

(72)

V5C2R6, , 4573
 V3J3N2, , 947
 V3H2T4, , 117
 V7R4P3, , 5551

(74)

:

(54)

1,2 -

1,2 - 가 , 가
 T - , , 가

1,2 - , 가

1,2 - 가 , T - , 가

([Hu, K. et al., Canadian Journal of Microbiology, 1998, 44, 1 072]), ([Mannila, et al, Phytochemistry, 1993, 33, 813]), (calcinno static) (EP 641,767) - ([Thakkar, K. et al., J. Med. Chem., 19 93, 36, 2950]) . (Photorhabdus) 5 - (2 -) - 2 - - 1,3 - 가 ([Webster et al, WO 01/42231]).

T (T -)가 (TNF), (IFN) (granulocyte) (macrophage) . T - (IL),

TNF- α 는 Th1 세포에서 분비되며, Th2 세포의 분화를 억제하고, IL-4, IL-10, IL-13의 생성을 감소시킨다. 또한, TNF- α 는 CD86 발현을 증가시켜 T 세포의 활성을 촉진한다. 반면, Th2 세포는 IL-4, IL-10, IL-13을 분비하며, TNF- α 의 효과를 억제한다. 이러한 상호작용은 면역 반응의 조절에 중요한 역할을 한다.

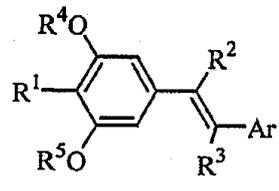
IL-8 (CXCL8)은 neutrophil을 끌어들이는 chemokine이다. IL-8은 neutrophil의 chemotaxis를 유도하며, myeloperoxidase를 활성화시킨다. 또한, IL-8은 T 세포의 down-regulation을 유도하여 negative feedback mechanism을 형성한다.

IL-2 (15 kDa)는 T 세포의 증식을 촉진하는 cytokine이다. IL-2는 B 세포와 T 세포의 상호작용을 조절하며, T 세포의 분화를 유도한다. [T.A.Waldmann, Immunol. Today, 14, 270 (1993)]

IFN- γ 는 Th1 세포에서 분비되며, CD8+ T 세포의 증식을 촉진한다. IFN- γ 는 MHC II 발현을 증가시켜 항원 제시를 촉진한다. 또한, IFN- γ 는 mast cell의 활성을 억제한다.

I 가 :

I



, R¹ a) H, b) (aralkyl), c) , d)
 CN, e) COOR⁶, f) NR⁷R⁸, g) S(O)₂NR⁷R⁸, h) COR⁹, i) OR¹⁰, j) S(O)_nR¹¹, n=0-2, k)
 ; R² R³ a) H, b)
 , c) , d) CN, e) COOR⁶, f) NR⁷R⁸, g) S(O)₂NR⁷R⁸, h) COR⁹, i) OR¹⁰, j)
 S(O)_nR¹¹, n=0-2, k) ; R⁴
 R⁵ a) H, b) , c)
 ; R⁶ a) H, b) ;
 R⁷ R⁸ a) H, b) ;
 ; R⁹ a) H, b) , c) NR⁷R⁸
 ; R¹⁰ a) H, b) ; R¹¹ a) H, b) ; Ar a)
 (, R² R³ H가), b) O, S / N ,
 5 , c) O, S / N ,
 6 . Ar a) (, R² R³ ,
 H가), b) O, S / N , 5 ,
 c) O, S / N , 6 .

I T- , , /
 가 . I .

R^1 a) H, b) , c) , d) CN, e) COOR⁶Ar a) , (, R² , R³ , b) O, S / N , 5
 H가 c) O, S / N , 6 .f) NR⁷ R⁸, g) S(O)₂NR⁷R⁸, h) COR⁹, i) OR¹⁰, j) S(O)_nR¹¹, n=0-2, k)
 R^2 R^3 a) H, b) , c) , d) CN, e) COOR⁶, f) NR⁷R⁸, g) S(O)₂NR⁷R⁸, h) COR⁹, i) OR¹⁰, j) S(O)
 nR^{11} , n=0-2, k) R^4 R^5
 a) H, b) , c)
 R^6 a) H, b)
 R^7 R^8 a) H, b)
 R^9 a) H, b)
 c) NR⁷R⁸ R^{10} a) H, b)
 , c) R^{11} a) H, b)
 , Ar a) , (, R² , R³ , b) O, S / N , 5 , Ar
 c) O, S / N , 6 . Ar
 a) H, b) , c) , d)
 CN, e) COOR⁶, f) NR⁷R⁸, g) S(O)₂NR⁷R⁸, h) COR⁹, i) OR¹⁰, j) S(O)_nR¹¹, n=0-2, k)

(E) (Z)

가

R^4 R^5 가 , R^1 :

5 - (1 - -2 -) -2 - i - -1,3 - (1);

5 - [1 - (4 -) -2 - (4 -)] -2 - i - -1,3 - (2);

5 - [1 - (3 -) -2 - (3 -)] -2 - i - -1,3 - (3);

5 - [1 - (3,5 -) -2 - (3,5 -)] -2 - i - -1,3 - (4);

5 - (1 - -2 -) -2 - i - -1,3 - (5);

2 - (3,5 - -4 - i -) -3 - (6);

2 - (3,5 - -4 - i -) -3 - (7);

5 - (2,2 -) -2 - i - -1,3 - (8);

3 - (3,5 - -4 - i -) -2 - (9);

3 - (3,5 - -4 - i -) -2 - (10);

1 - (3,5 - -4 - i -) -3 - (11);

(polyp) / (basophil) (degranulation)

T -

가 T - (Hashimoto) (Guillain - Barre) (polyp) (:)

A, FK506

() () (vehicle) 가

가 ()

가

가

가

가

1,3 -

(bland fixed)

(Ringer)

가

가

(tablet, troche, lozenge),

가

(elixir)

가

(arachis) (oil - in - water) (phosphatide), (soybean),

가 (gargle)).

[Remington 's Pharm

aceutical Science, Edition 17, Mack Publishing Company, Easton, PA.]

0.01 mg 140mg/ kg/ (day), 0.5mg 7g/ / 0.01 50mg / kg/ , 0.5 mg 3.5 g/ / , 2.5 mg 1 g/ / 가

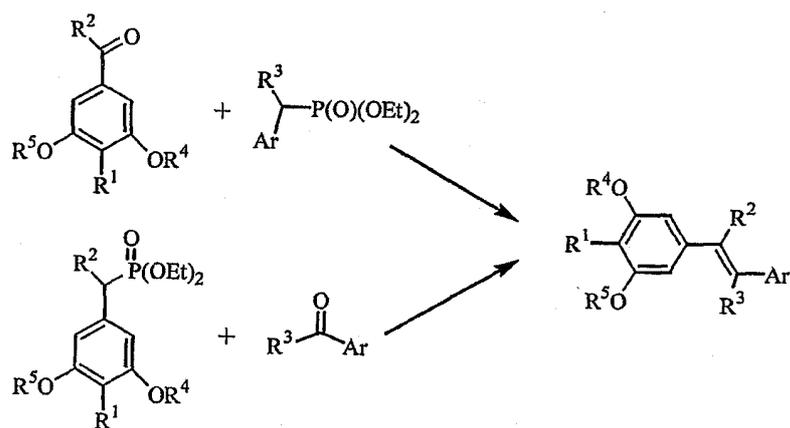
5 95%

1mg 0.5 mg 5g 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800 mg 1000mg

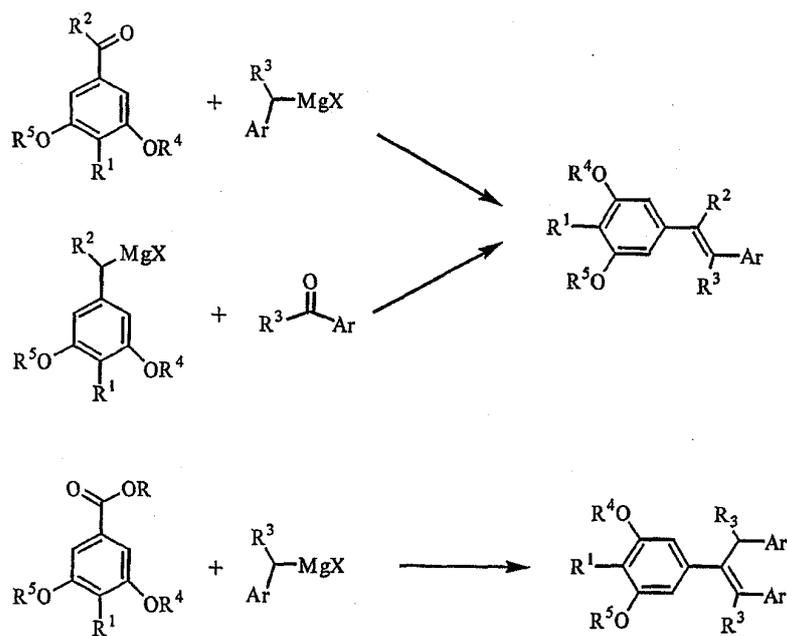
2231], [Treadwell , J. Org. Chem. 1999 (64), 8718 - 8723]; [Webster , WO 01/4 456] () , WO 1994/020

(2) (3) 1 - 3: (Wittig) (1), (Grinard)

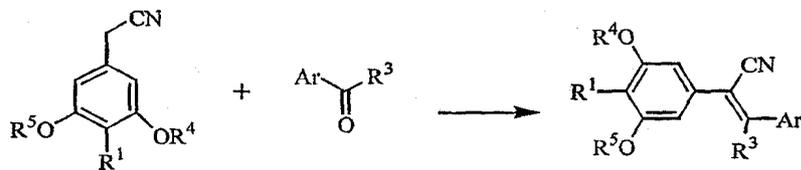
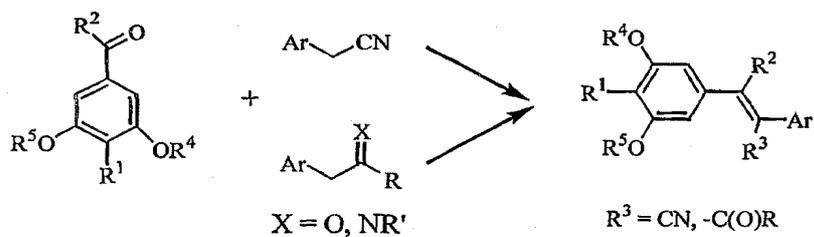
1: (Wittig olefination)



2: (Grignadr reaction)



3: (Aldol condensation)



()

1.

1. T (T -)

T -

T -

T -

RPMI - 1640
 M(Lymphocyte - M) (37
 2)
 37 2
 95%
 (Hank's solution)
 100ml , 5×10^5 M 2
 10,000
 (FCS),
 [^{3}H]
 BALB/C (2×10^5) C5
 [^{3}H] TdR; $1 \mu\text{Ci}/$) 가 ,
 , 16 가 .
 BALB/C
 5
 10mg
 25mM Hepes L - , 10%
 RPMI 1640)가 96
 (Costar Laboratories) ,
 C BALB/C (2×10^5) C5
 [^{3}H] TdR; $1 \mu\text{Ci}/$) 가 ,
 , 16 가 .
 BALB/C
 5
 10mg
 25mM Hepes L - , 10%
 RPMI 1640)가 96
 (Costar Laboratories) ,
 C BALB/C (2×10^5) C5
 [^{3}H] TdR; $1 \mu\text{Ci}/$) 가 ,
 , 16 가 .
 BALB/C
 5
 10mg
 25mM Hepes L - , 10%
 RPMI 1640)가 96
 (Costar Laboratories) ,
 C BALB/C (2×10^5) C5
 [^{3}H] TdR; $1 \mu\text{Ci}/$) 가 ,
 , 16 가 .

1

T -

[1] T - 50%

	IC ₅₀ (μM)
5 - (2 - 2 -) - 2 - i - - 1,3 -	1.15
5 - (2 - 2 -) - 1,3 -	4.65
2 - [2 - (3,5 - - 4 - i -)]	2.09
2 - (3,5 - - 4 - i -) - 3 -	3.50
5 - (1 - 2 -) - 2 - i - - 1,3 -	1.49
3 - (3,5 - - 4 - i -) - 2 -	1.81
2 - i - - 5 - (2 - 2 -) - 1,3 -	5.16

2. (IL - 2, IL - 4 IFN -)

T - IL - 2, IL - 4 IFN -

, T -

. T -

A (Con A)

(ELISA)

2 3

IL - 2 IL - 4

[2] IL - 2

	IC ₅₀ (μM)
5 - (2 - 2 -) - 2 - i - - 1,3 -	0.40
5 - (2 - 2 -) - 1,3 -	1.79
2 - (3,5 - - 4 - i -) - 3 -	0.13
2 - i - - 5 - (2 - 2 -) - 1,3 -	0.028

[3] IL - 4

(10 μM

%

)

	%
5 - (2 - 2 -) - 2 - i - - 1,3 -	0
5 - (2 - 2 -) - 1,3 -	0
5 - (1 - 2 -) - 2 - i - - 1,3 -	01
5 - (2,2 -) - 2 - i - - 1,3 -	47
3 - (3,5 - - 4 - i -) - 2 -	35
2 - i - - 5 - (2 - 2 -) - 1,3 -	23

IFN -

[4]

	IC ₅₀ (μ M)
2 - (3,5 - - 4 - i -) - 3 -	0.86
5 - (1 - - 2 -) - 2 - i - - 1,3 -	1.62
5 - (2,2 -) - 2 - i - - 1,3 -	1.71
3 - (3,5 - - 4 - i -) - 2 -	0.71
2 - i - - 5 - (2 - - 2 -) - 1,3 -	0.08

3.

TNF - (,) . CD86 , B
 CD86 T - 가 T - CD28 (pro -
 inflammatory) TNF - TNF - (pro -
 : DMEM 10% FCS (5 × 10⁴/)
 , N -
 가 37 , 5% CO₂ 24 , TNF - ELISA
 FACS CD86
 5 6 , 1 μ M TN
 F - CD86

[5] TNF - (10 μ M , %)

	%
5 - (2 - - 2 -) - 1,3 -	42
2 - [2 - (3,5 - - 4 - i -)]	75
2 - (3,5 - - 4 - i -) - 3 -	60
2 - i - - 5 - (2 - - 2 -) - 1,3 -	50

[6] CD86 (10 μ M , %)

	%
5 - (2 - - 2 -) - 2 - i - - 1,3 -	51
5 - (2 - - 2 -) - 1,3 -	90
2 - [2 - (3,5 - - 4 - i -)]	88
5 - (1 - - 2 -) - 2 - i - - 1,3 -	0
5 - (2,2 -) - 2 - i - - 1,3 -	10
3 - (3,5 - - 4 - i -) - 2 -	16
2 - i - - 5 - (2 - - 2 -) - 1,3 -	2

4.

C.), 1999. Biochem. Pharmacol 58:1869 - 1880] [N - (Tudan,
 (FMPL)] ()

(HBSS) pH 7.4 4% 80ml , 1 , 400ml , 15ml
 (Ficoll Paque) (Pharmacia) 5ml 5ml 가 . 500g 30 H
 BSS , 20 (hypotonic) 3 (1ml 5,000,000) 가 . 33 20
 , 37 10 , 가 . 37 90%

(7). , N - - - -
 (8).

[7] 5 - (2 - -2 -) - 2 - i - - 1,3 - (25 μ M)
 ((mV) , %)

()	%
1	23
2	10
3	7
4	6
5	6
7	16
10	29

[8] FMLP 25 μ M 5 - (2 - -2 -) - 2 - i - - 1,3 -
 ()

(mV)	%
	30

5.

[(Arquardt, C.) , 1986. Am Rev Respir Dis 133:1105 - 1109]

9 2 - i - - 5 - (2 - -2 -) - 1,3 -

[9]

	IC ₅₀ (μM)
2 - i - 5 - (2 - 2 -) - 1,3 -	18.9

6.

13 - (TPA) 20μℓ 가 TPA Balb/c 12 -
 TPA () 가
 TPA % 10
 2 - (3,5 - 4 - i -) - 3 -

[10] Balb/c

1 2 - (3,5 - 4 - i -) - 3 -
 () (%)

	%
2 - (3,5 - 4 - i -) - 3 -	85.2
0.01%	31.2

1.5 - (1 - 2 -) - 2 - i - 1,3 - (1).

a) WO 01/42231 A2 (Chen) 3,5 - 4 - i -
¹H NMR (CDCl₃, ppm): 1.32 (d, J=7.2Hz, 6H), 3.66 (, J=7.2Hz, 1H), 3.82 (s, 6H), 3.95 (s, 3H), 7.25 (s, 2H).

b) 2 - (3,5 - 4 - i -) - 1,3 - 2 -
 (5mL) Mg(0.252g, 10.4) (3mL) (1mL, 8.41mL)
 가 가 , 1 가 가 (15mL) 3,5 - 4 - i -
 (1.00g, 4.20) 가 가
 (10mL) 가 2N HCl(10mL) 가
 (3 × 50mL) Na₂SO₄ : (1 :9)
 (1.29g, 79%) , 2 - (3,5 - 4 - i -) - 1,3 - 2 -
¹H NMR (CDCl₃, ppm): 1.28 (d, J=7.2Hz, 6H), 3.08(d, J=13.3 Hz, 2H), 3.35 (d, J=13.3Hz, 2H), 3.6(m, 1H), 3.95 (s, 6H), 6.44 (s, 2H), 6.9 - 7.5 (m, 10H).

c) 5 - (1 - 2 -) - 2 - i - 1,3 - (1)

N_2 -78 CH_2Cl_2 (10mL) 2 - (3,5 - 4 - i -) - 1,3 - 2 - (0.63g, 1.6) BBr_3 (CH_2Cl_2 1M, 5.0mL, 5.0) 가 . -78 1 (50mL) 가 , 20% NaOH 가 pH 12 (2 x 10mL) . 6 N HCl pH 1 (3 x 50mL) (10mL) (10mL) Na_2SO_4 : (1:9) , 5 - (1 - 2 -) - 2 - i - - 1,3 - (1)(0.26g, 47%) (0) . $^1\text{H NMR}$ (CDCl_3 , ppm): 1.38 (d, J=7.1Hz, 6H), 3.52 (, J=7.1Hz, 1H), 4.08 (s, 2H), 6.51(s, 2H), 7.13 (s, 1H), 7.2 - 7.4 (m, 10H).

2.5 - [1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - (2).

a) 1,3 - (4 -) - 2 - (3,5 - 4 - i -) - 2 - .

1(b) 3,5 - 4 - i - 4 - 20% $^1\text{H NMR}$ (CDCl_3 , ppm): 1.30 (d, J=7.1Hz, 6H), 2.31 (s, 6H), 3.02 (d, J=13.5Hz, 2H), 3.25 (d, J=13.5Hz, 2H), 3.52 (m, 1H), 3.71 (s, 6H), 6.45 (s, 2H), 6.8 - 7.2 (m, 8H).

b) 5 - [1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - (2).

2 - (3,5 - 4 - i -) - 1,3 - (4 -) - 2 - (0.173g, 0.41) (0.432g, 3.72) 200 3 가 . 2N HCl(10mL) (15mL) 가 , (2 x 15mL) Na_2SO_4 : (1:9) , 5 - [1(Z) - 1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - (17.7mg), Z/E (79.4mg) 5 - [1(E) - 1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - (20.2mg) 77% $^1\text{H NMR}$ (CDCl_3 , ppm) : 5 - [1(Z) - 1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - : 1.38 (d, J=7.1Hz, 6H), 2.28 (s, 3H), 2.36 (s, 3H), 3.5 - 3.8 (m, 1H), 3.67 (s, 2H), 4.69 (s, 2H), 6.07 (s, 2H), 6.31 (s, 1H), 6.9 4 (s, 4H), 7.13 (s, 4H). 5 - [1(E) - 1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - : 1.36 (d, J=7.1Hz, 6H), 2.35 (s, 6H), 3.48 (m, 1H), 4.02 (s, 2H), 4.74 (s, 2H), 6.50 (s, 2H), 7.1 - 7.3 (m, 9H).

3.5 - [1 - (3 -) - 2 - (3 -)] - 2 - i - - 1,3 - (3).

a) 1,3 - (3 -) - 2 - (3,5 - 4 - i -) - 2 - .

1(b) 3,5 - 4 - i - 3 - 70% $^1\text{H NMR}$ (CDCl_3 , ppm): 1.29 (d, J=7.1Hz, 6H), 1.85 (s, 1H), 3.07 (d, J=13.3Hz, 2H), 3.29 (d, J=13.3Hz, 2H), 3.56 (, J=7.1Hz, 1H), 3.72 (s, 6H), 6.42 (s, 2H), 6.7 - 7.2 (m, 8H).

b) 5 - [1 - (3 -) - 2 - (3 -)] - 2 - i - - 1,3 - (3).

2(b) 1,3- (3-) - 2- (3,5- - 4-i-) - 2- 78% ¹H NMR (CDCl₃, ppm): 5- [1(Z)-1-(3-) - 2-(3-)] - 2-i- - 1,3- : 1.38 (d, J=7.1Hz, 6H), 3.44 (, J=7.1Hz, 1H), 3.72 (s, 2H), 4.8 (b, 2H), 6.04 (s, 2H), 6.33 (s, 1H), 6.6-7.3 (m, 8H). 5- [1(E)-1-(3-) - 2-(3-)] - 2-i- - 1,3- : 1.38 (d, J=7.1Hz, 6H), 3.45 (, J=7.1Hz, 1H), 4.03 (s, 2H), 5.00 (s, 2H), 6.49 (s, 2H), 6.8-7.3 (m, 9H).

4.5- [1-(3,5-) - 2-(3,5-)] - 2-i- - 1,3- (4).

a) 1,3- (3,5-) - 2-(3,5- - 4-i-) - 2- .

1(b) 1,3- 3,5- - 4-i- ¹H NMR (CDCl₃, ppm): 1.28 (d, J=7.0Hz, 6H), 1.83 (s, 1H), 3.04 (d, J=13.5Hz, 2H), 3.26 (d, J=13.5Hz, 2H), 3.56 (, J=7.0Hz, 1H), 3.74 (s, 6H), 6.40 (s, 2H), 6.5-6.8 (m, 6H).

b) 5- [1-(3,5-) - 2-(3,5-)] - 2-i- - 1,3- (4).

2(b) , 1,3- (3,5-) - 2-(3,5- - 4-i-) - 2- Z/E 70% ¹H NMR (CDCl₃, ppm). 1.38 (d, J=7.1Hz, 6H), 3.4 (m, 1H), 3.69, 3.99 (s, 2H), 6.04, 6.47 (s, 2H), 6.28, 6.98 (s, 1H), 6.49-6.78 (m, 6H).

5.5- (1- - 2-) - 2-i- - 1,3- (5).

a) 1- (3,5- - 4-i-) .

(100mL) Mg(2g, 82.2) (100mL) CH₃I(5mL, 80.4) 가
 가 , 1 , 0 . LiBH₄ (THF 2.0M, 25mL, 50
) 가 , (300mL) 3,5- - 4-i- (10.0g, 42.0)
 가 . 0 (50mL) 가 , 2N HCl(100mL) 가 .
 (4 x 200mL)

b) 3,5- - 4-i- .

(22.64g, 105.0) K₂CO₃ (2.3g)
 CH₂Cl₂ (80mL) 1 . TLC (1) ,
 600mL . (florisil) . TL
 C : (2:98
 1:9) 3,5- - 4-i- (3.65g,
 39%) ¹H NMR (CDCl₃, ppm): 1.31 (d, J=7.1Hz, 6H), 2.62 (s, 3H), 3.67
 (, J=7.1Hz, 1H), 3.90 (s, 6H), 7.16 (s, 2H).

c) 2- (3,5- - 4-i-) - 1- - 2- .

1(b) , 3,5- - 4-i- 78% ¹H NMR (CDCl₃, ppm): 1.32 (d, J=7.1Hz, 6H), 1.59 (s, 3H), 3.02 (d, J=13.9Hz, 2H), 3.18 (d, J=13.9Hz, 2H), 3.61 (, J=7.1 Hz, 1H), 3.81 (s, 6H), 6.60 (s, 2H), 7.0-7.4 (m, 6H).

d) 5-(1-(2-(3,5-4-iodophenyl)-1,3-dimethylbutyl)-2-iodophenyl)-1,3-dimethylbutane (5).

1(d) (100mL) LiAlH₄ (95%) (5.00g, 125mmol), (300mL) 3,5-4-iodophenyl (17.67g, 90.1mmol) 가 .
 BBr₃ 39% .¹H NMR (DMSO, ppm): 1.22 (d, J=7.0Hz, 6H), 2.12 (s, 3H), 3.4 (m, 1H), 6.44 (s, 2H), 6.69 (s, 1H), 7.3-7.6 (m, 5H), 9.03 (s, 2H).

6.2-(3,5-4-iodophenyl)-3-iodophenyl (6).

a) 3,5-4-iodophenyl .

N₂ 0 (100mL) LiAlH₄ (95%) (5.00g, 125mmol), (300mL) 3,5-4-iodophenyl (17.67g, 90.1mmol) 가 .
 1(b) 0 1 가 1 . 0 Na₂SO₄ (10mL) 가 .
 3,5-4-iodophenyl (13.76g, 88.3%) .¹H NMR (CDCl₃, ppm): 1.34 (d, J=7.2Hz, 6H), 3.65 (s, 1H, J=7.2Hz, 1H), 3.88 (s, 6H), 4.70 (s, 2H), 6.62 (s, 2H).

b) 3,5-4-iodophenyl .

0 (100mL) 3,5-4-iodophenyl (12.57g, 59.8mmol) PBr₃ (3.0mL, 31.2mmol) 가 . TLC (4mm), (180mL) 가 . (3x50mL) (20mL), Na₂CO₃ (20mL), (20mL) (20mL) .
 (14.93g, 91.4%) .¹H NMR (CDCl₃, ppm): 1.29 (d, J=7.1Hz, 6H), 3.64 (s, 1H, J=7.1Hz, 1H), 3.84 (s, 6H), 4.50 (s, 2H), 6.60 (s, 2H).

c) 3,5-4-iodophenyl .

DMF (30mL) (4.81g, 17.6mmol) NaCN (1.64g, 33.5mmol) 50 . TLC (200mL) . (2x50mL) , 3,5-4-iodophenyl (3.74g, 97%) .¹H NMR (CDCl₃, ppm): 1.29 (d, J=7.1Hz, 6H), 3.60 (s, 1H, J=7.1Hz, 1H), 3.74 (s, 2H), 3.84 (s, 6H), 6.51 (s, 2H).

d) 2-(3,5-4-iodophenyl)-3-iodophenyl (6).

3,5-4-iodophenyl (1.00g, 4.56mmol), (0.49g, 4.62mmol) 20% NaOH (15mL) (20mL) 5 .
 (6) (1.21g, 86%) .¹H NMR (CDCl₃, ppm): 1.32 (d, J=7.1Hz, 6H), 3.65 (s, 1H, J=7.1Hz, 1H), 3.91 (s, 6H), 6.85 (s, 2H), 7.4-7.6 (m, 4H), 7.8-8.0 (m, 2H).

7.2-(3,5-4-iodophenyl)-3-iodophenyl (7).

1(c) (6) BBr₃ .¹H NMR (DMSO, ppm): 1.23 (d, J=6.8Hz, 6H), 3.3-3.4 (m, 1H), 6.27 (s, 1H), 6.63 (s, 2H), 7.38 (s, 1H), 7.5-7.6 (m, 2H), 7.65 (s, 1H), 7.8-7.9 (m, 1H), 9.39 (s, 2H).

8.5-(2,2-(3,5-4-iodophenyl)-2-iodophenyl)-1,3-dimethylbutane (8).

a) 2-(3,5-4-iodophenyl)-1,1-dimethylbutane .

1(b) , Mg , 6(b) 3,5 - 4 - i -
 $^1\text{H NMR (CDCl}_3\text{, ppm): 1.24 (d, J=7.1Hz, 6H), 3.3 - 3.5 (m, 1H), 3.56 (s, 6H), 3.72 (d, J=15.4Hz, 2H), 6.04 (s, 2H), 7.2 - 7.7 (m, 10H).$

b) 5 - (2,2 -) - 2 - i - - 1,3 - (8).

1(c) , 2 - (3,5 - 4 - i -) - 1,1 -
 BBr_3 $^1\text{H NMR (CDCl}_3\text{, ppm): 1.41 (d, J=7.0Hz, 6H), 3.39 (m, J=7.0Hz, 1H), 6.00 (s, 2H), 6.78 (s, 1H), 7.2 - 7.5 (m, 10H).$

9.3 - (3,5 - 4 - i -) - 2 - (9).

a) 3,5 - 4 - i - .

6(a) 3,5 - 4 - i - (13.05g, 62.1)
 (33.92g, 157) K_2CO_3 (4.18g, 30) CH_2Cl_2 (100mL) 30
 (300mL) 가
 , 3,5 - 4 - i - (11.89g, 92%)
 $^1\text{H NMR (CDCl}_3\text{, ppm): 1.32 (d, J=7.2Hz, 6H), 3.68 (, J=7.2Hz, 1H), 3.92 (s, 6H), 7.12 (s, 2H), 9.96 (s, 1H).$

b) 3 - (3,5 - 4 - i -) - 2 - (9).

6(d) , 3,5 - 4 - i -
 $^1\text{H NMR (CDCl}_3\text{, ppm): 1.33 (d, J=7.1Hz, 6H), 3.73 (, J=7.1Hz, 1H), 3.91 (s, 6H), 7.15 (s, 2H), 7.4 - 7.5 (m, 4H), 7.6 - 7.8 (m, 2H).$

10.3 - (3,5 - 4 - i -) - 2 - (10).

2(b) , 3 - (3,5 - 4 - i -) - 2 -
 (9) $^1\text{H NMR (CDCl}_3\text{, ppm): 1.34 (d, J=7.0Hz, 6 H), 3.48 (, J=7.0Hz, 1H), 6.95 (s, 2H), 7.2 - 7.5 (m, 5H), 7.6 - 7.7 (m, 1H).$

11.1 - (3,5 - 4 - i -) - 2 - (11).

N_2 0 THF(100mL) (1 -) (8.72g, 36.0) NaH(60 %)(2.95g, 73.8) 가 . 가 , 0 1 , THF(100mL)
 9(a) 3,5 - 4 - i - (7.24g, 34.8) 가 0
 1 , 45 50 10 0 (50mL)
 가 , 2N HCl(200mL) 가 (3 × 200mL)
 Na_2SO_4 1 - (3,5 - 4 - i -) - 2 -
 . 10%

$^1\text{H NMR (CDCl}_3\text{, ppm): 1.33 (d, J=7.1Hz, 6H), 2.37 (d, J=1.3Hz, 3 H), 3.64 (, J=7.1Hz, 1H), 3.86 (s, 6H), 6.59 (s, 2H), 6.82 (m, 1H), 7.30 - 7.61 (m, 5H).$

12.5 - (2 - 2 -) - 2 - i - - 1,3 - (12).

1(c) , 1 - (3,5 - 4 - i -) - 2 - (11)
 BBr_3 63% $^1\text{H NMR (CDCl}_3\text{, ppm): 1.42 (d, J=7.0Hz, 6H), 2.32 (d, J=1.4Hz, 3H), 3.49 (, J=7.0Hz, 1H), 4.71 (s, 2H), 6.39 (s, 2H), 6.67 (m, 1H), 7.58 - 7.33 (m, 5H).$

13.1 - (3,5 -) - 2 - (13).

11, 3,5 - (1 -)
73% $^1\text{H NMR}$ (CDCl_3 , ppm): 2.33 (d, $J=1.2\text{Hz}$, 3H), 3.85 (s, 6H),
6.43 (t, $J=2.2\text{Hz}$, 1H), 6.56 (d, $J=2.2\text{Hz}$, 2H), 6.81 (d, $J=1.2\text{Hz}$, 1H), 7.3 - 7.7 (m, 5H).

14.5 - (2 - - 2 -) - 1,3 - (14).

1(c) 1 - (3,5 -) - 2 - (13) BBr_3
63% $^1\text{H NMR}$ ($\text{CD}_3\text{C(O)CD}_3$, ppm): 2.21 (d, $J=1.5\text{Hz}$, 3H), 6.23 (t, $J=2.2\text{Hz}$,
z, 1H), 6.36 (d, $J=2.2\text{Hz}$, 2H), 6.68 (m, 1H), 7.2 - 7.6 (m, 5H).

15.2 - [2 - (3,5 - - 4 - i -)] (15).

a) (3,5 - - 4 - i -) .

6(b) 3,5 - - 4 - i - (5.01g, 18.3) ((
4.7mL, 27.4) Bu_4Ni (0.05g) 110 130 가 .
110 (5.58g, 92%) $^1\text{H NMR}$ (CDCl_3 , ppm):
m): 1.27 (d, $J=7.1\text{Hz}$, 6H), 1.29 (t, $J=7.0\text{Hz}$, 6H), 3.12 (d, $J=21.5\text{Hz}$, 2H), 3.4 - 3.7 (m, 1H), 3.80 (s,
6H), 4.06 (dt, $J=7.1\text{Hz}$, 4H), 6.50 (d, $J=2.6\text{Hz}$, 2H).

b) 2 - [2 - (3,5 - - 4 - i -)] (15).

11,
41% $^1\text{H NMR}$ (CDCl_3 , ppm): 1.32 (d, $J=7.1\text{Hz}$, 6H), 3.65 (, $J=7.1\text{Hz}$, 1H),
3.88 (s, 6H), 6.81 (s, 2H), 7.15 (d, $J=16\text{Hz}$, 1H), 7.1 - 7.2 (m, 1H), 7.4 - 7.5 (m, 1H), 7.60 (d, $J=16\text{Hz}$,
1H), 7.70 (ddd, $J=7.9, 7.9, 1.8\text{Hz}$, 1H), 8.60 - 8.66 (m, 1H).

16.2 - [2 - (3,5 - - 4 - i -)] (16).

6N HCl 가 (16)
1(d) , 15(b) (15) BBr_3 27%
 $^1\text{H NMR}$ (DMSO, ppm): 1.22 (d, $J=7.0\text{Hz}$, 6H), 3.51 (, $J=7.0\text{Hz}$, 1H), 6.59 (s, 2
H), 7.13 (d, $J=16.4$, 1H), 7.6 - 7.9 (m, 2H), 8.3 - 8.5 (m, 2H), 8.72 (d, $J=6.4\text{Hz}$, 1H).

17.2 - [2 - (3,5 - - 4 - i -)] (17).

15(b) , 15(a) (3,5 - - 4 - i -)
) 78% $^1\text{H NMR}$ (CDCl_3 , ppm):
1.32 (d, $J=7.1\text{Hz}$, 6H), 3.70 (, $J=7.1\text{Hz}$, 1H), 3.89 (s, 6H), 6.69 (s, 2H), 6.90 (d, $J=16\text{Hz}$, 1H), 7.
0 - 7.3 (m, 4H).

18.2 - i - - 5 - (2 - - 2 -) - 1,3 - (18).

2(b) , 17 2 - [2 - (3,5 - - 4 - i -)]
) 24% $^1\text{H NMR}$ (CDCl_3 , ppm):
1.40 (d, $J=7.1\text{Hz}$), 3.47 (, $J=7.1\text{Hz}$, 1H), 4.8 (b, 2H), 6.48 (s, 2H), 6.74 (d, $J=16\text{Hz}$, 1H), 7.0 - 7.1
(m, 3H), 7.2 - 7.3 (m, 1H).

19.2 - [2 - (3,5 - - 4 - i -)] (19).

15(b) , 15(a) (3,5 - - 4 - i -)
) 2 - 56% .¹H NMR (CDCl₃, ppm): 1.32 (d, J=7.1Hz, 6H), 3.62 (, J=7.1Hz, 1H), 3.89 (s, 6H), 6.4 - 6.5 (m, 2H), 6.68 (s, 2H), 6.85 (d, J=16.2Hz, 1H), 7.06 (d, J=16.2Hz, 1H), 7.45 (b, 1H).

20.5 - (2 - - 2 -) - 2 - i - - 1,3 - (20).

0 (100mL) 5 - (2 - - 2 -) - 2 - i - - 1,3 - (12)(3.93)
 (10.8) 가 . TLC
 (30), (50mL) 가 . 2N HCl(30mL), H₂O(50mL), NaHCO₃ (50mL),
 H₂O(50mL) (50mL) 5%
 5 - (2 - - 2 -) - 2 - i - - 1,3 -
 (20)

21.2 - (3,5 - - 4 - i -) - 3 - (21).

2 - (3,5 - - 4 - i -) - 3 - (7)
 40% KOH , 2N HCl 가 pH 1 .
 3 Na₂SO₄
 (21)

22.3 - (3,5 - - 4 - i -) - 2 - (22).

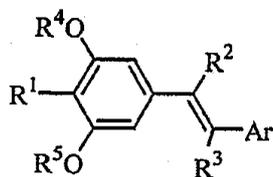
3 - (3,5 - - 4 - i -) - 2 - (10)
 (10) 40% KOH , 2N HCl 가 pH 1 .
 3 Na₂SO₄
 (22)

(57)

1.

I :

I



R¹

- a) H,
- b) , , , ,
- c) ,
- d) CN,
- e) COOR⁶,
- f) NR⁷R⁸,
- g) S(O)₂NR⁷R⁸,
- h) COR⁹,
- i) OR¹⁰,
- j) S(O)_nR¹¹, n=0 - 2,
- k)

;

R² R³

- a) H,
- b) , , , ,
- c) ,
- d) CN,
- e) COOR⁶,
- f) NR⁷R⁸,
- g) S(O)₂NR⁷R⁸,
- h) COR⁹,
- i) OR¹⁰,
- j) S(O)_nR¹¹, n=0 - 2,
- k)

;

$R^4 \quad R^5$

a) H,

b) , , ,

c)

;

R^6

a) H,

b) , , ;

$R^7 \quad R^8$

a) H,

b) , ,

;

R^9

a) H,

b) , , ,

c) $NR^7 R^8$

;

R^{10}

a) H,

b) , , ,

c)

;

R^{11}

a) H,

b) , ,

;

Ar

a) , (, R² R³ H가),

b) O, S / N , , 5 ,

c) O, S / N , , 6

;

Z E .

2.

1 , R¹ , , ,
.

3.

1 , R² R³

a) H,

b) , , ,

.

4.

3 , R¹ , , ,
.

5.

1 , R² R³

a) CN,

b) COOR⁶,

c) COR⁹

.

6.

5 , R¹ , , ,
.

7.

2, 4 6 , R¹

8.

7 , R¹

9.

1 , Ar

a) O, S / N , , 5 ,

b) O, S / N , , 6

10.

1 , Ar

11.

5 - (1 - 2 -) - 2 - i - - 1,3 - ;

5 - [1 - (4 -) - 2 - (4 -)] - 2 - i - - 1,3 - ;

5 - [1 - (3 -) - 2 - (3 -)] - 2 - i - - 1,3 - ;

5 - [1 - (3,5 -) - 2 - (3,5 -)] - 2 - i - - 1,3 - ;

5 - (1 - 2 -) - 2 - i - - 1,3 - ;

2 - (3,5 - - 4 - i -) - 3 - ;

2 - (3,5 - - 4 - i -) - 3 - ;

5 - (2,2 -) - 2 - i - - 1,3 - ;

3 - (3,5 - - 4 - i -) - 2 - ;

3 - (3,5 - - 4 - i -) - 2 - ;

1 - (3,5 - - 4 - i -) - 3 - ;

5 - (2 - 2 -) - 2 - i - - 1,3 - ;

2 - [2 - (3,5 - - 4 - i -)] ;

2 - [2 - (3,5 - -4 - i -)] ;

2 - [2 - (3,5 - -4 - i -)] ;

2 - i - -5 - (2 - -2 -) - 1,3 - ;

2 - [2 - (3,5 - -4 - i -)] ;

5 - (2 - -2 -) - 2 - i - - 1,3 - ;

2 - (3,5 - -4 - i -) - 3 - ;

3 - (3,5 - -4 - i -) - 2 -

| .

12.

1 | 가 .

13.

11 가 .

14.

, 1 | .

15.

11 .

16.

T - , (neutrophil), (macrophage) (cytokine)
1 | 11 .

17.

16 , , 가 .

18.

1 | 11 가 .