out with benzyl bromide under the reaction conditions shown in entry 1 (Table 1) to give (*Z*)-1,4-dibenzyloxybut-2-ene (**9**) in 50% yield.[5] In order to

improve the yield, the reaction time **A** and **B** were investigated in detail. When disodium salt of (*Z*)-but-2-ene-1,4-diol (**8**) was prepared for 6 h followed by benzylation with benzyl bromide for 13 h, dibenzyl ether (**9**) was obtained in 95% yield (entry 4).

Table 1. Synthesis of (*Z*)-1,4-Dibenzyloxybut-2-ene (**9**)

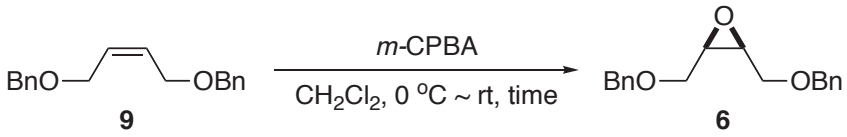


Entry	Time **A** (h)	Time **B** (h)	Yield (%)[a]
1	1	16	50
2	2	15	62
3	8	6	74
4	6	13	95

[a] Isolated yield.

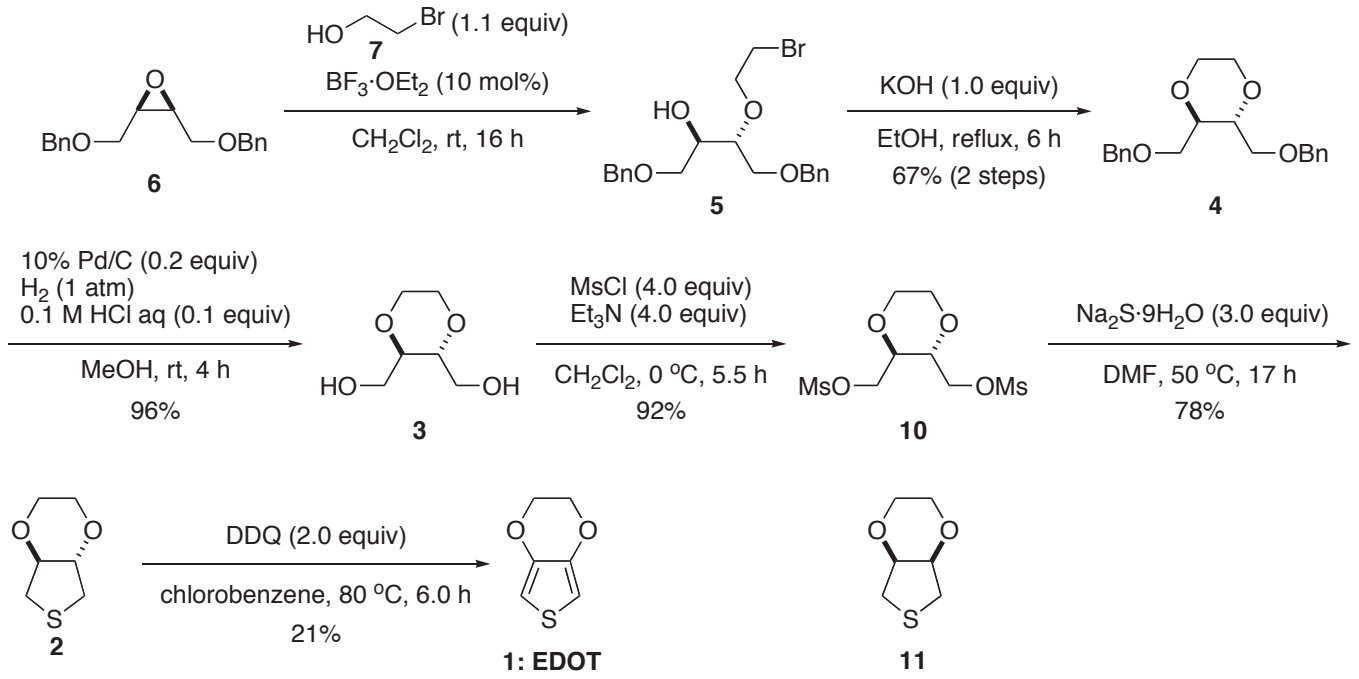
We next examined the epoxidation of the (*Z*)-1,4-dibenzyloxybut-2-ene (**9**) with *m*-CPBA.[6] Table 2 summarizes the results. The epoxidation reaction of (*Z*)-1,4-dibenzyloxybut-2-ene (**9**) with *m*-CPBA (1.1 equiv) for 17 h gave (2*R**,3*S**)-2,3-bis((benzyloxy)methyl)oxirane (**6**) in 86% yield (entry 1). When the epoxidation reaction with *m*-CPBA (1.2 equiv) was carried out for 24 h, the oxirane (**6**) was obtained in 91% yield (entry 2). Increasing the amounts of *m*-CPBA decreased the yields of oxirane (**6**) (entries 3 and 4).

Table 2. Synthesis of (2*R**,3*S**)-2,3-Bis((benzyloxy)methyl)oxirane (**6**)



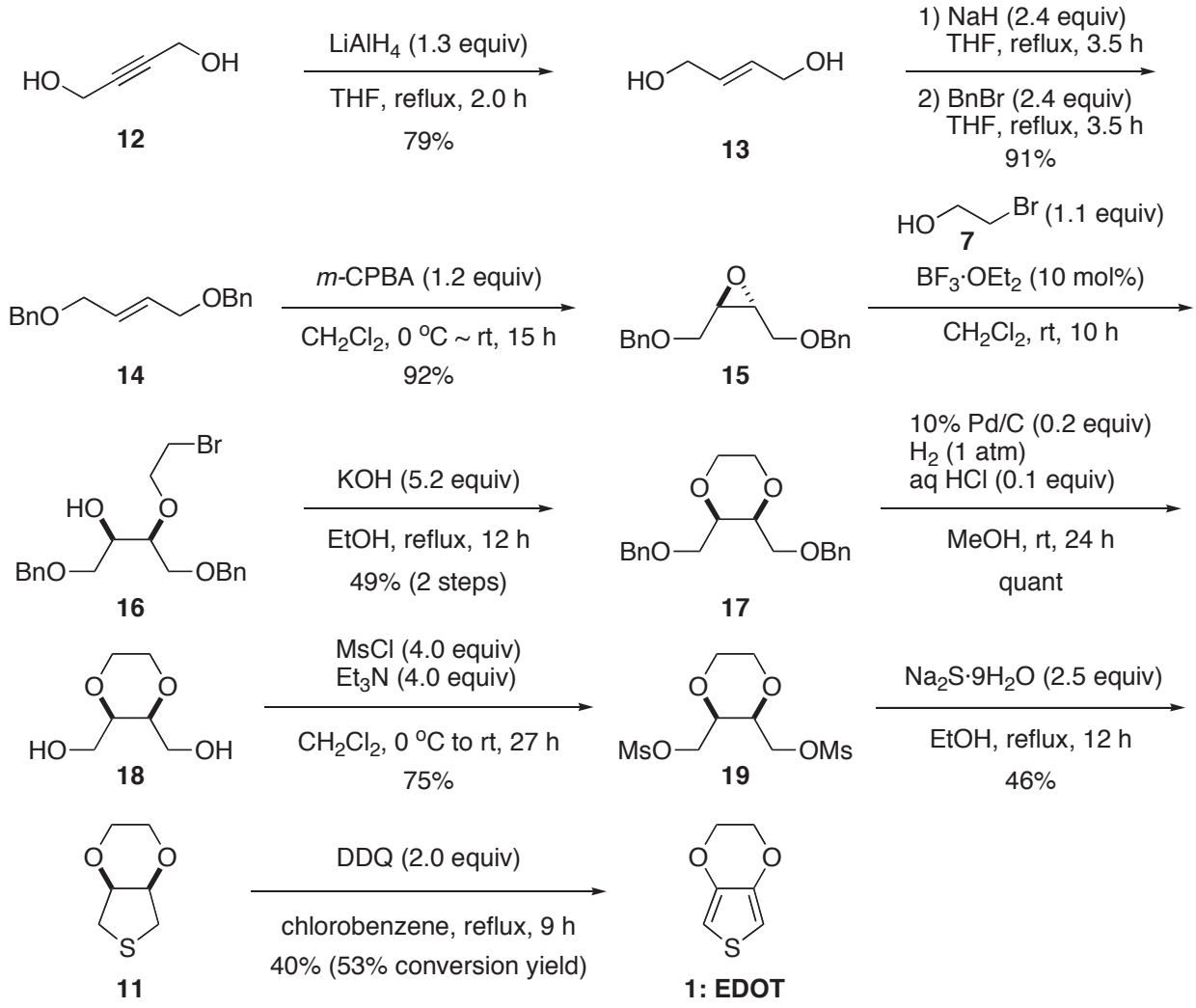
Entry	*m*-CPBA (equiv)	Time (h)	Yield (%)[a]
1	1.1	17	86
2	1.2	24	91
3	1.5	24	67
4	2.3	24	56

[a] Isolated yield.



Scheme 3. Synthesis of EDOT (**1**) via the *trans*-Tetrahydrothiophene Derivative (**2**)

BF_3·OEt_2 catalyzed ring-opening reaction of oxirane (**6**) with 2-bromoethanol (**7**) proceeded to give crude (2*R**,3*R**)-3-(2-chloroethoxy)-1,4-bis(benzyloxy)butan-2-ol (**5**),[7] and subsequent intramolecular etherification of the crude alcohol (**5**) using KOH as a base in EtOH under reflux gave 2,3-bis(benzyloxymethyl)-1,4-dioxane (**4**) in 67% yield. Debenzylation of **4** by hydrogenation gave (2*R**,3*R**)-2,3-bis(hydroxymethyl)-1,4-dioxane (**3**) in 96% yield,[8] which in turn was mesylated to give (2*R**,3*R**)-2,3-bis(methanesulfonyloxymethyl)-1,4-dioxane (**10**) in 92% yield. The reaction of the bismesylate (**10**) with sodium sulfide nonahydrate ($Na_2S·9H_2O$) gave (3*S**,4*S**)-tetrahydro-3,4-ethylenedioxythiophene (**2**) in 78% yield.[9] Finally, dehydrogenation of the tetrahydrothiophene derivative (**2**) using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave EDOT (**1**) in 21% yield (Scheme 3). However, the yield was not satisfied in the last dehydrogenation step. We next examined an alternative synthesis from *cis*-tetrahydrothiophene derivative (**11**). The *cis*-tetrahydrothiophene derivative (**11**) could be synthesized from (*E*)-but-2-ene-1,4-diol (**13**) instead of (*Z*)-but-2-ene-1,4-diol (**8**). Scheme 4 shows the synthetic route to the *cis*-derivative (**11**). Reduction of commercially available but-2-yne-1,4-diol (**12**) by $LiAlH_4$ gave (*E*)-but-2-ene-1,4-diol (**13**) in 79% yield.[10] The *cis*-tetrahydrothiophene derivative (**11**) was synthesized from (*E*)-but-2-ene-1,4-diol (**13**) in a similar manner to the *trans*-derivative (**2**). Dehydrogenation of the *cis*-derivative (**11**) using DDQ gave EDOT (**1**) in 40% yield (53% conversion yield) along with the recovered **11** in 23 % yield.



Scheme 4. Synthesis of EDOT (**1**) via the *cis*-Tetrahydrothiophene Derivative (**11**)

CONCLUSIONS

In conclusion, we have found a new synthetic route to 3,4-ethylenedioxythiophene (EDOT) via ring-opening of oxiranes (**6**) or (**15**) with 2-bromoethanol (**7**) followed by intramolecular etherification of bromo alcohols (**5**) or (**16**). The present method is an attractive synthetic route because several EDOT derivatives[11] can be synthesized using 2-bromo alcohol derivatives instead of 2-bromoethanol (**7**) in ring-opening of oxirane (**6**) or (**15**).

EXPERIMENTAL

General: Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL ECX-400 spectrometer (400 MHz) or a JEOL JNM α-500 spectrometer (500 MHz) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer (100 MHz) or a JEOL JNM α-500 spectrometer (126 MHz). Chemical shifts are reported in

δ units, parts per million from the central peak of $CDCl_3$ (δ 77.0) as an internal reference. High resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer. Purification of products was performed by column chromatography on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). All reactions were carried out under an argon atmosphere except for debenzylation of (2*R**,3*R**)-2,3-bis(benzyloxymethyl)-1,4-dioxane (**4**) by hydrogenation.

(*Z*)-1,4-Dibenzyloxybut-2-ene (9)[5]

Sodium hydride (11.0 g as a 60% dispersion in mineral oil, 272 mmol) was placed in a round-bottomed flask and the mineral oil was removed by washing with hexane (30 mL, 20 mL and 30 mL). A solution of (*Z*)-but-2-ene-1,4-diol (**8**) (10.0 g, 113 mmol) in THF (70 mL) was added to the flask at 0 ºC. The mixture was stirred under reflux for 6 h. Benzyl bromide (47.0 g, 272 mmol) was added to the mixture. The reaction mixture was stirred under reflux for 13 h and then cooled to room temperature. Water (200 mL) was added to quench the reaction. The phases were separated and the aqueous phase was extracted with Et_2O (100 mL x 2). The combined organic extracts were washed with sat. aqueous NH_4Cl (100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 8/1, as an eluent) to give (*Z*)-1,4-dibenzyloxybut-2-ene (**9**) (8.75 g, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.39 (m, 10H), 5.87-5.89 (m, 2H), 4.52 (s, 4H), 4.05 (dd, *J* = 1.4, 2.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 129.5, 128.4, 127.8, 127.6, 72.2, 65.8. IR (neat): 3087, 3063, 3028, 2855, 1496, 1454, 1383, 1361, 1329, 1247, 1203, 1090, 1028, 738, 670, 606 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{20}O_2$ 268.1463; [M^+]; found for 268. 1455.

(2*R,3*S**)-2,3-Bis((benzyloxy)methyl)oxirane (6)**[6]

m-CPBA (8.29 g as a 77% wt% solid, 37.0 mmol) in CH_2Cl_2 (70 ml) was added to a solution of (*Z*)-1,4-dibenzyloxybut-2-ene (**8**) (8.00 g, 29.8 mmol) in CH_2Cl_2 (30 mL) at 0 ºC. The reaction mixture was warmed to room temperature, stirred for 24 h, and then cooled to 0 ºC. The reaction mixture was filtered through a Celite pad to remove the precipitated *m*-chlorobenzoic acid and washed with sat. aqueous $NaHCO_3$ (100 mL), sat. aqueous $Na_2S_2O_3$ (100 mL), and brine (100 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 4/1, as an eluent) to give (2*R**,3*S**)-2,3-bis((benzyloxy)methyl)oxirane (**6**) (7.72 g, 91%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27-7.36 (m, 10H), 4.61 (d, *J* = 11.9 Hz, 2H), 4.51 (d, *J* = 11.9 Hz, 2H), 3.66-3.70 (m 2H), 3.50-3.55 (m, 2H), 3.24-3.27 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.7, 128.4,

127.7, 73.2, 68.0, 54.4. IR (neat): 3087, 3063, 3030, 2998, 2998, 2860, 1496, 1454, 1368, 1325, 1254, 1205, 1096, 1028, 991, 948, 907, 853, 820, 768, 737, 698, 607 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{20}O_3$ 284.1412; [M^+]; found for 284. 1410.

(2*R,3*R**)-2,3-Bis(benzyloxymethyl)-1,4-dioxane (4)**

$BF_3{\cdot}OEt_2$ (0.02 mL, 1 M in CH_2Cl_2, 0.02 mmol) was added to a mixture of (2*R**,3*S**)-2,3-bis((benzyloxy)methyl)oxirane (**6**) (60 mg, 0.21 mmol) and 2-bromoethanol (**7**) (30 mg, 0.23 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h and then concentrated in vacuo. To the residue including crude (2*R**,3*R**)-3-(2-bromoethoxy)-1,4-bis(benzyloxy)butan-2-ol (**5**) in EtOH (5 mL) was added a solution of KOH (12 mg, 0.21 mmol) in EtOH (5 mL) at room temperature. The reaction mixture was stirred under reflux for 6 h and then cooled to room temperature. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with EtOAc. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (*n*-Hex/EtOAc = 4/1, as an eluent) to give (2*R**,3*R**)-2,3-bis(benzyloxymethyl)-1,4-dioxane (**4**) (46.3 mg, 67%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22-7.34 (m, 10H), 4.54 (d, *J* = 12.2 Hz, 2H), 4.42 (d, *J* = 12.2 Hz, 2H), 3.62-3.80 (m, 6H), 3.50-3.55 (m 2H), 3.41-3.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.7, 128.2, 127.7, 127.5, 76.0, 73.4, 69.6, 66.7. IR (neat): 3064, 3029, 2997, 2859, 1496, 1454, 1367, 1326, 1253, 1204, 1096, 1028, 991, 948, 908, 849, 738, 698, 608 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{24}O_4$ 328.1675 [M^+]; found for 328.1672.

(2*R,3*R**)-2,3-Bis(hydroxymethyl)-1,4-dioxane (3)**

To 10% Pd/C (100 mg, 0.0940 mmol) was added a solution of (2*R**,3*R**)-2,3-bis(benzyloxymethyl)-1,4-dioxane (**4**) (1.55 g, 4.72 mmol) in MeOH (30 mL) and 0.1 M HCl (4.7 mL, 0.47 mmol). The mixture was stirred under H_2 (1 atm) at room temperature for 4 h. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with MeOH. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (EtOAc, as an eluent) to give (2*R**,3*R**)-2,3-bis(hydroxymethyl)-1,4-dioxane (**3**) (0.67 g, 96%) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51-3.90 (m, 10H), 3.15 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.8, 66.6, 62.5. IR (neat): 3416, 2961, 2919, 2861, 1449, 1371, 1267, 1120, 1078, 1009, 968, 908, 844, 790, 734, 650 cm^{-1}. HRMS (EI): calcd. for $C_6H_{12}O_4$ 148.0736 [M^+]; found for 148.0737.

(2*R,3*R**)-2,3-Bis(methanesulfonyloxymethyl)-1,4-dioxane (10)**

To a solution of (2*R**,3*R**)-2,3-bis(hydroxymethyl)-1,4-dioxane (**3**) (148 mg, 1.00 mmol) and Et_3N (399

mg, 3.94 mmol) in CH_2Cl_2 (5 mL) was added MsCl (459 mg, 4.01 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 5.5 h. Water (10 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 2/1, as an eluent) to give (2*R**,3*R**)-2,3-bis(methanesulfonyloxymethyl)-1,4-dioxane (**10**) (280 mg, 92%) as a white crystal.

Mp 103-104 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.33-4.39 (m, 4H), 3.71-3.91 (m, 6H), 3.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.7, 68.2, 66.7, 37.6. IR (KBr): 3025, 3014, 2965, 2953, 2935, 2875, 1452, 1350, 1289, 1249, 1173, 1126, 1088, 1043, 985, 920, 849, 816, 754, 743, 640 cm^{-1}. HRMS (EI): calcd. for $C_8H_{16}O_8S_2$ 304.0287 [M^+]; found for 304.0280.

(3*S,4*S**)- Tetrahydro-3,4-ethylenedioxythiophene (2)**

To (2*R**,3*R**)-2,3-bis(methanesulfonyloxymethyl)-1,4-dioxane (**10**) (36 mg, 0.12 mmol) was added DMF (3 mL) and sodium sulfide nonahydrate ($Na_2S{\cdot}9H_2O$) (87 mg, 0.36 mmol) at room temperature. The reaction mixture was stirred at 50 ºC for 17 h. H_2O (10 mL) was added to quench the reaction. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with EtOAc. The mixture was extracted with EtOAc (30 mL). The organic layers were washed with brine (30 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 2/1, as an eluent) to give (3*S**,4*S**)-tetrahydro-3,4-ethylenedioxythiophene (**2**) (13.5 mg, 78%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66-3.85 (m, 4H), 3.51-3.59 (m, 2H), 2.84-2.91 (m, 2H), 2.67-2.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.8, 66.4, 27.7. IR (neat): 2956, 2914, 2855, 1456, 1357, 1277, 1251, 1118, 1088, 985, 907, 875, 730, 629 cm^{-1}. HRMS (EI): calcd. for $C_6H_{10}O_2S$ 146.0402 [M^+]; found for 146. 0403.

EDOT (1)[12]

To DDQ (45 mg, 0.20 mmol) was added a solution of (3*S**,4*S**)-tetrahydro-3,4-ethylenedioxythiophene (**2**) (15 mg, 0.10 mmol) in chlorobenzene (5 mL) at room temperature. The mixture was stirred at 80 ºC for 6 h and then cooled to room temperature. 10% Aqueous sodium hydrogen sulfite (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 1/1, as an eluent) to give EDOT (**1**) (3.0 mg, 21%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (s, 2H), 4.19 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 99.5,

64.5. IR (neat): 3111, 2983, 2924, 2872, 1484, 1446, 1421, 1367, 1272, 1247, 1186, 1136, 1057, 1022, 934, 891, 860, 833, 765 cm^{-1}.

(*E*)-But-2-ene-1,4-diol (13)[10]

To a solution of $LiAlH_4$ (0.59 g, 15.5 mmol) in THF (50 mL) was added a solution of but-2-yne-1,4-diol (**12**) (1.02 g, 11.9 mmol) in THF (50 mL) at 0 ºC. The reaction mixture was stirred under reflux for 2 h and cooled to 0 ºC. 3 M NaOH was added slowly to the reaction mixture until no gas evolution was observed. The reaction mixture was then adjusted to a pH of 8; silica gel was added, and the solvent was removed in vacuo. The free-flowing product/silica gel mixture was loaded on the top of a prepacked silica gel column and flashed (*n*-Hex/EtOAc = 1/1, as an eluent) to give (*E*)-but-2-ene-1,4-diol **(13)** (0.83 g, 79%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89-5.91 (m, 2H), 4.17-4.19 (m, 4H), 1.63 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.5, 62.9. IR (neat): 3338, 2924, 2870, 1709, 1658, 1451, 1420, 1370, 1279, 1222, 1085, 991, 889, 769, 663 cm^{-1}. HRMS (EI): calcd. for $C_4H_8O_2$ 88.0524 [M^+]; found for 88.0525.

(*E*)-1,4-Dibenzyloxybut-2-ene (14)

Sodium hydride (2.01 g as a 60% dispersion in mineral oil, 50.2 mmol) was placed in a round-bottomed flask and the mineral oil was removed by washing with hexane (30 mL, 20 mL and 30 mL). A solution of (*E*)-2-butene-1,4-diol (**13**) (1.84 g, 20.9 mmol) in THF (30 mL) was added to the flask at 0 ºC. The mixture was stirred under reflux for 3.5 h. Benzyl bromide (8.59 g, 50.2 mmol) was added to the mixture. The reaction mixture was stirred under reflux for 3.5 h and then cooled to room temperature. Water (100 mL) was added to quench the reaction. The phases were separated and the aqueous phase was extracted with Et_2O (100 mL x 2). The combined organic extracts were washed with sat. aqueous NH_4Cl (100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 8/1, as an eluent) to give (*E*)-1,4-dibenzyloxybut-2-ene (**14**) (5.09 g, 91%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.36 (m, 10H), 5.78-5.80 (m, 2H), 4.49 (s, 4H), 4.06 (dd, *J* = 0.9, 2.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 129.5, 128.4, 127.7, 127.6, 72.2, 70.1. IR (neat): 3087, 3063, 3029, 2923, 2852, 1496, 1454, 1387, 1362, 1310, 1250, 1204, 1109, 1072, 1028, 970, 736, 697, 607 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{20}O_2$ 268.1463 [M^+]; found for 268.1474.

(2*R,3*R**)-2,3-Bis((benzyloxy)methyl)oxirane (15)**

m-CPBA (4.87 g as a 77% wt% solid, 21.7 mmol) in CH_2Cl_2 (50 mL) was added to a solution of (*E*)-1,4-dibenzyloxybut-2-ene (**14**) (5.05 g, 18.8 mmol) in CH_2Cl_2 (50 mL) at 0 ºC. The reaction mixture

was warmed to room temperature, stirred at room temperature for 15 h, and then cooled to 0 ºC. The reaction mixture was filtered through a Celite pad to remove the precipitated *m*-chlorobenzoic acid and washed with sat. aqueous $NaHCO_3$ (100 mL), sat. aqueous $Na_2S_2O_3$ (100 mL), and brine (100 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 4/1, as an eluent) to give (2*R**,3*R**)-2,3-bis((benzyloxy)methyl)oxirane (**15**) (4.94 g, 92%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.39 (m, 10H), 4.61 (d, *J* = 11.9 Hz, 2H), 4.55 (d, *J* = 11.9 Hz, 2H), 3.76 (dd, *J* = 2.8, 11.5 Hz, 2H), 3.51 (dd, *J* = 5.5, 11.5 Hz, 2H), 3.11-3.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 128.4, 128.2, 127.7, 73.3, 69.8, 54.4. IR (neat): 3087, 3063, 3030, 2998, 2858, 1496, 1454, 1366, 1315, 1241, 1207, 1107, 1028, 937, 906, 874, 737, 698, 608 cm^{-1}. $C_{18}H_{20}O_3$ 284.1412 [M^+]; found for 284.1405.

(2*R,3*S**)-2,3-Bis(benzyloxymethyl)-1,4-dioxane (17)**

BF_3·OEt_2 (0.02 mL, 1 M in CH_2Cl_2, 0.02 mmol) was added to a mixture of (2*R**,3*R**)-2,3-bis((benzyloxy)methyl)oxirane (**15**) (60 mg, 0.21 mmol) and 2-bromoethanol (**7**) (30 mg, 0.23 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 h and then concentrated in vacuo. To the residue including crude (2*R**,3*S**)-3-(2-bromoethoxy)-1,4-bis(benzyloxy)butan-2-ol (**16**) in EtOH (5 mL) was added a solution of KOH (60 mg, 1.1 mmol) in EtOH (5 mL) at room temperature. The reaction mixture was stirred under reflux for 12 h and then cooled to room temperature. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with EtOAc. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (*n*-Hex/EtOAc = 4/1, as an eluent) to give (2*R**,3*S**)-2,3-bis(benzyloxymethyl)-1,4-dioxane (**17**) (33.8 mg, 49%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.35 (m, 10H), 4.54 (d, *J* = 12.4 Hz, 2H), 4.50 (d, *J* = 12.4 Hz, 2H), 3.91-4.00 (m, 2H), 3.76-3.82 (m, 4H), 3.61-3.67 (m, 2H), 3.46-3.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 128.4, 127,7, 127.7, 74.0, 73.3, 67.2, 63.7. IR (neat): 3088, 3063, 3029, 2952, 2910, 2863, 1496, 1453, 1367, 1272, 1207, 1103, 1028, 909, 890, 737, 698, 610 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{24}O_4$ 328.1675 [M^+]; found for 328.1691.

(2*R,3*S**)-2,3-Bis(hydroxymethyl)-1,4-dioxane (18)**

To 10% Pd/C (194 mg, 0.182 mmol) was added a solution of (2*R**,3*S**)-2,3-bis(benzyloxymethyl)-1,4-dioxane (**17**) (2.99 g, 9.10 mmol) in MeOH (30 mL) and 0.1 M HCl (0.9 mL, 0.9 mmol). The mixture was stirred under H_2 (1 atm) at room temperature for 24 h. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with MeOH. The solvents were

evaporated in vacuo and then the residue was purified by chromatography on silica gel (EtOAc, as an eluent) to give (2*R**,3*S**)-2,3-bis(hydroxymethyl)-1,4-dioxane (**18**) (1.35 g, quant) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63-3.88 (m, 10H), 2.43 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.2, 63.7, 59.9. IR (neat): 3394, 2931, 2873, 1452, 1416, 1358, 1281, 1231, 1106, 1048, 1001, 953, 890, 862, 831, 795, 724, 675 cm^{-1}. HRMS (EI): calcd. for $C_6H_{12}O_4$ 148.0736 [M^+]; found for 148.0737.

(2*R,3*S**)-2,3-Bis(methanesulfonyloxymethyl)-1,4-dioxane (19)**

To a solution of (2*R**,3*S**)-2,3-bis(hydroxymethyl)-1,4-dioxane (**18**) (1.35g, 9.11 mmol) and Et_3N (3.70 g, 36.6 mmol) in CH_2Cl_2 (30 mL) was added MsCl (4.20 g, 36.7 mmol) at 0 ºC. The reaction mixture was warmed up to room temperature and then stirred at room temperature for 27 h. Water (100 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 2/1, as an eluent) to give (2*R**,3*S**)-2,3-bis(methanesulfonyloxymethyl)-1,4-dioxane (**19**) (2.08 g, 75%) as a white crystal.
Mp 109-112 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (dd, *J* = 7.3, 11.0 Hz, 2H), 4.29 (dd, *J* = 4.6, 11.0 Hz, 2H), 4.07-4.13 (m, 2H), 3.86-3.92 (m, 2H), 3.68-3.74 (m, 2H), 3.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 72.2, 65.4, 63.6, 37.8. IR (KBr): 3029, 2999, 2964, 2939, 2923, 2891, 2868, 1481, 1453, 1419, 1355, 1298, 1288, 1261, 1166, 1147, 1131, 1111, 1098, 1068, 1009, 987, 969, 912, 893, 874, 833, 811, 799, 766, 725 cm^{-1}. HRMS (EI): calcd. for $C_8H_{16}O_8S_2$ 304.0287 [M^+]; found for 304.0287.

(3*S,4*R**)-Tetrahydro-3,4-ethylenedioxythiophene (11)**

To (2*R**,3*S**)-2,3-bis(methanesulfonyloxymethyl)-1,4-dioxane (**19**) (2.08 g, 6.83 mmol) was added EtOH (40 mL) and sodium sulfide nonahydrate ($Na_2S{\cdot}9H_2O$) (4.13 g, 17.1 mmol) at room temperature. The reaction mixture was stirred under reflux for 12 h and then cooled to room temperature. The reaction mixture was filtered through a Celite pad. The Celite pad and the round-bottomed flask were rinsed with EtOAc. The mixture was extracted with EtOAc (50 mL). The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 2/1, as an eluent) to give (3*S**,4*R**)-tetrahydro-3,4-ethylenedioxythiophene (**11**) (0.46 g, 46%) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16-4.20 (m, 2H), 3.82-3.88 (m 2H), 3.55-3.62 (m, 2H), 3.04-3.08 (m, 2H), 2.84-2.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.4, 62.8, 29.2. IR (neat): 2944, 2865, 1441, 1347, 1291, 1274, 1252, 1215, 1181, 1105, 1087, 1058, 1033, 1006, 925, 904, 870, 819, 754, 675, 629 cm^{-1}. HRMS (EI): calcd. for $C_6H_{10}O_2S$ 146.0402 [M^+]; found for 146. 0402.

EDOT (1)

To DDQ (123 mg, 0.54 mmol) was added a solution of (3*S**,4*R**)-tetrahydro-3,4-ethylenedioxythiophene (**11**) (40.0 mg, 0.27 mmol) in chlorobenzene (5 mL) at room temperature. The mixture was stirred under reflux for 9 h and then cooled to room temperature. 10% Aqueous sodium hydrogen sulfite (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over sodium sulfate, and filtered. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-Hex/EtOAc = 9/1, as an eluent) to give EDOT (**1**) (15.3 mg, 40% (53% conversion yield)) as a pale yellow oil and the recovered (**11**) (9.1 mg, 23 %) as a yellow oil.

REFERENCES AND NOTES

1. For a review, see: L. Groenendaal, F. Jonas, D. Freitag, H. Pielartzik, and J. R. Reynolds, *Adv. Mater*., 2000, **12**, 481 and references therein.
2. Q. Pei, G. Zuccarello, M. Ahlskog, and O. Inganäs, *Polymer*, 1994, **35**, 1347.
3. (a) K. Zong, L. Madrigal, L. Groenendaal, and J. R. Reynolds, *Chem. Commun*., 2002, 2498. (b) D. Caras-Quintero, and P. Bäuerle, *Chem. Commun*., 2002, 2690.
4. Short step synthesis of EDOT via *p*-TsOH catalyzed transetherification of 3,4-dimethoxythiophene with ethylene glycol, see: F. von Kieseritzky, F. Allared, E. Dahlstedt, and J. Hellberg, *Tetrahedron Lett*., 2004, **45**, 6049.
5. C.-Y. Chuang, V. C. Vassar, Z. Ma, R. Geney, and I. Ojima, *Chirality*, 2002, **14**, 151.
6. A. Thurner, F. Faigl, L. Tóke, A. Mordini, M. Valacchi, G. Reginato, and G. Czira, *Tetrahedron*, 2001, **57**, 8173.
7. G. Prestat, C. Baylon, M.-P. Heck, and C. Mioskowski, *Tetrahedron Lett*., 2000, **41**, 3829.
8. J.-E. Goujon, D. Gueyrard, P. Compain, O. R. Martin, K. Ikeda, A. Kato, and N. Asano, *Bioorg. Med. Chem*., 2005, **13**, 2313.
9. J. Shiina, R. Obata, H. Tomoda, and S. Nishiyama, *Eur. J. Org. Chem*., 2006, 2362.
10. M. G. Organ, J. T. Cooper, L. R. Rogers, F. Soleymanzadeh, and T. Paul, *J. Org. Chem*., 2000, **65**, 7959.
11. J. L. Segura, R. Gómez, E. Reinold, and P. Bäuerle, *Org. Lett*., 2005, **7**, 2345.
12. ^{1}H NMR, ^{13}C NMR, and IR spectra of the synthetic and the commercially available EDOT (**1**) were identical.