

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. ⁷
C07D 471/04

(11)
(43)

2002 - 0005767
2002 01 17

(21)	10 - 2001 - 7015412
(22)	2001 11 30
	2001 11 30
(86)	PCT/US2000/15154
(86)	2000 06 01

(87)

WO 2000/72846
2000 12 07

[illegible]

(30) 60/137,004 1999 06 01 (US)

(71)

19103

(72)

19426

132

19382

911

19426

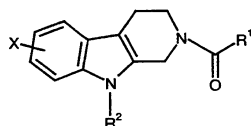
2015

(74)

(54)

Fab I , I .

< I >



,

R^1 Ar Het ,

R^2 H, C_{1-6} Ar - C_{0-6} ,

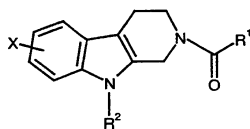
X H, C_{1-4} , OR', SR', C_{1-4} , C_{1-4} , CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , C
ON(R')₂, COR', NR'C(O)R', F, Cl, Br, I $CF_3S(O)_r$, R' H, C_{1-6} Ar - C_{0-6}
, r 0, 1 2 .

, , Fab I

Fab I , .

(ACP) , (FAS)
1 2
FAS , FAS
, ACP ,

Fab I(EnvM) 4
 - ACP ([Bergler, et al, (1994),J. Biol. Chem. 269, 5493 - 5496]).
 , 1 β - - ACP , - ACP - CoA(FabH,
 III) . - ACP - ACP(FabB FabF, I II)
 . 2 NADPH - β - - ACP (FabG) .
 β - - ACP (FabA FabZ) - 2 - - ACP
 , NADH - - ACP (Fab I) - ACP 2
 가 가 - ACP(16C) ,
 - ACP Fab I 가 [Heath, et al, (1996),J. Biol. Chem. 271,
 1833 - 1836]. , Fab I
 . , Fab I .
 가 , (LPS) ,
 Fab I . [Grassberger, et al (1984)J. Med Chem 27 947 - 953]
 2b18 Fab I ([Bergler, et al, (1994),J. Biol. Chem. 269, 5493 - 5
 496]). (S. typhimurium) Fab I
 (E. coli) ([Turnowsky, et al, (1989),J. Bacteriol., 171, 6555 - 6565]).
 , Fab I Fab I
 . Fab I ([Bergler, et al (1994),J. Biol. Chem. 26
 9, 5493 - 5496]).
 Fab I (triclosan) ([McMurr
 y, et al, (1998)Nature394, 531 - 532]). NAD Fab I
 Fab I , ([Levy, et a
 I, (1999)Nature398, 383 - 384]). [Ward et al., (1999)Biochem. 38, 12514 - 12525]
 Fab I 가 Fab I
 가 . NAD Fab I Fab I
 .
 , Fab I , 가 ,
 .
 < >
 Fab I , I .
 , I .
 , Fab I .
 .
 I .

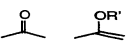


R^1 Ar Het ,

R^2 H, C_{1-6} Ar - C_{0-6} ,

X H, C_{1-4} , OR', SR', C_{1-4} , C_{1-4} , CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I $CF_3S(O)_{r-}$, R' H, C_{1-6} Ar - C_{0-6} , r 0, 1 2 .

가 , 1 -

(Z) (E)  R' 1

가 I

I Fab I . ,

I :

R^1 C_{1-4} , OR', $N(R')_2$, F, Cl, Br, I CF_3 (, R' H C_{1-6}) 1 3 .

R^1 C_{1-4} , OR', $N(R')_2$, F, Cl, Br, I CF_3 (, R' H C_{1-6})

R^2 H, C_{1-6} - C_{0-6} , C_{1-4} , OR'', CO_2R' , $N(R')_2$, F, Cl, Br, I CF_3 (, R' H C_{1-6} , R'' H, C) 1 3 .

X H, C_{1-4} , OR', CN, $N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , F, Cl, Br I(, R' H C_{1-6}) .

1 24 .

[Eur. J. Biochem, 158, 9 (1984)]

IUPAC - IUB

n- C_{1-4} , n- t - C_{1-6} , n- C_{0-4} , n- C_{0-6}

C_{1-4} , C_{1-6} , R^x , C_{1-4} , OR' , SR' , C_{1-4} , C_1 , -4 , $-CF_3$, $-CO_2R'$, $-CON(R')_2$, $-COR'$, $-NR'C(O)R'$, F , Cl , Br , I , $-CN$, $N(R')_2$, $CH_2N(R')_2$, $-NO$, $CF_3S(O)_r$, $(R')_r$, I

F, Cl, Br I

Ar 1 3

[illegible]

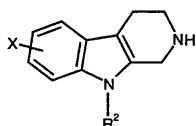
Het _____, 3

, Fmoc , t - Bu 3 , Boc t -
 , Ph , Cbz
 , Bn , Me , Et , Ac
 , Alk C₁₋₄ , Nph 1 - 2 - , cHex . Te
 t 5 - .

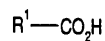
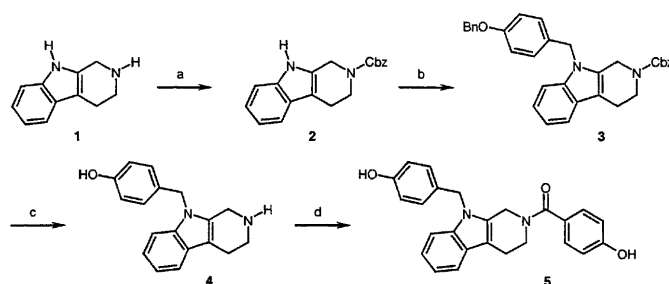
, EDC 1 - (3 -) - 3 - , DMAP , HOBT 1
 , THF , DIEA ,
 DEAD , PPh₃ , DIAD ,
 , DME , DMF , NBS N -
 , Pd/C , PPA , DPPA
 , BOP - 1 - (-)
 , HF , TEA , TFA
 , PCC .

가, EDC HOBT, II, III, , , ,

11



III


 $R^1, R^2 \quad X$


: (a) N - () , Et_3N , DMF; (b) 4 - , NaH, DMF; (c) H_2 , 10% Pd/C, HCl, MeOH, , (d) 4 - , EDC, HOBT · H_2O , (i - Pr) $_2$ NEt, DMF.

가 1,2,3,4 -
(Cbz)

- 9H -

[3,4 - b] (I - 1)
I - 2

가

[Greene, " Protective Groups in Organic Synthe

sis" (published by Wiley - Interscience)]

N -

I - 3

, LDA $LiN(TMS)_2$
THF, DMF

. Cbz

(Pd/C)

I - 4)가 . Cbz

(Greene)

(I - 5)

, 4 -

DMF, CH_2Cl_2 CH_3C
(Et_3N),

EDC HOBT
N (I - 4)
((i - Pr) $_2$ NEt)

가 가

가

["

Compendium of Organic Synthetic Methods" , Vol. I - VI (published by Wiley - Interscience)]

[Bo

dansky, " The Practice of Peptide Synthesis" (published by Springer - Verlag)]

. EDC, DCC, DPPA, PPA, B

OP , HOBT, N -

1 - (HOBt) (DMAP)

(DCC)

N - , DMAP

(THF)

가 ,
 ,
 가 .
 ,
 . Li⁺, Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺ NH⁴⁺
 .

가 (terra alba), 20 mg 1 g

, (,)

Fab I , (,), (,), (,), CNS(,), (,), (, 가 , , , (bacterial myositis)) (,)

0 mg 가 10 mg 100 1 50 mg 500 mg 가 5% 가 가 (bolus)

FabI :

fabI (S. aureus strain) WCUH29 DNA
TaqDNA (BRL) 5' - CGCCTCGAGATGTTAAATCTTGAAAACAAAACA T
A TGTC - 3' 5' - CGCGGATCCAATCAAGTCAGGTTGAAATATCCA - 3'(XhoI BamHI)
XhoI BamHI ,XhoI - BamHI - pET - 16b()
pET - His10 - fabI .fabI (Applied Biosystem model) 377 . pET - His10 - fabI NcoI NdeI
, His 10 tag, Xa FabI 8 97 bp , F
abl 8 2
pET - fabI (version) pET - fabI
(5' - CATGGGCTTAAATCTTGAAAACAAAACA - 3' 5' - TATGTTTTGTTTTCAAGATTT
AAGCC - 3') . pET - fabI FabI
가 FabI pET - fabI BL21(DE3)()
BL21(DE3): pET - fabI

FabI

15L 400 g 10% 가
FabI (lyse) ,
3 : (15Q), - ()

(12) . FabI (pool) ,

FabI

FabI PCR DNA PCR , TOPO TA
 PCR+ . FabI BL21(DE3) . FabI PCR
 pBluePet (Coomassie) , DNA FabI (~28 Kda) SDS
 PAGE (Coomassie) FabI DNA 가 . N'
 FabI

FabI

(broth) 3L 120 g ,
 15% 가 , 3 FabI : (15Q), - ()
 (12) . FabI ,

FabI (NADH)

, 96 가 . 100 mL NaADA, pH 6.5 (ADA=N - [2 -] - 2 -
), 4% , 0.25 mL CoA, 1 mM NADH FabI
 50 - uL 가 . 0.01 10 uM
 . 340 nm 30 20 NADH . t=0
 (fit) IC₅₀ 가 , , 4 -
 , FabI ± S.D.
 30.0 0.010 IC₅₀ .

FabI (NADPH)

, 96 가 . 100 mL NaADA, pH 6.5 (ADA=N - [2 -] - 2 -
), 4% , 0.25 mL CoA, 50 μ M NADPH FabI
 150 - uL 가 . 0.01 10 uM
 . 340 nm 30 20 NADH . t=0
 (fit) IC₅₀ 가 , , 4 -
 , FabI ± S.D.

FabI :

, 96 가 . 100 mL NaADA, pH 6.5 (ADA=N - [2 -] - 2 -
), 4% , 0.25 mL CoA, 50 μ M NADH FabI 150
 - uL 가 . 0.01 10 uM . 3
 40 nm 30 20 NADH . t=0
 (fit) IC₅₀ 가 , , 4 -
 , FabI $\pm$ S.D.
 45.0 2.0 IC₅₀ .

(NCCLS)가 , (Document) M7 - A4, "
 " .
 0.06 64 mcg/mL 가 : Oxford, WCU
 H29, (Streptococcus pneumoniae)R6, ERY2, 1629, N 138
 7, (Streptococcus pyogenes)CN10, (Enterococcus faecalis)I,
 7, (Haemophilus influenzae)Q1, NEMC1,
 (Moraxella Catarrhalis)1502, DC0, ESS, 7623AcrAB+, 120 AcrAB -, MG165
 5, MG1658, (Klebsiella pneumoniae)E70, (Pseudomonas aeruginosa)K799wt. 가
 가 (MIC) . MIC

256 μ g/mL MIC .
 , 128 μ g/mL MIC . 가 ,
 64 μ g/mL MIC .

(¹H NMR) 300 MHz , (TMS)
 () . NMR : s= , d=2
 , t= 3 , q= 4 , m= , dd= 2 2 , dt= 2 3 , app= , br= , J H
 ertz NMR . CDCl₃ , DMSO - d₆
 , CD₃ OD (ES)
 (Quantitative Technologies Inc.)
 (Thomas - Hoover melting point appatus) ,
 (Analtech silica Gel GF) (E. Merck
 silica Gel) 60 F - 254 60
 (E. Merck Kieselgel)(230 - 400) . HPLC (Beckman)
 . HPLC (Gilson)
 ODS . YMC ODS - AQ() ODS
 , (YMC Co. Ltd.) . PRP - 1() ()
 - () , (Hamilton Co.)
 () - , (Man
 ville Corp.) .

1

9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 1,3,4,9 - - 2H - [3,4 - b]

DMF(150 mL) 1,2,3,4 - - 9H - [3,4 - b] (20.0 g, 116.2 mmol)
 N - () (31.84 g, 127.76 mmol) (13.0 g, 127.76 mmol)
 l) 가 . 12 , (150 mL) , EtOAc(2 × 200 mL) .
 , Na₂SO₄ . (/EtOAc, 4:1)
 (34.48 g, 97%) . MS (ES) m/e 307 (M+H)⁺ .

b) 2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

DMF(150 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (17.75
 g, 58.0 mmol) 4 - (14.85 g, 63.8 mmol) 가 . 10 , 60% N
 aH(2.78 g, 69.6 mmol) 가 , RT 가 , 12 . (/EtOAc, 4:1)
 200 mL) , EtOAc(2 × 200 mL) . , Na₂SO₄
 (27.13 g, 93%) . MS (ES) m/e 503 (M+H)⁺ .

c) 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

가 (25 mL) HCl(10 mL, 1M) (50 mL)
 2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] (5.0 g,
 9.96 mmol) 10% Pd/C(0.5 g) 가 . 5 4₅ psi H₂ .
 () (2.79 g, 89%) . MS (ES) m/e 279 (M+H - HCl)⁺ .

2

9 - - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF (75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (5.0 g,
 16.3 mmol) 60% NaH(0.7 g, 17.5 mmol) 가 . 10 , (11.57 g, 81.
 5 mmol) 가 , 가 12 . (100 mL) , Et
 OAc(2 × 100 mL) . , Na₂SO₄ . MS
 (ES) m/e 321 (M+H)⁺ . (/EtOAc, 1:1) (5.17 g, 99%) .

b) 9 - - 1,3,4,9 - - 2H - [3,4 - b]

가 (100 mL), EtOAc(25 mL) HCl(17 mL, 1M)
 2 - - 9 - - 1,3,4,9 - - 2H - [3,4 - b] (5.17 g, 16.2 mmol) 10
 % Pd/C(0.5 g) 가 . 6 4₅ psi H₂ . ()
 (3.19 g, 92%) . MS (ES) m/e 187 (M+H - HCl)⁺ .

3

9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF(75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (5.82 g, 19.0 mmol)
60% NaH(1.10 g, 28.5 mmol) 가 . 10 , 4 -
(5.0 g, 20.9 mmol) 가 , 가 12 . (100 mL) , EtOAc(2 × 100 mL) . , Na₂SO₄
(/EtOAc, 4:1) , (8.73 g, 99%)
. MS (ES) m/e 465 (M+H)⁺ .

b) 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

가 (50 mL), (50 mL) HCl(19 mL, 1M) 2 -
- 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b] (8.73 g, 18.81 mmol)
10% Pd/C(0.5 g) 가 . 6 45 psi H₂ .
() ,
(6.33 g, 92%) . MS (ES) m/e 331 (M+H - HCl)⁺ .

4

2 - - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 1,3,4,9 - - 2H - [3,4 - b]

DMF(20 mL) 1,2,3,4 - - 9H - [3,4 - b] (2.0 g, 11.6 mmol)
(1.56 g, 12.77 mmol), 1 - (1.72 g, 12.77 mmol)
(1.65 g, 12.77 mmol) 가 . 10 , EDC(2.44 g, 12.77 mmol) 가 , 12
(100 mL) , EtOAc(2 × 200 mL) .
, Na₂SO₄ . (/EtOAc, 1:1)
(3.0 g, 94%) . MS (ES) m/e 277 (M+H)⁺ .

5

9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF(75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (5.0 g, 16.33 mmol)
60% NaH(0.98 g, 24.5 mmol) 가 . 10 , 4 -
(3.40 g, 18.0 mmol) 가 , 가 , 12 . (100 mL)
, EtOAc(2 × 100 mL) . , Na₂SO₄
(/EtOAc, 4:1) (6.42 g, 95%)
. MS (ES) m/e 415 (M+H)⁺ .

b) 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

가 (50 mL), (50 mL) HCl(19 mL, 1M) 2
 - 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b] (5.28 g, 12.
 7 mmol) 10% Pd/C(0.5 g) 가 6 4 5 psi H₂ .
 () ,
 (3.61 g, 90%) . MS (ES) m/e 281 (M+H - HCl) ⁺ .

6

4 - (1,2,3,4 - - 9 - })

a) 2 - - 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF(75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (5.0 g, 1
 6.33 mmol) 60% NaH(0.98 g, 24.5 mmol) 가 . 10 , 4 - ()
 (4.12 g, 18.0 mmol) 가 , 가 12 . (1
 00 mL) , EtOAc(2 × 100 mL) , Na₂SO₄
 (/EtOAc, 4:1) (6.91 g, 93%)
 . MS (ES) m/e 455 (M+H) ⁺ .

b) 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b]

가 (50 mL), (50 mL) HCl(19 mL, 1M) 2
 - 9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b] (6.91 g
 15.22 mmol) 10% Pd/C(0.5 g) 가 6 4 5 psi H₂ .
 () ,
 (5.22 g, 90%) . MS (ES) m/e 345 (M+H - HCl) ⁺ .

1

2 - - 9 - - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF(75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (3.0 g. 10.9 mmol)
 60% NaH(0.52 g, 13.1 mmol) 가 . 10 , (7.80 g, 55 mmol)
 가 , 가 , 12 . (50 mL) , EtOAc(2 × 100
 mL) , Na₂SO₄ .
 (/EtOAc, 1:1) (3.14 g, 99%) . MS (ES) m/e 291 (M
 +H) ⁺ .

2

2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

5 DMF(75 mL) 2 - - 1,3,4,9 - - 2H - [3,4 - b] (17.75 g, 58.0 mmol)
 ol) 60% NaH(2.78 g, 69.6 mmol) 가 . 10 , 4 - (14.85 g, 63.8 mmol) 가 , 가 12 . (150 mL) ,
 EtOAc(2 × 150 mL) . , Na₂SO₄ .
 (/EtOAc, 1:1) (26.61 g, 97%) . MS (ES) m/e 473 (M+H)⁺ .

3

2 - (3 -) - 9 - - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - [3 - ()] - 9 - - 1,3,4,9 - - 2H - [3,4 - b] (385820)

DMF(20 mL) 9 - - 1,3,4,9 - - 2H - [3,4 - b]
 (0.35 g, 1.59 mmol) 3 - (0.24 g, 1.75 mmol), 1 -
 (0.24 g, 1.75 mmol) (0.45 g, 3.50 mmol) 가 . 10 , EDC(0.33 g, 1.75 mmol)
 mol) 가 , 12 . (100 mL) , EtOAc(2 × 150 mL)
 . , Na₂SO₄ .
 (CH₃Cl₃/CH₃OH, 95:5) (0.45 g, 92%) . MS
 (ES) m/e 306 (M+H)⁺ .

4

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

DMF(25 mL) 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]
 (0.50 g, 1.59 mmol) 4 - (0.24 g, 1.75 mmol), 1 -
 (0.24 g, 1.75 mmol) (0.45 g, 3.50 mmol) 가 . 10 ,
 EDC(0.33 g, 1.75 mmol) 가 , 12 . (100 mL) , EtO
 Ac(2 × 150 mL) . , Na₂SO₄ .
 (/EtOAc, 1:2) (0.55 g, 91%) . MS (ES) m/e 383 (M+H)⁺ .

5

2 - - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - - 9 - [4 - (0)] - 1,3,4,9 - - 2H - [3,4 - b]

(0.21 g, 1.75 mmol) 4 - 4 ,
 (0.60 g, 90%) , (/EtOAc, 1:2) . MS
 (ES) m/e 383 (M+H)⁺ .

6

2 - (3,4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (3,4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

(0.29 g, 1.75 mmol) 4 -

(0.69 g, 93%)

MS (ES) m/e 427 (M+H) ⁺.

7

2 - (2 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (2 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

2 - (0.24 g, 1.75 mmol) 4 -

(0.62 g, 89%)

. MS (ES) m/e 399 (M+H) ⁺.

8

2 - (3 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (3 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

5 - (0.28 g, 1.75 mmol) 4 -

(0.63 g, 85%)

. MS (ES) m/e 423 (M+H) ⁺.

9

2 - (6 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (6 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

6 - (0.24 g, 1.75 mmol) 4 -

(0.58 g, 83%)

. MS (ES) m/e 400 (M+H) ⁺.

10

2 - (6 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (6 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

6 - (0.24 g, 1.75 mmol) 4 -

(0.60 g, 87%)

. MS (ES) m/e 399 (M+H) ⁺.

11

2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

4 - (0.26 g, 1.75 mmol) 4 - 4
, (0.61 g, 85%) , (/EtOAc, 1:2)
. MS (ES) m/e 412 (M+H) ⁺ .

12

2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

4 - (0.24 g, 1.75 mmol) 4 - 4
, (0.56 g, 80%) , (/EtOAc, 1:2)
. MS (ES) m/e 398 (M+H) ⁺ .

13

2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

4 - (0.27 g, 1.75 mmol) 4 - 4
, (0.63 g, 96%) , (/EtOAc, 1:2)
. MS (ES) m/e 417 (M+H) ⁺ .

14

2 - (3,5 - - 4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (3,5 - - 4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

3,5 - - 4 - (0.36 g, 1.75 mmol) 4 -
4 , (0.70 g, 94%) , (/EtOAc, 1:2)
. MS (ES) m/e 468 (M+H) ⁺ .

15

2 - (3 - - 4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (3 - - 4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

3 - - 4 - (0.32 g, 1.75 mmol) 4 -
4 , (0.62 g, 91%) , (/EtOAc, 1:2)
. MS (ES) m/e 434 (M+H) ⁺ .

16

2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

a) 2 - (4 -) - 9 - [4 - ()] - 1,3,4,9 - - 2H - [3,4 - b]

9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b] (0.
50 g, 1.37 mmol) 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]
4 , (0.55 g, 90%) ,
(/EtOAc, 1:2) . MS (ES) m/e 451 (M+H) ⁺ .

17

4 - ({2 - [(4 -)] - 1,2,3,4 - - 9 - })

9 - {[4 - ()] } - 1,3,4,9 - - 2H - [3,4 - b] (0.76
g, 2.0 mmol) 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]
4 , (0.87 g, 94%) ,
(/EtOAc, 1:2) . MS (ES) m/e 466 (M+H) ⁺ .

18

2 - (4 - - 2 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

4 - - 2 - (0.19 g, 1.10 mmol) 4 - 4
, (0.44 g, 95%) , (/EtOAc, 1:2)
. MS (ES) m/e 469 (M+H) ⁺ .

19

2 - (5 - - 2 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

5 - - 2 - (0.19 g, 1.10 mmol) 4 - 4
, (0.44 g, 94%) , (/EtOAc, 1:2)
. MS (ES) m/e 469 (M+H) ⁺ .

20

2 - (4 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b] (0.50 g, 1.
58 mmol) 9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b]
4 , (0.58 g, 92%) ,
(/EtOAc, 1:1) . MS (ES) m/e 401 (M+H) ⁺ .

21

2 - (3 - - 4 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b] (0.50 g, 1.58 mmol)
 9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b]
 , 3 - - 4 - (0.32 g, 1.75 mmol) 4 -
 4 (0.60 g, 95%)
 EtOAc, 1:1) . MS (ES) m/e 436 (M+H) ⁺ .

22

2 - (3,5 - - 4 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b] (0.50 g, 1.58 mmol)
 9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b]
 , 3,5 - - 4 - (0.36 g, 1.75 mmol) 4 -
 4 (0.68 g, 92%)
 1) . MS (ES) m/e 470 (M+H) ⁺ .

23

2 - (3 - - 4 -) - 9 - [(4 -)] - } 1,3,4,9 - - 2H - [3,4 - b]

9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b] (0.50 g, 1.37 mmol)
 9 - [(4 -)] - 1,3,4,9 - - 2H - - [3,4 - b]
 , 3 - - 4 - (0.27 g, 1.51 mmol) 4 -
 4 (0.56 g, 90%)
 (/EtOAc, 1:1) . MS (ES) m/e 453 (M+H) ⁺ .

24

2 - (2 - - 4 -) - 9 - [(4 -)] 1,3,4,9 - - 2H - [3,4 - b]

2 - - 4 - (0.27 g, 1.75 mmol) 4 -
 , (0.62 g, 95%)
 . MS (ES) m/e 413 (M+H) ⁺ .

25

5 mL 1 20 mg 20 mg 1
 (D5W) 20 mL 가 25 mL , 5%
 , D5W ,
 (bag)
 가 .

26

, 1 50 mg 75 mg 5 mg

27

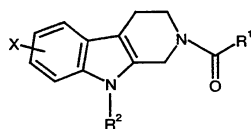
20 mg, 150 mg 1 50 mg 10%
mg 10 mg, 5 mg 3

(57)

1.

I

< I >



R^1 Ar Het ,

R^2 H, C_{1-6} Ar - C_{0-6} ,

X H, C_{1-4} , OR' , SR' , C_{1-4} , C_{1-4} , CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , C
ON(R')₂, COR', NR'C(O)R', F, Cl, Br, I $CF_3S(O)_r$ - , R' H, C_{1-6} Ar - C_{0-6}
, r 0, 1 2 .

2.

1 , R^1 C_{1-4} , OR' , $N(R')_2$, F, Cl, Br, I
 CF_3 (, R' H C_{1-6}) 1 3

3.

1, R¹ C₁₋₄, OR', N(R')₂, F, Cl, Br, I CF₃ (, R' H C₁₋₆)

4.

1, R² H, C₁₋₆ - C₀₋₆, C₁₋₄, OR'', CO₂R', N(R')₂, F, Cl, Br, I CF₃ (, R' H C₁₋₆, R'' H, C₁₋₆)

5.

1, X H, C₁₋₄, OR', CN, N(R')₂, NO₂, CF₃, CO₂R', CON(R')₂, COR', F, Cl, Br I (, R' H C₁₋₆)

6.

1,

2 - - 1,3,4,9 - - 2H - [3,4 - b],

2 - - 9 - - 1,3,4,9 - - 2H - [3,4 - b],

2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (3,4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (2 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (3 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (6 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (6 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (3 -) - 9 - - 1,3,4,9 - - 2H - [3,4 - b],

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b],

2 - (3,5 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

2 - (3 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] ,
 4 - ({2 - [(4 -)] - 1,2,3,4 - - - 9 - }) ,
 2 - (4 - - 2 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] ,
 2 - (5 - - 2 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] ,
 2 - (4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] ,
 2 - (3 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b] ,
 2 - (3,5 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b
] ,
 2 - (3 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,
 4 - b] ,
 2 - (2 - - 4 -) - 9 - [(4 -)] - 1,3,4,9 - - 2H - [3,4 - b]

7.

1 .

8.

1 , Fab I .

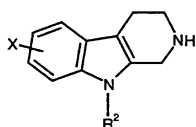
9.

1 , .

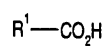
10.

EDC HOBT , II III
 , 1
 I .

< II >



< III >



,

R^1, R^2 X I .

11.

1 6 , .

12.

, 1 I .

13.

Fab I 가 , 1 I .