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Discokiolide B의 합성에 관한 연구

金洪碩* · 金相和 · 李周泳
경북대학교 공과대학 공업화학과
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Synthetic Studies on Discokiolide B

Hong-Seok Kim*, Sang Hwa Kim, and Ju-Young Lee
Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701, Korea
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요 약. 해양천연물 Discokiolide B의 옥사졸 골격인 discokiic acid **1**을 합성하였다. 2[2′-(4-Phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(**4a**)와 methyl propionate의 리튬 enolate와의 알돌반응으로부터 discokiic acid methyl ester를 합성하였다. 중요한 반응중간체인 2[2′-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(**4a**)는 디아조 말론알데히드와 니트릴을 로듐촉매하에서 반응시켜 얻었다. Discokiic acid의 오른쪽 측쇄 부분인 3-hydroxy-2-methyl 프로판산 부분의 상대적인 입체화학을 ^{1}H와 ^{13}C 핵자기공명 데이터에 근거하여 결정하였다.

ABSTRACT. A synthesis of the oxazole skeleton of discokiolide B, represented by discokiic acid **1**, is described. Aldol condensation of 2[2′-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(**4a**) with lithium enolate of methyl propionate provided the discokiic acid methyl ester. The key intermediate 2[2′-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(**4a**) has been synthesized from the rhodium-catalyzed cycloaddition of diazomalonaldehyde with nitrile. The relative stereochemistry of the 3-hydroxy-2-methylpropanoate unit of discokiic acid was assigned on the basis of ^{1}H and ^{13}C NMR data.

INTRODUCTION

Discokiolide B is a novel cytotoxic cyclic depsipeptide which was recently isolated from the marine sponge *Discodermia kiiensis*.[1] It shows a potent proliferation effect *in vitro*. Discokiolide B attracted our synthetic interest because it represents a new class of cyclic peptide, on which contains a unique oxazole ring system in its skeleton. Our retrosynthetic analysis of discokiolide B is depicted in *Scheme* **1**. We planned to construct the oxazole moiety via dirhodium tetraacetate-catalyzed decomposition of α-diazo-β-dicarbonyl compounds in the presence of nitrile.

α-Diazo-β-dicarbonyl compounds have found great utility in organic synthesis.[2] Among the diazocarbonyl compounds, diazomalonaldehyde, ethyl α-formyldiazoacetate, and ethyl diazomalonate have been used in oxazole synthesis.[3]

Herein we describe our investigation on the construction of the oxazole skeleton of discokiolide B.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover melting point apparatus, and are un-

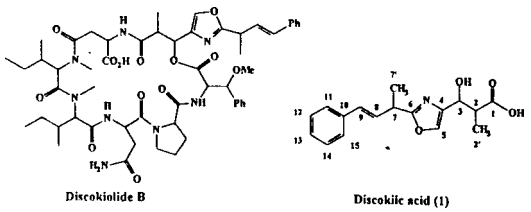


Fig. 1.

corrected. IR spectra were obtained on a Matton GL-6030E spectrophotometer using KBr pellets or thin film on NaCl. The ^1H and ^{13}C NMR spectra were measured on either Bruker AM-300 or Varian Unity Plus-300 instruments, and unless otherwise noted all NMR were performed in $CDCl_3$ solution. The chemical shifts of ^1H NMR spectra (300.1 MHz) are given in ppm downfield of internal TMS with coupling constants in hertz and assignments of ^{13}C NMR spectra (75.5 MHz) were made from DEPT, COSY, and comparison with spectra of similar compounds. The low resolution mass spectra were recorded on a Shimadzu QP-1000 spectrometer with electron energy of 20 or 70 eV and direct sample introduction. All reactions were performed under an atmosphere of argon. Solvents were dried and distilled following standard procedures.[4] Solutions were dried over anhydrous sodium sulfate. *trans*-4-Phenyl-3-buten-2-one, sodium borohydride, cerium(III) chloride heptahydrate, iodomethane, sodium hydride, methyl propionate, and dirhodium(II) tetraacetate were purchased from Aldrich and used as received. 2-Phenyl-1,3-oxazole-4-carboxaldehyde(**4d**),[3l] trimethylsilyl cyanide,[5] triphenylmethyl perchlorate,[6] diazomalonaldehyde(**2a**),[7] ethyl α-formyldiazoacetate (**2b**),[8] ethyl diazomalonate(**2c**)[9] were prepared according to the known procedure.

***trans*-4-Phenyl-3-buten-2-ol.**[10] To a stirred solution of $NaBH_4$(1.29 g, 34.1 mmol) in 30 mL of methanol was added $CeCl_3 \cdot 7H_2O$(40 mg) in an ice bath, and then trans-4-phenyl-3-buten-2-one (4.99 g, 33.4 mmol) was added. The resulting solution was stirred for 2 hr at room temperature. After removal of solvent under reduced pressure, extracted with ethyl acetate, dried, evaporated to dryness. The residue was chromatographed on silica gel column, eluting with ethyl acetate/hexane (1 : 4), to give 4.52 g(89%) of *trans*-4-phenyl-3-buten-2-ol as colorless oil: IR(neat) 3376(OH), 3030, 2974, 2926, 1665(C=C), 1493, 1369, 1264, 1139, 1061, 969 cm $^{-1}$; ^1H NMR δ 7.36~7.17(m, 5H, Ar-H), 6.53(d, 1H, J=15.9 Hz, C_6H_5CH=), 6.23(dd, 1H, J=6.3 and 15.9 Hz, C_6H_5CH=C*H*-), 4.43(dq, 1H, J=6.3 and 6.5 Hz, CH_3CH(OH)-), 2.22(bs, 1H, OH), 1.34(d, 3H, J=6.5 Hz, CH_3); MS(m/z) 148(M^+, 42), 133(21), 115(22), 105(74), 91(46), 77(35), 45(base).

***trans*-3-Methoxy-1-phenylbutene.**[11] To a solution of 5% NaH(1.62 g, 67.0 mmol) in 50 mL of dried diethyl ether was added *trans*-4-phenyl-3-buten-2-ol(7.68 g, 51.8 mmol) in 15 mL of dried diethyl ether. The mixture was refluxed for 1 hr and cooled to room temperature, then was added portionwise 5.16 mL(82.9 mmol) of CH_3I. The resulting solution was refluxed for 8 hr. After the reaction was completed, 50 mL of water was added and the solution was extracted twice with 30 mL portions of diethyl ether. The combined organic extracts were dried, concentrated in vacuo and the crude product was purified by flash chromatography, eluting with 10% ethyl acetate in hexane, to produce 7.14 g(85%) of *trans*-3-methoxy-1-phenylbutene as yellow oil: IR(neat) 3287, 3212, 3118, 2924, 2859, 1718(C=C), 1597, 1456, 1263, 1079 cm $^{-1}$; ^1H NMR δ 7.41~7.21(m, 5H, Ar-H), 6.53(d, 1H, J=16.0 Hz, C_6H_5CH=), 6.09(dd, 1H, J=7.6 and 16.0 Hz, C_6H_5CH=C*H*-), 3.89(dq, 1H, J=6.3 and 7.6 Hz, CH_3CH(OCH_3)-), 3.32(s, 1H, OCH_3), 1.33(d, 3H, J=6.3 Hz, CH_3); MS(m/z) 162(M^+, 12), 147 (22), 131(11), 91(29), 45(base).

***trans*-4-Phenyl-3-buten-2-nitrile(3).**[5] To a solution of *trans*-3-methoxy-1-phenylbutene(921 mg, 5.68 mmol) and trimethylsilyl cyanide(845 mg, 8.52 mmol) in 25 mL of CH_2Cl_2 was added triphenylmethyl perchlorate(44 mg, 0.42 mmol) for 30 min at −20 ℃. The resulting solution was stirred for 30 min at room temperature, then solvent was removed under reduced pressure. The residue was purified by flash chromatography, eluting with 5% ethyl acetate in hexane, to give 514 mg(58%) of **3** as yellow oil: IR(neat) 3033, 2991, 2242(CN), 1598, 1493, 1451, 1327, 1131, 1069, 969, 749, 695 cm $^{-1}$; ^1H NMR δ 7.38~7.23(m, 5H, Ar-H), 6.71(d, 1H, J=15.9 Hz, C_6H_5CH=), 6.04(dd, 1H, J=6.1 and 15.9 Hz, C_6H_5CH=C*H*-), 3.47(dq, 1H, J=6.1 and 7.2 Hz, CH_3CH(CN)-), 1.49(d, 3H, J=7.3 Hz, CH_3); MS(m/z) 157(M^+, 84), 156(base), 142(43), 129(23), 91(27).

2[2'-(4-Phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(4a). To a solution of $Rh_2(OAc)_4$(10

mg, 0.02 mmol), **3**(345 mg, 2.20 mmol) in 3 mL of fluorobenzene was added a solution of diazomalonaldehyde(**2a**, 323 mg, 3.30 mmol) in 5 mL of fluorobenzene with syringe pump for 10 hr at 80 ℃. After the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane(1 : 4), to give 95 mg(19%) of **4a** as white solid.: mp 66~68 ℃(Et_2O); IR(KBr) 3118, 3079, 3029, 2994, 2940, 1675(C=O), 1582, 1451, 1393, 1115, 972, 791, 741, 691 cm^{-1}; ^1H NMR δ 9.93(s, 1H, -C*H*O), 9.19 (s, 1H, H-5), 7.38~7.23(m, 5H, Ph-H), 6.54(d, 1H, J=15.9 Hz, C_6H_5CH=), 6.33(dd, 1H, J=7.5 and 15.9 Hz, C_6H_5CH=C*H*-), 3.91(dq, 1H, J=7.0 and 7.5 Hz, C_6H_5CH=CHC*H*(CH_3)-), 1.59(d, 3H, J=7.0 Hz, C*H*$_3$); ^{13}C NMR δ 184.0(C-3), 168.0(C-6), 144.2(C-5), 140.9(C-4), 136.5(C-10), 131.8(C-13), 128.6(C-11, 15), 128.5(C-9), 127.8(C-8), 126.4(C-12, 14), 37.1 (C-7), 18.5(C-7'); MS(m/z) 227(M^+, 58), 210(8), 156(12), 142(22), 125(base), 115(56), 91(53).

4-Carbethoxy-2[2'-(4-phenyl-3-butenyl)]-1,3-oxazole(4b). To a stirred solution of $Rh_2(OAc)_4$(10 mg, 0.02 mmol), **3**(345 mg, 2.20 mmol) in 3 mL of fluorobenzene was added a solution of ethyl α-formyldiazoacetate(**2b**, 409 mg, 3.30 mmol) in 5 mL of fluorobenzene with syringe pump for 8 hr at 80 ℃. After the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane(1 : 4) to give 125 mg(21%) of **4b** as yellow oil: IR(neat) 2982, 2937, 1736(C=O), 1579, 1449, 1370, 1314, 1108, 1022 cm^{-1}; ^1H NMR δ 8.16(s, 1H, H-5), 7.38~7.22(m, 5H, Ar-H), 6.52(d, 1H, J= 15.9 Hz, C_6H_5CH=), 6.34(dd, 1H, J=7.5 and 15.9 Hz, C_6H_5CH=C*H*-), 4.39(q, 2H, J=7.1 Hz, -OC*H*$_2$ CH_3), 3.92(dq, 1H, J=7.0 and 7.5 Hz, C_6H_5CH= CHC*H*(CH_3)-), 1.59(d, 3H, J=7.0 Hz, C_6H_5CH= CHCH(C*H*$_3$)-), 1.38(t, 3H, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR δ 167.2(C-3), 161.3(C-6), 143.7(C-5), 136.5 (C-10), 133.4(C-4), 131.5(C-9), 128.8(C-11, 15), 128.5(C-8), 127.6(C-13), 126.3(C-12, 14), 61.1(-OCH_2-CH_3), 37.2(C-7), 18.5(C-7'), 14.2(-OCH_2CH_3); MS (m/z) 271(M^+, 67), 197(38), 169(base), 156(35), 141 (20), 131(30), 123(51), 115(58), 105(48), 91(17).

4-Carbethoxy-5-ethoxy-2[2'-(4-phenyl-3-butenyl)]-1,3-oxazole(4c). Using the same procedure, from $Rh_2(OAc)_4$(10 mg, 0.02 mmol), **3**(345 mg, 2.20 mmol), and ethyl diazomalonate(**2c**, 613 mg, 3.30 mmol) was obtained 173 mg(25%) of **4c** as yellow oil(silica gel chromatography, eluting with ethyl acetate/hexane, 1 : 4): IR(neat) 2981, 2933, 1743 (C=O), 1447, 1369, 1288, 1228, 1094, 1023 cm^{-1}; ^1H NMR δ 7.37~7.22(m, 5H, Ar-H), 6.49(d, 1H, J=15.9 Hz, C_6H_5CH=), 6.29(dd, 1H, J=7.5 and 15.9 Hz, C_6H_5CH=C*H*-), 4.46(q, 2H, J=7.0 Hz, OCH_2 CH_3), 4.36(q, 2H, J=7.2 Hz, -$CO_2CH_2CH_3$), 3.76(dq, 1H, J=7.5 and 7.0 Hz, C_6H_5CH=CH-C*H*(CH_3)-), 1.53(d, 3H, J=7.0 Hz, C_6H_5CH=CHCH(C*H*$_3$)-), 1.45 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.37(t, 3H, J=7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ 161.6(C-3), 161.3(C-6), 155.7(C-5), 136.7(C-10), 131.3(C-9), 128.9(C-11, 15), 128.5(C-8), 127.6(C-13), 126.3(C-12, 14), 69.9 (OCH_2CH_3), 60.5($CO_2CH_2CH_3$), 37.2(C-7), 18.2(C-7'), 14.9(OCH_2CH_3), 14.4($CO_2CH_2CH_3$); MS(m/z) 315 (M^+, 61), 270(11), 242(21), 213(base), 197(21), 185 (14), 167(12), 130(11), 129(19), 123(11), 115(51), 105 (21), 91(12).

2-Phenyl-1,3-oxazole-4-carboxaldehyde(4d). This compound was prepared by the literature method.[3f]

***syn*-Methyl 3-[2'-phenyl-1,3-oxazole-4'-yl]-2-methyl-3-hydroxypropionate(5), and *anti*-methyl 3-[2'-phenyl-1,3-oxazole-4'-yl]-2-methyl-3-hydroxypropionate(6).** In a 25 mL flask, 2M THF solution of LDA(0.15 mL, 0.3 mmol) was dissolved in 3 mL of THF, cooled to −78 ℃ and treated with methyl propionate(28 mg, 0.3 mmol). After 45 min, a solution of 2-phenyl-1,3-oxazole-4-carboxaldehyde(**4d**, 40 mg, 0.23 mmol) in 2 mL of THF was added slowly. The resulting solution was stirred for 30 min, and the reaction was quenched with saturated NH_4Cl solution. The resulting mixture was extracted with ethyl acetate, dried, and evaporated to dryness. The residue was purified by medium-pressure liquid chromatography(MPLC) with an FMI pump on Merck LiChroprep Si 60 (40~63 μm) column, eluting with 10% ethyl acetate in hexane, to give **5**(24 mg, 40%) and **6**(20

mg, 33%).

Compound **5**: colorless oil; IR(neat) 3459(OH), 3091, 2924, 1731(C=O), 1551, 1450, 1200, 1061 cm^{-1}; ^{1}H NMR δ 8.04~7.99(m, 2H, H-8, 12), 7.65 (s, 1H, H-5), 7.46~7.44(m, 3H, H-9, 10, 11), 5.15 (dd, 2H, J=3.9 and 5.1 Hz, H-3), 3.74(s, 3H, OCH_3), 3.28(d, 1H, J=5.1 Hz, OH), 3.10(dq, 1H, J=3.9 and 7.2 Hz, H-2), 1.21(d, 3H, J=7.2 Hz, H-2'); ^{13}C NMR δ 176.1(C-1), 161.7(C-6), 142.5(C-5), 135.3 (C-4), 130.4(C-7), 128.7(C-9, 11), 127.4(C-10), 126.4 (C-8, 12), 68.3(C-3), 51.9(C-1'), 43.8(C-2), 10.9(C-2'); MS(m/z) 261(M$^+$, 20), 260(10), 201(24), 174(base), 118(88), 105(60), 91(36), 77(76).

Compound **6**: 121~121.5 ℃(Et_2O/hexane); IR (KBr) 3478(OH), 3113, 2955, 2922, 2854, 1707(C=O), 1446, 1377, 1251, 1174, 1024 cm^{-1}; ^{1}H NMR δ 8.04~8.00(m, 2H, H-8, 12), 7.64(s, 1H, H-5), 7.46~7.43(m, 3H, H-9, 10, 11), 4.81(dd, 1H, J=7.2 and 7.2 Hz, H-3), 3.72(s, 3H, OCH_3), 3.55(d, 1H, J=7.2 Hz, OH), 3.14(dq, 1H, J=7.2 and 7.2 Hz, H-2), 1.22 (d, 3H, J=7.2 Hz, H-2'); ^{13}C NMR δ 176.0(C-1), 161.9(C-6), 142.7(C-5), 135.2(C-4), 130.6(C-7), 128.7 (C-9, 11), 127.3(C-10), 126.5(C-8, 12), 69.3(C-3), 51.9(C-1'), 44.6(C-2), 14.2(C-2'); MS(m/z) 261(M$^+$, 21), 260(19), 202(15), 174(base), 118(52), 91(26), 77 (32).

Discokiic acid methyl ester. In a 25 mL flask, 1M hexane solution of lithium bis(trimethylsilyl) amide(0.18 mL, 0.18 mmol) was dissolved in 2 mL of THF, cooled to −78 ℃ and treated with methyl propionate(13 mg, 0.15 mmol). After 45 min, 2[2'-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde(**4a**, 14 mg, 0.06 mmol) was dissolved in 2 mL of THF and added slowly. The resulting solution was stirred for 30 min, and the reaction was quenched with saturated NH_4Cl solution. The resulting mixture was extracted with ethyl acetate, dried, and evaporated to dryness. The residue was purified by MPLC with an FMI pump on Merck LiChroprep Si 60(40~63 μm) column, eluting with 10% ethyl acetate in hexane, to give **7**(6 mg, 31%) and **8**(3 mg, 16%).

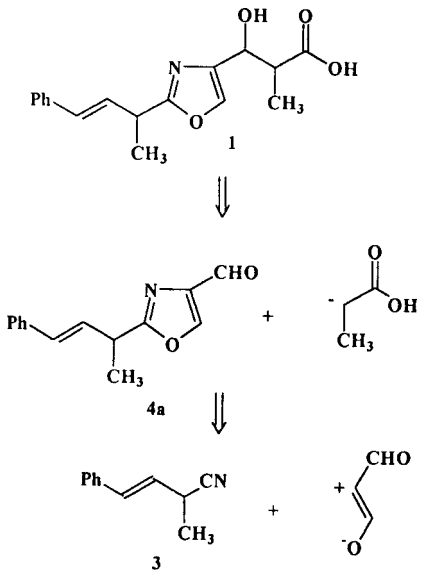
Compound **7**: colorless oil; IR(neat) 3428(OH), 3028, 2980, 2939, 1734(C=O), 1562, 1454, 1266, 1203, 1093, 1067, 967 cm^{-1}; ^{1}H NMR δ 7.52(d, 1H, J=1.2 Hz, H-5), 7.35(m, 1H, H-11, 15), 7.30(m, 1H, H-12, 14), 7.26(m, 1H, H-13), 6.48(d, 1H, J=15.6 Hz, H-19), 6.34(dd, 1H, J=15.9 and 7.5 Hz, H-8), 5.05(dd, 1H, J=4.2 and 1.2 Hz, H-3), 3.82(qd, 1H, J=7.5 and 7.2 Hz, H-7), 3.71(s, 3H, OCH_3), 3.01(qd, 1H, J=7.2 and 4.2 Hz, H-2), 1.52(d, 3H, J=7.2 Hz, 7-CH_3), 1.17(d, 3H, J=7.2 Hz, 2-CH_3); ^{13}C NMR δ 176.1(C-1), 166.6(C-6), 140.1(C-5), 136.7(C-10), 135.1(C-4), 131.0(C-9), 128.9(C-8), 128.5(C-12, 14), 127.6(C-13), 126.3(C-11, 15), 68.2(C-3), 52.0(-OCH_3), 43.8(C-2), 37.2(C-7), 18.7(7-Me), 11.1(2-Me); MS (m/z) 315(M$^+$, 73), 256(18), 239(23), 228(50), 213 (20), 195(30), 163(16), 131(base), 129(27), 115(43), 105(12), 91(96); R_f: 0.67(1 : 1 EtOAc : hexane).

Compound **8**: colorless oil; IR(neat) 3381(OH), 2931, 1735(C=O), 1570, 1450, 1375, 1260, 1120, 1169, 1035 cm^{-1}; ^{1}H NMR δ 7.52(d, 1H, J=0.9 Hz, H-5), 7.35(m, 1H, H-11, 15), 7.30(m, 1H, H-12, 14), 7.26(m, 1H, H-13), 6.48(d, 1H, J=15.9 Hz, H-9), 6.36(dd, 1H, J=15.9 and 7.2 Hz, H-8), 4.73(dd, 1H, J=7.2 and 7.2 Hz, H-3), 3.83(qd, 1H, J=7.2 and 7.2 Hz, H-7), 3.71(s, 3H, OCH_3), 3.06(qd, 1H, J=7.2 and 7.2 Hz, H-2), 1.53(d, 3H, J=7.2 Hz, 7'-CH_3), 1.18(d, 3H, J=7.2 Hz, 2-CH_3); MS(m/z) 315(M$^+$, 86), 314(13), 256(12), 239(17), 228(53), 213(17), 195 (41), 163(15), 131(base), 129(25), 115(39), 91(77); R_f: 0.58(1 : 1 EtOAc : hexane).

RESULTS AND DISCUSSION

Previous work on the transition metal catalyzed reaction of diazomalonaldehyde with nitriles showed that dirhodium tetraacetate gives 2-substituted-1,3-oxazole-4-carboxaldehydes in good yields.[3] Application of this process to the synthesis of the above-mentioned key intermediate, 2[2'-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde **4a** and its subsequent conversion to discokiic acid **1** would demonstrate the usefulness of the α-diazo-β-dicarbonyl compounds.

Since discokiic acid **1** was isolated in 1992 from the marine sponge *Discodermia kiiensis* as a part of discokiolide B, the relative stereochemistry of the 3-hydroxy-2-methylpropionate unit of discokiic acid remains unclear.[1] Thus the synthesis of

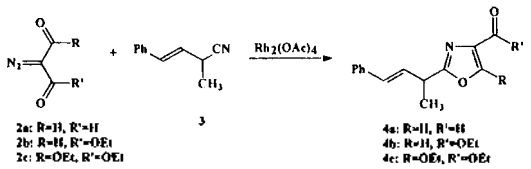


Scheme 1.

discokiic acid **1** was planned as shown in *Scheme* 1, starting from the known *trans*-4-phenyl-3-buten-2-nitrile **3** prepared from *trans*-4-phenyl-3-buten-2-one.

Our retrosynthetic analysis of compound **1** shows two main fragments: a propionic acid residue, and a 2,4-disubstituted-oxazole portion **4a** (*Scheme* 1). In turn, compound **4a** should in principle be obtained by reaction of a suitably substituted nitrile with diazomalonaldehyde. It was envisioned that discokiic acid could be elaborated in its final stage by the aldol condensation of compound **4a** with the formal carbanionic species(methyl propionate). Accordingly, we attempted to achieve formation of compound **4a** via cycloaddition of *trans*-4-phenyl-3-buten-2-nitrile **3** with diazomalonaldehyde **2a**.

Synthesis of compound **3** was started from commercially available *trans*-4-phenyl-3-buten-2-one. Reduction of *trans*-4-phenyl-3-buten-2-one with $NaBH_4$-$CeCl_3$ in methanol solution gave *trans*-4-phenyl-3-buten-2-ol in 89% yield. Transformation of the latter to *trans*-3-methoxy-1-phenylbutene was achieved by the reaction of *trans*-4-phenyl-3-buten-2-ol with sodium hydride and iodomethane in 85% yield. The required *trans*-4-phenyl-3-buten-2-nitrile(**3**) was prepared by reaction of *trans*-3-methoxy-1-phenylbutene with $(CH_3)_3SiCN$-$TrClO_4$ in 58% yield.[8]



Scheme 2.

Utilizing methodology already developed in our laboratory,[3a] we could synthesize 2[2'-(4-phenyl-3-butenyl)]-1,3-oxazole-4-carboxaldehyde **4a** from diazomalonaldehyde **2a** and compound **3** in 19% yield based on nitrile(*Scheme* 2). Although we varied the solvent($ClCH_2CH_2Cl$, fluorobenzene), the dropping time of the diazo compound and the relative ratio of nitrile/diazo(1 to 2), the yield could not be improved. Earlier work by Helquist[3b] and Yoo[3c] had demonstrated that the reactions of nitrile with ethyl α-formyldiazoacetate and ethyl diazomalonate provided the corresponding oxazoles in better yield. Thus compound **4a** was reacted with α-formyldiazoacetate **2b** and ethyl diazomalonate **2c** under various conditions to give compounds **4b** and **4c** in 21% and 25% yields, respectively. The resulting oxazoles **4b** and **4c** could be converted to compound **4a** by reduction with $LiEt_3BH$ followed by PCC oxidation.[3g]

In order to determine the relative stereochemistry of the 3-hydroxy-2-methylpropanoic acid unit in compound **1**, we now performed the aldol reaction between 2-phenyl-1,3-oxazole-4-carboxaldehyde **4d** and lithium enolate of methyl propionate as a model reaction. Both the *syn*- and *anti*-3-hydroxy-2-methyl ester isomers are frequently embedded in natural products of propionate origin such as macrolide antibiotics.[12] A variety of excellent methods has been developed for the efficient construction of the *syn*- and *anti*-3-hydroxy-2-methylpropionate unit.[13~15] Treatment of compound **4d** with the lithium enolate, formed in situ from methyl propionate deprotonated by LDA in THF solution at −78 ℃, provided a 55 : 45 mixture of the *syn*(**5**) and *anti*(**6**) diastereoisomers in

Table 1. ^{1}H NMR chemical shifts for 3-Hydroxy-2-Methylpropionate derivatives

Compound	2-Methine	2-Methyl	Carbinol-3H
1[a]	2.93 (qd, 7.0, 10.8 Hz)	0.84 (d, 7.0 Hz)	5.87 (d, 10.8 Hz)
5	3.10 (qd, 7.2, 3.9 Hz)	1.21 (d, 7.2 Hz)	5.15 (dd, 5.1, 3.9 Hz)
6	3.14 (qd, 7.2, 7.2 Hz)	1.23 (d, 7.2 Hz)	4.81 (dd, 7.2, 7.2 Hz)
7	3.01 (qd, 7.2, 4.2 Hz)	1.17 (d, 7.2 Hz)	5.05 (qd, 4.2, 1.2 Hz)
8	3.06 (qd, 7.2, 7.2 Hz)	1.18 (d, 7.2 Hz)	4.73 (qd, 7.2, 7.2 Hz)
9[b]			5.15 (d, 3.1 Hz)
10[b]			4.80 (d, 9.4 Hz)

[a]Chemical shifts were taken from lit. 1.; [b]Chemical shifts were taken from lit. 14b.

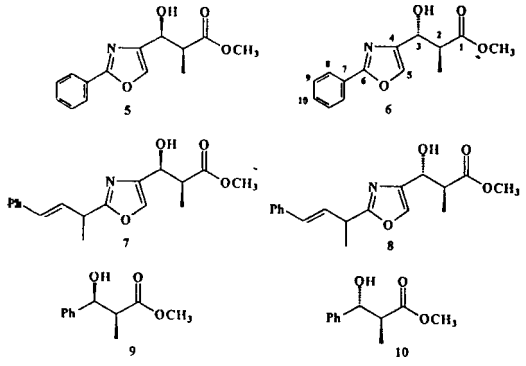


Fig. 2.

77% yield. The *syn*(**5**) and *anti*(**6**) product mixture was separated by silica gel chromatography and analyzed by NMR spectroscopy. Stereostructures of aldol products **5** and **6** were assigned on the basis of their ^{1}H and ^{13}C NMR spectra. As shown in *Table* 1, the ^{1}H NMR chemical shifts of compound **5** and **6** were compared with the known data of compound **9** and **10**. In the ^{1}H NMR spectra, the proton signal on the carbinol carbon of the *syn*-isomer shifted more downfield than that of the *anti*-isomer, *i.e.* while in compound **5** this signal showed at 5.15 ppm as a doublet of doublets with coupling constants 5.1 and 3.9 Hz, in compound **6** the same signal appeared at 4.81 ppm as a doublet of doublets with coupling constants 7.2 and 7.2 Hz. These differences in chemical shifts and coupling constants are in agreement with known literature values.[14] In the ^{13}C NMR spectra, the crucial resonance is the 2-methyl carbon which appears at 10.9 and 14.2 ppm for **5** and **6**, respectively.[15]

Table 2. ^{13}C NMR chemical shifts for 3-Hydroxy-2-Methylpropionate derivatives

Compound	2-Methine	2-Methyl	3-Carbinol
1[a]	43.8	14.5	70.9
5	43.8	10.9	68.3
6	44.6	14.2	69.3
7	43.8	11.1	68.2
9[b]	46.6	10.8	73.6
10[b]	47.1	14.4	76.3

[a]Chemical shifts were taken from lit. 1.; [b]Chemical shifts were taken from lit. 15.

Aldol reaction of compound **4a** with lithium enolate generated from methyl propionate deprotonated by lithium bis(trimethylsilyl)amide in THF gave a 66 : 34 mixture of the *syn*(**7**) and *anti*(**8**) isomer in 47% yield. The *syn* and *anti* mixture was separated by silica gel chromatography. In the ^{1}H NMR spectrum, the 3-proton of compound **7** appeared at 5.05 ppm as a doublet of doublets with coupling constants 4.2 and 1.2 Hz, which is coincident with the known *syn* coupling constant(3~4 Hz).[14] For compound **8**, the 3-proton appeared at 4.73 ppm as a doublet of doublets with coupling constants 7.2 and 7.2 Hz, which is also coincident with *anti* coupling constant(7~9 Hz). The ^{13}C NMR chemical shift of the 2-methyl carbon(11.1 ppm) in compound **7** indicates that compound **7** is the *syn*-isomer. Although we could not obtain ^{13}C NMR spectral data for compound **8**, we could assigned the configuration of compound **8** as *anti*.

Based on the *syn* and *anti* ^{1}H NMR chemical shifts and coupling constants for the compounds **7** and **8**, and on the dissimilarity of the ^{13}C NMR chemical shifts of compound **7** and discokiic acid (**1**),[1] we assigned compound **1** as the *anti*-isomer.

Further support for the structure of compound

8 was derived from IR (hydroxyl absorption band at 3381 and carbonyl absorption band at 1735 cm^{-1}), and MS data(molecular ion peak at 315).

In summary, discokiic acid methyl ester has been prepared from nitrile using rhodium catalyzed cyclization-aldol condensation, and we could assign the stereochemistry of the right-hand side of the latter. Further investigation on the synthesis of discokiolide B is now in progress.

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