(19) (KR)
(12) (B1)

(45) 2010 04 21
(11) 10-0953990
(24) 2010 04 13

(51) Int. Cl.
C07C 323/18 (2006.01) *C07C 317/14* (2006.01)
(21) 10-2008-7015303( )
(22) ( ) 1998 05 14
2008 06 23
(85) 2008 06 23
(65) 10-2008-0066885
(43) 2008 07 16
(62) 10-2006-7026799
( ) 1998 05 14
2006 12 19
(86) PCT/US1998/009781
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60/047,020 1997 05 14 (US)
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EP0190682 A2*
JP02085246 A*
JP02520161 B9*
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(73)
,
30004
8995
(72)
.
30350 7935
.
30319 1162
( )
(74)

: 22 :

(54) -1

(57)

VCAM-1(vascular cell adhesion molecule-1) , ,
VCAM-1 .

(72) .
.
30092
30136 412 3353-

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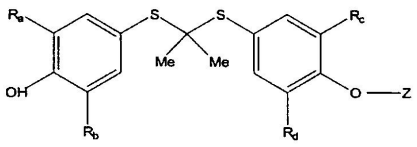
II :



(II)

, R_a, R_b, R_c R_d , , , ,

; R_a, R_b, R_c R_d , , , , , ,

, , ,

Z , , , , , , , , -(CH_2)-R_e

,

R_e , , , , , NH_2, NHR, NR_2, - - , ,

, , COOH, COOR, -$CH(OH)R_k$, , $C(O)NH_2$, C(O)NHR, $C(O)NR_2$,

R , , , , -COOH, -COO , -COO , ,

2 R 5 7

C_{1-10} ,

,

-O- ,

, ,

, , , , , ,

C(O)R' , R' , ,

-O- ,

, , , , , , , , ,

, , , , , , ,

1 .

11

10 , R_a, R_b, R_c R_d , C_{1-10} , Z

, , , -(CH_2)-R_e

.

12

11 , II

:

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

R_a=1- ,R_b=t- ,R_c= , R_d= ;Z=4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=t- ;

R_a=t- ,R_b=t- ,R_c=H, R_d=H;Z=4- ;

R_a=t- ,R_b=t- ,R_c=H, R_d=H;Z=3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-(2-);

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-2- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=CO- ( );

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -2- - ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- -2- :

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3-(2- -2-) -2- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4-N,N- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3-(N,N-) ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=1,3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3-(1,3-) ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,- -4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3-(5- -5-) ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CH_2CONH-(CH_2)CH(NH_2)COOH;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=$CH_2CONHCH$(COOet)CH_2CH_2(COOet);

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,4,5,6- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=2- -3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=2- -3- ;

R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=$CH_2CH(OH)CH_2NH$(2,3,4,5,6- .

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(ACE) β-
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37

38

39

15 17 , .

40

39 , 5 1500 mg .

41

39 , 25 750 mg .

42

15 17 , .

43

15 17 , .

44

15 17 , .

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15 17 , .

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15 17 , .

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15 17 , .

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15 17 , .

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15 17 , .

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15 17 , .

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15 17 , .

[0001] VCAM-1 , , VCAM-1 .

[0002] (CHD) . CHD .

[0003] . (foam cells) . . , .

[0004] , , VCAM-1 .

[0005] VCAM-1

[0006] (endothelium) ,
.
.
-1 (vascular cell adhesion molecule-1: VCAM-1), -1 (intracellular adhesion molecule-1: ICAM-1) E- (E-selectin)
, (,) .
VLA-4 VCAM-1
. ( ) VLA-4 , VCAM-1
. ,
, , , , , ,
(chemoattractants)
.

[0007] VCAM-1 , . ,
VCAM-1 ICAM-1 . Pilewski, J.M. , Am. J. Respir. Cell Mol. Biol. 12, 1-3 (1995); Ohkawara, Y. , Am. J. Respir. Cell Mol. Biol, 12, 4-12 (1995). , VCAM-1 ICAM-1 (VLA-4 LFA-1)
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, , VCAM-1
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[0009] VCAM-1 (LPS) (TNF-α) -1 (IL-1)
.
.

[0010] Medford 5,380,747
.

[0011] Medford 5,750,351 Emory University WO95/30415
(LDL: low density lopoproein) ("PUFAs": polyunsaturated fatty acids) ("ox-PUFAs")
VCAM-1 , -1 (ICAM-1)
E- . VCAM-1
.

[0012] , , , , (13-HPODE)
(15-HPETE) VCAM-1 - ICAM-1 E-
. ( ) ( ) VCAM-1, ICAM-1 E-
.

[0013] PUFAs VCAM-1 (PDTC)

. ,
(,), (,) ,

.

[0014]

. PUFAs ox-PUFAs
.

[0015] , WO95/30415 ($C_{18}\Delta^{9,12}$), ($C_{18}\Delta^{6,9,12}$), ($C_{20}\Delta^{5,8,11,14}$) ($C_{20}\Delta^{8,11,14}$) ( )
, , , -
, , (angina), VCAM-1
.

[0016] VCAM-1 , ,
.

[0017] _____

[0018] .
. : (chylomicrons),
(VLDL: very low-density lipoproteins), (LDL: low-density lipoproteins),
(HDL: high-density lipoproteins).
. VLDL
. LDL
. HDL .
LDL . Brown Goldstein, Ann. Rev. Biochem. 52, 223 (1983); Miller, Ann. Rev. Med. 31, 97 (1980). LDL .

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LDL (ox-LDL)
. LDL ,
-
. (13-HPODE) R
LDL .

[0020] LDL
. . LDL
. ,
, (PUFA)
.
, (PUFA) .

[0021] LDL HPLC ,
LDL 13-HPODE . LDL
- VCAM-1
.

[0022] , LDL
. , , , / LDL ox-LDL
. LDL (take up) LDL , " "
ox-LDL , LDL ,

. , ox-LDL (fatty streak)
- - .

[0023] . , 1984 12 ,
National Institute of Health Consesnsus Development Conference Panel (
)
.

[0024] , , (VLDL),
(LDL) (HDL) - . LDL
LDL HDL
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LDL , HDL
[Patton , Clin. Chem. 29, 1980(1983)].
LDL
.

[0025] , LDL LDL
/
.
. , LDL
. , /
LDL .
, LDL /
[Parthasarathy , J. Clin. Invest. 77,641 (1986)]. ,
LDL .

[0026] (restenosis), , (xanthoma)
. , , , ,
.

[0027] LDL ( ) , LDL
. LDL ,
( ), 3- -3- A (HMG CoA) .
(Probucol) , . HMG CoA
(statins) (vastatins) .
(Pravchol, Bristol Myers Squibb),
(Warner Lambert/Pfizer), (Zocor , Merck), (Mecavor , Merck),
(Lescol) .

[0028] (LDL)
. LDL .
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LDL- - .
,
.

[0029] 2,[3]-3 - -4- (BHA) 2,6- -3 - -4-
(BHT) . 4,4'-( ) (2,6- -3 -
) .

[0030] .
Lorelco™ . ,

. ,

. ,

. ,

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20 . (Kazuya , J. Lipid Res.32; 197-204 (1991)

50 μM 24 1 μg /10^6

.

[0031] Parthasarathy 5,262,439 2

, . ,

, , , , , - -

. , , ,

, , ,

- - .

[0032] :

FR 2168137 (-4-); FR 2140771 ( ); FR 2140769 ( ); FR 2134810 (-(3- -5-t- -4- -5-)) ; FR 2133024 (-(4-) ; FR 2130975 ((4-)).

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[0035] Hall 4,752,616 . .

[0036] Adir et Compagnie . Reginer 5,206,247 5,627,205 (621 255) 763 527 .

[0037] Nippon Shinyaku Co. Ltd. WO97/15546 , , PTCA .

[0038] Dow Chemical Company 2-(3,5- -3 - -4-) . , Wagner 4,029,812 , 4,076,841 4,078,084 , .

[0039] , 90% , . , , VCAM-1 . .

[0040] ,
.

[0041] LDL .

[0042]
.

[0043] LDL .

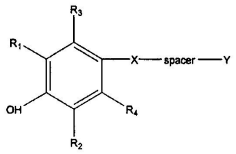
[0044] VCAM-1 ,
.

[0045] , MCP-1, IL-6
.

[0046] _____

[0047] VCAM-1 , , , I
II ,
, VCAM-1 .

[0048] [I]



(I)

[0049]

[0050] , X O, S, SO, SO_2, CH_2 NH;

[0051] (spacer) $-(CH_2)_n-$, $-(CH_2)_n-CO-$, $-(CH_2)_n-N-$, $-(CH_2)_n-O-$, $-(CH_2)_n-S-$, $-(CH_2O)-$, $-(OCH_2)-$, $-(SCH_2)-$, $-(CH_2S-)$, -(-O)-, -(O-)-, -(-O)-, -(O-)-;

[0052] n 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 10;

[0053] Y , , , ,
, , ,
, , ,
, NH_2, NHR, NR_2, SO_2-OH, OC(O)R, C(O)OH, C(O)OR, $C(O)NH_2$, C(O)NHR, $C(O)NR_2$, SO_2NH_2, SO_2NHR, SO_2NR_2;

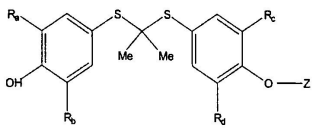
[0054] R , , , , , , , , -COOH, -COO ,
-COO , , , , 2 R 5 7
;

[0055] R^1 R^2 , , , , ,
, , ; R^1 R^2 , , , ,
, , , , ;

[0056] R^3 R^4 H, H,
R^1 .

[0057] II :

[0058] [II]



(II)

[0059]

[0060] , R_a, R_b, R_c R_d

, , , , , , ,

, , ; R_a, R_b, R_c R_d ,

, , , , , , , , ;

[0061] Z , , , , , , , , ,

, , , -(CH_2)-R_e, -C(O)-R_g, -C(O)-$(CH_2)_n$-R_h, (a) R_a, R_b, R_c R_d

t- , Z (b) R_a, R_b, R_c R_d t- Z

;

[0062] R_e , , , , , , , , ,

, NH_2, NHR, NR_2, - - , , , ,

, , , COOH, COOR, -CH(OH)R_k, , C(O)NH_2, C(O)NHR, C(O)NR_2;

[0063] R_g , , , , , , , , ,

, NH_2, NHR, NR_2, - - , , , ,

;

[0064] R_h , , , , , , , , ,

, NH_2, NHR, NR_2, - - , , , ,

, , , COOH, COOR, -CH(OH)R_k, , O- , C(O)NH_2, C(O)NHR,

C(O)NR_2 ;

[0065] , , R_e, R_g R_h , C(O)- -SO_3H

( ), C(O)- -SO_3M (M

), C(O)- -PO_3H_2, C(O)- -PO_3M_2, C(O)- -

PO_3HM, C(O)- -PO_4H, C(O)- -PO_4M, SO_3M, -PO_3H_2, -PO_3M_2,-PO_3HM, ,

, , (CO)- -$[O(C_{1-3})_p]_n$ (n , p 1, 2, 3),

-$[O(C_{1-3})_p]_n$, , , N,N- ,

, , , , , ,

, , N- , , N- ,

, , , .

[0066] I II

.

[0067] I II LDL

.

[0068] , , -

-

.

[0069] -

(IL-1β), (MCP-1), (IL-6), (VCAM-1 E-) .

[0070] , C_{1-10} , 1 , 2 , 3 , , , , , , , t- , , , , , , , , , 3- , 2,2- , 2,3- . , , , , , , , , , , , , , , , , , , , Greene Protective Groups in Organic Synthesis, John Wiley and Sons, 2 , 1991 ( ) .

[0071] C_{1-5} , ( ) .

[0072] 1 10 (hydrocarbyldiyl) . , 1,2- - , 1,1- - , 1,3- - , 1,2- - , 1,3- -3 , 1,4- - . , , , , , , , , , , , , , , , , , , Greene Protective Groups in Organic Synthesis, John Wiley and Sons, 2 , 1991 ( ) .

[0073] "-$(CH_2)_n$-" . "n" 0 10 . "-$(CH_2)_n$-" (, n=0), , 1,2- 1,3- .

[0074] , , , . . , , . , , , , , , , , , , , , , , , , , , Greene Protective Groups in Organic Synthesis, John Wiley and Sons, 2 , 1991 . ; ; ; ; 3,4,5- ; 3,4,5- ; 3,4,5- ; 4- ; 4- ; 3,5- -3 -4- ; 4- ; 4- -1- ; 2- -1- ; 2- ; 4- ; 4-3 ; 4-3 .

[0075] " " , , , . .

[0076] , , .

[0077] , , O- , .

[0078] C(O)R' , R' , , , , , , .

[0079] (PUFA) 2 (C_{8-24}), ($C_{18}\Delta^{9,12}$), ($C_{18}\Delta^{6,9,12}$), ($C_{20}\Delta^{5,8,11,14}$)

.

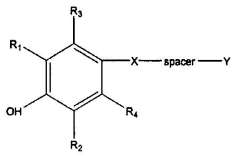
[0080] (ox-PUFA)
. 13-HPODE 15-HPETE .

[0081]
. (a)
(, , , , ,), , , , , ,
, , , , , , ,
; (b) , , , , , , ,
, , , , , ,
N,N- , D- , ,
; (c) (a) (b) ; , .
4 , ~NR⁺A⁻ 4 ,
, R , A , , , O- ,
, , , , (, ,
, , , , , , , ,
, , ,) .

[0082] VCAM-1 , - , ,
, , , , , , ,
.

[0083] , I , VCAM-1
:

[0084] I



(I)

[0085]

[0086] , X O, S, SO, SO_2, CH_2 NH;

[0087] (spacer) $-(CH_2)_n-$, $-(CH_2)_n-CO-$, $-(CH_2)_n-N-$, $-(CH_2)_n-O-$, $-(CH_2)_n-S-$, $-(CH_2O)-$, $-(OCH_2)-$, $-(SCH_2)-$, $-(CH_2S-)$, -(-O)-, -(O-)-, -(-O)-, -(O-)-;

[0088] n 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 10;

[0089] Y , , , ,
, , ,
, , ,
, NH_2, NHR, NR_2, SO_2-OH, OC(O)R, C(O)OH, C(O)OR, $C(O)NH_2$, C(O)NHR, $C(O)NR_2$, SO_2NH_2, SO_2NHR, SO_2NR_2;

[0090] R , , , , , , , , -COOH, -COO ,
-COO , , , , 2 R 5 7
;

[0091] R^1 R^2 , , , , ,
, , ; R^1 R^2 , , , ,
, , , , ;

[0092] R^3 R^4 H, H,

R^1 .

[0093] :

[0094] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y , , ,
, NH_2, NHR, NR_2, , , , ; R , , ,
, -COOH, -COO , -COO , , ,
, 2 R 5 7 ; R^1 R^2 ,
C_{1-10} ; R^3 R^4 , R^1 I .

[0095] :

[0096] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y , , ,
, NH_2, NHR, NR_2, , , , ; R , , ,
, -COOH, -COO , -COO , , ,
, 2 R 5 7 ; R^1 R^2 ,
C_{1-5} ; R^3 R^4 I .

[0097] :

[0098] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , ,
, , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), ,
- , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR -
; ; , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR -
; NH_2; NHR; NR_2; ; OCOR, SO_2OH, COOH COOR ,
; OCOR; R , , , , -COOH, -COO , -COO ,
, , , 2 R 5 7
; R^1 R^2 , C_{1-5} ; R^3 R^4
I .

[0099] :

[0100] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , ,
, , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), ,
- , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR -
; R , , , , -COOH, -COO , -COO , ,
, , 2 R 5 7 ; R^1 R^2
C_{1-5} ; R^3 R^4 I .

[0101] :

[0102] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , ,
, , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), ,
- , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR -
; R , , , , -COOH, -COO , -COO , , ,
, , 2 R 5 7 ; R^1 R^2
C_{1-5} ; R^3 R^4 I .

[0103] :

[0104] X S, SO, SO_2; $-(CH_2)_n-$; n 0-10, Y ; , , , , , , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), , - , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR - ; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R , - COOH, -COO ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0105] :

[0106] X S, SO, SO_2; $-(CH_2)_nCO-$; n 0-10, Y ; , , , , , , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), , - , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR - ; R , , , -COOH, -COO , -COO , , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0107] :

[0108] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , , , , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), , - , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR - ; R , -COOH, -COO , -COO , , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0109] :

[0110] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , , , , COOH, COOR, $CONH_2$, CONHR, $CONR_2$, $-(CH_2)_m-OH$ (m 0-10), , - , , SO_2OH, SO_2NH_2, SO_2NHR, SO_2NR_2 OCOR - ; R , -COOH, -COO , -COO , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0111] :

[0112] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y ; , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR - ; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0113] :

[0114] X S, SO, SO_2; $-(CH_2)_n-$; n 0-10, Y ; , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR - ; R , , , , -COOH,

-COO , -COO , , , , 2
R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4
I .

[0115] :

[0116] X S, SO, SO_2; -$(CH_2)_nCO$-; n 0-10, Y ; , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR -; R , , , , -COOH, -COO , -COO , , , 2
R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4
I .

[0117] :

[0118] X S, SO, SO_2; -$(CH_2)_n$- -$(CH_2)_nCO$-; n 0-10, Y , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR ; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0119] :

[0120] X S, SO, SO_2; -$(CH_2)_n$- -$(CH_2)_nCO$-; n 0-10, Y , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR ; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0121] :

[0122] X S, SO, SO_2; -$(CH_2)_n$- -$(CH_2)_nCO$-; n 0-10, Y , , , CH_2NH_2, CH_2NHR, CH_2NR_2, COOH, COOR ; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0123] :

[0124] X S, SO, SO_2; -$(CH_2)_n$- -$(CH_2)_nCO$-; n 0-10, Y NH_2, NHR, NR_2; R , , , , -COOH, -COO , -COO , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0125] :

[0126] X S, SO, SO_2; -$(CH_2)_n$- -$(CH_2)_nCO$-; n 0-10, Y NH_2, NHR, NR_2; R , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0127] :

[0128] X S, SO, SO_2; $-(CH_2)_n-$; n 0-10, Y NH_2, NHR, NR_2; R , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0129] :

[0130] X S, SO, SO_2; $-(CH_2)_nCO-$; n 0-10, Y NH_2, NHR, NR_2; R , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0131] :

[0132] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y , ; OCOR, SO_2OH, COOH COOR , , ; OCOR ; R , , , , 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0133] :

[0134] X S, SO, SO_2; $-(CH_2)_n-$ $-(CH_2)_nCO-$; n 0-10, Y , ; OCOR, SO_2OH, COOH COOR , , ; OCOR ; R 2 R 5 7 ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0135] :

[0136] X S, SO, SO_2; $-(CH_2)_n-$; n 0-10, Y , ; OCOR, SO_2OH, COOH COOR , , ; COOR ; R ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0137] :

[0138] X S, SO, SO_2; $-(CH_2)_nCO-$; n 0-10, Y , ; OCOR , , ; R ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0139] :

[0140] X S, SO, SO_2; $-(CH_2)_n-$; n 0-10, Y OCOR; R ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0141] :

[0142] X S, SO, SO_2; $-(CH_2)_nCO-$; n 0-10, Y OCOR; R ; R^1 R^2 C_{1-5} ; R^3 R^4 I .

[0143] I :

[0144] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0145] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0146] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-$(CH_2)_2$-;Y=4- ;

[0147] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=2- ;

[0148] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=3,5- -t- -4- ;

[0149] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0150] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=1- -1- ;

[0151] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=3- ;

[0152] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=2,4- ;

[0153] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0154] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=2- ;

[0155] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4-(N,N-) ;

[0156] X=SO;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0157] X=SO_2;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0158] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0159] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0160] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4- ;

[0161] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y= ;

[0162] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=2- ;

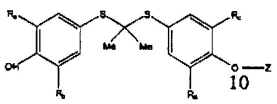
[0163] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-$(CH_2)_3$-;Y= ;

[0164] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-$(CH_2)_5$-;Y= ;

[0165] X=S;R^1=t- ;R^2=t- ;R^3=H;R^4=H; =-CH_2-;Y=4-(2-) .

[0166] II II , VCAM-1 :

[0167] II

[0168]  (II)

[0169] , R_a, R_b, R_c R_d , , (3 -) ,
, , , , , ,
; R_a, R_b, R_c R_d , , , , , , ,
, , ;

[0170] Z , , , , , , , , , ,
, , , -(CH_2)-R_e, -C(O)-R_g, -C(O)-$(CH_2)_n$-R_h, (a) R_a, R_b, R_c R_d
t- , Z (b) R_a, R_b, R_c R_d t- Z
;

[0171] R_e , , , , , , , , ,
, NH_2, NHR, NR_2, - - , , , ,
, , , COOH, COOR, -CH(OH)R_k, , C(O)NH_2, C(O)NHR, C(O)NR_2;

[0172] R_g , , , , , , , , ,
, NH_2, NHR, NR_2, - - , , , ,
;

[0173] R_h , , , , , , , , ,
, NH_2, NHR, NR_2, - - , , , ,
, , , COOH, COOR, -CH(OH)R_k, , O- , C(O)NH_2, C(O)NHR, C(O)NR_2
;

[0174] , , R_e, R_g R_h , C(O)- -SO_3H
( ), C(O)- -SO_3M (M
), C(O)- -PO_3H_2, C(O)- -PO_3M_2, C(O)- -
PO_3HM, C(O)- -PO_4H, C(O)- -PO_4M, SO_3M, -PO_3H_2, -PO_3M_2, -PO_3HM, ,
, , (CO)- -[O(C_{1-3})$_p$]$_n$ (n , p 1, 2, 3),
-[O(C_{1-3})$_p$]$_n$, , , N,N- ,
, , , , ,
, , N- , , N- ,
, , , .

[0175] , , , , , , , ,
, , , , COOR, $CONH_2$, CONHR, $CONR_2$, , , -
, CH_2-OR, CH_2-OH, OCOR, O- , SO_2-NH_2, SO_2-NHR, SO_2-NR_2 .

[0176] :

[0177] R_a, R_b, R_c R_d , C_{1-10} ; Z , , ,
, , , , , -(CH_2)-R_e, -C(O)-R_g, -C(O)-$(CH_2)_n$-R_h
II .

[0178] :

[0179] R_a, R_b, R_c R_d , C_{1-5} ; Z , , ,
, , , , , -(CH_2)-R_e, -C(O)-R_g, -C(O)-$(CH_2)_n$-R_h
II .

[0180] :

[0181] R_a, R_b, R_c R_d , C_{1-5} ; Z , , , , , , -CH_2- , , -(CH_2)-NR_2, -CH_2- , -CH_2-CHOH, -CH_2- , -CH_2- , -CH_2- , -CH_2-OCO- , -CH_2-OCO- , -CH_2-COOR, -$CH_2CH(OH)CH_2NHCH_2COOR$, -CH_2-CH(OH)- (, CH_2OH, CH_2OCHOH-), -CO- , -CO- , -CO- , -CO- , -CO$(CH_2)_n$-COOR, -CO-$(CH_2)_n$-OH, -CO-$(CH_2)_n$- , -CO$(CH_2)_n$- , -CO-$(CH_2)_n$-CONH(CH_2)COOR, -CO-$(CH_2)_n$-CON$((CH_2)COOR)_2$, , II .

[0182] :

[0183] R_a, R_b, R_c R_d , C_{1-5} ; Z , , , , , - , , , , , , , , , , , - , - , - , , , , , , , , N,N- , , ( ) ( ) , , , CO- , CO- , CO- , CO- , CO- , CO- , CO- , CO- , CO- , CO- , CO-( )( ) , , CO- II .

[0184] II :

[0185] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

[0186] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-$(CH_2)_2$-COOH;

[0187] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-(5- -2-);

[0188] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

[0189] R_a=1- ,R_b=t- ,R_c= , R_d= ;Z=4- ;

[0190] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

[0191] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

[0192] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=t- ;

[0193] R_a=t- ,R_b=t- ,R_c=H, R_d=H;Z=4- ;

[0194] R_a=t- ,R_b=t- ,R_c=H, R_d=H;Z=3- ;

[0195] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0196] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2-($CONH_2$) ;

[0197] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO- ;

[0198] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-(2-);

[0199] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-(2-);

[0200] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO- ;

[0201] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-3- ;

[0202] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

[0203] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-2- ;

[0204] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=CO- ( ):

[0205] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -2- - ;

[0206] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- -2- :

[0207] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3-(2- -2-) -2- ;

[0208] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0209] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3- ;

[0210] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,4- ;

[0211] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3- ;

[0212] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3- ;

[0213] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0214] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

[0215] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4-N,N- ;

[0216] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-2- ;

[0217] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-2- (L-);

[0218] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

[0219] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

[0220] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0221] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3-(N,N-) ;

[0222] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- ;

[0223] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0224] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=1,3- ;

[0225] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3-(1,3-) ;

[0226] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,- -4- ;

[0227] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2- -3-(5- -5-) ;

[0228] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

[0229] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=4- ;

[0230] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0231] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CO-3- ;

[0232] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=3- ;

[0233] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CH_2CONH-(CH_2)CH(NH_2)COOH;

[0234] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=CH_2CONHCH(COOet)CH_2CH_2(COOet);

[0235] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z= ;

[0236] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ;Z=2,3,4,5,6- ;

[0237] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=CO-3-(2-) ;

[0238] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=CO-2,2- -3- ;

[0239] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=2- -3- ;

[0240] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=2- -3- ;

[0241] R_a=t- ,R_b=t- ,R_c=t- , R_d=t- ; Z=CH_2CH(OH)CH_2NH(2,3,4,5,6- .

[0242] I . I Scheme A . , .

[0243] Scheme A

[0244] , 4- -2,6- -t- (Laufer 3,129,262 ,). , .

[0245] 4- -2,6- -t- 0.5M 1,2 (5N) . 5 , 1,2 24 . 1N HCl pH 7 . .

[0246] Scheme A . , (I) , , 2,6- -3 -4- 3,576,883 , 3,952,064 , 3,479,407 73-28425 .

[0247] , I , 2,6- -4- ( ) .

[0248] 2,6- - . , , 2- , , t- ; 1- ; ; ; . .

[0249] Scheme A . . , "g" ;, "mmol" ; "mL" ; "bp" ; " " ; "mmHg" ; "mp" ; "mg" ; "μM" ; "μg" .

[0250] , VCAM-1 VCAM-1 , VCAM-1 .

[0251] **1**

[0252] **2,6- -3 - -4- (4'-( ))**

[0253] :

[0254] 2,6- -t- -4- (238mg, 1mmol) (0.7mL) 0 . 5N NaOH(0.6mL, 3mmol) 4-( ) (229mg, 1mmol) . 0.5 . 1N HCl (3.5mL) (25mL) . (1x5mL) (1x5mL) $MgSO_4$. 50:50 / (2,6- -3 - -4- (4'-( )) 170mg .

^{1}H NMR ($CDCl_3$, 400 MHZ): δ 7.24 (s, 2 H), 7.17 (d, J = 8.4 Hz, 2 H), 7.11 (d, J = 8.4 Hz, 2 H), 5.20 (s, 1 H), 3.91 (s, 2 H), 3.59 (s, 2 H), 1.33 (s, 18 H).

[0255]

[0256] **2**

[0257] **2,6- -3 - -4- (4'-)**

[0258] :

[0259] 0.5mL EtOH 0.28 mmol(68mg) 2,6- -t- -4- 0 NaOH (5N) 0.3 mmol (0.06ml) . 5 , 4- 0.29 mmol (62mg) . TLC (1:1 - $-CH_2Cl_2$; UV PMA/) . 2 . NaCl-EtOAc . 2x2ml EtOAc ; $MgSO_4$. ; . 2 x 500 μ 1:1 $-CH_2Cl_2$ (pTLC) . (2,6- -3 - -4- (4'-)) 86% (90mg) .

^{1}H NMR ($CDCl_3$, 400 MHZ): δ 8.10 (d, J = 8.8 Hz, 2 H), 7.25 (d, J = 8.8 Hz, 2 H), 7.04 (s, 2 H), 5.28 (s, 1 H), 3.98 (s, 2 H), 1.34 (H).

[0260]

[0261] **3**

[0262] **2,6- -3 - -4- (4'-)**

[0263] :

[0264] 2,6- -t- -4- (0.48mmol, 115 mg) THF 2 mL 2 . (60%) 0.67mmol(27mg) , . 4- (0.49mmol; 135mg) . TLC (3x10: 1 $-CH_2Cl_2$; UV PMA/) (NaCl-EtOAc). 2x5 ml EtOAc $MgSO_4$ . . (radial) (10:1 $-CH_2Cl_2$; 4 mm) 2,6- -3 - -4- (4'-) 93mg (50%) . ^{1}H

NMR ($CDCl_3$, 400 MHZ): δ 8.15 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.24 (s, 2 H), 5.26 (s, 1 H), 3.11 (t, J = 7.2 Hz, 2 H), 3.09 (t, J = 7.6 Hz, 2 H), 1.43 (s, 18 H).

[0265]

[0266] **4**

[0267] **2,6- -3 - -4- (3'-)**

[0268] :

[0269] 3- (0.42mmol, 72 mg) 2,6- -3 - (0.42mmol; 100mg) 0.7 mL EtOH 92 μL NaOH (5N) . 19.5 NaCl EtOAc . EtOAc (2x10mL) . , Na_2SO_4 . 2 . 4:1 -EtOAc 2mm(SiO_2) , 2,6- -3 - -4- (3'-) (108mg, 69%) .

8.07 (app d, J = 7.6 Hz, 1 H), 7.87 (s, 1 H), 7.48 (AB d, J = 7.6 Hz, 1 H), 7.42 (AB m, J = 7.6, 8.0 Hz, 1 H), 7.05 (s, 2 H), 5.27 (s, 1 H), 3.99 (s, 2 H), 1.34 (s, 18 H).

[0270]

[0271] **5**

[0272] **2,6- -3 - -4- (2',4'-)**

[0273] :

[0274] 2,4- (0.42mmol, 72 mg) 2,6- -3 - (0.42mmol; 100mg) 0.7 mL EtOH 92 μL NaOH (5N) . 19.5 NaCl EtOAc (25mL) . EtOAc (2x10mL) . , Na_2SO_4 . 4:1 -EtOAc 2mm(SiO_2) , 2,6- -3 - -4- (2',4'-) (37mg, 21%) . ^{1}H NMR($CDCl^3$, 400MHZ); δ8.74(app d, J=2.4Hz, 1) H), 8.24 (dd, J = 8.8, 2.4 Hz, 1 H), 7.29 (d, J = 8.8 Hz, 1 H), 6.98 (s, 2 H), 5.35 (s, 1 H), 4.36 (s, 2 H), 1.34 (s, 18 H).

[0275]

[0276] **6**

[0277] **(2,6- -3 - -4- (4'-( ))**

[0278] :

[0279] 4-( ) (0.42mmol, 72 mg) 2,6- -3 - (0.42mmol; 100mg) 0.7 mL EtOH 92 μL NaOH (5N) . 30 , . 22 NaCl EtOAc . EtOAc (2x10mL) . Na_2SO_4 . 4:1 -EtOAc 2mm(SiO_2) , (2,6- -3 - -4- (4'-( )) (140mg, 84%) .

^{1}H NMR ($CDCl_3$, 400 MHZ): δ 7.48 (AB d, J = 8.0 Hz, 2 H), 7.20 (AB d, J = 8.0 Hz, 2 H), 7.01 (s, 2 H), 5.24 (s, 1 H), 3.93 (s, 2 H), 1.33 (s, 18 H).

[0280]

[0281] **7**

[0282] **2,6- -3 - -4- ((2'-)-5-)**

[0283] :

[0284] 2,6- -3 - (0.49mmol; 116mg) THF (2mL) (0.58 mmol; 23mg; 60%) . 5-( )-2- (0.54mmol; 95mg) . 22 . EtOAc (3x3mL) Na_2SO_4 . 2x500 μ (SiO_2 ; 1:1 -CH_2Cl_2) (132mg; 72%). (0.35mmol; 132mg) 4:1 MeOH-THF-H_2O (3mL) LiOH (1.2mmol; 50mg) . 18 2,6- -3 - -4-)(2'-)-5-) (94mg; 74%) .

[0285] ^{1}H NMR ($CDCl_3$, 400 MHZ): δ 7.21 (d, J = 3.2 Hz, 1 H), 7.19 (s, 2 H), 6.17 (d, J = 3.2 Hz, 1 H), 5.30 (br s, 1 H), 4.00 (s, 2 H), 1.40 (s, 18 H).

[0286] **8**

[0287] **(2,6- -3 - -4- (4'- -N,N-)**

[0288] :

[0289] 2,6- -t- -4- (180mg, 0.755mmol) (1.5ml) 5N NaOH (0.15ml, 0.75 mmol) . 5 , (1.5mL) 4-(N,N-) (210mg, 0.755) . 3 . 1N HCl pH 7 (3mL) (10mL) , $MgSO_4$. 30:70 / , 40:60 ' . 160mg .

[0290] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.08 (s, 2 H), 5.27 (s, 1 H), 2.69 (s, 6 H), 1.36 (s, 18 H).

[0291] **9**

[0292] **2,6- -3 - -4- (4'-)**

[0293] :

[0294] 2,6- -3 - -4- (3'-) (157mg, 0.42mmol) (4.2mL) mCPBA . 15 (15ml) (2x5mL), (1x5ml) (1x5ml) . $MgSO_4$. 30:70 / 80:20 / . (Rf=0.2, 80:20 /) 2,6- -3 - -4- (3'-) 50mg .

[0295] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 8.8 Hz, 2 H), 7.07 (br s, 4 H), 5.57 (br s, 1 H), 4.13 (d, J = 12.4 Hz, 2 H), 4.01 (d, J = 12.4 Hz, 2 H), 1.36 (s, 18 H).

[0296] **10**

[0297] **2,6- -3 - -4-(-(4'-)**

[0298] :

[0299] 2,6- -3 - -4- (3'-) (157mg, 0.42mmol) (4.2ml) mCPBA . 15 , (15ml) (2x5ml),

(1x5ml) (1x5ml) . $MgSO_4$, .
30:70 / 80:20 /
. (Rf=0.5, 80:20 /) 72mg .

[0300] 8.16 (d, J=8.4 Hz, 2 H), 7.38 (s, 2 H), 7.29 (d, J=8.4 Hz, 2 H), 5,84 (s, 1 H), 4.35 (s, 18 H).

[0301] **11**

[0302] **2,6- -3 - -4- (4'-)**

[0303]

[0304] DMF (4.2ml) 2,6- -3 - (0.46mmol; 110mg) (0.63mmol; 25mg; 60%) 15 . 4-( ) (0.42mmol; 77mg) . 6.5 EtOAc (20ml) H_2O (25 ml) . NaCl . 4:1 -EtOAc (SiO_2) 2,6- -3 - -4- (4'-) (38mg, 21%).

[0305] ^1H NMR ($CDCl_3$, 400 MHz): δ 7.17 (AB d, J = 8.8 Hz, 2 H), 7.10 (s, 2 H), 6.97 (AB d, J = 8.8 Hz, 2 H), 5.23 (s, 1 H), 3.94 (s, 2 H), 2.29 (s, 3 H), 1.37 (s, 18 H).

[0306] **12**

[0307] **2,6- -3 - -4- (4'-)**

[0308]

[0309] 1.6 ml THF 2,6- -3 - 0.64mmol (153mg) (60%) 0.85mmol(34mg) - . 4- (0.66mmol; 122mg) . . TLC (;UV PMA/) . 24 , TLC (PMA -). NaCl-EtOAc . 2x5ml EtOAc ; $MgSO_4$.
2x500μ TLC (SiO_2) 2 .
(2,6- -3 - -4- (4'-)) 32% .

[0310] ^1H NMR ($CDCl_3$, 400 MHz): δ 7.10 (s, 2 H), 7.07 (s, 4 H), 5.22 (s, 1 H), 3.94 (s, 2 H), 2.33 (s, 3 H), 1.38 (s, 18 H).

[0311] **13**

[0312] **2,6- -3 - -4- (4'-)**

[0313]

[0314] 0.7ml EtOH 2,6- -3 - (0.46mmol; 110mg) NaOH (5N) 92μL . 4- (0.42mmol; 52μL) 24 . NaCl EtOAc (20mL) . 2x10ml EtOAc . Na_2SO_4 . 100% 19:1 -1EtOAc MPLC (SiO_2) 119mg . 2x500μ SiO_2 19:1 -EtOAc (pTLC) 2,6- -3 - -4- (4'-) (34mg; 34%) .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09 (AB t, J = 8.8 Hz, 2 H), 7.07 (s, 2 H), 6.92 (AB t, J = 8.8 Hz, 2 H), 5.23 (s, 1 H), 3.91 (s, 2 H), 1.36 (s, 18 H).

[0315]

[0316] **14**

[0317] **2,6- -3 - -4- (3'-)**

[0318]

[0319] EtOH 2,6- -3 - (0.84mmol; 200mg) 3- (0.92mmol; 207mg) NaOH(5N) 0.18 mL . 90 0.3N HCl 1 ml 10mL EtOAc . $MgSO_4$, SiO_2 ( ), ; 100% CH_2Cl_2 4:1 CH_2Cl_2-MeOH (100mL) 0.4mL AcOH 4:1 CH_2Cl_2-MeOH. 2,6- -3 - -4- (3'-) (126mg; 42%).

^{1}H NMR ($(CD_3)_2SO$, 400 MHz): δ 7.06 (s, 2 H), 2.88 (app t, J = 7.2, 7.6 Hz, 2 H), 2.52-2.48 (m, 2 H), 1.88 (s, 2 H), 1.80 (pent, J = 7.2, 7.6 Hz, 2 H), 1.35 (s, 18 H). LRMS: Neg. Ion ES 359 (M-H).

[0320]

[0321] **15**

[0322] **2,6- -3 - -4- (5'- -2'-(( )))**

[0323]

[0324] 2.4ml THF 2,6- -3 - -4- (0.24mmol; 112mg) 2-(( ))-5-( ) (0.13mmol; 25 mg) 0.13 mmol(32mg) . 60 . (2mm SiO_2 ; 95:5 CH_2Cl_2-MeOH) 7.3mg (7.5%) .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s, 2 H), 6.22 (d, J = 3.2 Hz, 1 H), 5.97 (d, J = 3.2 Hz, 1 H), 5.22 (br s H), 3.95 (s, 2 H), 3.72 (s, 2 H), 2.37 (s, 6 H), 1.40 (s, 18 H).

[0325]

[0326] **16**

[0327] **2,6- -3 - -4- (3'-( )))**

[0328]

[0329] DMF 1.5mL 0.5 mmol(119mg) 2,6- -3 - (60%) 0.55 mmol(22mg) . 3-( ) (0.5mmol; 79mg) 2 . TLC(1:1 -CH_2Cl_2; UV PMA/) . 0.5mmol NaOH (5N) . TLC UV- (Rf;) . NaCl-EtOAc . EtOAc $MgSO_4$ . . . 2 x 500μ (SiO_2) EtOH (pTLC) 2,6- -3 - -4- (3'-( )))) (61mg; 37%) .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (s, 2 H), 5.20 (s, 1 H), 2.85 (t, J = 7.6, 7.2 Hz, 2 H), 2.37 (t, J = 7.6, 7.2 Hz, 2 H), 2.20 (s, 6 H), 1.77 (q, J = 7.6, 7.0 Hz, 2 H), 1.42 (s, 18 H).

[0330]

[0331] **17**

[0332] **2,6- -3 - -4- ((1'-( ))**

[0333]

[0334] 2,6- -3 - -4- (0.84mmol; 200mg) 7.6ml DMF NaH(60%) 1.1 mmol(46mg) . 15 , 5- 0.76 mmol(0.12ml) . 25 EtOAc 20ml H_2O (25ml) . . (2mm SiO_2 ; 85:15 -EtOAc) 2,6- -3 - -4- ((1'-( )) (93mg, 30%) .

[0335] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 2 H), 5.20 (s, 1 H), 4.05 (app t, J = 6.4, 7.2 Hz, 2 H),

[0336] 2.83 (app t, J = 6.8, 7.2 Hz, 2 H), 2.04 (s, 3 H), 1.66-1.58 (br m, 4 H), 1.50-1.42 (br m, 2 H), 1.43 (s, 18 H).

[0337] **18**

[0338] **2,6- -3 - -1- -4- (4'-))**

[0339]

[0340] (2,6- -3 -4- (4'-( )) (60mg, 0.15mmol) (0.75 ml), (9mg, 0.225mmol) 60% (0.014ml, 0.225 mmol) . 0.5 1N HCl (1ml) (10ml) . (1x3ml) (1x3ml) $MgSO_4$. 1:99 / 20mg .

[0341] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.01 (s, 2 H), 3.93 (s, 2 H), 3.60 (s, 3 H), 1.33 (s, 18 H).

[0342] **19**

[0343] **2,6- -3 - -4- (4'-( )))**

[0344]

[0345] 1 (300mg, 0.86 mmol) THF(17.2mL) -78 . - (THF 2M, 1.72ml, 1.72mmol) . 0 , HCl (0.5ml) . (25ml) , (1x5ml), 1N NaOH (1x5ml) (1x5ml) . $MgSO_4$, 40:60 / 198mg .

[0346] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (s, 4 H), 7.09 (s, 2 H), 5.21 (s, 1 H), 3.94 (s, 2 H), 3.84 (br s, 2 H), 2.84 (t, J = 6.8 Hz, 2 H), 1.36 (s, 18 H).

[0347] Z II , . Z II Scheme B , .

[0348] Scheme B

[0349] 0.1M (Sigma Chemicals) 2

30 . 1 3
16 . 1N HCl .
.
, .
.

[0350] Z II Mitsunobu (Synthesis, 1981, 1)
1 .

[0351] Z II Ando (Bull. Chem. Soc. Jpn., 55, 1982, 2504-2507) 1
.

[0352] Z II
. Z II Scheme C ,
.

[0353] Scheme C

[0354] 0.1M 2 30
. 3 16 .
1N HCl .
, .
. .

[0355]
. Sigma Chemicals .

[0356] Scheme B C .
.

[0357] **20**

[0358] **, 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-,6- (1,1-)**

[0359]

[0360] THF (25ml) (2.8g, 5.5mmol) (528mg, 13.2mmol) 60%
(0.751ml, 6.6mmol) . 2
(3ml) (10ml) . (50ml) , 0:100
/ 20:80 '
. 500mg .

[0361] 7.63 (s, 2 H), 7.45 (s, 2 H), 5.82 (s, 1 H), 3.71 (s, 3 H), 2.73 (t, J = 7.6 Hz, 2 H), 2.50 (t, J = 7.2 Hz, 2 H), 2.07 (pent, J = 7.6 Hz, 2 H), 1.47 (s, 6 H), 1.44 (s, * 18 H), 1.34 (s, 18 H).

[0362] **21**

[0363] **, 4-[[1-[[3,5- (1,1-)4-[(4-)]]]-1-]]2,6- (1,1-)-**

[0364]

[0365] DMF (1ml) (0.19mmol; 100mg) (0.28 mmol; 11mg;
60%), 4- (0.24mmol, 63mg) . 18
. Et_2O 3 x 2 ml .

$MgSO_4$, . (2mm ; 1:1 $-CH_2Cl_2$) (53mg; 43%).

^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J = 7.6 Hz, 2 H), 7.35 (s, 2 H), 7.14 (d, J = 7.2 Hz, 2 H), 6.79 (s, 2 H), 5.41 (s, 1 H), 3.13 (s, 2 H), 1.45-1.43 (overlapping s, 21 H), 1.14 (s, 21 H).

[0366]

[0367] **22**

[0368] **, 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]**

[0369]

[0370] 50mL (1.0g, 1.93 mmol) (16ml) . (0.23g, 5.75 mmol) 60% . THF (12ml) (0.58g, 5.8mmol) . 3 . 1N HCl (25 ml) (50ml) 2 . MgSO , . 70:30 ; 0:100 ; (170mg, 0.276 mmol, 14%). TLC (, 60:40 / + 10 HOAc, R_f = 0.35);

^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (s, 2 H), 7.43 (s, 2 H), 5.38 (s, 1 H), 2.97 (t, J = 6.8 Hz, 2 H), 2.76 (t, J = 6.8 Hz, 2 H), 1.45 (s, 8 H), 1.42 (s, 16 H), 1.32 (s, 18 H).

[0371]

[0372] **23**

[0373] **2- , 5- , 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)**

[0374]

[0375] THF (3.9ml) 0.39mmol(200mg) (0.58mmol; 23mg; 60%) 10 . 4- (0.77mmol; 136mg) . 47 . Et_2O (40 ml) H_2O(15ml) Na_2SO_4 - . (2mm SiO_2 ; 1:1 $-CH_2Cl_2$) 4,4'-( )[O-(5"- -2"-)-2',6'- -3 -]-[2,6- -3 -] (83mg; 33%) .

^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (s, 2 H), 7.50 (d, J = 4.0 Hz, 1 H), 7.45 (d, J = 3.6 Hz, 1 H), 7.45 (s, 2 H), 5.39 (s, 1 H), 1.50 (s, 6 H), 1.45 (s, 14 H), 1.35 (s, 22 H).

[0376]

[0377] **24**

[0378] **,4-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6-]-**

[0379]

[0380] DMF (5.5mL) 4,4'-( )[2',6'- -][2,6- -3 -](0.55mmol; 0.24g) . (1.38mmol; 33mg) 4- (0.83mmol; 188mg) . 4.5 . 0.3N HCl (6ml) . Et_2O (25ml) H_2O (10ml) (10ml) . $MgSO_4$. MPLC ((SiO_2; : 100%

95:5 -Et_2O 90:10 -Et_2O 80:20 -Et_2O)

(197mg; 67%) . (.35mmol; 187 mg) 4:1:1 MeOH-THF-H_2O (3.5ml)

. LiOH (1.05mmol; 44mg) , 1.75 .

0.1N HCl pH 4 . EtOAc 3 x 15 ml $MgSO_4$

. MPLC (SiO_2; : 100% 60:40

Et_2O- ( ))

4,4'-( )[O-(γ-)- 2',6'- -] [2,6- -3 -]

(100mg, 55%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.44 (s, 2 H), 7.25 (s, 2 H), 5.38 (s, 1 H), 3.83 (app t, J = 6.0 Hz, 2 H), 2.68 (app t, J = 8.0 Hz, 2 H), 2.25 (s, 6 H), 2.14 (m, 2 H), 1.47 (s, 6 H), 1.45 (s, 18 H).

[0381]

[0382] **25**

[0383] **, 4-[[1-[[4-(4-)-3,5- (1,1-)]]-1 -]]2,6- (1,1-)**

[0384]

[0385] 4,4'-( )[2',6'- -][2,6- -3 -] (1.44mmol; 622 mg) DMF (14.4ml) (3.6mmol; 144 mg) . (0.72mmol; 266 mg) (N-) (2.2mmol, 608mg) . 17 . 0.3N HCl (6mL) Et_2O (100ml) . H_2O (50ml) (50ml) . NaCl Et_2O . $MgSO_4$. MPLC (SiO_2; : 100% 75:25 -Et_2O) (750mg; 82%) . (0.89mmol; 563 mg) DMF (8.9mL) ((27mmol; 0.83ml) . 42 . 1N HCl (8.9ml) 1.5 ; $NaHCO_3$ pH 7 EtOAc (2x15ml) $MgSO_4$. MPLC (SiO_2; : 50:50 MeOH-CH_2Cl_2 49.5:49.5:1 MeOH-CH_2Cl_2-NH_4OH) 4,4'-( )[O-( )-2',6'- -][2,6- -3 -](93mg; 21%) .

^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, 2 H), 7.22 (s, 2 H), 5.55 (s, 1 H), 3.76 (app t, J = 6.8 Hz, 2 H), 2.78 (app t, J = 6.8 Hz, 2 H), 2.24 (s, 6 H), 1.83 (m, 2 H), 1.66 (m, 2 H), 1.45 (s, 6 H), 1.42 (s, 18 H).

[0386]

[0387] **26**

[0388] **, 4-[[1-[[4-(4-)-3,5- (1,1-)]]-1-]]2,6- (1,1-)**

[0389]

[0390] DMF (14.5ml) (9.7mmol, 5g) (48.4 mmol; 7.03 g) KF (N-) (13.6mmol; 3.82g) . 18 80 4 . H_2O (10ml) Et_2O (10ml) . Et_2O (200ml) H_2O (50ml (50ml) . $MgSO_4$. MPLC (SiO_2; : 100% 80:20 -Et_2O)

(346mg; 5%) . (0.44mmol; 314mg) DMF (4.4mL)
(13mmol; 0.41mL) . 16 1N HCl (4.7ml)
1.5 . $NaHCO_3$ pH 7 . 2 x 30 ml
EtOAc (20ml) $MgSO_4$
. MPLC (SiO_2; : 100% CH_2Cl_2 90:10 CH_2cl_2-MeOH)
4,4'-( )[O-( )-2',6'- -3 -][2,6- -3 -]
(182mg; 71%) .

^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s, 2 H), 7.44 (s, 2 H), 5.28 (s, 1 H), 5.25 (br s, 2 H), 3.72-3.69 (m, 2 H), 2.92-2.88 (m, 2 H), 1.94-1.90 (m, 2 H), 1.73-1.69 (m, 2 H), 1.43 (s, 22 H), 1.40 (s, 20 H).

[0391]

[0392] **27**

[0393] **, 4- , 4-[[1-[3,5- (1,1-)-4-]]-1-] -2,6-** (1,1-)

[0394]

[0395] -78 THF (200ml) 22 (6.17g, 10 mmol) - (10ml, THF 2M) .
. 0 , (37%, 4ml) .
(100 ml) (100ml) . 1N
(100ml) (100ml) .
( ) . /
(5.5 g). MP: 138-139 .

^1H-NMR (400 MHz, $CDCl_3$): 7.63 (s, 2 H), 7.45 (s, 2 H), 5.38 (s, 1 H), 3.76 (t, 2 H), 2.79 (t, 2 H), 2.01 (m, 2 H), 1.47 (s, 6 H), 1.44 (s, 18 H), 1.34 (s, 18 H).

[0396]

[0397] **28**

[0398] **, 2,2- -, [4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6-** (1,1-)]

[0399]

[0400] (30ml) (5.17g, 10mmol) (6.0g, 40 mmol)
(8.0g, 40%) . 18 .
(100ml) . (100ml)
. (; 4:1)
(0.39g) .

^1H-NMR (400 MHz, $CDCl_3$): 7.59 (s, 2 H), 7.45 (s, 2 H), 5.49 (s, 2 H), 5.38 (s, 1H), 1.464 (s, 6 H), 1.457 (s, 18 H), 1.445 (s, 18 H), 1.28 (s, 9 H).

[0401]

[0402] **29**

[0403] **,4-[[1-[[4-(4-)]]-1-]]-2,6-** (1,1-)-

[0404] *

[0405] DMF 2ml 4,4'-( )[ ][2,6- -3 -] (0.18mmol; 75mg)

0.23 mmol (9mg) (60%) . N-(4-) (0.22mmol, 63 mg) NaI 0.22 mmol (33mg) . 120 . 24 , TLC (SiO_2; CH_2Cl_2 ; UV , PMA/) . Et_2O NaCl 3ml . 3ml Et_2O ; $MgSO_4$, . (SiO_2; 20x170mm ; CH_2Cl_2) 69% (69mg). (0.11mmol; 69 mg) 1ml DMF . (0.16mmol; 8 μL) . 1 . TLC . (10.3 mmol; 0.5 mL) ; 24 . 12N HCl pH 3 . 5 , $NaHCO_3$ (pH=7). EtOAc , EtOAc 2 x 2 ml . $MgSO_4$, . (SiO_2; 15 x 110 mm ; EtOH) 4,4'-( )[O-( )][2,6- -3 -] (25mg; 48%) .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J = 8.4 Hz, 2 H), 7.42 (s, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 5.36 (br s, 1 H), 3.97 (br m, 2 H), 3.10 (br m, 2 H), 2.01-1.86 (overlapping m, 4 H), 1.43 (s, 24 H).

[0406]

[0407] **30**

[0408] **, 4,4-[[1-[3,5- (1,1-)-4-]]-1-]]]-**

[0409]

[0410] DMF 6ml 4,4'-( )[ ][2,6- -3 -] (0.6mmol; 242mg) 1.3mmol (53 mg) (60%) . 0.9mmol (131 μL) 4- . CH_2Cl_2 TLC (UV , PMA/). 24 , TLC . NaCl Et_2O . 2 x 6 ml Et_2O ; $MgSO_4$, . CH_2Cl_2 (SiO_2; 20 x 185 mm) 232 mg (77%) 4:1:1 MeOH-THF-H_2O 3 mL . 0.92 mmol(39mg) LiOH . (18) 12N HCl pH 2 ( ). Et_2O (5ml) ; 2 x 5 ml Et_2O . $MgSO_4$, . (SiO_2; 15 x 180 mm ; 3:1 -EtOH) 4,4'-( )[O-(γ-)][2,6- -3 -] (62 mg. 40%) .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J = 8.0 Hz, 2 H), 7.40 (s, 2 H), 6.80 (d, J = 7.6 Hz, 2 H), 5.35 (s, 1 H), 3.93 (br m, 2 H), 2.51 (br m, 2 H), 2.07 (br m, 2 H), 1.42 (s, 18 H), 1.25 (s, 6 H).

[0411]

[0412] **31**

[0413] **, 4-[[1-[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]-**

[0414]

[0415] (1.5ml) (0.5g, 0.967 mmol) -2- (0.31g, 1.45 mmol) 40% (0.7 g) 24 . (25ml) (2x 5 ml) . $MgSO_4$. 5:95 / 160mg . THF:H_2O:MeOH (4:1:1) (4ml) LiOH-H_2O(50mg) 1 . 1N HCl (2x10ml) $MgSO_4$, . 50:50 / 90mg .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (s, 2 H), 7.40 (s, 2 H), 5.35 (s, 1 H), 4.40 (s, 2 H), 1.43 (s, 6 H), 1.41 (s, 9 H), 1.39 (s, 9 H).

[0416]

[0417] **32**

[0418] **, 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)**

[0419]

[0420] THF (58ml) (3.0g, 5.8mmol) 60% (1.16g, 29.0mmol) 0.5 . 0.5 . (150 ml) (5ml) (2x50ml) (1x50ml) . $MgSO_4$, . 10% / 20% / 610mg . DMF (8.6 ml) (0.136ml, 2.34mmol) . 1N HCl (5ml) 1 . (25ml) $NaHCO_3$ (aq) (1x10ml) . $MgSo_4$, 1% / 1.5% / 334 mg .

7.64 (s, 2 H), 7.45 (s, 2 H), 5.39 (br s, 1 H), 3.76 (s, 2 H), 1.48 (s, 6 H), 1.44 (s, 18 H), 1.33 (s, 18 H).

[0421]

[0422] **33**

[0423] **, 4-[[1-[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]**

[0424]

[0425] 50ml (1.0g, 1.93mmol) (20ml) . (0.16g, 4 mmol) 60% . THF (12ml) (0.170g, 3 mmol) . 3 . 1 N HCl (25 ml) (50ml) 2 . $MgSO_4$, . 70:30 ; 0:100 / . . 7.62 (s,2H), 7.45 (s, 2H)

5.37 (s, 1 H), 2.75 (t, J = 7.2 Hz, 2 H), 2.55 (t, J = 7.2 Hz, 2 H), 2.09 (m, 2 H), 1.47 (s, 6 H), 1.44 (s, 18 H), 1.43 (H).

[0426]

[0427] **34**

[0428] , 4-[4-[[1-[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]-

[0429]

[0430] DMF (15ml) 4- (3.1g, 13.6mmol) (5g, 9.7mmol) . (7g, 48 mmol) 40% . (50ml) (2x20ml) (1x20ml) . $MgSO_4$, 10:90 / 60:40 / . 442mg . $THF:MeOH:H_2O$ (4:1:1) (5ml) (63mg, 1.5mmol) . 2.5 1N HCl (3mL) (15ml) . (3ml) $MgSo_4$, . , 10:90 / 50:50 / 308mg .

[0431] 7.53 (s, 2 H), 7.45 (s, 2 H), 5.37 (s, 1 H), 3.77 (t, J = 6.8 Hz, 2 H), 2.55 (t, J = 7.6 Hz, 2 H), 2.16 (m, 2 H), 1.44 (s, 24 H), 1.41 (s, 18 H).

[0432] 35

[0433] , α-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]-;

[0434] ,3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]-;

[0435] , α-[[3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]]]]]-

[0436] (50ml) (5.16g, 10mmol) 1,3- (1.6ml, 20mmol) (2.9g, 20mmol, 40%) . 18 . (150ml) (2x100ml) . (/ 2:1, 1:1, 1:2) , α-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]- (0.47g), , 3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]- (0.15g) , α-[[3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]]]]]- (0.05g) .

[0437] , α-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]-:

[0438] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (s, 2 H), 7.45 (s, 2 H), 5.38 (s, 1 H), 4.10-4.17 (m, 1 H), 3.83-3.97 (m, 2 H), 3.27-3.32 (m, 1 H), 2.83-2.94 (m, 2 H), 2.18 (br. s, 1 H), 1.46 (s, 6 H), 1.45 (s, 18 H), 1.44 (s, 18 H).

[0439] ,3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]-:

[0440] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (s, 2 H), 7.45 (s, 2 H), 5.39 (s, 1 H), 4.38 (m, 2 H), 4.00 (m, 2 H), 3.89 (m, 2 H), 1.34-1.41 (m, 42 H).

[0441] , α-[[3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1

-)]]]]]-

[0442] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2 H), 7.45 (s, 2 H), 5.39 (s, 1 H), 4.24 (br. m, 1 H), 3.93 (m, 1 H), 3.81 (m, 1 H), 3.77 (br. m, 1 H), 3.16 (m, 1 H), 3.06 (m, 1 H), 2.91 (m, 1 H), 2.85 (m, 2 H), 2.84 (m, 1 H), 2.75 (m, 2 H), 1.41-1.44 (m, 42 H).

[0443] **36**

[0444] **, 4-[[1-[[3,5- (1,1-)-4-(0] -1-]]-2,6- (1,1-**)-

[0445] 0 THF (50ml) (2.58g, 5 mmol) (0.66ml, 10mmol), (2.62g, 10mmol), (1.57ml, 10mmol) . 48 . (/ 4:1, 2:1) (1.01g).

[0446] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (s, 2 H), 7.44 (s, 2 H), 5.39 (s, 1 H), 4.40 (m, 1 H), 3.75 (m, 1 H), 3.39 (m, 1 H), 2.91 (m, 1 H), 2.77 (m, 1 H), 1.40-1.49 (m, 42 H).

[0447] **37**

[0448] **, N-[3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-**)]-2-]-

[0449] (10ml) , 4-[[1-[[3,5- (1,1-)-4-(0] -1-]]-2,6- (1,1-)- (0.17g, 0.28mmol) (43mg, 0.57mmol) (1ml) . . . . (/ 10:1 1:1) (99mg) .

[0450] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.52 (s, 2 H), 7.43 (s, 2 H), 5.37 (s, 1 H), 4.58 (br. s, 1 H), 3.79 (br. m, 2 H), 3.67 (m, 1 H), 3.30 (m, 1 H), 3.21 (m, 1 H), 3.13 (m, 1 H), 1.43 (s, 18 H), 1.41 (s, 6 H), 1.38 (s, 18 H).

[0451] **38**

[0452] **1,2,3- ,4-[4-[[1-[[3,5- (1,1-)-4-]** =1-] -2,6- (1,1-)-]-2-]-

[0453] (0.15g) , α-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]-(0.15g) (1ml) (10) . 48 (50ml) , (3x50ml) . (/ 3:1) (26mg) .

[0454] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2 H), 7.43 (s, 2 H), 5.36 (s, 1 H), 4.27 (m, 2 H), 3. 98 (m, 2 H), 3.75 (m, 2 H), 1.36-1.44 (m, 42 H).

[0455] **39**

[0456] **, 4-[[1-[[3,5- (1,1-)-4-(3- -2-**)]]-1-]]-2,6- (1,1-)-;

[0457] **1,2- ,3-[4-[[1-[[3,5- (1,1-)-4-]**]-1-]]-2,6- (1,1-)]-

[0458] * (10ml) , α-[[[3-[[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]]]] - (0.32 g) 1N (1.5ml) . (50ml) (50ml) . (50ml) . (/ 1:1, / 4:1) 1,2- , 3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]- (58 mg) , 4-[[1-[[3,5- (1,1-)-4-(3- -2-)]]-1-] -2,6- (1,1 -)- (/ 5:1 -) , 4-[[1-[[3,5- (1,1-)-4-(3- -2-)]]-1-]]-2,6- (1,1-)- (52mg).

[0459] **, 4-[[1-[[3,5- (1,1-)-4-(3- -2-)]]-1-]]-2,6-** (1,1-)-:

[0460] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.55 (s, 2 H), 7.45 (s, 2H), 5.38 (s, 1 H), 4.35 (m, 1 H), 4.11 (m, 1 H), 3.83 (m, 2 H), 3.62 (m, 1 H), 3.57 (m, 2 H), 1.43-1.46 (m, 42 H), 1.22 (t, 3 H).

[0461] 1,2- ,3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-

[0462] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (s, 2 H), 7.45 (s, 2 H), 5.38 (s, 1 H), 4.32 (m, 1 H), 3.94 (dd, 1 H), 3.85 (m, 1 H), 3.77 (m, 1 H), 3.66 (m, 1 H), 1.40-1.44 (m, 42 H).

[0463] **40**

[0464] **,4-[[1-[[3,5- (1,1-)-4-]]-1-]**]-2,6- (1,1-)-

[0465] **2- ,3-[4-[[1-[[3,5- (1,1-)-4-]**]-1-]]-2,6- (1,1-)]-, , (E)-

[0466] 2- ,3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-, , (E)-

[0467] THF (50ml) (5.16g, 10mmol) (1.2ml, 12 mmol) (7ml, 50 mmol) . 1 . (100ml) , (3x100ml) . (/ 9:1) ,4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)- (0.51g), 2- ,3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-, , (E)- (0.37g), 2- ,3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-, , (E)- (0.54 g) .

[0468] **,4-[[1-[[3,5- (1,1-)-4-]]-1-]**]-2,6- (1,1-)-:

[0469] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.52 (s, 2 H), 7.45 (s, 2 H), 5.37 (s, 1 H), 3.76 (quad., 2 H), 1.39-1.45 (m, 45 H).

[0470] **2- ,3-[4-[[1-[[3,5- (1,1-)-4-]**]-1-]]-2,6- (1,1-)]-, , (E)-

[0471] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.62 (s, 2 H), 7.44 (s, 2 H), 6.40 (d, 1 H), 5.38 (s, 1 H), 5.02 (d, 1 H), 4.23 (quad., 2 H), 1.47 (s, 6 H), 1.44 (s, 18 H), 1.42 (s, 18 H), 1.30 (t, 3 H).

[0472] **2- ,3-[4-[[1-[[3,5- (1,1-)-4-]**]-1-]]-2,6- (1,1-

)]-, , (E)-

^{1}H-NMR (400 MHz, CDCl3): 7.62 (s, 2 H), 7.51 (s, 2 H), 6.40 (d, 1 H), 5.03 (d, 1 H), 4.23 (quad., 2 H), 3.76 (quad., 2 H), 1.25-1.48 (m, 48 H).

[0473]

[0474] **41**

[0475] **, [4-[[1-[[3,5- (1,1-)-4-]]1-**]]-2,6- (1,1-)]

[0476] :

[0477] 22 (1.13 g, 1.83mmol) DMF (3.6ml) 60% (183mg, 4.6mmol) 0.25 (0.342mL, 5.5mmol) . . (2mL) (50ml) . (2x10ml) (1x10ml) $MgSO_4$. 0:100 / 40:60 / 556mg . THF:MeOH:H_2O (4:1:1) (5ml) (63mg, 1.5mmol) . 2.5 , 1N HCl (3ml) (15ml) . (3ml) $MgSO_4$, . 10:90 / 50:50 / 400mg .

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 2 H), 7.45 (s, 2 H), 5.37 (s, 1 H), 3.71 (s, 3 H), 2.75 (t, *J* = 7.2 Hz, 2 H), 2.55 (t, *J* = 7.2 Hz, 2 H), 2.09 (m, 2 H), 1.46 (s, 6 H), 1.44 (s, 18 H), 1.42 (s, 18 H).

[0478]

[0479] **42**

[0480] **,4-[[1-[[4-[2-[4-( )] -3,5- (1,1-**)] -1-]]-2,6- (1,1-)-

[0481]

[0482] THF (11.6ml) (1.16mmol; 600 mg) (2.3mmol; 608mg), (2.3 mmol; 0.37mL), 4-( ) (2.3mmol; 383 mg) . 41.5 . . 4,4'-( )[O-4"-( ))-2',6'- -3 -][2,6- -3 -] (256mg; 33%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s, 2 H), 7.45 (s, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 6.74 (br d, *J* = 8.0 Hz, 2 H), 5.38 (s, 1 H), 3.84 (app t, *J* = 8.0, 8.8 Hz, 2 H), 3.09 (app t, *J* = 7.6, 8.8 Hz, 2 H), 2.93 (s, 6 H), 1.45-1.44 (overlapping s, 42 H).

[0483]

[0484] **43**

[0485] **,4,4'-[(1-) [[2,6- (1,1-**)-4,1-] -2,1-]] [N,N - -

[0486]

[0487] THF (11.6ml) (1.16mmol; 600 mg) (2.3mmol; 608mg), (2.3 mmol; 0.37mL), 4-( ) (2.3mmol; 383 mg) . 41.5 . . 4,4'-( )[4"-( ))-2,6- -3 -][2,6- -3 -] (155mg; 16%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (s, 4 H), 7.12 (d, J = 8.8 Hz, 4 H), 6.74 (br d, J = 8.0 Hz, 4 H), 3.84 (app t, J = 7.6, 8.8 Hz, 4 H), 3.09 (app t, J = 8.0, 8.8 Hz, 4 H), 2.93 (s, 12 H), 1.43-1.42 (overlapping s, 42 H).

[0488]

[0489] **44**

[0490] **L- , [4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]**

[0491]

[0492] (30ml) 22 (1.67g, 2.7mmol) L- (0.47 g, 2.7 mmol) . 2 . . . (1.75g) . MP: 185-190

^{1}H-NMR (400 MHz, CDCl3): 7.60 (s, 2 H), 7.42 (s, 2 H), 5.37 (s, 1 H), 3.64 (br. s, 1 H), 3.11 (br. s, 2 H), 2.96 (br. s, 2 H), 2.58 (br. s, 2 H), 1.41-1.44 (m, 26 H), 1.23-1.31 (m, 20 H).

[0493]

[0494] **45**

[0495] **2- ,3-[4-[[1-[[3,5- 91,1-)-4-]]-1-]]-2,6- (1,1-)]-, (E)-**

[0496]

[0497] THF (5ml) 2- , 3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-, , (E)-(0.16g, 0.26 mmol) (2ml) (42mg, 1mmol) . . (50ml) , . (/ 4:1) (22mg) . ^{1}H-NMR (400MHz, $CDCl_3$): 7.63 (s, 2 H), 7.44 (s, 2 H), 6.52 (d, 1 H), 5.39 (s, 1 H), 5.08 (d, 1 H), 1.47 (s, 6 H), 1.44 (s, 18 H), 1.42 (s, 18 H).

[0498]

[0499] **46**

[0500] **α-D- , 6-0-4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6-** (1,1-)]-1,2:3,4- -O-(1-)

[0501]

[0502] THF (100ml) (2.58g, 5 mmol) 1,2,3,4- -O- -D- (1.8 ml, 10mmol) (2.62g, 10mmol) (1.57ml, 10mmol) . 72 . . (/ 30:1) (0.16g) .

^{1}H-NMR (400 MHz, CDCl3): 7.53 (s, 2 H), 7.45 (s, 2 H), 5.60 (s, 1 H), 4.65 (m, 2 H),4.35 (m, 4 H), 1.59 (s, 6 H), 1.44 (s, 18 H), 1.43 (s, 18 H), 1.37 (s, 6 H), 1.33 (s, 6 H).

[0503]

[0504] **47**

[0505] **,4-[[1-[[4-[3-( )]-3,5- (1,1-)]]-1-]** -2,6- (1,1-)-

[0506]

[0507] 0 THF (0.5g, 0.97 mmol) 3- (0.287 ml, 1.94 mmol) (0.508g, 1.94 mmol) (0.31ml, 1.94 mmol) . 30 . 20:80 / .

[0508] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (s, 2 H), 7.27 (s, 2 H), 3.74 (t, J = 1.6 Hz, 2 H), 2.56 (q, J = 7.2 Hz, 2 H), 2.03 (pent, J = 7.6 Hz, 2 H), 1.44 (q, J = 3.2 Hz, 4 H), 1.42 (s, 24 H), 1.25 (t, J = 3.3 Hz, 6 H).

[0509] **48**

[0510] **,N-[[4-[[1-[[3,5- (1,1-)-4-]]-1,-]]-2,6- (1,1-)]]-**

[0511]

[0512] , (0.87ml) [4-[[1-3,5- (1,1-)-4-]]-1-]]2,6- (1,1-)-(50mg, 0.087 mmol) (15.8mg, 0.11 mmol), 1-(3- -3- (22mg, 0.11 mmol) (28mg, 0.23 mmol) . . (10ml) (2x3ml) , $MgSO_4$, . 50:50 / 50mg . THF:H_2O:MeOH (2:1:1) (1ml) LiOH-H20(15mg) 1 . 1N HCl (2x10ml) , $MgSO_4$, 25 mg .

[0513] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 2 H), 7.42 (s, 2 H), 5.39 (br s, 1 H), 4.31 (s, 2 H), 4.22 (d, J = 5.2 Hz, 2 H), 1.44 (s, 6 H), 1.42 (s, 9 H), 1.39 (s, 9 H).

[0514] **49**

[0515] **, N-[[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]]-**

[0516]

[0517] , (1.8ml) [4-[[1-3,5- (1,1-)-4-]]-1-]]2,6- (1,1-)-(100mg, 0.174 mmol) (54mg, 0.22 mmol), 1-(3- -3- (44mg, 0.22 mmol) (55mg, 0.45 mmol) . . (10ml) (2x3ml) , $MgSO_4$, . 50:50 / . THF:H_2O:MeOH (2:1:1) (3ml) LiOH-$H_2$0(100mg) 1 . 1N HCl (2x10ml) , $MgSO_4$, 45 mg .

[0518] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 2 H), 7.42 (s, 2 H), 5.37 (s, 1 H), 4.83 (m, 1 H), 4.28 (s, 2 H), 2.56 (m, 2 H), 1.44 (s, 6 H), 1.43 (s, 9 H), 1.41 (s, 9 H).

[0519] **50**

[0520] **L- , N-[3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-**

)]-2-]- -,

[0521]

[0522] * (15ml) , 4-[[1-[[3,5- (1,1-)-4-( )]]-1-]]-2,6- (1,1-)-(0.12g, 0.20mmol) L- (0.24g, 1mmol) (2ml) . 18 . . (/ 5:1) (/ 10:1) (16mg) .

[0523] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.53 (s, 2 H), 7.42 (s, 2 H), 5.36 (s, 1 H), 4.90 (m, 1 H), 3.85 (m, 2 H), 3.55-3.75 (m, 7 H), 2.01 (m, 2 H), 1.39-1.42 (m, 48 H), 1.23 (m, 2 H).

[0524] **51**

[0525] **2- , 4-[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)]**

[0526]

[0527] THF (50ml) (2.58g, 5 mmol) 4- (1.0ml, 10 mmol), (2.62g, 10 mmol) (1.57ml, 10 mmol) . 1 . . (/ 4:1) (0.92g) .

[0528] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2 H), 7.46 (s, 2 H), 6.42 (dd, 1 H), 6.14 (dd, 1 H), 5.84 (dd, 1 H), 5.38 (s, 1 H), 4.23 (t, 2 H), 3.75 (t, 2 H), 1.97 (m, 2 H), 1.82 (m, 2 H), 1.46 (s, 6 H), 1.45 (s, 18 H), 1.42 (s, 18 H).

[0529] **52**

[0530] **, 4-[[1-[[3,5- (1,1-)-4-(4-)]]-1-]]-2,6- (1,1-)-**

[0531]

[0532] (20ml) 2- , 4-[4-[[1-[[3,5- (1,1-)-4-]]-1-] -2,6- (1,1-)] (0.82g) (0.5g) . . (50ml) , (2x50ml) . (/ 4:1) (0.52g) .

[0533] ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2 H), 7.46 (s, 2 H), 3.71-3.77 (m, 4 H), 1.96 (m, 2H), 1.72 (m, 2 H), 1.46 (s, 6 H), 1.45 (s, 18 H), 1.43 (s, 18 H).

[0534] **53**

[0535] **β-D- , 6-O-4-[[1-[[3,5- (1,1-)-4-( ]]-1-]]-2,6- (1,1-)]-**

[0536]

[0537] THF (20ml) (1.8g, 3.5 mmol) 1,2,3,4- -O- -β-D- (1.0g, 2.9 mmol), (0.92g, 3.5 mmol) (0.55ml, 3.5 mmol) . 2 . . (/ 4:1) (0.92g) .

[0538] ^{1}H-NMR (400 MHz, CDCl3): 7.53 (s, 2 H), 7.45 (s, 2 H), 5.80 (d, 1 H), 5.38 (s, 1 H), 5.33 (dd, 1 H), 5.16 (dd, 1 H), 4.90 (dd, 1 H), 4.19 (m, 1 H), 3.88 (m, 1 H), 3.74 (m, 1 H), 2.14 (s, 3 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.45 (s, 18 + 6 H), 1.38 (s, 18 H).

[0539] **54**

[0540] **1-H- -1- , 4-[[1-[[3,5- (1,1-)-4-( ]]-1-]]-** 2,6- (1,1-)

[0541]

[0542] THF (10ml) , 4- -, 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-) (60mg, 0.1mmol) 1H- (14mg, 0.2 mmol), (52mg, 0.2mmol) (0.03ml, 0.2mmol) . 2 . . (/ 4:1) (57mg) .

[0543] ^{1}H-NMR (400 MHz, $CDCl_3$): 8.56 (s, 1 H), 7.64 (s, 2 H), 7.45 (s, 2 H), 5.39 (s, 1 H), 4.84 (t, 2 H), 2.74 (t, 2 H), 2.47 (m, 2 H), 1.47 (s, 6 H), 1.45 (s, 18 H), 1.33 (s, 18 H).

[0544] **55**

[0545] **, 4-[[1-[[3,5- (1,1-)-4-[[3- -1-)]]]-1-]]-2,6-** (1,1-)-

[0546]

[0547] THF (15ml) 2- , 3-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]-, , (E)- (65mg, 0.1mmol) (1ml, THF 1M) . . (20ml) 0.5 . (3x50ml) . (/ 4:1) (46mg) .

[0548] ^{1}H-NMR (400 MHz, CDCl3): 7.61 (s, 2 H), 7.45 (s, 2 H), 5.99 (d, 1 H), 5.39 (s, 1 H), 4.84 (m, 1 H), 4.46 (m, 2 H), 1.47 (s, 6 H), 1.45 (s, 18 H), 1.42

[0549] **56**

[0550] **)-4-]]-1-L- , N^6-[[4-[[1-[[3,5- (1,1-**]]-2,6- 91,1-)]]-

[0551]

[0552] (1.8ml) , [4-[[1-[[3,5- (1,1-)-4-]]-1-]]2,6- (1,1-)]- (150mg, 0.26 mmol) (79 mg, 0.34mmol), 1-(3- -3- (130mg, 0.67mmol) (82mg, 0.67mmol) . . (10ml) (2x3 ml) $MgSO_4$, . 50:50 / 70:30 / 128mg . THF:H_2O:MeOH (2:1:1) (3ml) LiOH-H_2O (50mg) 1 . 20:80 / 67mg .

7.58 (s, 2 H),
7.44 (s, 2 H), 6.86 (m, 1 H), 5.39 (s, 1 H), 4.75 (m, 1 H), 4.29 (d, J = 7.2 Hz, 2 H), 3.44 (m, 2 H), 2.10 (m, 2 H), 1.95 (m, 2 H), 1.82 (m, 2 H), 1.46 (s, 6 H), 1.44 (s, 9 H), 1.42 (s, 9 H).

[0553]

[0554] **57**

[0555] **D- , 6-O-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6-** (1,1-)]-

[0556]

[0557] (50ml) β-D- , 6-O-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- 91,1-)]-(0.68g) 91g) . (200mg) (3x 150ml) (100ml) . (/ 10:1 5:1) (0.26g) .

^{1}H-NMR (400 MHz, $CDCl_3$): 7.52 (s, 2 H), 7.44 (s, 2 H), 5.36 (s, 1 H), 5.31 (s) and 4.78 (br. s, 1 H), 3.30-4.38 (br. m, 6 H), 1.38-1.43 (m, 42 H).

[0558]

[0559] **58**

[0560] **D- , 6-O-[4-[[1-[[3,5- (1,1-)-4-]**]-1-]]-2,6- 91,1-)]-

[0561]

[0562] THF (5ml) D- , 6-O-[4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-)]- (70mg) 2 . (2ml) 1 . (50ml) (3x50ml) . . (/ 100:12) (19mg) .

^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (s, 2 H), 7.44 (s, 2 H), 5.36 (s, 1 H), 4.35 (m 1 H), 3.30-4.10 (m, 7 H), 1.40-1.44 (m, 42 H).

[0563]

[0564] **59**

[0565] **,**
4-[[(2-)]]-4-[[1-[[3,5- (1,1-)-4-]-]-1-]]-2,6- (1,1-)

[0566]

[0567] (1ml) , 4- -, 4-[[1-[[3,5- (1,1-)-4-]]-1- }]-2,6- (1,1-) (60mg, 0.1mmol0 1,2- (21mg, 0.11mmol) 1 . (10ml) . (1ml) (0.5ml) 0.5 . (50ml) (2 50ml) . . (/ 5:1) (21mg) .

^{1}H-NMR (400 MHz, $CDCl_3$): 7.58 (s, 2 H), 7.44 (s, 2 H), 7.15 (br. s, 1 H), 6.87 (br. s, 2 H), 6.71 (br. s, 1 H), 5.37 (s, 1 H), 3.97 (br. s, 2 H), 2.48 (br. s, 2 H), 1.83 (br. s, 2 H), 1.45 (s, 6 H), 1.43 (s, 18 H), 1.24 (s, 18 H).

[0568]

[0569] **60**

[0570] , **4- -3,3- -,4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6-** (1,1-)

[0571]

[0572] (2.3g, 4.46mmol) (23ml) . (0.23g, 5.75 mmol) 60% . 2,2- (1g, 7.6mmol) . 3 . 1N HCl (25ml) (50ml) 2 . $MgSO_4$, . 70:30 / 0:100 / . 700mg . (214mg, 0.332 mmol) THF (6ml) - (THF 2M, 0.665ml, 0.664mmol) 6 . HCl (0.100ml) . (25ml) (1x5ml), $NaHCO_3$(1x5ml) (1x5ml) . $MgSO_4$, . 100:0 / 50:50 / 85mg .

[0573] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (s, 2 H), 7.46 (s, 2 H), 5.39 (s, 1 H), 3.48 (d, J = 6.8 Hz, 2 H), 2.73 (s, 2 H), 1.47 (s, 6 H), 1.45 (s, 9 H), 1.35 (s, 9 H), 1.11 (s, 6 H).

[0574] **61**

[0575] **, 4-( )-, 1-[4-[[3,5- (1,1-)-4-( ]]-1-]]-2,6-** (1,1-)]

[0576]

[0577] DMF (150ml) , 4- -, 4-[[1-[[3,5- (1,1-)-4-]]-1-]]-2,6- (1,1-) (12.5 g, 20.75mmol) (12.5g, 87.5mmol) . . (100ml) (2x50ml) . (75ml) . . (/ 10:1, 5:1) .

[0578] THF (200ml) . (5ml) NaOH(0.8g, 20mmol) . 2 . 1N NaOH (200ml) 0.5 . 1N NaOH (200ml) 0.5 . (9.23g) .

[0579] LDL I II .

[0580] " " .

[0581] I . .

[0582] **62**

[0583] **IC_{50}**

[0584] **HEPG2 :**

[0585] HEPG2 10ml MEM, 10% FBS, 1mM . . MEM, 10% FBS, 1mM 4x96 50%

.

[0586] **1 :**

[0587] 100 µl DMEM, 1% RSA 24 . DMSO . IC_{50} , 10 µM-40 µM , 3 .

[0588] , 4x96- NuncIMmunoSorb ApoB 1D1 (1:1000 1XPBS, pH7.4) . .

[0589] **2 ApoB ELISA:**

[0590] 1XPBS , pH 7.4, -0.05% Tween 20 3 . 100 µL . ApoB 6.25, 3.12, 1.56, 0.78, 0.39ng 3 .

[0591] **:**

[0592] 1XPBS 90 µl, pH 7.4, -0.05% Tween 20 . 10 µl HEPG2 ApoB ELISA . 2 .

[0593] 1XPBS, pH 7.4, -0.05% Tween 20 3 . Boehringer Mannheim ApoB 100 µl (1XPBS, pH7.4, -0.05% Tween 20 1:2000). 1 . 1XPBS, pH7.4, -0.05% Tween 20 3 . - IgG (1XPBS, pH7.4, -0.05% Tween 20 1:2000) 100 µl . 1 . 1XPBS, pH7.4, -0.05% Tween 20 3 . (10ml, TMB (10mg/ml) 100 µl, 1 µl) 100 µl . 8N 25 µl . MicroPlate Reader VCAM-1 450nM . ApoB . IC_{50} .

[0594] **63**

[0595] **VCAM-1**

[0596] **:**

[0597] 2 4 (confluent) P150 50mL . , .

[0598] 36,000 /mL 1mL .

[0599] 24 . 90-95% . 8 .

[0600] **:**

[0601] _____

[0602] 50 µM 10 µM . 50mM . 5mM 1mM . 5mM 10 µL (1ml /), 50 µM . 1mM 10 µL 10 µM .

[0603] _____

[0604] 25mM DMSO . . 1mL . , 50 µM , 1 mL 25mM 2 µL . 50mM .

[0605] _____

[0606] (2). VCAM

ICAM .

[0607] , TNF . 100 /ml TNF . TNF , . , . 100 /ml , TNF 10 /μL 10μL .

[0608] 37 , 5% CO_2 (16). . , , ( ) .

[0609] **64**

[0610] **ELISA**

[0611] MCP-1 , (500μL) -70 . 1ml/ Hanks Balance Salt Solution (HBSS) PBS 1 . . (1) 250μl/ HBSS +5% FCCS HBSS +5% FCS 250μL/ 1 . .5ml/ HBSS PBS 2 . HBSS+5%FCS 250μl/ HRP- 2 (1) . 37 30 . .5ml/ HBSS PBS 4 . 250μl/ . ( ) . (15-30). 75μL/ (8N), A450nm .

[0612] _____

[0613] 1. :

[0614] 10mL

[0615] 30% 1μL

[0616] TMB (3,3',5,5'-) 100μL

[0617] TMB : 10mg TMB 1mL . 4 .

[0618] 2. VCAM-1 Ab: 1μg/μL 0.25μg/mL

[0619] 25μL VCAM-1 (Southern Biotechnology) 10mL HBSS+5% FCS

[0620] 3. ICAM-1 Ab: . 1μg/μL 0.25μg/mL

[0621] 25μL ICAM-1 (Southern Biotechnology) 10mL HBSS+5% FCS

[0622] 4. 2 Ab:HRP- IgG (1:500)

[0623] 20μL VCAM-1 (Southern Biotechnology) 10mL HBSS+5% FCS

[0624] I II 62-64 . 1 .

1a

화합물	VCAM-1 IC_{50} 또는 % 억제 [μM]	LD_{50}	ApoB/HepG2 IC_{50} 또는 % 억제 [μM]
2,6-디-3차-부틸-4-티오(4'-(메틸)페닐아세트산))페놀	80	200	15에서 7%
2,6-디-3차-부틸-4-티오(4'-니트로벤질)페놀	10	200	27
2,6-디-3차-부틸-4-티오(4'-니트로페네틸)페놀	15	0.4	NE
2,6-디-3차-부틸-4-티오(부타노인산)페놀	75	200	NE
2,6-디-3차-부틸-4-티오(3',5'-디-3차-부틸, 4'-히드록시부탄디온산 에스테르)페놀	6	50	NE
2,6-디-3차-부틸-4-티오(4'-(메틸)벤조산)페놀	NE	>100	NE
2,6-디-3차-부틸-4-티오(2'-아세톡시,2'-메틸프로필)페놀	50		NE
2,6-디-3차-부틸-4-티오(3'-니트로벤질)페놀	13	200	20
2,6-디-3차-부틸-4-티오(2',4'-디니트로벤질)페놀	8	400	32
2,6-디-3차-부틸-4-티오4'-(트리플루오로메틸)벤질)페놀	5	300	16
2,6-디-3차-부틸-4-티오(2'-퓨란카르복실산)-5-메틸)페놀	40	400	NE
2,6-디-3차-부틸-4-티오(4'-메틸-N,N-디메틸벤젠설폰아미드)페놀	20	350	31
2,6-디-3차-부틸-4-설피닐(4'-니트로벤질)페놀	50	<100	NE
2,6-디-3차-부틸-4-(설포닐-(4'-니트로벤질))페놀	40	100	25
2,6-디-3차-부틸-4-티오(4'-아세톡시벤질)페놀	18	75	40
2,6-디-3차-부틸-4-티오(4'-메틸벤질)페놀	75		22
2,6-디-3차-부틸-4-티오(4'-플루오로벤질)페놀	35		30
2,6-디-3차-부틸-4-티오(3'-프로판설폰산)페놀	50에서 25%		
2,6-디-3차-부틸-4-티오(5'-메틸-2'-(9디메틸아미노)메틸)퓨란)페놀	10		19
2,6-디-3차-부틸-4-티오(3'-(디메틸아미노)프로필))페놀	50에서 30%	100	
2,6-디-3차-부틸-4-티오((1'-(아세톡시)펜틸)페놀	50에서 40%	100	30
2,6-디-3차-부틸-1-메톡시-4-티오(4'-트리플루오로메틸)벤질)벤젠	NE		<10
2,6-디-3차-부틸-4-티오(4'-(메틸)페닐에틸알코올))페놀	15	50	15에서 53%
페놀,4-[[1-[3,5-비스(1,1-디메틸에틸)4-[(4-니트로페닐)메톡시]페닐]티오]-1-메틸에틸]티오]2,6-비스(1,1-디메틸에틸)-	50에서 30%	>100	15에서 17%
부탄디온산, 모노 [4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐[티오]-1-메틸에틸]티오]2,6-비스(1,1-디메틸에틸)페닐]에스테르	5.6	23	15에서 65%
2-퓨란카르복실산, 5-니트로, 4-[[1-[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	25	400	15에서 17%
부타노인산, 4-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]2,6-디메틸에틸페녹시]-	19	75	15에서 41%
페놀, 4-[[1-[[4-(4-아미노부톡시)-3,5-비스(1,1-디메틸에틸)페닐]티오]-1-메틸에틸)페닐]티오]-1-메틸에틸]티오]2,6-비스(1,1-디메틸에틸)-	8	25	
페놀, 4-[[1-[[4-(4-아미노부톡시)-3,5-비스(1,1-디메틸에틸)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	9	25	
부타노인산, 4-히드록시-, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	6	250	15에서 81%
프로파노인산, 2,2-디메틸-, [4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]메틸 에스테르	25에서 25%		

[0625]

1b

페놀, 4-[[1-[[4-(4-아미노부톡시)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	5	12.5	
부타노인산, 4-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]페녹시]-	19	>100	15에서 47%
아세트산, [4-[[1-[[3,5-비흐(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스91,1-디메틸에틸)페녹시]-	10	50	NE
부타노인산, 4-아미노-4-옥소-, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	8	25	
글라이신, 4-[[1-[[3,5-비스91,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-디메틸페닐 에스테르	20에서 10%	35	
부타노인산, 모노[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오)-1-메틸에틸)-2,6-디메틸페닐]에스테르	8	20	
부타노인산, 모노[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오)-1-메틸에틸)티오-2,6-비스(1,1-디메틸에틸]페닐메틸에스테르	100에서 40%		
글라이신, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	5	25	5에서 30%
펜타노인산, (1-메틸에틸리덴)비스(티오(2,6-비스(1,1-디메틸에틸)-4,1-페닐렌)]에스테르	NE	25	
펜타노인산, 모노[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오)-1-메틸에틸)티오]-2,6-비스(1,1-디메틸에틸)페닐]에스테르	8.7	25	15에서 70%
부타노인산, 4-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-	11	25	15에서 77%
부타노인산, (1-메틸에틸리덴)비스[티오[2,6-비스(1,1-디메틸에틸]-4,1-페닐렌]]에스테르	NE	25	
글라이신, (1-메틸에틸리덴)비스[비스[티오-2,6-비스91,1-디메틸에틸)-4,1-페닐렌]]에스테르, 이염산염	NE		
옥시란메탄올, α-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스91,1-디메틸에틸)페녹시]메틸]-	45		
옥시란메탄올, 3-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸티오]-2,6-비스91,1-디메틸에틸)페녹시]메틸]-	>100		NE
옥시란메탄올, α-[[3-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오-2,6-비스91,1-디메틸에틸)페녹시메틸]옥시라닐]메톡시]메틸-	60		
페놀, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-(옥시라닐메톡시)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	50에서 NE		

[0626]

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글라이신, N-[3-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시] 2-히드록시프로필]-	16	50	15에서 45%
1,2,3-부탄트리올,4-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-2-히드록시프로필-	6	20	1에서 6%
페놀,4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-(3-에톡시-2-히드록시프로폭시)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	75		
1,2-프로판디올, 3[-4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페톡시]-	30		15에서 40%
페놀, 4-[[1-3,5-비스91,1-디메틸에틸)-4-에톡시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디매틸에틸)-	50에서 NE		
2-프로페노인산,3-[4-[[1-[3,5-비스91,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-,에틸 에스테르, (E)-	50에서 NE		
부타노인산, 모노[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-메톡시페닐]티오]-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐]에스테르	NE		15에서 89%
페놀,4-[[1-[[4-[2-[4-(디메틸아미노)페닐]에톡시]-3,5-비스91,1-디메틸에틸)페닐]티오]-1-메틸에틸]티오]-2,6-비스91,1-디메틸에틸)-	55		
벤젠아민,4,4'-[(1-메틸에틸리덴)비스[티오[2,6-비스(1,1-디메틸에틸)-4,1-페닐렌]옥시]2,1-에탄디일]]비스[N,N-e디메틸-	NE		
L-아르기닌, 모노[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐부탄디오에이트]	15	50	15에서 93%
펜탄디오인산, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-6-비스(1,1-디메틸에틸)페닐메틸 에스테르	80		NE
2-프로페노인산,3-[4-[[1-[[3,5-비스91,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-(E)-	30		NE
α-D-갈락토피라노스,6-O-[4-[[1-[[3,5-비스(1,1-디메틸에틸O-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐]-1,2:3,4-비스-O-(1-메틸에틸리덴)	45		
페놀,4-[[1-[[4-[3-(디메틸아미노)프로폭시]-3,5-비스91,1-디메틸에틸)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)]	50에서 22%		
글라이신,N-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)4-히드록시페닐]티오]-1,메틸에틸]티오]-2,6-비스91,1-디메틸에틸)페녹시]아세틸]-	15		15에서 83%
글루탐산, N-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-아세틸]-	75		15에서 94%
L-글루탐산, N-[3-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-2-히드록시프로필]-디-, 디에틸 에스테르	10	50	

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글라이신, N_[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오-2,6-비스(1,1-디메틸에틸)페녹시]-2,3-디히드록시부틸]-	50	>100	
L-라이신, N^{b}-[3-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-2-히드록시프로필]-	75	100	
2-프로페노인산, 4-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]-부틸 에스테르	75		
페놀,4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-(4-히드록시부톡시)페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	125		
β-D-글루코피라노스,6-O-4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐]-	50에서 30%		
1-H-테트라졸-1-부타노인산, 4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에태ㅣ르]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	50에서 25%		
페놀, 4-[세[1-[[3,5-비스(1,1-디메티레틸)-4-[[3-히드록시-1-프로페닐)옥시]페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)-	55		
L-라이신, N^{b}-[[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페녹시]아세틸]-	50에서 30%	NE	
D-글루코피라노스,6-O-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐]-	10	50	
D-글루시톨,6-O-[4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐]-	15	50	
부타노인산, 4-[[히드록시페녹시)포스포닐]옥시]-4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록히페닐]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	43	75	
부타노인산,4-히드록시-3,3-디메틸-,4-[[1-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸)페닐 에스테르	110		15에서 90%
부타노인산, 4-(설폭시)-, 1-[4-[[3,5-비스(1,1-디메틸에틸)-4-히드록시페닐]티오]-1-메틸에틸]티오]-2,6-비스(1,1-디메틸에틸}페닐]에스테르	20	50	NE

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