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An Efficient Synthesis of (+)-Subersic Acid

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This paper describes a concise and practical route to (+)-subersic acid from naturally occurring (−)-Sclareol in 7 steps. The key step of this route relied on the cross coupling of the diterpene with the arene fragment using the arylation of allylic acetate followed by *β*-acetoxy elimination type Heck reaction.

Keywords (+)-subersic acid, (−)-Sclareol, cross coupling, Heck reaction

Introduction

(−)-Subersic acid, an inhibitor of human 15-lipoxygenase, was firstly isolated by Crews and co-workers from the Papua New Guinean sponge *Suberea sp*.[1] The absolute configuration of (−)-subersic acid was confirmed to be (5*R*, 10*R*) by Mori and co-workers through total synthesis.[2] While (+)-subersic acid was firstly synthesized by Pilar Basabe and co-workers as the enantiomer of (−)-subersic acid in 2003.[3] Later then, it was isolated by Andersen *et al*. in 2004 from the Indonesian marine sponge *Acanthodendrilla sp.* and reported to be a MAPKAP kinase 2 (MK2, IC_{50}=9.6 μmol/L) inhibitor involved in various inflammatory processes.[4]

In this paper, a short synthetic route to (+)-subersic acid is reported. It is easy to observe that the structure of (+)-subersic acid was constructed with a diterpene fragment which could be derived from naturally occurring (−)-Sclareol and an arene unit. Therefore, the key step of its synthesis lies in the cross coupling of these two fragments (Scheme 1).

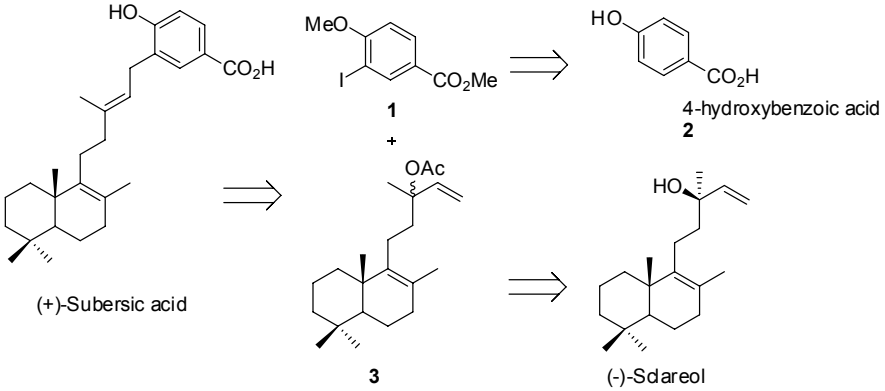
Experimental

General information

Unless stated otherwise, all reagents and solvents were obtained from commercial sources without further purification. Column chromatography was carried out on silica gel (300−400 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard. HRMS data were determined by EI ionization.

Methyl 3-iodo-4-methoxybenzoate (1) To a stirred solution of 4-hydroxybenzoic acid (5.0 g, 36 mmol) in ammonia (200 mL) was added iodine (9.2 g,

Scheme 1 Retrosynthesis of (+)-subersic acid



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36 mmol) and KI (29.4 g, 180 mmol) in water (100 mL) portionwise at room temperature. After the addition, the mixture was stirred overnight at the same temperature. Then, hydrochloric acid (2.0 mol/L) was added in to adjust the pH of the mixture to pH＝2.0 and white solid material precipitated. After filtration, the filtercake was washed with water. The white solid material was dried and then dissolved in DMF (100 mL). Then, K_2CO_3 (20.0 g, 72 mmol) was added to the mixture, and it was stirred for 1 h at room temperature before MeI (10.0 mL, 144 mmol) was added, and stirring was continued overnight. The mixture was diluted with water and extracted with ethyl acetate (120 mL×2). The organic layer was washed with water and then dried with anhydrous sodium sulfate. After the concentration under vacuum, the crude product was purified by column chromatography to give compound **1** (8.4 g, 79%) as white solid. m.p. 94.7－95.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (d, J＝2.0 Hz, 1H), 8.01 (dd, J＝8.4, 2.0 Hz, 1H), 6.83 (d, J＝8.8 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 161.2, 140.1, 131.2, 123.9, 109.5, 84.9, 56.1, 51.7; HRMS (EI) calcd for $C_9H_9O_3I$ 291.9596, found 291.9594.

4-((1*R*,2*R*,8*aS*)-2-Hydroxy-2,5,5,8*a*-tetramethyldecahydronaphthalen-1-yl)butan-2-one (5)[5] To a stirred solution of (–)-Sclareol (30.8 g, 0.1 mol) in acetone (500 mL) was added a mixture of $KMnO_4$ (55.3 g, 0.35 mol) and $MgSO_4$ (60.2 g, 0.5 mol) portionwise at 0 ℃. After the addition, the mixture was stirred overnight at room temperature. The solid material was removed by filtration. The filtrate was concentrated under reduced pressure to give compound **5** (25.8 g) which was used for the next step without further purification.

4-((8*aS*)-2,5,5,8*a*-Tetramethyl-3,4,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl)butan-2-one (6)[5] To a stirred solution of compound **5** (28.0 g, 0.1 mol) in toluene (2.0 L) was added iodine (1.3 g, 5.0 mmol). Then, the mixture was heated to 150 ℃ with Dean-Stark equipment for 3 h. Upon cooling, aqueous $Na_2S_2O_3$ was added to quench the reaction. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography to give compound **6** (23.6 g, 82% over two steps) as a yellow oil. $[\alpha]_D^{25}$ ＋74.5 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (t, J＝8.4 Hz, 2H), 2.25－2.33 (m, 1H), 2.16－2.19 (m, 1H), 2.14 (s, 3H), 1.91－2.02 (m, 2H), 1.78 (br, J＝12.4 Hz, 1H), 1.63－1.66 (m, 1H), 1.58－1.61 (m, 1H), 1.53 (s, 3H), 1.47－1.48 (m, 1H), 1.42－1.45 (m, 1H), 1.37－1.40 (m, 1H), 1.12－1.17 (m, 1H), 1.09 (d, J＝11.6 Hz, 1H), 0.96－1.05 (m, 1H), 0.88 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 139.2, 126.6, 52.0, 44.6, 41.7, 39.1, 36.9, 33.6, 33.3, 29.8, 21.7, 21.6, 19.9, 19.4, 19.0.

3-Methyl-5-((8*aS*)-2,5,5,8*a*-tetramethyl-3,4,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl)pent-1-en-3-ol (7) To a stirred solution of compound **6** (8.5 g, 32.4 mmol) in THF (500 mL) was added dropwise vinyl magnesium bromide (97.0 mL, 97 mmol, 1.0 mol/L in THF) at 0 ℃. After the addition, the mixture was stirred at room temperature for another 3 h. Then, water was added to quench the reaction. THF was removed under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography to give compound **7** (7.7 g, 82.3%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.89－5.97 (m, 1H), 5.20－5.24 (m, 1H), 5.05－5.08 (m, 1H), 1.77－2.10 (m, 5H), 1.57－1.70 (m, 4H), 1.32－1.57 (m, 7H), 1.29 (s, 3H), 1.08－1.19 (m, 3H), 0.93 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.1, 145.0, 140.1, 140.0, 125.8, 111.9, 111.8, 73.7, 52.0, 42.6, 41.9, 39.2, 37.2, 33.7, 33.5, 33.4, 27.7, 27.5, 22.2, 21.8, 20.2, 19.6, 19.2; HRMS (EI) calcd for $C_{20}H_{34}O$ 290.2610, found 290.2613.

3-Methyl-5-((8*aS*)-2,5,5,8*a*-tetramethyl-3,4,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl)pent-1-en-3-yl acetate (3) To the stirred solution of compound **7** (480 mg, 1.7 mmol) in *N*,*N*-dimethyl aniline (5 mL) and DCM (10 mL) was added dropwise acetyl chloride (0.7 mL, 10 mmol) at 0 ℃. Then, the mixture was heated to 50 ℃ and stirred overnight. Ethyl acetate was added to dilute the mixture after the starting material was consumed. The mixture was washed with hydrochloric acid (1.0 mol/L) until it turned to colorless. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography to give compound **3** (494 mg, 90%) as white solid. $[\alpha]_D^{24}$ ＋57.0 (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.99 (dd, J＝17.0, 11.5 Hz, 1H), 5.15－5.20 (m, 2H), 2.65 (d, J＝12.0 Hz, 1H), 2.05 (s, 3H), 1.69－2.12 (m, 5H), 1.55－1.68 (m, 4H), 1.31－1.54 (m, 6H), 1.30 (s, 3H), 1.07－1.20 (m, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 111.8 (111.7), 139.7 (139.6), 126.2, 113.1, 83.2 (83.1), 51.9, 41.8, 40.3, 39.1, 37.0, 33.7, 33.3, 23.3, 23.2, 22.2, 21.7, 20.2, 19.4, 19.1; HRMS (EI) calcd for $C_{22}H_{36}O_2$ 332.2715, found 332.2717.

Methyl 4-methoxy-3-(3-methyl-5-((4*aS*,8*aS*)-2,5,5,8a-tetramethyl-3,4,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl)pent-2-enyl)benzoate (8) To a solution of compound **3** (50 mg, 0.15 mmol) and compound **1** (60 mg, 0.2 mmol) in DMF (5.0 mL) in a sealed tube was added TBAC (63 mg, 0.23 mmol), $Pd(OAc)_2$ and triethylamine (0.2 mL, 1.2 mmol). Then, the mixture was sealed up and heated to 120 ℃ for 12 h. Upon cooling, the mixture was filtered to remove the solid material. The filtrate was washed with water and dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography to give compound **8** (23 mg, mixture of E∶Z＝1∶1 36.2%, $[\alpha]_D^{25}$ ＋22.0 (c 1.31, $CHCl_3$)) as a colorless oil in which small amount of sample was separated by

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preparative chromatography to run a ^{1}H NMR for identification propose. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, J=8.8, 22 Hz, 1H), 7.83 (d, J=2.0 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 5.31 (t, J=7.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.33 (d, J=8 Hz, 2H), 1.76−2.16 (m, 8H), 1.73 (s, 3H), 1.61−1.72 (m, 2H), 1.58 (s, 3H), 1.34−1.50 (m, 4H), 1.10−1.30 (m, 4H), 0.94 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H). HRMS (EI) calcd for $C_{29}H_{42}O_3$ 438.3134, found 438.3129.

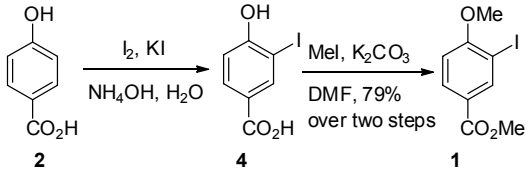
Methyl-4-hydroxy-3-((*E*)-3-methyl-5-((4*aS*,8*aS*)-2,5,5,8*a*-tetramethyl-3,4,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl)pent-2-enyl)benzoate (9) The mixture of compound **8** (200 mg, 0.45 mmol), PhSH (0.05 mL, 0.45 mmol) and K_2CO_3 (3.2 mg, 0.02 mmol) in NMP (5.0 mL) was heated to reflux for 1 h. Upon cooling, ethyl acetate (20.0 mL) was added in. Then, the mixture was washed with water and the organic layer was dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was further purified by preparative chromatography to give compound ***E*-9** (78 mg, 40%) as colorless oil. $[\alpha]_D^{26}$ +19.9 (c 1.2, $CHCl_3$); ^{1}H NMR (400 MHz , $CDCl_3$) δ: 7.80−7.83 (m, 2H), 6.84 (d, J=8.2 Hz, 1H), 6.10 (brs, 1H), 5.34 (t, J=7.0 Hz, 1H), 3.88 (s, 3H), 3.39 (d, J=7.1 Hz, 2H), 1.78−2.16 (m, 7H), 1.81 (s, 3H), 1.61−1.69 (m, 2H), 1.27 (s, 3H), 1.36−1.50 (m, 3H), 1.10−1.20 (m, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 158.9, 140.3 (2C), 132.0, 129.8, 127.0, 126.2, 122.5, 120.4, 115.7, 52.0 (2C), 41.9, 40.6, 39.2, 37.2, 33.8, 33.5 (2C), 29.6, 27.2, 21.8, 20.3, 19.6, 19.2 (2C), 16.5; HRMS (EI) calcd for $C_{28}H_{40}O_3$ 424.2977, found 424.2976.

(+)-Subersic acid To a stirred solution of ***E*-9** (595 mg, 1.4 mmol) in MeOH (30.0 mL) and water (10.0 mL) was added NaOH (944 mg, 16.8 mmol). Then, the mixture was heated to reflux for 5 h. The mixture was diluted with ethyl acetate and acidified to pH=5.0 with hydrochloric acid (1.0 mol/L). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and concentration, the crude product was further separated by flash column to give a colorless amorphous solid (+)-subersic acid (513 mg, 89%). $[\alpha]_D^{20}$ +49.0 (c 0.78, $CHCl_3$) [Lit[3]. $[\alpha]_D^{20}$ +45.0 (c 0.78, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (s, 1H), 7.89 (d, J=2.0 Hz, 1H), 6.86 (d, J=8.8 Hz 1H), 5.35 (t, J=7.0 Hz, 1H), 3.42 (d, J=7.2 Hz, 2H), 2.17−1.91 (m, 7H), 1.82 (s, 3H), 1.70−1.62 (m, 2H), 1.57 (s, 3H), 1.50−1.36 (m, 3H), 1.20−1.10 (m, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$) δ: 171.7, 159.7, 140.7, 140.3, 132.7, 130.6, 127.0, 126.2, 121.8, 120.3, 115.9, 52.1 (2C), 42.0, 40.6, 39.2, 37.2, 33.8, 33.5 (2C), 29.7, 27.2, 21.9, 20.3, 19.7, 19.2(2C), 16.5; HRMS-EI calcd for $C_{27}H_{38}O_3$ 410.2811, found 410.2816.

Results and Discussion

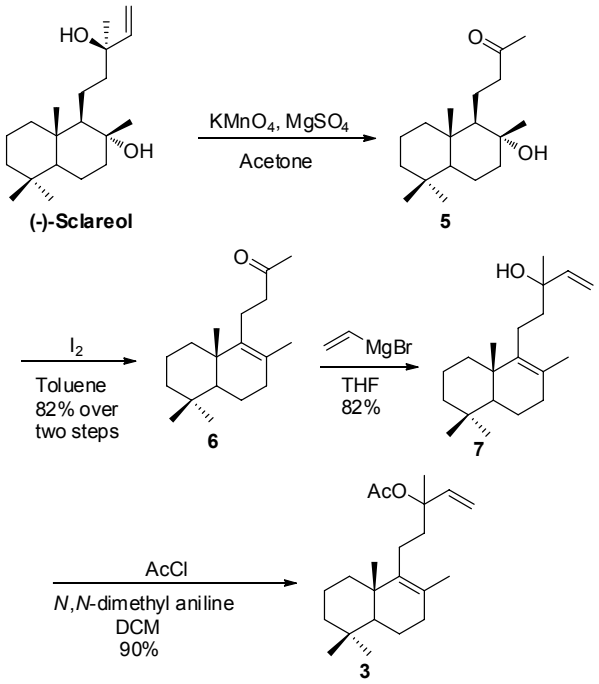
The synthesis of the arene fragment was summarized in Scheme 2. The starting 4-hydroxybenzoic acid **1** was iodinated to give **4** which was then treated with methyl iodide and potassium carbonate to furnish the arene intermediate **3** with 79% overall yield (Scheme 2).

Scheme 2 Construction of the arene fragment



Then, attentions were focused on the construction of the diterpene fragment. Oxidized by $KMnO_4$, (−)-Sclareol was transformed to the ketone **5** which was dehydrated to **6** in the presence of a catalytic amount of I_2.[5] Diterpene fragment **3** was easily obtained by Grignard addition of vinylmagnesium bromide to **6** followed by acetylation of its free hydroxyl group (Scheme 3).

Scheme 3 The construction of the diterpene fragment



With these two fragments in hand, the key issue became the cross coupling reaction. There were lots of reports about the arylation of allylic acetates followed by β-acetoxy elimination type Heck reaction which could be used to construct the skeleton of (+)-subersic acid.[6] Therefore, various conditions were screened and finally $Pd(OAc)_2$ was chosen as the proper catalyst in DMF to give a higher yield of coupling product with E : Z=1 : 1 (Table 1).

Finally, the protecting groups of the arene were removed by PhSH and NaOH to give pure (+)-subersic acid in which the characteristic data were identical to the previously reported (Scheme 4).[3,7]

Scheme 4 Synthesis towards (+)-subersic acid

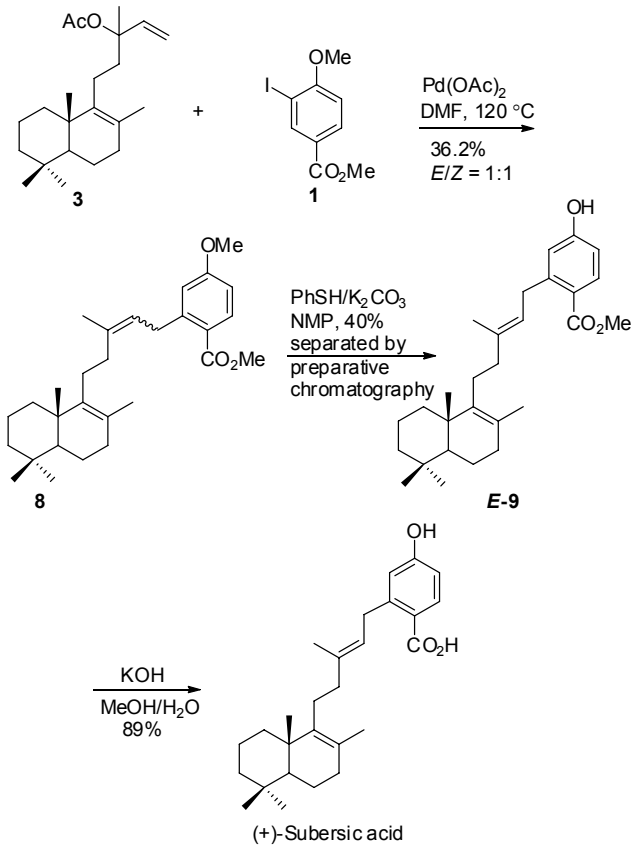


Table 1 Screening for the cross coupling reaction

Entry	Cat.	Solvent	*T*/℃	Yield[a]/%
1	$Pd(OAc)_2$	MeCN	120	34.1
2	Pd/C	MeCN	120	18.8
3	$PdCl_2$	MeCN	120	21.1
4	$Pd_2(dba)_3$	MeCN	120	8.2
5	$Pd(PPh_3)_4$	MeCN	120	3.0
6	$Pd_2(dba)_3{\cdot}CHCl_3$	MeCN	120	12.9
7	$PdCl_2(MeCN)_2$	MeCN	120	8.9
8	**$Pd(OAc)_2$**	**DMF**	**120**	**36.2**
9	$Pd(OAc)_2$	DMSO	120	20.4
10	$Pd(OAc)_2$	DMF	150	13.1
11	$Pd(OAc)_2$	DMF	100	10.5

[a] Isolated yields, $E:Z=1:1$.

Conclusions

In summary, (+)-subersic acid was synthesized from (−)-Sclareol in 7 steps. The key point of the route relied on the cross coupling of the diterpene with the arene fragment using the arylation of allylic acetates followed by *β*-acetoxy elimination type Heck reaction. Although the stereoselectivity of *E*/*Z* isomer was not resolved, this paper provided a convenient route to (+)-subersic acid as well as its derivatives.

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