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SUPERINTENDENGIA DE. INDUSTRAY COMLR00

Senora

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NO. 01.01885.00013-00
FecMa: 200907.28 163929
Alix Carmenza CØsnedes d

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, 444 RcSPUESTAREQUE Folios: 36
Jefe de Division de Nuevas Creaci&..t. _-.----- - SUPERINTENDENaA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia: Expediente No. 01.018.857
Solicitud de Patente de Invención: "Inhibidores a base de Pirrolidina
fusionada con ciclopropilo de dipeptidil peptidasa IV, proceso para su
prcparación y su uso"

Solicitante: Bristol Myers Squibb Company

RESPUESTA AL OFICIO NOTIFICADO POR FIJACION EN USIA
DEL 28 DE MAYO DE 2009, OFICIO No. 0666 (ART 46 BIJSQUEDA DE ANTERIORIDADES)

ALvo COR.REA ORDOEz, mayor de edad y vecino de Bogota D.C., identifleado tal como aparece al pie de ml firma, en ml carÆcterde apoderado de la sociedÆden referencia, doy respuesta al oficio emanado por ese Despacho dentro del tØrmino legal:

1. Presentaclôn de los documentos requerldos de conformidad al articulo 46 de la DecisIon 486

Presento copia completa de las siguientes publicaciones:
1) 1-IANESSIAN S ET AL: "Probing the importance of spacial and conformational domains in captopril analogs for angiotensin converting enzyme activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol 8, no.16,18 August 1998 (1998-08-18), pages 2123-2128, XP00413723 1. ISSN:0960-894X

lb

2) TVEROZOVSKY V V El AL: "Synthesis of (2S, 3R, 4S)-3,4-methanoproline and
analogues by cyclopropylidene insertion" TETHRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no.43, 27 october 1997 (1997-10-27), pages 14773-14792, XP004 1063 07.ISSN:0040-4020

3) SAGNARD I El AL: "Enantioselective synthesis of cyclopropane alpha-amino
acids: Synthesis of N-Boe-cis-(2S, 3R, 4S)-3,4-methanoproline and N-Boc-(2S,3R, 4S)- 3,4-metbanoproline and N-Boc-(2S, 3R, 4R, 4S)-3,4-methanoglutamic acid" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol 36, no 18, 1 May 1995 (1995-05-01), pages 3149-3152, XP004028212ASSN:0040-

4039.

2. Informo a su Despacho que las anteriores publicaciones corresponden a la categorIa
A, segiin se observa del informe de la b(zsqueda internacional (Copia adjunta). Es decir, los documentos solicitados por su Despacho se definen como el estado del arte general, y por Jo tanto no se consideran que tengan relevancia en particular.

En virtud de Jo anterior, solicito que se proceda con el anÆlisis de patentabilidad para la invención que se tramita en este expediente.

Atentamente,

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79.143.366 do Usaquen
81

Anexos: Copia del informe de la Bi’isqueda Internacional
Copia do Ia publicación HANSSIAN S ETA AL
Copia de la publieación TVEREZOVSKY V V ET AL
Copia de Ia publicación SAGNARD I ET AL

MGTIROGDMS4l$$59-Vl-pOO_01857.0720.1XC

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I11III1(LNAIIV1’(AL bLAIKU11 EI!,1UIU Interr iiai Application No

PC1/US 01/07151

A. CLASSIFICATION OF SUBJEC1 MATTER

IPC 7 C07D209/52 A61K31/403 A61P3/04 A61P3/06 61P3/10

According to International Patent Classification (IPC) or to both national classIfication and IPC --
8. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C070

Documentation searched other than minimum documentation to the extent that such documents are Included in the fields searched

Electronic data base consulted during the International search (name 01 data base and, where practical. search ten used)

EPO-Internal, CHEM ABS Data

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My Further documents are listed In the continuation 01 box C. [J Patent family members arelisted in annex.

SpeclaI categories of cited documents: T’ later document published after a International filing date or priority date and not In con A document defining the general slate of the an which IS not cited to understand the princi

Ict with the application but

Ia or theory underlying the considered to be of particular relevance Invention

E earlier document but published on or after the international document of particular releva filing date the claimed invention

cannot be considered novel oi

L’ document which may throw doubts on prloilly claim(s) or Involve an tnvenllvestep what
Is cited to establish the publication date of another NY.

cannot be considered to
the document Is taken alone

Which IOfparticular reteva citation or other special reason (as specified) cannot be considered to Invoh

the claimed Invention e an Inventive step when the
10’ document referring to an oral disclosure, use, exhibition or document Is combined with or
other means mania, such combination beth a or more other such docu-

obvious to a person skilled

P document published prior to the international filing date but In the art
later than the priority date claimed &’ document member of the same patent family
Date of the actual completion of the International search I Date of mailing of the Internet at search report

16. October 2001 1 23/10/2001
Name and mailing address of the ISA Authorized officer
European Patent Office. P.B. 5818 Patentiaan 2 I

NI 2260 I-tV Rijswijk I Tel (+31-70) 340-2040. Tx. 31 651 epo ft.

Fax: (+31-70) 340-3016 Hass, C

Ofl PC17iSAf21O lasoond sheotJ (July lass)

(12) INTERNATIONAL 4,PPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property OrganizationInternational Bureau 11111 1101

(43) International Publication Date (1 lot roatlonal Publication Number

20 September 2001 (20.09.2001) PCT 0 01/68603 A3

(51) International Patent Clg ssificati0n7 C07D 209/52 (74) Agents: &LGII rRl, Aldo, A ci al Bristol Myers Squibb
A611(31/403 A61 1/0 1/06 3/10 Co P0 Box 4000, Lawrenceville Princeton Rd Prince-
ton,NJ(543(IS).
(21) International Applicati n Number: PCTIIJSOI/07151..

(81) Designated Sta es (nalIcnaD: AB, AG, AL, AM, AT, AU, (22) International Filing Date: 5 March 2001 (0501 2001) AZ BA B, B’,BR BY, CA, CH CN CR, CU CZ, DE,
DK DM DZ, E, ES, M. GB, (3D, GE, CH. GM HR, HU,
(25) Filing Language English ID IL,’R4, Is, M, KB, KG KP KR, KZ LC LK Lk, LS
LT, LU, JX, MA, MD, MG. MK, MN, MW. MX, NO, Ni
(26) Publication Language English PL, PT 0, RU SD SB SG SI 5K, SL TJ TM TR II’
’17..UA. L)G,US, UZ VN,YU,ZA,W,
(30) Priority Data:

60/188,555 10 March 2000(1001 2000) US (84) Designated States (regional) ARIPO patent ((314, OM,
ICE. LS MW Z, SD, SL, SZ 17., UG ZW) Eurasian

(71) Applicant (for all designated States except US) BIUS- patent (dl,AZ BY, KG 1(2, MD RU,TJ TM) European TOL-MYERS SQUIBI CO (US/US] P.O.Box 4000 patent BE ’H CY DE DK ES F! FR GB CR IB, Lawrenceville-Princeton Road, Princeton NJ 08543 (US) IT LU, iC, N,PT SE TR) OAPI patent (lIP, 8.1, CF.
CC), Cl.:M, G GN, ML MR, NE, SN, TD, TG). (72) Inventors; and
(75) Inventors/Applicants (/,* US onlj’): ROBLI Jeffrey, Published: A. [US/US]; 7 Tulip Drive.

SULSKZ Richard, B.

Newtown, PA 18940 (US).
S/US]; 2 Coventry Square, West -with internatioi alsearch re or!
Trenton NJ 08628 (US) 1

107 Carter Road Pnncc

AUGERI, David, J (US/US],
n NJ 08540 (US) MAGNIN, (88) Date of abBe ition ofthe international search report
David, II [US/US], 40C nage Court Hamilton, NJ 08690 14 February 2002 (US). HAMANN, Lawn net, C. [US/US]; 24 East Riding
Drive, Cherry Hill, NJ 08003 (US), BETEBENNER, For two-letter codes 4 ind other dbbrevfartons, refer to the "Guid-David, A [US/US], 3] iston Court, Lawrenceville, NJ once Notes on Codes andAbbreviations"appearzng at the in.
08648 (US). ning ofeach, gular issue ofth PCTGazette.

S

(54) Title CYCLOPROPYL USED PYRROLIDINE-BASED INHIBiTORS OF DII 1EPTIDYL IV PROCESSES FOR THl PREPARATION, AND THEII USE

(57) Abstract: Dipeptidyl peptiØas
IV (liP 4) inhibiting compounds I ar
provided having the formula (I) wirer
R

1 a2

r(I)

xis0orl and yisoori(provide
that x I when =0 and x =0 whe

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N y=I),nis0orl XisHorCN

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n y and wherein R’, R2, R3 and R4 are a

4 A 0 X described herein. A method is also
provided for treating diabetes an

Cdiabetes, other

related diseases,
set out inhibitor a inhibitor

another antidiabetic mett’ormln, glyburide, troglitazone, and/or-on
more hypoilpidetnic anti-obesity other thempet age

C. Continuation)

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Application

01/07151

No

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C.(Conttnuation) DOCUMENTS CONSIDERED TO SE RELEVANT
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Acids: Synth sis of
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S Blooc & ChwubtrY LMtm 8 (IM2l2I28

PROBING THE 111PORTANCE OF AND CONFORMATIONAL I) CAPIUPRILMALOGS FORMOIOTENSIN CONVERTING ENZYME

Stephen ifanessian,’ lUnch Reinhold, Midiel SauWer, and Stephen Clan

Dqwftgw UthesvUi deMond C.?. 6124 &cmWe Can MonirØaI QuŒbecC.4W4D4 11SC 3J7

ReceIved 29 April 1998; accepted 9 July 1998

Abstiset A new synthesis of4,5-seth L-prcflns and th*. eazymatle activity of Ike mercapto-2’R-methyl-proplonyt) analogs as inhibitors of angiozensin convefling enzyme a 01998 MwdorSuit= Ud. MI A&M cscrved.
Target and cheridsisy-dilven drug design based on molecular interactions with en recent years as a stimulating area of researcl eudeav& Although there are a muhbs enzyme Inhibitors, even at UM concentrations in vitro, the process oftheir development ii is arduous to say the least One of the remarkably succeasibi attempts at drug desig Interactions with an enzyme Is eaernpliSed in ouptopil.2 an Inhibitor of angioteirsin car used tbrThe treatnient of’hypertension (PIgure 1).

FIgure 1. Captoprll,Ramlpailat and new constrained analogs

c02N

0 CO2B
Ramiprila 2

CO2B

Captopril, 1

0

R=t-lluO,S R i-BoO, 7

BIOOSWAMC&
MSDIaNALVHEMIS1RY
Lffilan

-S has emerged In
of small-molecule
a marketable drug
med on molecular
ting enzyme, and

3

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,10

The discovery ofcaptapnil, an exquisitely simple molecule by today’s standards 4IncreasIng molecular complexity,Is; classic example ofdesign based on a knowledge of possible interactions etween the drug and

S

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P17: $0960-*94X(98)00377-1

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2124 S. Wwwssian or/Bioorg. MeL Chem. Left. 8(1998) 2123-2128

the active she &the enzyme This was also aided by e*tensive analog synthesis ofprolive peptides, which led to the conclUsion that captopril appears to offer effective interactions with the functional 8rcups on the surface ofthe enzyme that involve charge, H-bonding and hydrophobic contact?
The importance at such multiple interactions has been discussed in 643 and was the bash of an intense effort directed at the discovery of analogs otcaptopril,21.1 sUch as enalapdl,3’ s$ of 2. Since the cLr-orientation of the cyclopentane in ramiptilat in Important for biological activity the relevance of the hydrophobic interaction ofthat region OFthI prcflne moiety with the enzyme can be a
Our interest isthe synthesis of conlbnnationaily constrained heterocydes, vcup1d with the desire to fUrther probe the role of substituants on the enzymatic activity of captopril, inedgatd the research work reported in this paper.
Previous work in our IabOTalCryM (Scheme 1) has described methodsforthe synthsia ofBoa derivatives
of methano-L-prolhie3, cLM metbunoL-pndine 5, frwrs-5,6-methano-L.-pipcd11c acid, 7, and cia-5,6-methano-L-pipecoflc add, P. It was furth& observed that the proline ring in the N. Boo derivative 3 was virtually flattened (rims, 0,003 A) compared to 5 (ruts, 0.013 A) and Boc-L-proline (ruts,.0l8 A).$ While the reasons for this lauainal. effhct were not evident, we anticipated that such constrain pndine derivatives should be *zplcrcd fltrther as surrogates for L-proftne In a selected group of medidnelb relevant compounds.

,

We thus set out to prepare the (2R)-methyl..3-mervapto N-proplonyl amides of the above mentioned 0-methano-L-prollnes and L-pipecoiio adds as constrained analogs of captopril, and to ptudy their inhibitory activity cn ACE (anglotensin conveailngeuzyme).

Scheme 1. I

3

nMe3

MPS2,
TM

1.LiEtBii.
Boch

80

1 317

Coal!OR nu0,1 OR

Equilibrate

Mal

1. UMSBH lloc$

Zseps
2. TFA

OR n=0.l OR
2344e6ano-prolines have been previously reported by a number of groups cia- end frans-3,4-Methano-pr4lines were described by Wilkop and coworkers’ in 1971. We were awake of one synthesis of macnile 4,5-methano-pnline aznldes9 which was based’ on a Beckerami Iarrangemem of cia-bicyclo(3.I.O3bexau-2’.one to a 8-lactam followed by chlorination and ring contraction.

2126 S. Hwze.cslon etaL Irnoorg. MeeL Chem. Lea. 8(1998)2123-2128

X-ray structure and solid stale eonfcnna*icnal characteristics of 16 mvvaled ctzulden pyrrolidine ring (ama 0.09 A) compared to L-proline (tins 0.181 A), A H-bond was
protonated amine and the cmbonylate group, (Plgure 2).

Figure 2.

The predominance ofthe cls4,5-xnethano Isomer 14 in the cyciopropanadon macli
the tin-mediated inilnium Ion cydlizalico protocol’ (Scheme 1) favored the forination oft
steric factors imposed by a bulky resident group. Most probably, the r*-oyclopropanal
- anchozing effectofthe zinc species with the ester group In 12, thus delivering the nuci side to give 14.
Acyistiun ofthe free amino acidswith the readily available S-acetyl-2-Q)-me1hyI
saponification afforded the captoptil analogs 4 and 6. The L-plpecolia acid analog 8 ’a
from the precuracramino add.5
Inhibition ofACE obtained from rabbit lung and partially purified, was studied ii
as a substrate following the procedure ofCushman and Cheung.’6 The results shown Ii the cis- and emts.5-metbano analogs oft-prollne 4,6, and theraw..L-p1pecdic add anal inhibitors, eves surpassing captopril The cLc4A-caabocydic analog of captopril, ram] active than the corresponding Owu4somer, in this respect ills ofinterest that the cia active an the own-analog 4. Clearly, this study has shown thatsmall rings can be tolem otcaptopril with cip or ffans.Orientadons. It also appears that the degree ofring flatten relative to captopril Is not having an adverse affect on enzyme inhibitory activity, ar advantage.
Analogs 4,6, and 8, were inactive against neutral endopeptidase 24.11 enzyme against endothelin converting enzyme at 1 pt The selectivity described herein exhibik methane analogs 4, 6, and 8 towards ACE is obviously of interest. Future we incorporation of4,5-mcthano prolines and 5,6-metheno pipecolic adds into strategic poi ofthe corresponding natural amino acidsin pharmacologically relevantmolecules.

L]

flattening of the
Icut between the

Is of intczest, since
hun-Isomer due to
ii Is the remit of an
simile from the anne

lcayl chloride and
similarly prepared

ng hippuryl-Bis-Lau
Table I indicate that
g are highly potent
dIet 2, is much more
malogd is equally as
A at the 4,5-position
ig in time derivatives
I it could even be an

10 as well as

by captoprit and the
will focus on the
Ions as replacements

4

S. Hwwiwg et al. /Bioorg. Mott Chem. Lct& 8(1998) 2/23-2128

Our synthesis of the analogs 3,5,71 and 9, relied on the ielmmclomilar himethylstanmjlmethyl luctams via the corresponding linluiwn.saIis’ The cLi- or cycicprapane ring could be controlled by the D- or x-dlsposfticn of the turned Telpectively via-A-vip the steseocontroiling substituent In the corresponding derivatives

scheme 2.

B

2. PM, MeOB
Boc?(

EtZnFCI1 65%

1. UBEt3B,fliP, 95%

3. NB4CI, 150°C 2. Boc20, DMAP
20.100 mmHg, 81%
CO2Et Cop

CB2CI,75%

11

1. LiOR, McOWH20
13
2. RCO2H

(quanL)

15

12

l.Ac&-XCOCl

CO2c12, EtN
2. sq. NB40n
40% (2 steps)

1. UGH, MeOWH20 1.AcSiJ1

2. HCO2H CH2c12 Bt3N

(quazu.) &)2H 2. eq. NH4OH
56% (2 steps)

13

1),

2125

of a-
of the
group

.16 6

We have now devised an expedient route to 4,5..methano-prolines that affords the cuanliopure derivatives 3 and 510 essentially eight steps from commezdUy available L-pyrugluta4 acid (Scheme 2) Thus reduction ofthe lantern carbonyl In U with lithium tuiethyThorohydside followed by transformation to the methory hemiarninal carbamate and elimination ofmethanol In the presence of ammoc1un chloride’0 led to the enecaibaunate analog 12 In good yield." Originally, we had used other published motIods12 to effect the dehydration, but in our hands, yields were modest and reproducibility depended on the s ofthe reaction. Application ofthe modified SimmonsSmith cyclopropanado&3 reaction to the enecathamite 12 followed by protection ofthe amine with Boo anhydride, led to a mixture ofthe frans-4,5-rnethdno-L-prcliue analog 13 and the concspcmdlng cv-4,54sorner 14-in a ratio of 1:4 iwa combined yield of 75%.14 This expedient method based on a well-known reaction," proceeds in good overall ylcid and it Is 3 steps shorter then our previous syzzthesis5 which utilized an organotin reagent It has allowed us to prepare gram quaitlties of both 4,5-methano-L-prolincs which were easily separable by column chromatography astheirN.Boc derivatives 13 and
14. Hydrolysis with LIOH in sq. methanol gave the known respective 4,5-methano-N-oc-L-prollnes5 as crystalline solids Treatment of 13 with aq, base followed by formic acid gave the free add I5 as a white solid In quantitative yield. Analogous hydrolysis of 14 gave the isomeric free add 16 as a crystalline solid. The

4

S. lianesslan at al. /Bfoorg. Med Chain. LaU. 8(1998) 21234128

Table 1 inhibition Tests on Angiotensin Converting Enzyme (ACE)’ Compounct Eso

7.6 Ok 07 aM)

CO2H

HSç 6,6 (* 0.3 aM)

O2H

aft

HO

N 5.3 O.2 aM)

Me

13.O(–1nM)

I,Captcpril

a. For assay method, see ref 16

2127

Adedgunents, We gratefully acicnowlcdge 8nancial assistance from NSERC uider the Medicinal Chemistry Chair program. We are Indebted to Dr. Arco Y. lang (Novarils, Summit, NJ fur the enzymatic asaaya. We think Dr. Michel Simard ofthe X-ray crystallography laboratory at the UniynrsltØ do MontrØal
for structure determinations.

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1. 4.nku 1"6,1097.
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Often. DE3,324,263 (Cl. C07D209/2); Chain. Abs#. 1985,103, P 54461q; for a reli mixtures c(dlastcreomrrs, we also it Pe!licciati, L Azniazu, P. Do CaprarUs, B. N A..GsIli, J. Client. Soc. Perkt,,I. 1995,1251.
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Ii. Typical procedure: A mixture contahdngN-Bo-5..niethoxy-(ZS)pyrrdidine-1-carb (1.2 & 4.4 mad) and amumonhun chloride (0.044, 0.15 equlv) was heated under 100 mm Hg) In a flask equipped with it rethur condenser. The reaction mixture ’o room temperature, and the resultant oil was purified by flash chromatography on al acetate, 91) to afford the product 12(0.854 g, 81%) as a colorless oil.
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24. Typic4d procedure: To a cooled solution of 12 (0.5708 & 2,366 nimol) in dry 1, nitrogen was added dropwlse 1.1 equlv of diethyl zinc Et2Zn, 1.OM solution In be tuL) said 1.5 erpriv, ofdilodomethane (3.55 mmcl, 0.29 niL) at 0 °C. The reaction r 30 min at 0°C then 6 b at room temperature and quenched with dilute NaHCO, (7 it (40 niL), and the aqueous layer was extracted with dichloromcthane (4 x 50 niL) a The residue after evaporation was purified by flash chromatography (methanol. 1:5:13) to aftotd the isomeric mixture ofproducts (0.3328,65%) as a pale-yellow ci Into the N-Eec derivatives (BocO, DMAF, Et3N, CB20), and separated by clan and 14(75%yield, 1:4retlo)
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A.; Besslres, B.; La
Ic H.; Holt, B. M.;
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D.Synle#1994,575;
B. M. Tetrahedron:

CM P.; Kale, J. M.;
mica of cyclopropyl
,KE.;Cas*aldI,M.

& H. Becker, Oar.
example Involving
n, M. Marinozzi,

T. J. Am. Chain,

VC acid ethyl ester
Wed pressure (20
allowed to cool to
gel (homes-ethyl

Pardo, D.G..S)rt

Jicidoroethane under
we, 2.603 mmol, 16
xture was stirred for

.). Water was added
I processed as usual.
axanes-cthyl acetate,
that was trunsfoimed
isatogrby to give 13

r, L.P. Synlett 1995,
1"6,19,336.

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Temthedjwn, Vol. 53, No 43, pp. 14773-14792,W97
1997 BI*ovlcr $olflco US
M dghtsecvcd. ftintcd 1 Gou Nub

PlI S0040-4020(97)009li8-5 $11.00 + 000

Synthesis of(^3k 4S)-3,4.Methaii9prolineaud
by Cydupropylidgue Insertion

\rmchesjav V. Tverezovskt, Mark S. Baird" and ban G. BoICSOVb

’D.par$nient of Ual1, ofWales, Bangor b Department ofChaudatry, S niveraity ofMoscow, Moscow

AbMwr hbuwbmftIrowtimofaia1eczanSeaesotcick,ropyItemIn10 5,64whaled
with nM&4*mc(aw*rwv"=ymmcbbb4aWm 01997 Sleovler Science Ltd.

Although methanoprollne (1) was Isolated some years ago from the American hozsł chesaut, 4asculsss it is still auracthtg considerable attwgioo.X3 It was shown to be a potent uhlbitor of praline mntabolimn’ assuch it wastargeted an apotential chemical control agent in the production ¶bbrldwhe&In addition, methanoproilne inhibits the proline transport system ofEsdwfchb coil,’ while a thde derivatives of xnetbenoprolhii are inhibitors of angloteusin converting enzyme.1 Although a munbor of routes to rucendo thanoproline havebeen repnna&* only one synthetis ofenantiomericatly pure (i) and on synthesis oftheN-
Boo derivative have appeared.° The first involves the cyclopropermatton ofdehydroprolirre i4 a reaction widob Is
Mveay diastereoselective and from which the major product is the trans-Isomer (2).

C

The second Involvesthe coupling oftwo shire! starting materials, (3) and (2R)-gly1
by zyclisation and flavtit*mat group intesconvetllon to giveN-Boo protected 1) In seven 19
oflessthus25 We tupoeted some years ago that 2diinofllethyl-1,1-dlbfOUIOCYcl
reactwith xnethylRthhm to give 3-azabIcycIoI3.I.O]hexanes (5) by a itrid hmsartioii ofthS dane or a related carbenold Into the CH-bond adjacent to nitrogen and 5,64elated to the c

-_MaLi

It has alsobeen shown that a abnilar Insution ofcyclopropylldenee derived float

14773

Viflats, followed
with overail yield
panes such as (4)
ved cyclopzvpyil-
no ccntr&r

ft) and(6b)

A

 1

I

14174 V. V. TVaREZOVSKY a: al.

by reaction with methyflithiurn leads to the 3..oxablc ot3.l.O]bsxaces (ia) and (Th) w1th dlastercosclectivfty for Risomer’2

404C’ ’

+ "0’
(5a.(–),RVInyI) (786RyL75%,endcIeso17:1) I

i moderate to high

(lb’(. R a IPfSCHCH) (Th R t.PtiCH=CH1 41 % endc#w 7)

We nowreport the application ofthe insertion reaedon to the snthcds ofmethanopmllne and ofit number ofrelated corspounds each as a do&aawOww. Themethod hasthe a vantage that 01oug4 lovolft a number ofstep; the staitlng matmials are cheap ant) readily available on a large scale and the rectlons Involved are geum*ocaamely high moreover It maybevatted to produce in principle any requid stereolsonier and a range ofanalogues.
Reaction of methyl methactylate with bromotbrm and base leads very read to 2,24bromo-1 meth4oyclopropane carboxylic acid.13 this Is simply resolved using dehydroablctylanifne Lateethanol to give (S. R) and its enandoiner, and the absolute acharniaby ofthe antide of(3, It) has been Cetabilahed by X.ray eriagmp)ryN The corresponding non-methylated acid (9, B.) and its enantion2er were readily obtained on a nashi.gmm scale by oxidation of I,1-dibromo-2..’dnylcyclopmpane with potassium "M4, guac to give 2,2. dlbrornocyclopropane caibo*yilo acid followed by riolution ofthiswith de4*oablct)tumh0e.14

Me or H or

R) tbr (5. RI

The acid (8 S) (99% i.e.) was converted into the corresponding add chloride byreaction with thlonyl chloride, and tide was reduced to the alcohol (11) by reaction wlthlithiuin aluminium hydride. This route was chosen in ceder to avoid competing reduction ofthe 0bronrocyclopmpaneto the couespo$lnglsomerio mono-bromides. Itwas necessary to add a solution aftho add chloride In etherto lithium alwrthd4mhydride In ether at
- 80 OC, a okkion oftbe hydd& to the add ddoftled to up to 30 % ofan am&ded by nudon offt product alcOhol with theacid chloride. Mbigherteirçeratures monobroinides were ibemed ir addition to dibrumi-des. The alcohoL (11) was converted into the corresponding bromidi (12) by reaction With 1,2.bie(dlpheayl-pbosphino)cthane and bromine, and reaction ofthla with drberailylamine or benaylamiac gave the ammnes (13) and (14’

* Attempted dhoct reduction ofainides ofacid S) to amines with LAK Naa*1 or BWSM; led to abdurve ofproducts. Attempts to make the tosylatsfrom the alcohol (11)led so cly amoderate yield.

Synthesis of SR4S-34-uDthancpsoline

(11,55%)

Sr M* Sr AN RCINHz

caOo S

C(13R fx V98%)
(15.RPh,O5%) ç14,RhaG%)

Bsisiisquenceofon Ow d9,R)(93%efled1ntothedt
in enewenli yield of86%. Msenpla topxara(*1)fiom 1,14brom-24omoykcicprcp (9R) ybyreaotionwfthdmhiehioonly8O%tddof(fl)after4daysat5C

(5)50012
(i4LiMH4

(i5) diphee, Br2
5000 C5v) B*512
(9,5) (v)Th55r

s(I(14)ectedssththBocdndentives(15)a 16)l inaction oft
lithisenJed ton of the*rcnvhlchwesus ab1relat3,1,0Thcxa respectively. The yields ofew*ofibe products were highly dependent on the reaction conditic sttseochcssistsy ofthe allyt imd pb1gioups In (iSa) or (180) was assigned onthe busis ofthe forB4Inthe protonNMR specimen in each case appeared us a a1nlet ratherlisa the donlM .plms Moreover, In each vas, these compounds showed the signals fortwo tow=s boi by 1H anti NMR; deprotection gave the amman (21a)and (ith) uIddi abound cniy the cx signals in 1H and "C?DAL

(1RVbtyI) MeU H Pet, 1M0
C1.RPh) 0’c3,Itthi9 1’(+ +
me

A7__

i* H VInłi - (W ROW" (’
21Ht) H (15biRPh)

14715

4amlns (Vfl
dotived linen

tesewithenetbyl
s(18s) or(liii)
a Tublc I). The
atthddoOpd
expected forthe
the anddebond
ected U=AW of

14176 V.V.TveRov$uetaL

Eeaetle*s uf*5) med (26) wIth mrthI Uddim

bl

Teosasdn
readxC’

C4uyWk%"
(183 j39)_
OR 20 40 45 9 :. 2
40 50 19 17 7 31
. 60 -61 8 -16 2
42 29 8 1
(30) 20
90 8 I? 3 24

J)AOixix5W l75oc)ixsamea83aym asei. heteedyIstd cthlebsomdazmebasidee’

AhbouitlmpmLSed)e1d ofs1$e)obtthzed h thisway was only 47 Itcould be convreted Into
the nitthanopzolhte analogue (23) bp.addadon with rutheafuni tehoxido gadin aihi ¶oniRu4thilowed by deprotection. Attempted cuonolyals *lso led to (22) but In this case a second product was the lactam (24)

H Mu H W H Mu H Mu H Mu
CFAW

- ’ ’ +;

23.89%) Z60%) I 415)

11mwuloc(1sbednwhhbe4bm*uletolve(25). leon
zylamise (2$) reacted with mcthyflithiumto give the endo.phenyl isomer(26) as the m

of me
Mau

30tft Ph

_ Ph
+ f
(583 Ph (283 Ph (27) Ph Ph
Table 2 Reaction atCompound (25) wIthme"ftWlu

o(16)the4lbeu
aduct (Thbl. 2):

I
I T (25) (283 (29)
L 20 5651 1 33
9° 1

wa Ph

Synthesis of (2S,3R,48>3,4iuethanoproline

It coold beobinlund pmby fmmdofihe lepwlties (28) and (20) by selectiv debcazylsdon a catalyst (5%Pd/C,0.0I moteq, I h) Mowed byflaahchroniatogrephy.
The undo antine (26) was dthalatedto (30) under more vigorous condItions (0.05 catalyst 15 h). P onbytillhmroacetyladon, then oxidation ofthe phenyl group by react tatrodda at 80T, for 3 hpve (34 and then deçrotecticn gave the ainlnoacid (33), a second is of methanopiuline. It is Interesting to note the remarkable stability of CU and CU2 groui oxidation under these conditions. It Iswell known that ethersRC3%0Me (it-Ph or AJk) can to esters with rutI*nhsmteIzodde even at room temperature Mtemptsto oxidiso (31) with r at20Cevcnusingmore cata1yat and for 1 day wave un*acccssfbl. In the caseofthcBoc-pz’ ruthenhentetioside oxidation atroom temperature led to ring opening to give (35).

H Me H Me
PhPh__Koo

(sb) L.PhH

BOB

(3 (CFjCO/ 95%) (34,81%)

Ph

Mc H Me

’ rRuo1 KOH J) P HOOctJ)

MeOH

CoCE COCFi
(5195%) (*93%)

14711

hydrogen and

eq. ofthe anne
with rotheninan
Id analogue
nitrogen to
be oxidised
in tetroidde

amIne (34),

(35,44%)

Ma

01%)

Reaction of (17) wIth methpi lithium gave one major product (36) together with a number ofminor products with structures typical of those usually obtained in similer reactions of non-lint tionalised dihalo-
CycIOprOpansL0

Ph

Ph (41,1.6%)

Ph Ph

+ +

Fh) ?ph

!11

34778 V. V. TVEUEZOVSKY at aL

flmstereocbnnbuy ofthe blcyclopropyfideuws (40) and (41) is not certain, while tha1 of(39) in assigned
on the basis *fNCQ3 studier. The use ofmodified reaction conditions to increase theyklds¶bonovel opliaafly active bicyclopropylidenes Is bagexamined.
Thereason forftsmarsal Inthes$crcocbeatistiy ofthe nuor uzabl’c1as (26) and (3) compared to tint of(18*) and (lSb) is not yet clear, but may reflect the inmeased stesic demand ofthe Boo 1gruup compared to bmqk or more probablythe s*lc endelectronic effect ofthe NCObond ofthe it ermedlses leading to (1k) and (lob) compamdtothe N.Cl1,bond ofthoseleadingto (26) and (36). Thdsed theNMR spetra oftheproducts (18*) and (ISh) em characterfard by the presence eftwe ruramnem about this bond.
Debenzyletlonof(36)(93 %e.e.) followed by protection as a trifluorcacetate gave crr$aflMe (42)(81%
yiald, 100% on. bydthal gic., with baselineresolution, ace ala egerneut). Oxidation as L1efbre and deproteq-
tion gavethe final enilnoacid (1) with nNMR spectrum which was identical tothat inthsl?vature.’Tbojdjj,20 (.141J1 was also In good agreement with the literature value ([u] 1440),5 The overall dcld of(1)from (9, B) was 4l%.

H H

H H H H H
(II Pdso uj
, I COOH

KOH f.4cooH

I It MOM
Coors cocF, H
(3O 03% ee.) (42 01%. 100% e.e.) (43,88 %)

The reactions described above Indicate that the Insertion clfcYcioProPYUdencs Witoaff bonds can occur ins higidy stereocontrolled maimer and may offer a valuable route to a number of active mono and polycyclic systems.

MknoeIedgnecst 1*w kwłoudd riththuppa1 cftheflTMpmpae
111813$
28V1$M*sapplØna 501111$’ 5 cOteWbprOVidrdonIutiCe.

Z*p.rlmeztal Section
P patewere obtained finer conunereW opIiers am) wemusedwithout flutherpu
Diddorometheurwas ovtroticlum hydride. Diethyl ether and tetrabydrofliran war
wive. Petmwas herofboIIing point 40.60°Cor60-8UC and wasdi5tflk
anhydrous conditions were performed using oven dried glassware (250 °C) that was ci
siltengen orargon a diheenpalmentawara conducted under a positive atnsoqbere ofone i
III sohnloue weredried over anhydnuis nwgavsium WWWft a4unless stated, ware avaporati quoted are fbrthe purified compounds unless stated.
AD new compounds were homogeneous by tic orby gin. Ole was conducted using
III P17PLD, onacaplia ycolwnn(30mx0.32mmldPbase,D05 split ratio of5O:l) using

cation unless statcd.
liatifled over sodium
Reactions niqaldug
ad under either dry
these gases, Organic
at 14 mumUg. Yields

i-ELmerModel
ascairlergas.

IP

Synthesis at(23R,43)-3,4methanujollne

*was conducted using a -340umvaceI1-K-cyc10dextth1 fined silica column ID, 0,2mm), using helium as a ceniesgas at 2 barpresaize (see acletowledgement). Th wa hellicagel 60 plates(1254). Compomi6vievev1suaWoldmr by examination under an
or by exposure to iodine vapour. Column cbromatograpby was conducted with Merck 77 medium presaure
points amwcotmcted. Inflared spechnsrere obtained on a Perkln-Elnier 1600
as liquid fihus unless otherwise stated. Low resolution mass epebtra were b*talned using a i spectrometer. Mass meamrcmeelsmVto 19Br and ’C1 isotopes unlessstated and were obtained Mass Spectrometiy Service. Microanalyses were pertbnncd with a Cado-Eft Model 1106 CE Wows were recorded in CDCI5 unless otherwise stated caBroker AC250at 250 Mffzibr p100 rcatbous and lathe latter vase were broad-bad dccoupted In most oteesDEPT spectra me signs ofsignals Cli, CH,-for CN,) areIndicated onthe data forthe broad-band decoupin signalswith no sign in such a epeceum are quatelnamy.

(S)-(+).2lbrum4l-1-wethylcycleplwpaneCarbOnyI chlor1de
Thonyl chloride (25 nil, 0.34 mole) was added to (8)-(-)4,2-dlbromo-1-mcth3lcycboj
acid (4, S), [u]55.1 (a 1.015, CISCI5), >99% e.e. (26.4 & 102.4 mniole) and the utixtu 2 ii. The excess ot’thionyl dulOdde was removed by distillation and the residue was distilled mmffg) to give (S)-(+)-2 2.dih I..arethylcyclopropanecutbonyl chkrlde (10) (21.2g.! (forraccuaste see ref’ 181 14m40,3, (a 1.104, CHCI3), asp. -15 ’C, which showed bw 1.77 ii, 18.0Hz), 2.52 (10, d, I 8.0 Hz); 66 21.76+, 27.61,34.31-, 42.97,156.35; v,,, 1783 8. 145 12971240 To, 10gSm,lOS6 mi 029 in, 951s91n790;721 To, 6SSn626mCr

14779

Zip

40 m 0.23 mm
- using
Uzvlo1et source
i Avg Rd under

1K spectrometer
iniganMat 1020
nra the Swansea
a_.NMR
is and 62.9 MHz
also run and the
spectrum. Those

apace carboxylic
wasrefluxed for
139-40 ’C 0.8
.4 masols, 96%)
3}I,$), 1.78 (IN,
in, 1421 in, 134

(S+2,2-Dlbromo.]hydroIymethyI-Z.methylCycIopi1panCi
A solution of()-(+).2,2.d1broino.I-mcthylcyclopropnnecarb0nyl chloride (24.7g. 9.4 mmole) in dry ether (20mb) was added with stirring to lithium aluminium hydride (3.66g. 89.4 mmobe) In dry ether (400 nil) at 45 ’C undernitrogen over 20 ntin. After 10 niln at 45 ’C, ethyl acetate (40 nil) was slowly added and the mixture was warmed to ’C and sat.eq. amnuzonlura chloride (IM mb) was added. The aqueous layer vas extractedwith ether (100 ml). The combined organic layers were dried and solvent was removed to give cude product(21.1 g), which was sublimed at 5 imuNg and 70 ’C to yield (22-di6romo-J-I91dr4aatIli44-metIP1I-cvkropane (11) (19.5g. 80.0 masole, 89%) (Found: C 24.41,113.50. Calculated for CJBr50: C 24.62,11 3.31), nip. 53-54 ’C, [a] +38.8’ (a 1,050, CHCI,) (for racemate see reEl9) which showd 6,: 1.47 (20, d, 17.4 1.51 (311, 411.62 (In ii, 17.4 1.89 (111, dii, 18.3,3.913.70 (IK dii, 111.9,3,9), 386 (111, dii,.1 1-1.9, 8.3); 6; 20.52+,31.39,32.$S-, 35.75,69.W, v, 3258 br.s, 2931 in, 1453 as, 10508. l07 a, 1023 s, 7878.
763 s,d9lscm4.

(SH+)2,2-DlbromO.1bmm0methyl-1.methylCyduproPInt.
A echelon ofboiuine (0.55 in!, 16.5 inmole) in dlobloromethane (2 rub) wasslowly am
g, 8,63 renal.) In dichlorcasethane (25 ml) at ’C (l)-(+)-2,2-Dibromo.1-hydroxylnethYl-1.
(3.668, 15.O mmole) hr dicbborometbares(15 ml) wasthen added at 0 ’C and the mixture was

to diphos (3.44

for3h.Ether

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(50 uil) was added, she sohisianwasfiltered and solvent wasremoved to *a cnide produà which was purIfied by short column chromatography oversilica ebling with petrol and ether (4:1) to yield (9-’+)-Z2-a7mnas-1-broraamct1v4-J-meIhy1cyck4avprge (12) (4,54g, 14.8 amoln, 99%), [u]° +26,4 (c Q.884, COC!) (ft recanale asrd2O) whiCh showed b: 1,57 (311, a), 166(10,4,37.8Hz), 1.70 (111, d, I 78 Hz), 3.55(10,4, 110.5 Hi), 3.73(10,4,110.5Hz), 22.21+,30.31, 35.6&, 36.63, 41.97.; v,,, 2994 a, 2965 a, 2929 a, 2868 m,1451a,1427a,13811%1320m,1270m,1227a,1150m1078510488,10265,959a,900jn,866m,839 in, 703 a, 642 scm"1.

(S+)-N-MIyI-2bmmo-1.mtthyiqalopropylmethylanzlnr (S(+)-22.y1.4-meyolopi’opane (1.53 g,5.0 nunole) wa added to allylarnine
(3.8 ml, 50 nirnole)uibeazana (5 nil) and refluxed fbi 15 h, then astractedwIth 5% sq, eodmhythmdde (5 ml,
6nimoie) andwashedwith brine (5 ml). The organic layer was dried and the solvent wasremoved to give ($4.)- N1-Z2-bromo-1-methylcyclopropybnethylombm (12) (1388,4.8* mmoln, 98%), (a3°.15.4D (00.968,
CHCl,)’wblch showed 1.40 (10, a), 1.43 (UI. 4,37.4Hz), 1.43 (31%, 1.53 (UI, 4,3 14 Hz), 2.75(10,4,

I..

3 12.40z),2,*6 (ill, 4,312.4Hz), 3.29(10, ddd, 36.0, 1.6, 3.0Hz), 5.11 (111,ddt, 110., 1.6, 1.0 Hz), 5.20
- (10, dde, 3 17.1, 1.6, 1.6 Hz), 5.91 (10, dde, 3 17.!, 10.2, 6.0 Hz); b0: 21.78+, 29.90,33.55.., 37.31, 52.39., 57.13-,116.04-,136.774,, v 3076 in, 2967 a, 2927 a, 2849 a, 2820 a, 1643 in, 1455 s,1428 ni, 1381 in, 1148
W in, 1114s, 1071 %,1040 a, 1020a,993 s,919s,lSPni,690s’c&.

(SX-)-N-Br-22-dlbromo-1-mthyyclupropy!methy)amlne,
A solution of(9)-(+)2,2- browo4broinomeihy!-1 ylcyclopropane (1,848, 6.0 zumole) InDMSO
(5 ml) wasaddadto bcnzylambie(1.93 S. 18.0 nude)in DMSO (10 ml) and stirred for 20 b. It was diluted with
water (60 ml) and uxtracted with ether(3 x25 rid) and the organic layerswere combined and dried. After removing the so)vent the crude productwas purified bycolunm chromatography over silica to give startingmateriel (0.14 S, 0.5 =mole) and ($4.)-N-hn y14,2 J-rnctjIcw1opropytmeU’1ornIaw (14) (1.808,5,41 mmoln, 98 1.41(111,4,17.5Hz),
1.48 QA a), 1.49(10,4,17.5Hz), 1,58 (IA 8)) 2.72(10,4,112.411z), 2.86(10,4,3 12.4 Hz). 3.81 (20, a),
7,20-7.37 (54 in); be 21,27+,30.4 33.53-, 37.45, 53.93-,S%31-, 127.03+, 128.11+, 128.41+, 140.29; v:
3026m,2989 to, 2927ni,2890in.2842vu, 1494 m. 1453s, 1113 in, 1071174 1042m, 1027:m,139a,698 a wO,

(S(+)-N-t-BuoenrboN-z22d1biwmo1-msthylcyeloprepyJmethy3amInea P’Potauiwn carbonate (0.74 9, 7.0 nunole) was added to (SX-)-N-aIlyl-2,2.dilromo-1-methylcyclo-propylnzethylainine (0.99g, 3.50 mmole) and t-butczycathonylanhyddde (0.969,4.38 mJ1e!e) inTO (10 tnt).
dwnwas vigorouSly stirred %r2 h, thee filtered and TOF was ovaporetert A solution ofsodium hydroidde (0.12g,3mmole)inetbsnol(lOmI)wasaddedso the rcaldueand thembrturewasstirred firr 1 b. The solventwas
rmnoved and the crude product was purified by short column chromatography oversilica r1utbig withpetrol and
ether (3:1) to yield ($4+) f(4w -f.QJcl-2,onroJ.ntetkvkcbprop,lmtF1ptumfne (15) (1.29
3.37 zumole, 96%), jt9V+220 (c 1.116, CRCl,) which showed ba, 1.36 (3% a), 1.49 (100,s), 1.54 (10, 4, 38.5Hz), 3.30-3.90(30, bi.m), 3.99(111, dd, 3102,5.51b), 5.11.5,19 (20, in), 5.82(111,4th, 117.0,10.4, 5.5 Hz); 6. 21.00+,233-8+.(33A 33.80)-. 37,27, 48.98-, ($1.90, 52.37>., 79.86, 136.23., 133.63+; v: 2975 s,2931m,1698s,1455s1408a,1365a,1319to, 1245a, 1172s,1148a,955m,923m, $73 in, 774 m, 694mcm4.

Synthesis of (2S.3R,4-3,4-methanoproIine 14781

(S)-(+)-N-t-Butoz7caiteeyl-N-bmasjl-2,2-dlbrwaio-1-m.Ihykydepropybnethylambie.
PotassIum bicarbonate (0.34 & 4.0 rurnole) was added to
cyioproy1methj4ainlne(O.27g, 081 mmole) and t-butozycwbonylauhyddde (0.22 g, LOl mmoie) hr fliP (5 ml). Thembrtwewas vigorously edited for 18 h, theitfihured and THF was evapoated. Work up above and short coirurm claumatography over An dufingwith petrol and ether (2) gave (-(+)-N-t-bthoapJ-N-benzi1-Z2Sb’roao-1.mcvvl1opyb,ve09’Iamlne (16) (0.33g, 0.17 mmole, 95%), [e]° +16.0’(c 1.373, CHCI3) which showed 1.34.. 1.50 (14K a); 3.20-3.70(211, br.in), 4.43 (1ff, br4 115.4 Hz), 4i57 (111, d, 115.8 Hz), 7,18-7.58(511, m); 6,4 21.07+,28,40t (33.46,33.90)-, 36.02, (49.85,49.98)-, 52.38.., 00.29,127. 11+, 127.22+, 128.44+,138.37,(156,06,156.36), v 3064 in, 3030 in, 2969s, 2929 s, 1700 br.a, 1496 a, 1454S, 14161366s, 1309s 1250s, 1180 1122s, IMok 1066n n% 169m, 698 scm4.

(1lX+)-22-Dbremoprepinecsston31 chloride.
Tbionyl chloride (12 ml, 164 maple) was added to +)-2,2-dlbomacyclopropanerathoxyflc add (5,
R); (Ia)?+129.4’ (o1.036, CHCI3), 92.5% e.o), (10.00 g, 41.0 inmate) and the mixture refluxed for 2 h. The excess ofthionyl chloride was removed by distillation to give +)-2-dlbrolOnropaneAVboJlyl chloride (10.72 g, 40.9 mmole, 100 %), (a)? +109.7’ (c 1.063, CHCI3) ’which showed 218 (111, rid, 39.2, 7.9Hz), 2.27()11, dd, 17.97.6Hz), 3.12(111, dd, 39.2,7.6 Ez); 19.34,31.1%,42.63+, 16806; 1779 br.s,1417m13478,1104 in, 1069s,1001s,940 in, 836s,1411n,689500(1.

(R)-(+)-2,2-Dlbromo-1-hydroiymethylcyclopropaue.

A solution oflRX+)-2,2-d omocyctapropylcaibonyl chlorIde (10,68g. 40.7 mmole) In dry ether (20 ml) was added to a stirred solution ot’litlthnn aluminhar hydride (1;64 & 40 tamale) in dry ether 150 nil) at 45 ’C under nitrogen over 30 niki. After 10 raIn at -45 ’C, work up asfor (6) and removal ofthe solvent gave (Il-(+)- 22-dI4romo-14*orpzethylCyclOpropofle (9.02 g, 39.2 mmo1e 96%) as colourless oil, [4J0ei +2.4’ (a 1.234, QICI3) (for racenrate see ret: 21) which showed 8W 1,43 (lit rid, 37.5,7.3Hz), 1.82(111, dcl, 110.4,7.3 Hz), 1.97(111. dddd, 310.4,8.5,7.5,5.1 Hz), 2,33 (111, s), 3.62 (Krid, 112,2,8.5 lIz), 3.91 (111, 4d, 112.2,5.1Hz); b,6 26.01,26.45-, 32.33+,64.84--, v,,,,: 3346 bi. a, 2934 a, 2*79 ru, 1462 in, 1432 in, 1390 ni, 1240 Ui, 1103 $,
1042 9, 682 scm1. S

RH-)-Z2-Dtbroeio-1.brornomethylcyciopropane.
A solution ofbromIne (2.21 nil, 42.9 inmate) In diohlorornethane (5 ml) was slowly added to a sQhWQU of
diphos (L93 g, 22.4 nunol In dichioromethane (150 rid) at O.T.(RX+)..2,2-Dibronro-1*hydroxyinethyl-
cyclopropane (8.99g. 39.1 urazole) in dlcbloromethane 00nil) wasthen added at’C and tho reaction mixture
’ was stirred for 3 It, The solution was evaporated to a volume of 100 inland ether(100 m)) wnsadded and the

solution was separated from a solid. The solid was dissolved In dlclilprornethanc (50 rid) and (100 ml) was S added. The solution wasseparated from precipitate and the last procedure wasrepeated 4 threa, until there was
rio product In the organic layer by gb. AN sobitlons were combined and the solvent wasrenioed to give a crude
pmdumwhich was purified by short column chromatography oversilica elutbig with pctrol and ether (kJ) to yield (R)..(.)_2,2.dlbronro.l-brrarjvmethykyckqiropwai (11.08g. 37.8 miuote,97 %), [u]0 (c 0.962, CHC1J)
(ibriscemate see iaft. 20,22) which showed ô: 1.46 (111, dd,37.7,7.41!z), 1.95 (111, dd,il0.1,7.4Hz), 2,10

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(UI, ddt, 110-1. 7.7,75 HA 3.46 ML d, 17.5 Hz); 2062,23.58-, 25,61+,26.W- ’
in, 1215; 1191 m,11060,1047 nk 1011 m,931ni690s,621 mcrn4.

143016 1366; 1230

(R).(+)-N.Bfr2dbroyclorcpylmethylamlue.
A solution of(1tX-)-Z2-dlbromo-1-broniomethy1c,cIopz,pane (5.86 & 20.0 mmoe) 1n1MSO (20 m))
was added to bsoz5dwnlne (6.43 g, 60.0 snmole) biDMSO (20ml). The inb4umwasstirred fbi4 11 at 60 C, diluted withwaler(lOOnd),and5%aq.ofaodIanhydundde(20ml,2.5minds)was added and the nÆizbirewaswrtrar*ed with ether (3*100 ml). The orgaido layers were combined and dried. After removing the solvent, the crude product was purified by chromatography over silica (patroletber, 1:1) to give +)-enzyl.2.2-dlbromo-cIpykwlhy1an,Inc (6.01 g,18.8 mmcl; 94%), (Founik W. 318.9394. Calculated r C1 N75Br"Br. 318.9394), (nJ’ +1,5(o 1348, CBCI0)wblch showed ô: 1.34 (lii, dd, 37.1,6.8 Hz), 1.75 (111, 111.78 (111, dd, 110.4,6.8Hz), 1.86(10. dddd, 1 10.4,8.0,7.1,5.2Hz). 2.72 (111. dd, 1 12.8, 8.0 Hz), 2.89(10, dii. 112.8, 5.2 Hz), 3,87 (111, ii, 113.1 Hz), 3.89(10. d,J 13.1 Hz), 7.26- 7.38 (5H,m); 6: 15.34,27.29-, 30.94+, 52.00-, 53.67-,127.13+,12&16, 12830f, 139.92; v,, 3061 3026; 2891 in, 2830 a, 1494 454 a, 1358 in, 1108
a, 1044 in, 1028 as, 734; 698;679 a (m\%): 321.2; 320,2,319, 3; 318,3; 3172(M’); 316, 2; 255,
2,146,20100,24;91,100,

(*+)-NN-Dlbc4moqdupropyhuetbylamlne.
Sodium carbonate (3.11 g, 35.0 mmcc) in water (20 ml) was added to ç1t)-(+)-14enzyl-2,2-dlbmołyclopropylniethylaznin.(5.428,17.0 nunolc) and benzylbrondde (6.035 aimole) in dloblorometbane (20 ml) and the mb&ture wasrethixed and stirred 1br 15 h.The waterlayer was extracted with dlchioromethane (2 *5 ml). The organic layers were combined, dried and the solvent wasremoved. Most oftsc beuzyibromidowas evaporated In iunuo (100 T, I mmHg). The residue was pu!iOed by chromatography over Silica (petrol - ether, 2:98) to give (J)-(+)-NZtT-berezy1-2,2-thbromucyc1opvpytmeihylamiiw (11) (6.808, 16.6 mmcl; 98 %) as colowices, very ’viscous oil (Food- W, 403.9864. Calculated for CHZ Bt’1BT 403.9864), tujr,° +17.00(0 1.024, CITCIa) which showed oH: 1.23 (10, dd, 37.2,5.8 Hz), 1.81(10 dd, 3 10.6, 5.8 #zj 1.83 (lB. dddd, I 10.6,7.2,6.4,5.1 Hz), 2.66 (10, dd, 113.7,5.1Hz), 2.81 (10, dd, 1 13.1,6,4 Hz), 3.65 (20, ii, 113.6 Hz), 3.80 313.6Hz), 1.25-1.45(1011, Zn); h 27.60..29.43,29.09 +, 55.17-, 58.30-, 127.034, 123.30+, 128.80
I-, 139.41;v,,,,3084m,3061 to, 3026s,2925m,2801 a, 1494s, 1453 a, 1368s, 1247rn4l1I0s, 1074iii, 1028 s,973m,746;698s,618 a, cm’;(m\z,.%): 411,3; 410,3;409,4;408,4; 407; 3 00;406, 1; 210,30; 149,4; 92,12,91,100.

(10, 48, 5S)-N-t-Dutarbon4-metbvni-3-awab1cdoI3.1.0heasne1
A 13 Msohrtion ofnlsth,viilthbnn In et1 (3.03 ml, 4,55 macIc) was added to (S)-N-s-butoxycarboayl-N..aily1-2,2-dibromo-1-methyicydopropy1methlandne (1,66 g, 4.33 mutole) In thy ether(50 inI) under nitrogen at-60 "CoserS 7UxbftvmsftWfbr3Ombtlhmmt sq, enmmonlum chloride (20 rut) was added. The water layer was extracted with ether (50 ml), The combined organic layers were evap!za*ed and purIfied by chrumatogruphy over silica (ether-petrol, 19) to give (!& 43
w,abirr.yclo(3.I.O/herww (1k), (453 mg, 2.03 mots, 47%) as mixture oftwo rotamers In ratio 1.5:1, (uJ°
-382’(c0.976, CHCl)w icbsbowedv 2976m, 1699a, 1449m, 1405 s, 1388; 1366m, 1176m, 1123 a,

IN 7.-.-... -,--

Synthesis of (23,3R,48)-3,4-mcthanoproline 14783

833 inc&; (m(z, %) 213,9,21; 10(M); 198. 12; 197, 14; 169, 44; 168,59; 167,39,142,;7; 141,38; 140, 13; 108,20; 96,24; majorrotawer,
(10, d, 110.6 Hz), 3.61 (IR 4,110.6 Hz), 4.27 (14 d, 36.5Hz), 5.03-5.18(20 in), 5,69-.88 (1114 in); Oc: 15.39.., M60,27.07, X131+, 28.49+, 51.7$-, 6220+,7921,11422-, 139.00+,154.73; mhnirotawer, N. 0.39 (10, in), 0.54 (10, in), 1.07 (10, in), 1.23 (34 a), 1.43(90. a), 3.11(10,4,110.61b), 3.55 (?,28.43+,52.41-,

H, 4,310.6Hz),
4.32(10,4,35.9Hz), 5.03-5.18(211, in), 5,69.5.88(10, łi), 6 15.31-, 18.55+,
61.51+,79.21,114.31-, 137.53+,154,51. S
Also w elsolatedN-allyf-N4-6W &aryt..N-2..nctThuas-Z3.en,jJon*s (19a) (5* mg, 0.26 minute, 6%)(4æchshowà1b 1.4*a(90), 1.68 (3H,t, 13.1), 3.12(4H,br. s), 4.65(20,ni), 5.12(* in), 5.15(10. my,66 15,91+, 28.34+, 48.74-, 15.23-, 79,53 95.62, 116.20-, 116.63-, 133.76+, 155.52,206.44; v, 2978 in, 2929 an, 1698 s, 1456 in, 14015,1366 an, 1244 a, 1167 a 0164;N-oJyI-N-1-buWxycarboiiyl-N-(2-bromo-J. meUytcythpnpyhnethyiJaniIne (20a) (188 nag, 0.62 minute, 14%) whIch sbwed 6: 0.69(10,44, 16.4,4.5 lIz), 0.87(30, 44,17.4,6.4Hz), 1.25(30, a), 1.47(904 s), 2.95(10, hr. s), 3.30-4.00(40, br. in), 5.01.5,17 (211, in), 5.74(10, ddt, 1)7.0,10.5,5.6Hz); v: 3079w, 2977 in, 2930 in, 1694s. 14S6m 1410 in, 1366 in,

- 0 1246m,1172s cm4.
(10, 48,
A 1.5 M solutlouofnaeth litbiun In other (0.44ml, 0.66mold) was added to(SX+)-N4-butozy-carbonl-N-22-1-methmetldamine(260aug. 0.60minute) In day ether (10 ml) wider idbogca at 20Cover 5 miii. The solutionwas eliued 30 mlii then aat.aq. ammonbuan chlorIde (5 ml) was added. The waterlayerwas emanated wI&ather(10 nil). Evaporation ofthe combined organic layers and chromatography over silica (ether.pctrol, 3:17) gave (19 45’, 53)-N-t-bvnyl-1-mall$4..phenyl-3.łablcyclo(3.LOj-hexwv (18b), (65 nag, 0.24 inmule, 40%) asamlxtureoftwa zotaniersin ratio 21, (0]0in4$,2 (oO.108, CH") which showed v 2978 an, 2929 m, 2W8 in, 2250 in, 1684 a, 1473 in, 145$ in, 140$ a, ’!° s.. 1367 in, 1172 a, 1127 a, 90$ 9,879 M 731 a,699 a, 649 in cm4; major rotanier, &: 00(lH, a), 0.69 (1H, in), 125 (lit in), 1.27 (9K a), 135 (31L s), 3.44(10,4,110.7Hz), 3.75(10,4,110.7Hz), 4.69 (10, s), 7.19 7.36 (SK in), 6: 16.80-, 19,77+,22.91,2825+,30.14+,53.26-, 64.32+,79,38, 126.54+,128.28+.143.8$,1$4i’,56, athaor retainer,
6 0.52 (111, ci), 0.69 (IA in), 3.25 (10, in), 1.32 (3H, a), 1.41 (90,. a), 3.37(10,4,3 10.8Hz4 3.69 (10, 4,1
10.8 Hz), 4.89 (111, s), 7.19 -7.36 (SIT, in); 16.35-,18.564; 23.49,2023+,29.19+,53.46-, 63.45+, 79,38,
126,91i’, 128.47+,243.17,154.33.
Also isolated was antixtute of’(19b), (20b) and starting nmleaial (90 m& 27:7:11 b$sed on 2IINMR. of Bucdepcednihutnre)wblcbhowedv,_, 3030ni,2916s,2930a, 1961 a, 1694 a, 1496m,, 1454 9, 1413 a,
H 13659,1242 a,, 11695,11245,877 in, 768 in, 699 sara,N.bsyI-N.I-biaci?cm*ol4yl..N-2..nretIyIbWa-2,3-thaplianthie (19b) ghowed (Oemthis ndxture) P, 1.51 (90, in), 1,68 (30, in), 3.80 (2K in), 4.45 (2K in), 4.73
(20, in), 1.21-7,39 (SB, an); b: 15.95, 28.39, 48.62, 7$.37, 95.41, 127.09, 128.36, 128.*8, 137.5, 156.31,
206.83, This iniz*wn (90 nig)was depsotected by reaction with ttifluoroacctlo acid to gIve 69mg ofanahass which
were separated by cctwim chinmatogrephy to yield N-beasy1-!?3-nveIftvThukz-Z3.theryIwnbna (31 mg, 0.18 nnno1e,27%) which shawcd 4 1.70(30,t,13.1 Hz), 3.20(20,5,13.0Hz), 3.27 (1}I,br. a), 3.35 (2K 44.76
(20, qt, 13.1, 3.0 Hz), 725-734(50, iii), v,0 1960 a cm4; N’6yt-N.(2-hs-1-amthylà,wlqflvpy&wethyQ-dvathae(11 mg,0.045 inmole,7 Vv) whlch showed 8j 0,68(11144,36.4,4.3Nil 1.04 (30, 44,18.1, 6.4 Hz), 1.33 (3K a), 1,55 (10, a), 2.46 (In 4,112.3Hz), 2.62(10,4,112.3 Hz), 2.89(10.44,3 8.1, 4.3 Hz), 3.79 (24

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a), 7-24-732(50, rn)1 (nh, %) 255, 5, 254,7; 253, S (M’); 252,7; 174, 12; 160, 11,120,41; 91,100; 65, 14.

(IR, 4$, es-1-Methyw.vinhqdep.1bex.
(IR, 4$, 58 c-1-u3-azahicyd3.LO)hasane (30.0 ing, 0.134 nunole)was dissolved in&Swoftdm(0,5 ml) and uifluoniscetic add (0.5 ml) was added and the solution was stirred for 30 win. The vologeswemranasved hrvacuo and I % eq. sodIum hydroxide (2 nil, 0.5 =mole) was added and the product was wdrected withold rofitm(Zx2 ml). oabhied organic layersWW With I % eq. sodium hydroxide (2 ml) and thee dried. The solvent was removed to yield (JR. 43, 5S)-J-mgtJ’i-4-vby1-3-arabicyclo(3. LO)hexane (21*) l5.8 nig, 0.128 nnnole, 96 %), (Pound: M’, 123.1050. Calculated fbr C,iluN 123.1048). [a]’° -5.4" (*0.67, VUCI.,) which showed b: 0.42-0.50(20, as), LOS (114 dd, 17.3,4.4 Hz), 1.26 (30,s), 2;02 (10, 5). 2,81 (211, a), 3.52 (10, d, 36.7 lb), 5.02 (IN, ddd, 110.3, 1.8, 1.0 Hz). 5.13 (10, ddd, I 17.0.1.8.1.315.97 (19 ddd, 3 17.0, 10.3,6.7 Hz), 6,4 13.60w, 18.39+,24.35,28.23+,52.1% 62.10+, 113.36’, 10.73+,,3318b9,309m,24392866*,1639w,1450w,1423m,1381w,1101n1,1019m,916s,890 as cm1; (n,/z, %), 124, 10; 123,48 (M"), 122,25; 100,49; 96, 100; 94,31; 80, 34.

.

’fl (10, 48, SS)-1-Methyl.4-phewhiol3.LOIhei*ne, (IF, 4S, 5S)-0-t-flu 1-meth44pbenyl-3-ezabhyclo(3.E0jhexane (25mg, 0.091 ulasoIc) was dissolved in dichloromedmac (0.5 nil) and Ulfluoroacctic acid (0.5 nIL) was added and the solution was stirred for 30 eli. The vu swemmuasvedlniarno sod 1 % eq. sodIum hydroxide (2 ml, 0.5 asmole) was added and the productwee actedvtthlorolbml(2 2 ml). The combined oi gc1ayesswerewasbed with I 1/64q. sudiwu hydroxide (2 ml) and thee dried. The solvent was removed to yield (JR, 48. 53).J-snetkyl-4-phenyl-3-wablcycIof3.I,01herone (21b) (1 *4 wg, 0.081 mmdc, 89%), (Pound: W, 113.1205. calculated for C11113N: 173.12051 m.p. 34-35 "C, [e1 -100 (a 0.81, CHC1) which showed: 0.59-0.64(20, as), 1.2$ (10, dd, 17.1,4.98z), 1.34 (34 $12.81 (20, a), 4.20 (JA s), 4.32 (lB. br.$), 7.22-7,37(50, as); 8: 14.65., 18.15+,
25.19,29.30+,51.77-, 64.09+, 126.96+, 127.28+, 128.65+, 143.46; v 3313 br. ra, 3060 in, 3027w, 2985 ni, 29414 2US s, 1492w, 1453*, 1408w, 1387w, 1370w, 1101 as, 1028m, 880w, 755m,700scm’1;(nilz,%): 174,44; 113,58 04+),172,56,,158,27-,149.29-.117,55; 91,100; 83,39; 57,44.

(111,40, 5S).N.t-Rutoxycsrbonyl-1-rnetbyl3-ambk do(3J.0Jhcxsue.4curbozy1ic add. N+inxyrnrbónyl-1-n 1-vhl34aabicyolo[3i.O]bexane (200mg, 0.896 mmole) was
dissolved incinbon teusobloslde (2 ml) and acetonMe(2 nwetorQ nil), periodic acid (1.07 & 4.7 nainole. 5.25 eq.) end n*=hmtdeModdel9*ate (4.0M& 0.02 eq.) were added. The reaction mixturewas xigorously stirred for 3 h ctmomtmnperature, thtu ether (5 ml) was added. The black organic solution was separated, and the water layer was washed With ether (2 x $ ml). The ether *olutious were combined, dried twice with magnesium with vigcous shaking (until all colourwent Into the solid phase and the solution became colourless and trans-parent) and the solvent was removed In vacua to GIve oR, 48. sr-bvl-i-nsstIri4-3-wahftjelo-(3.J.0)hemme.4-cm*oxy$csed(22)(193 nag, 0,808 nmd*,90%) as amixture oftwo i’otarners (1:1), m.p. 117-119 "C, 46.3" 0.730, CHC) which showed Œ4: 0.51 (10, dd, 35.2,3.8Hz), 0.55 (10, *1*1,35.2,3.8 Hz). 0.11 (211,. dd. 37.6,5.2 Hz), 121 (311, e), 128 (3H, a), 1.43 (OK s), 1.49 (90, s), 1,50 (2Kus), 3,37 (01,

Synthesis of (25,3R,48).3.4-methanoproline 14785

$), 985(20, a) 6 15.75-, 16.00-, 18,17+, 18.264,22.51,23.14,25,13+, 26.14+, 28.23+, 28.35+, 53.07-, 53.36-, 61.65+,62.06+,50.44,80.68,1$4.59,155.54,176,$9,177.90,* v,,(CCl,) 3150 bi ni, 29720, 29518,2881,, 1736s,136s,147143$8,143281407m,1368 in, 13261n,1248s,1214m,1191$,fl6ls,1135s,898

(1k, 48, 5S)-I.Mathy1-3-szablqdo3.1.0heui*4-varboiylk acid. $$)N.t.Th,$oxygazbonyl_l..niethyl..3assbicycloL3.1.0]he ane.4-carboxyflc said (163 nig, 0.676
=note) was dissolved In dieldoromethane (2 ad) and trifluoroacedc add (2 ml) was added and the solution was stirred for 2 Ii. The volatiles were removed In weuo end the residue was dissolved in weer and desalted on a column ofDowex 50W - X8 resin In the hydrogen form. The endue acid was elated from the column with SM snunonia. Aftevupcalicnbz wasas and drying overphosphorus pntexid; (IR. 4S, S$)-1.metkyl-3-aaabwydo-(3.1.0J1wrrvre4-carktivtIc acidwas obtained (23) (85 nig, 0.606 mm* 89%), m.p. 236-240 ’C (decomp.), e’-79°(c 0.758, HO) which showed 61(102O) 0.59 (10, dd, 16,4,4.2 Hz), 0.89 (IH, dd, 18.3,6.4 Hz), 129(30, s), L75(1H, dd, 18.3,4.2Hz),3.39(IH,d,1 1121b),3.44(1H,41 11.20z),4.08 (10, a); 80(D50): 16.71. 19.304,25.26, 28,06+ 53,80-, 66.45+, 176.43; v,,,, (KUr): 3420 hr. w, 3264w, 2944w, 2300-2800 hr. 1616 s 137616 1312m, 1275 w, 1202in, 669wcall,

Ozawolysis of(114 48, 5S).N-t-butoxycntónyl-1-wcthy)4-vfrk7c1013.1.OJIICU0C.
Ozone (5 % in oxygen) was passed through a solution of(1R, 48, SS)-N-t-butoxy-carbouyl-1-methyl’4-iinyl-3-azabicyclo[3.1.0]hexene (31.5 lug, 0.141 uinio)e) in acetone (10 nil) at -78 ’Cfor 5 Wand the reaction mixture was kept at -18 ’C for 30 mlii, then allowed to warm to 0’C and Jones reagent (005 gofCrO In I nil of15% sulSuic acid)was added. /afler I batroom temperature chromium salts were uttered ofi’end acetone was removed in vacuo. The residue was dissolved in ether (5 ml) and this solution was extracted with 0-IM sodium hydroxIde (5 0.5 nimole). The orgzude layer was dried with magnesium sulfhte to give siler evapointlon ofthe solvent (JR. 5*N4bvtl-I. neyU -3-aacbicyctof3.LQ)hexaIle (24) (13.7 mg 0.065 romole, 46 %)wbichsbowed 0,96 (10, dd, 14.7,3.1 Hz), 1.12(10, dd, 18.7, 4.7 On), 137(30, a). 1.53 (90, s), 1,81 (10, dd, 18.7,3.1Hz), 3.57(10,4, 110.9 Hz), 3.76 (11t d, 1 10.9 Hz); 6 18-62+,19-371-,27.74,28.03+, 59.92’1, 82.52,150.29, 174.12; (CC1.I) 29788, 2932 s6 17899,1749 s, 1714s, 1480 in, 1454 ni, l369, 1351 a, 13225, 1293 a, 1259 1159 8,10910% 1056m, 1007 913 in, 856 rn, 781 mcm".11ydrcIilorioacid(1 ml, I M, I macole) was added to the waterlayer and thiswas extracted with ether(2 x 3 ml). The organic 6iclioas were combined end dried to give after ovaporsthm ofthe solvent (JR, 4 erab$cyclo(3.1.0)hcdne-4-1x*boxyJIC avid(22) (14.0 nig, 0.058 nunole, 41 %), identical to that above.

(S4+NN..DIbenzyI2breme-1.n1ethYicYeIOPrOpY$mtth71aJulfle.
A solution ofsodium carbonate (1.06 & 10 inmate) in water(3 ml) was added to a solution of(S)-(’.)-14-benl-2,2romo4-me1oprcpybnntllamine (1.53g. 4.59 muncIe) and berr4ibronzidc (1.03 g. 6.0 nirnol in didiloronicllmno (10 ml) and thendxtuzewasreftunnid and stirred for days.The waterInyerwas eudmcted with dlchiorometbane (10 m), The Combined organic layers were dried and solvent was removed The residue was dissolved In ethanol (15 ml) end sodium hydroxIde (0.28,5 mmole)was added. The mixture was rethrxcd I h, thesolverurwaaranssved and water (10 ml) and petrol (15 ml) were added. The waterlayer was extracted with

t9

9611 ’WPV! ’W1,6Z1 ’W ’ LLfl 1?fl Sp6fPI UEVO9IME’SME LH ’ZL6fl +Y1Z! ’+!flZE ’+sołgi4+ipzzi ’+!0/X! ’+W91 ’+1L19 ’-w6 s699 ’+1’6OE

’6c1z ’+1 61 ’isiIt ’g (w HO!) or. - 9Z (z t ’P ’rn) 6Lt ’(ZR ’p ’III) WE ’(zn ti
’P ’Hi) ott ’(zł 9’8 ii’ Wwe
1,1-0.419 pOqS1PPP (913fl3 ’OCO 3) rct+ ORCIVI ’(L9rt9z:M3 PMTj3 114911C9Z pimoj) CS ’aoww 991,0 ’SW g) (9z) xwnqfoI ff)
*AIR oi(96p ’od-.wqia) ijop dflauZq8noqipPs%dMcpoid *p pu pcuazod* ’pipsuoputoc eq x qis ipu pisxc i *Pvp si*(atoww 9.0 ’Pu apxoz$q umwoc
i %I pa p*zodi loumpa ’puig cpu NnPqmwrm cip ioipCq*punq I SCS".ijy papp oiu(Euz c)3iPr% c ium(Zoww0O ’iui tro) pp upopcipAjy pa(Iiu çt) joumpuu pascp flu
(qowuz ooro ’Sw ctc) d-q-L-2I*q*(sc ’as’ ’Hi) 0p1U3 (q
W 9561 8LL0Z ’L6E1 ’+L&’$ZI ’+PZIVE +489Z1 ’t’9’96 ’ILCL ’6LS ’-LcLç
’+Z691:ç - WL. ’itt b 9LP Is ’HI’) Ott ’i ’Hz) LOt ’(ZR It f

’P

’st j,);ind pm ’(% 96 ’PjOWW 6E ’S too) ’fiz) i,aqfrrJaaiqe-j*agJi*pau-r-Ii&q-N-(gc

’S
in

ppp *(B ip puqumU wij x)iap UU!$I 3UBJO ou płppi W&(iw ç) Mppw ’znduwswaoi o) q £
SRM wMxp uopwi allpppe Ojm tba coc ’ft ot) wpqapmMn ’npqmi pa (b si ’G;oww L18) ppe o!pod ’Ow ri) xqm ’(w *0) appown pa Ow ro) MwWaM
(’;otuw t.tvo ’04 ç99) uq(o’r°t łq u--owo z--uqd--pcqsp.t.(ss 40 11)
’PP’ 3fttIuVq(mIOpt ’

*JU3W869’$
PPII ’LU IOVI ’S 6=1 ’W ItlIl ’Lu 6151 ’ 501.1 A (ZRV1.tf’b)OY951 ’806t1 ’46EIZI ’+$69Zt 6W1 ’(zj ’I’) p1911 ’40V59 ’i-w05 :9 ’On ’Es) gfL ’(zI ’iii) LES ’(zg pó1 ’P ’in) ’(ZR Vol ’P fr*t LP ’91 £ ’PPP Wi Is ’110 csi ’(211

1.WGBOOLs0SL ’Lu 1.68 to £95 ’UISZOI 1W Leo1 ’Lu

’I..’L

Ow

4788 V. V. TVERBZ0vSKY or aL

With magnesiwn sulfate and solveet was removed In vacuo to give ffit 41 5S)-J-nwdyII-fr(t1uorixwe(’I4. wabico(3.I.111Amee4.carboxyI(oacid(32)(54.5 ing, 0.230 annals, 93%) nsa ndnture oftwo rotamers (5:1), ["]D20 196.1’ (C 0.96, CH4) which showed 0.76 (113, dd, I SO, 5.6 Ha), 0.98 (10, dd, 15.6,4.0 Hz), 1.34 (30, a), 1.74 (19 ddd, 18.0,5.3,4.0Hz), 3.68(111,4,110.3Hz), 3.95(111,4,1 10.3 Hz), 446(111,4,15.3Hz), 9.59 (10, a), 15.35-,19.92+,24.72-, 25.36,,54,77-, 62.35+, 115.83 (q, 1281.1 liz), 156.45 (q, 737.2Hz), 13.6 v,,.1(CC1320Obr.s,2958m,2931 in, 1726s,l708s, 1450 s, 1264m, 12299,1176 5, 11506,761m, 721 237, 5 (M; 193,14; 192,100-,164, 10; 122,S-,84, 39. In addition to the signals forthe MOWrutamer given above, the minor rotamer showed 6,: 1.35(311,5), 5.55(113,4,75.1Hz).

(11% 416 SS)-1-Methyt-3-azabkydol3.1.Ojhexsu*4-carboiyfle add.
(IR, 41k 5S)-1 -Meth 1-N-tiifluoroacetyl-3-azablcyclo[3J.0]he ne-4-cazboxylic (35.5 lag, 0.149
mmole) was dissolved in aIM solution ofpotassium hydroxide In methanol (0.5 ml) and thl was stirred for 2 b.
Solvent wasremoved In vamand the residue was dissolved water, neuiralizd with 2M hydrochloric acid and
desalted on a column ofDowez SOW - X8 In the hydrogen Ibnn, The amino acid was eluted from the coiimm

with

3M ammonia After evaporation by vacua and drying over phosphorus pentoxide (JA 44 5S)-I-mellipl-3-
. uzcibkycIof3.J.0)hamu-4.cw’boxylIc acW(33) was obtained (19.1 nig, 0.135 inmate, 91 3’.), m.p. 234-237 ’C (decomp.), (aJ?+107’(c 0.63, HO) which showed 8a(DO) 0.89- 0.99 (2H. in), 1.53(311. a), 2.04 (1R, ddd,
18.3,4.4,4.0Hz), 3,56(111,4,711.4Hz), 3.12(113,4,711.4Hz), 4.59 (IA 4,14.4Hz); fic (D%. 13.41’, 19.42+,26.04,27.39+,53.99.,.65.61+,176.09; v,JKBr): 3421 hr. w, 2940w, 2300-2800w, 1599 s, 1458w,
1393 a, 1372s, 1341 s,702mcsn’1.

(131.411, SS)-N-t-Unycnbu4-methyl-4-pbbdof3j,Ojhexnne.
Crude (10,411, 58 -1-methy1-4-phenyl-3-azabicyc1o.LO]hsaane (425 mg, 40% SAYby gIn andPM
was dissolved in THF (15 ml) and potassium carbonate (0.53 g,5.0 niniole) and t-butoxycarbonylanbydrlde (0.61 g. 2.8 annals)were added. The mixture was vigorously atinndfbr 3 h, Shared and TOP wasremoved. Aq. sodhun hydro;ddo (0.09 & 2 mmale)in othand (10 M) was added to the nddue and the MbMnWas Stirred tori it. The solvent was removed and the crude product was pwiSed by passing through a column ofsilica (the Ihater the cohmm, the Idgbertheyield) dotingwith petrol and ether (9:1) to yield (II?. 41% 5S)-N-t-bu1oxycarbo,ytJ.metI4-4-phertj4.3.azab1cyclo(3.LOjhaiww (34) (391 pig, 1.43 nunol; 61 ’is), [uJ+153.3’(c 1.002, CUd3) which showed b: 0.38 (10, dd, 37.9,5.4Hz), 0.63 (11L Lw. a), 1.12 (911, br. a), 1.20 (39 a), 1.56(10, ddd, 17.9,4.9, 4.3 lIz), 3.49(144,3.10.4Hz), 3.74(111,4, 310.4 Hz), 4.98(111,4,74.3Hz), 7,12 - 7.32004 in); 66 15.09-, 19.52+,23.29,27,99+,31,96+,56.11;1 63.64+,79.33,125.W, 12623+,127.80,155.47; v,, 3054 in, 3030 ni2973s,2928s,28704 1694s, 1496m,1479m, 1454s, 1372s, l348, 1326m41282m, 1177s, 112$s, 1101 tn,1076m1029m,SSlm,760m,750m,7olscur’.

(10, 28)-2-B zoyl-1-methylcyduprvpana-1-enrbozyiic actiL
(IR, 411, 5S).N-t-Butoxycarbonyl-1-metbyl4-pbenyl-3-azabicyclo(3.l.0]herrane (12,3 mg, 0,045 minds)
was dissolved In carbon tetrachloride (0.2 ml) and noetoulbile (0,2 ml), water(0.3 ml), periodic acid (146 mg, 0.64 inmate, 14.2 eq.), and ruthenium trlobloside hydrate (0.5 mg, 0.05 sq.) were added. The mixture was vigorously stirred 3 batroomtemperature, then ether (0.5 ml) was added. The black organic sohithat was separated and

OLEI ’S ESIFT ’S t,6tt ’S 56/. ’UE ZZ6Z ’W 196Z ’S 9ZOC Am Z90C: s66Ct ’+6C8t1 ’44Z8Z1 ’+989Z1 8C

’Z69S ’89LE ’+t’jOE ’+LçEZ ’-zvzz; (w ’not) WL Lvi. ’(Zil LEL VP ’Hz) 08c ’(zn cç. ’p ’iw) 69g ’(Zn cc ’zfl f ’pp Hz) trz ’(Zn cc ’zci ’pp ’in) viz ’(’ ’in) WI ’(ZH 61’ ’06£ ’PP ’in) o ’(zg c,s 159 4t’9 ’o’o r WWHO io’(zł 64’ ’y9 ’pp ’at) oro:E p*o ip (’rJiO ’4’Z D)P(*)] ’(ccc ’zqi - lo.nd of,0 ’9t60’EVt lWifl63 9E604’f ’ UflO no snoosç %W11=103SB No 91 ’010M’w98) 6f qdwüp q-)*-t Wtoot ’16 ’El ’901 1C18c1 L’ZL1 0Z’461 SI ’R’V’(Ji) 1c’5PtL1 ’ow (%’S,n’).wDsooL’SocL’wzLU u99fl ’S5111 ’S £601 ’s $6LZ ’S LWE ’UI 199E P?V4’I ’6E04’1 ’+099 ’-Lo4’c "+fVc ’+PLZV ’+54191 ’096 Q
(w 6414 ’(s ’Hi) 60, ’(Zn WHO 04’I I WHO WE’(H IT ’061 ’PP /.6Z
’(zg 06 I ’p t ’(Zn i ’Zt ’t’L ’Wi. I ’pppp ’Hi) 691 VE ’EL ’8L I ’ppp

121cr6tz

() WC ’wi) z9 ’cg cz ’99 ’001 ’16 96 ’z6 ’L ’sit ’oil pc ’iizc ’g’(jz)i. ’64V9 ’ow:(%’zpu)was9’S BU ’S Mt t ’S 09CI ’S çp ’Spl ’Sfc61 ’SL6LV It MZ Is 9ZOE ’S 1190C ’tu c EEC 06Oz ’cC6c1 ’466111 ’+grgzi +6691I ’+54195 ’-CS’PL ’-zVLc ’.ij:p ’(iii ’n*t) PC’L 4’VL ’(Zn 9’9’1 L t ’U ’in) g ’(Zn ’99 f ’p ’Hz) 4’L’P ’(s ’zw) L9’C ’(214 St

’A puno) (% 54’ ’Sp1WW 1L0 ’ 9Ll) (SE) pamog=aOSlY

t’9 ’sic ’(.w) 56 6t’Z 001 ’051 (% ’z/W) ’-UI3 9669’S W’s ço ’w oszi ’UI z’si ’S 190 ’S ES4’I ’S L6ti Is 9*LV ’W looc ’IU 090E:’& LZ’14’1 ’59’6E1 ’+irszi ’+EP1Zt 1+11*811 +SçLVt ’+PI’LZI ’+IL’911 ’+/.119 ’6L95 ’+96EV

01 pappz ss (aiounu 4191 ’jW 601) APIq umiIEqIawo uonios wcz v

 18 ’LL 1I ’16 I-ODI ’Sot 08 ’851 14Z ’651 15 ’981 ’.91 ’181 ’(ii) s ’stz;(% ’(asa-ap) 2/UI) ’UiO UI

’.4

14790 V. V. TvaazovsKy a: aL

in, 1172 s,, 1128 in, 1074 in, 102$m %) 346,5; 345, 17-,344’ 12; 343,14 CM’)’, 342,,5; 210,62; 91, 100; one isomer ofbIçedçvvThkne (41) (72 ing, 0.145.mmole, 1.8 %), R10 17 (petrol ether, 5:95), +70,2°(c 1224, CHCl,)whith showe4N 0.89 (111, in, 134 0%in), 1.71 (14br. 612.37 (IA 64313.1,7.2 1142.74(111, dd, 113.1, 5.7 lIz), 3.63(21!, 4.113.

.9 Hz), 3.78(211 d, 3 13.8 Hz), 721 7.42 (1011, in),
8.60.., 13.93+, 56.4*-, 57.95.., 115.12, 126.79+, 129,.22+,129.72+,140.03; v 3061 m, 3027 8,2969 in, 2794 s, 1494; 1453; 13675, 1126 in, 1074 in, 7345,69*8 cur’; a second isomer ofl4cyvlopvpylldene (40) (143 nw, 0.29awk3.6 %),R0.I3 (petrol- etheç 5:94 [a]?+23.6°(c 1.010, CHCl,) which showed 05: 0.96 (111, M). 1.39(I4m), 1.79(IF4bi. 5)2.54(1Hdd,,113.3,6.20z),2.67(3H,dd,1 13,3,6.51143.63(211, d,3 13.8 Hi), 3.80 (2K d, 313.8 Hz), 7.26-7.49(1011, in), 6 8.80-, 13.57+,56.75-,57.94-, 115.34, 126.76+, 128.19+, 120.75+,140.09; v,,; 3062 9% 3M7 16 2957 k 2627 9. 27% s6 14948,1454; 1368; 112510, 1074m, 1028 in, 7358,6975cm4; (nilz, %): 500, 100; 499,63 (M’); 423,9; 408,17; 407, 11; 210, 13; 107, 9.

(1, 28,sPbewblqdo4l.Lojbezane.
(Ht, 28, 5S)N-Benzyl-2-pbcuy5.3-ainbicyda(3.1.0]hexane (2.598, 10,4 nunote) was dissolved In ethanol
(50 and 3N hydrocblwic acId (6.9 ml, 20.8 mmolc) and 5% Pd/C (1,3 g) were added. Mcistirring for 2 Ii under hydrogen, the mixture was filtered, ethanol was evapointad and 2 % sq. sodium hydroiddc (50 ml, 25 mniole) was added. The undue was extracted with ether (3 a 50 ml), the organic sohitlon was dried and solvent wasremoved to give (1R 4 5$)-2-phesl-3.mrbIcycle(3.1.OJbexane (1.618,10.1 mmolo 97%) (Foundi M’, 159.1048. Calculated for CH15N: 159.1048), (al?.117.9 0 (a 1.062, COd3) which showed N. 0.37-0.51(21!, m), 1.44 (IA in), 1.60(111, in), 2.06 (111, s), 3.01 (lH,d,3 11.11143.05 (111, dd,J 11.1, 2.9H44,30(I14 d, 332Hz), 7.15-7.43(511, in), ö. 3.58.., 1627+, 20.89+, 49.23-, 62.53+, 127.08+, 127.2+, 128.36+, 141.69; v,,3317br.9,3061 m,3031;2925s,2864s1495m,1451s,1089m, 1032m,927m,7453,700scin";(n*, 159, 100 (M’), 158,90,144,12,,129,16; 105,23; 104,32, 92, 15; 91,28; 83, 27; 82,42; 54, 17.

(1R 28, 5S)-2-Phniyl..N4rifluoace4-rsabicjdol3.LOJhexane.
(lR, 28, 5S)-2-Plienyl-3-azahicyclo(3.1.Ojhexane (1.53g, 9.61 nunole) was dissolved in d1oroiIiane
(30 ml) and tdfboroecetic =hydride (10 ml, 50 minds) was added. The solution was stirred fbi 2 1*, then the voladleswere removed iuvacuo and the residue was dissolved in ether(50 nil) and this solutionwas extracted with phosphate bufthr (2 a 30 ml. p116.88) The organic solution was dried afterremoving the solved, (114 4
(42) (2.44 g, 9.56 inmole, 99 3k9) was obtained, m.p.
94-97°C, a]° -170.4° (02.004, CRC,), 93.3% e.a by chital g,l.o. (155°C). ’This crud9 pwduct was mays-WbW bernie- eth4 acate(20 nil, 173) and the mother ilipror after this was reciyst4lllsed as well to yield (A 4£)-Z-phreIyI-!(-bfiuomac4’l-3.erablc,cZofS.J.OJhaxwre (42) (2.06 & 8.07 mmQla, 84%)(Found: C 61.03, 11 4.74,1’l 5.49. Calculated fbrC,H,?’1OF3: C 61.18,114.65, N. 5.66), m.p. 107- 108 ’C, [a]° -192.7° (c 0.999, dIG,), 100.0% e^ by chiral gJ.c (155 "C) wldcbshowed 6n 0.46 (lit ddd, 36.1,4.1,4.1 Hz), 0,68 (14 ddd, 38.1,7.9,6.11141.87(111, dddd, 17.9,7.6,5.0,4.1Hz), 2.03 (111, dddd, 38.1, 76, 5.5, 4.1 Hz), 3.99 (10, d,J 10.7 Hz), 4.11 (14 dd, 310.7,5.0Hz), 5.38 (UI, d, 15.51147.09-7.40(50,, m) 6: 10.10-, 17.81+, 23.85+, 51.09 (-, q, 33.8Hz), 64.70+, 116.20 (q, 3288.2 Hz), 125.08+,127.02+, 128.46*, 139.02, 156.49 (q, 336.9Hz);v(CCI4): 2900 w, 1694; 1495m, 1453 a; 1370m,, 1345m, 12248,1146; 1079 in, 836m,784 in, 749 in, 701 a urn4; (rn/a, %): 256,42 (M’); 254,100,142,45; 129,29; 117,31; 104,33; 91,21; 81, 19.

zt,

Synthesis of (2S,3R,4S)-3,4’-nicthanoproline

(ZR, 28, 5S)-N-TrmuuvoIc bkyc1o1OJbezane-2-carbox7IIc acid.

14791

(IR, 28, 5S)-2-Ph N-ftifluorocetyI-3-azblcyoIot3,LO]heicaxie(1,68 & 6.58 asmolu,) was dissolved
In ntetmcldcalde(161zd) and acetoidnileQsnal), water (24 ml) and periodic add (21.75 g,95.4 minole, 14.5
eq.) were added. Aftcradilitionofz,i0ssinn friddodde hydrate (74mg. 0.05 eq.) Lbo solution tqecama lih& The V8001100 mixturewaswarmed to 80°C with vigorous stkrhig when oxidation began (the black.o1our changed to yellowish and gas began to be evolved). After 2.75 h the reactiuu mixture became black again 4nd after I Ii more it was cooled to morn temperature and ether(SO ad)was added. The organic sobdion was aea4ed and the water layer was wsbed with ether(2 x 50u4 The combined ether layers were dried and the sofvcit wasremoved in vacua to give (iJ?, 23, SS)-N- uocace(y1-3’.arabiqwu1o(3J.OJhan,e-2.carbor,lic ai*1 (43) (Poimd: M, 223.0456. Calculated forCH,NO3V 223.0456) (1.29 g, 5.78 mmdc, 88%) as a mixture ofto rolatnon (ratio 11:41 (ct]° -116.5° (c 0.96, CHCI,) which thowed v,,,: 3260 bri, 1726s, 1696s, 1451 as, 121 9, 1180a, 1068 wcm4; (in!; %):223,2 (M’), 179, 12; 178, 100; 126,7; 69,31; major retainer, an: 0.73 - 0.0 (211, in), 3,82-2.19(211, in), 3,84 - 4.03 (211, as), 4.63 (114 d, 35.5Hz), 11.08(111, a), &: 9.06-, 17.68+. 18,58+. 50.18 (-, q, 13.4 Hz), 61.97+, 115.81 (;3 286,9 HZ), 156.86 (q, 338.1 lIz), 174.00; mInor retainer,: 0.49-0.55(111, as), 0.13 - 0.90 (111, as), 1.82-2.19(211, in), 3.84- 4.03 (211, in), 5.48 (10, d, 15.4Hz), 11.08 (11% a); be: 9,12-, 19.19+,50.40-,64.00+, 115.81 (q, 1286.9 Hz), 156.52 (q6138.4 Hz), 160.79.

(ZR, 28, SS)-3-Azabicydof3.1.Ojhexane-2-carbozyllc acid.
Ø R, 28, 5S).N-Tiifluomacetyi.3ambiuycio13.L0Jhamne.2-carbuitylic acid (1.24 g, 5.56 nimole) was
dissolved In a 3M solution ofpotnashun hydroxide In methanol (15 ml) and this wan stirred 1br2 h. Then solvent wasieinovedln iuruo and the residuewas dissolved in wag, neutralized with 2M roo1doricadd and desahed on a cokumi ofDower SOW - X8 resin In the hydrogen (hun. The amino add was elated fron the column with 5M ammonia. After evaporation in vacua, diylng over phosphorus pentoxide and reciystallIsig from ethanol - acetone (19 2$, 53)-3.azablcyc!of3.I,0jhexans-2.carboxylic acid (1) was obtained (557 nil 4.38 nimolc 79 %), (Found: C, 55.90; 0,7.00; N. 10,80. RequIred for CH,NO C 56.68, H 7.35, N 11.04 u.p. 240-241 ’C (decoinp.), (lit.’ 235-245°C), [a],’ -141.8° (0 0.776, 1120), (1I0 (uJ -132’; lit.9 [u),,° -144 which showed 11(D2O): 0.48 (lit ddd. 16.5,4.2,4.2 Hz), 0.77 (10, ddd, 18.2,8.2, 6.5 lIz), 1.83 (10, as), 2,05 (11L dddd. 18.2,6.7,44 4.2 Hz), 3.48 (20, ci, 12,0 Hz), 4.28 (1ff, d, 14.6 Hz), 6 (D20) 7.05-, 18.261’, 21.24+, 50.30-, 65.23+,175.93; v,,JKBr): 3432 br. w, 2980w, 2300-2800w, 1630s, 16039, 138$ a, 2355m, 706 m cat4.

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14792 V.V.TVERRZ0VSiYeta1.

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OO40-4O39(95)OO48.3

Enantloselectl’ve Synthesis of Cyclopropane a-Amino Acids:

Synthesis of N-Boc.cis.’(2S93R94S)u304.MethanoproIine and N-Boc-(2S,3R,48)3,4-MetbnJutamjc Acid
Isabella Sagnard, N, Andre Sasakl, Mrgtle Chiaruni, Claude Riche and Pierre Potier

lusther de c indesSmecesNsancl1es,as,Mdalam,91198 0l1-sur-Yveus6Fsuncu

Abstract: 774 tijlt compoaaLs ware synshealzed by a 5-step ladle sraarjbnnation af. She key buemxJazc 4, ks4abhthi,dbya ane-ors4’oaa-we&tued eye opropanadonfrom cow*who (Rj-Iaft).gycidylp?a1e.

Naturally uceuning and synthetic cycloprepane u-amino acids belong to a unique class of non-c1einogelic amino acids, They constitute an unusu1 form of conformnasfoually constrained u-wninoacids with pardcu1ad) Interesting biological pwpertl& Example; are i-amlnocyclopropanccarboxylic acid (ACC), known as plant gmwth regujalor2, or u-(methylcuecyclopropyl)-glyclne, with lethal hypoglycemic effects, isoltcd fnm Litchi chlnensis.3 Despise the apparent simplicity of their structures, the preparation of etiantlomercaUy pure Isom esenisaccoslderable synthetic challenge.
We have recently reported an efficient general methodology for chirospecific synthesis of 2,5-6substItuTcl pynolidinessensing fnnn the versatile chlralsynthon 1 (or he anhipode) and (2S)- cr(2R)-glycldyi lr1flate2,a depicted in Scheme L’

1ment
which and

On
the In SItU
toahydan
a novel as

r SO2Ph’
+

V’Z"08UL,0’›:?R.W.

mP

L Has
1 2 3

Scheme 1

,fthe dilitbiated species of I with g15.ddyt tilflato 2 at -60°C smoothly affords P4poxy sulfone 3 rgoes epoxide ring opening In ’one-pot" exclusively via a*-cycllzudon pathway to provide 2,5-ci pyrtolidines.
he other had, as we have pruviouslydesciThed in the synthesis of optically pure cyclualkylglyclam. iddhkm ofone more equivalent ofn.BuU to 3 generatas a new sulfonyl caxbaulon which may lend ynerthybycloplupyl sulfonc compuemd.5 in this communication we combine these two concepts for I concise Approach to the cnanUosciccdrc synthesis of cyclopxopanc u-amino acids. Thus, Ch-

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4

4

.4S)-3,4-me*banopro1lnc, isolated from seeds of Aescufu: parvlflora,6and (2S,3R,4S)-3,4-gIuamlc acid; a selective synthetic N.methyl-D-aspartic acid (NMDA) receptor agouis9 ware prepared derivatives, Sand 11. respectively (Scheme 2)

SWOU

MsO.S?h L[

Hq?c It

H 4 H COSH 30BM

0HL 8j"

nos

12
Scheme 2

Reagents and eoadl*imr a) 2 eq n-Bnli, ThP, 12 eq (2R).$31c147$ frlfla$s 2.-79’C-, Ii) 1 eq n-RuLI,THP, -WC It; c) 1 eq MSCVBt3N,VU5Cli. d) 1.1 eq NaUi 111SF, a) Ei011,1).l eq pyvidlniuin p-iolüeaesutroesto, WC, 3h;
06%Na.Ug,NfideOfl,oQg)Zoneaoz1daUon, MUM, OT, Th,b)3cq JNLIOH,McOH,,t, 1h

Shortly after addition of(2R)-glycldyl triflais 2 to the dillibluun anion species of(R).1 (about 15 min),
one note equiv of n-BUM was added at -60CC to afford the key lmenniedlarc4 In 73% yield after purification by flash hmnuatography together with unrcacicd (15)1(7%). Mcsyladon of4 followcd by ft: alment with NaH In DM1 provided a mixture ofthe mesylate 5 and the bicyclic product 6I86% yield On 2 steps) and in a 1:3 rado,rcspccdvdy. ’These two products were easily separated by flash chromatography (EtOAchn-heprane,l/1). Rcmval ofthe THP group from 6 by treatment with pyrldhnlum p-toiucncsulfonatc gave the sulfono alcohol 7 In qun1iradve yield. Reductive dcstdfunyladon by 6% Na-Hg followed by Jones o,ddadóa provIded S In 55% yield (In 3 steps). X-ray structure analysis of ’7 (FIgure 1) deruonsuatcs unambiguously that the major

. 4

cydlizes ’ii
dedvativc
subjected
1:3mlxtu

analysis (I
1. The sep
the NMI’

as the (35
isolated fr

NMDA
NMDA

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or formed by sulfóon-uiedlated oyclopropanallon Is indeed the sulfonc alcohol 12 which further
ithe mesylared Intennedhee to give 6. Based on this result, we attempted the synthesis ofthe N-Boo
f a potent NMDA receptor agonIst 11 in enandoincrically pure fone. The key Intermediate 4 was
the removal ofThP group followed by reductive desulfonyladon and Jones osidation to afford a
: of 9 and 10, respectively, In 80% overall yield. The structure of 10 was confirmed by X-ray [gum 2).10 Itsabsolutc configuration was deduced from the known C2..(R) chirality ofthe synthon ration of 10 from 9 was effected by simple recrysiallisudon (EtOAc/n-beptane). Finally, treatment of amide 10 with 1NUOH afforded 11 In 72% yield. The dicaxboxylic acid 91s tentatively assigned 48)-stereomer of 11 which Is the N-Boo protected form of a naturally occuning a-amino acid
m the unripe fittits ofAerculaspa,vUlora andBlighia sopId60
approach may find application In the facile synthesis ofthe enanilomerofii, anotherknown potent
onlst,11 or enamlomatically pure 2-amino-3,4-methano-5-phospbonopcntanolc acid, a potential

1 X-ray structure of 7 Flgure2 X-ray strucune of 10

AND NOTES

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maces cited therein.

8. selec ddata 7.mp39.40°C1t4D20=+22(c2.6,MeOH); 2HNMR (250 MHz, CDCI3,TMS)81,20
(in, 11), 1.33 (a, 90), 1.95 (in, 20), 2.48 (in, 10), 3.48 (in, 40), 4.20 (mu, 10); ’C NMR (62.9 MHz, CDC 3)8 14.43 (Cd), 23.07 (C3), 28.31 (CO3 Boo), 49.50 (CS), 61.85 (C2), 64.82 (C7), 128.69,

I,

3152

129.66 (Ph), 134.23 (Cq Ph), 155.90 (CO Boo). 8, mp 148-15(PC;23 [a]o -68(c 1.13, MeOH)13
10 NMR 80.65 (in 10), 0.75 (in, 10), 1.39 (a, PH), 1,60 - 1.86 (in, 20), 3.55 (ta, 290.71 (s,30), 4.34 (d,.1 4.0 lIz, 10); 13C NMR 8 8.70, 16.37, 20.71, 28.29 (CO3 Boa), 49.95 (CS), 6060 (0), 80.81 (Cq floe), 154.43 (CO Boo), 177.12. 9,14 mp 7345*C EaID20 = + 112 (o 1.5, CHCl); 211 NMR 8 1.05 (in, 10), 1.25 (in, UI), 1.43 (a, 94 1.74 094 20), 3.65 (s, 211), 3.95 (in, 114), 5.22 (d, 111); SaC NMR 8 13.06 (Cl), 17.74 (C4), 24.13 (C2),28.27 (CR3 Boo), 51.95 (CR3 ester), 52.60 (CH cater), 54.90 (Cl), 155.92 (CO Boo), 171.76,173.66.-10.15 nip. 79-81110, (st]020 =.129 (C 1.13, MeDH); SH NMR 8 1.12 (in, 111), 128 (in, 111), 1.42 (s 911), 2.20 (in, 21!), 4.75 (d, Im 6,0 Hz); ISC NMR 39.06 (C6).14.78 (CS), 21.46 (C4),27.86 (CRS floe), 58.55 (C2), 84.05 (Cq Hoc), 14931 (CO

Boo), 172.81, 174.18. 11.14 sib KZIDin + 95 (a = 0.83, CO2C12); ifi NMR 8 1.15 (in, 111), 1.27 (in, 111), 1.45 (a. 90), 1.50 (in, IH), 1.65 (in, IH), 3.10 (a, 30), 3.72 (a, 30), 4.33 (in, UI), $23 (4, Ui); SaC NMR 8 12.48 (CS), 18.72 (C4), 23.61 (C2), 28.41 (CR3 Hoc), 51.98, 52.42, 77.59 (Cq Hoc), 152.55 (CO Hoc), 169.71, 169.87.
9. Crystal data for compound 7. C17IiNO5 8, molecular weight 353.44, crystals obtained from slow evaposadon ofBtOAvIn.hcpinne orthorhonthic system, space group P 212121, Z 4, a = 6.663 (3), b 13.517 (6), c = 20.235(9) A. V = 1822 (2) A, dc = 1.29 g cm-3,]r(000) 752,X (Cu Ku) = 1.5418 A, It = 1.75 nun4; 2293 measured bncnshics on a Noidus CAP4 d1ffictometcr, (0-20) scan technique up to = 65, 2281 unique rcflcxlons (Rim a 0.027), 2155 observed with 1>3.0 u(1); B. 0.043 and Rn, 0.056 (Rn,’ (Zw ur0l)2/wFo2J1a), 1/2(Fo)+o.00011 Fo2J.
10. Crystal data forcompound 10.Cii0N0,molecular weIght 241.24;
o

rthorhombic system, space group
P212121, Z = 4, a 9.088 (3), b = 11,181 (6), c 12.531 (6) A, V = 1273 (1) Ad0 = 1.26g cnr3, F(000) = 512, L (CM Ku) 1.5418 A, P= 0.8 mml; 1755 measured IntensIties, 1641 unique reflexions

(Rim = 0.037), 1567 observed with 1>3.0 uØ); R 0.047, 0.053, w = 1/U2(Po).
The structures were solved by direct methods using SUEZX586 and refined by full matrix 1eaat-squares minhalning the function EwWo-IFc02, with the progrem SHELX76. The hydrogen atoms, loptcd In difference Pourlermaps, were Introduced In the acflnement at theoretical positions (C-B ix LOG) using experimental torsional angles and assigned an isohopic thctmal factor equivalent to that ofthe bonded parent atom, plus 10%. ’fire absolute configuration o17 was assured by comparison ofselected 0jvcet pairs of reflexions using the anomalous dispersion of the sulfur atom. In the crystal of 7, an Intranioleenlar hydrogen bond links the hydruxyl group 011 to 08 (O"O 2.717 A). In 10, 012-H Is hydrogen bonded atom 013 of nelghboiüing (0-0 = 2.834 A). Mondc coordinates have been deposited at the Cambridge Crysiaflogruphia Data Center, UL
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12. Dappen, M.S.; PcJllcclarI, R.; Natabnl, B.; Monahan, LB.; Chiorn, C.; Cordi, A.A.Z. McS Chant.

13. Dicyclohezylanrine salt.
14. Dbncthyi ester by steaunenu with CO2N3,
15 Methyl esterby treatment with CR3N2.

AS: 97.065 COC r ...

AaNACIBI*-Iii 06-We -’V

FORMULAR1O UMCO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NAC1ONAL

SOUCI1UD DE:
Patents tie lnvenciôn.D Patente de Modelo tie UWkiad.

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NUmero....22720 TPJ9436-
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5 PCT(86)
Solicitud Internacional No. PCTIUS2003/038558 Fecha 04-12-2003
Pub!icación Intemacional No. WO 2004/052850 A2 Fecha..24-06-2004

TItulo (54): MET000S Y COMPUESTOS PARA PRODUCIR INHIBIDORES DE DIPEPTIE)JL PEPTIDASA
IVY SUSINTERMEDIARIOS S

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REIVINDICACIONES

CI) Compuesto que coxnprende la estructura de
formula IA:

IA

0 una sal farrnacØuticamente aceptable, caracterizada porque:
se selecciona ’del grupo que consists de H y OH;
R2 se selecciona del grupo que consiste de -C(0) -
CO,R4 (=O)NR5R6, (X)-COR4 y -C-NR7R8COR4,
en donde
ISH X es un haiógeno;
nesdel-2

R4 se selecciona del rupo que consiste de 0-
aiquilo, NH2 y OH; y S
R5, 1k6, R7 y RB cada uno se selecciona del grupo que
29 consists de H y C00R91.en donde R9 esun aiquilo sustituido 0 insustituido; y
()se selecciona del grupo que consiste de H, OH y
en donde R’° es NHR"C (0) R’,

es R13COOH, :

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10 MØtodo para producir un irthibicior basado en
pirrolidina fusionado con ciciopropilo de la dipeptidul
peptidasa IV, caracterizaclo porque comprericie:
(a) acoplar el Æcido (<aS)-<a[N1,1-dimetiletoxi)
carboriil] amino] -3-hidroxitriciclo t3. 3.1. i’J decano-1-ac6tico
o su sal de 1,4-diazabiciclo(2.2,2loctano a la iS,3S,5S)-2-j

L1c1o[3 1. 0]hexano-3-carboxamida/para producir 111-
dimeti6ster del Æcido 3-(aminocarboriil)-<aS)-<a-(3- k. hidroxitriciclo3.3.l,13’7)dec-il)-<b-oo-(1S,3S,5S)-2-
azabiciclo [3. 1. 0] hexano-2-etancarbÆmico;
(b) deshidratar 1,1-dimetiletil ester del Æcido 3-

(aminocarbonil)-<aS)-<a- (3-hidroxitriciclo[3. 3.1. 17]dec-1- 0 I

"

il)-<b-oxo-(1S,3S,5S)-2-azabic.clo(3.1.0]hexano-2-
?20 etancarbÆmico para producir 1,1-dimetiletil ester del Æcido
3-ciano-(<aS)-<a-(3-hidroxitriciclp[3.3.l.13"]dec-1-il)<b-oxo-(1S,3S,5S)-2-azabiciclo(3.0)hexaflO-2etaflcarbÆmiCo y
(c) hidrolizar 1,1-dimetiletil ester del Æcido 3-
ciano- (<aS) -<a- (3-hidroxitriciclo [3.3.1. 13"]dec-1-il) -<b-oxo-
25 (1S,3S,5S)-2-azabiciclo[3.1.0]hexano-2--etaflCarbrfliCO para

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ormar el inhibidor de la dipeptidil peptidasa IV.
MØtado de conformidad con la reivindicación
10, caracterizado porque ci. Acido

dimetiletoxi) carbonil3 amino] -3-hidroxitricic1o[3.3.1. i’]. yj
decano-1-ac6tico, etapa (a) es producido protegiendo con BOC ci Acido (<aS)-<a- amino- 3-hidr’oxitriciclo[3.3.1,13’7]decano-1-acØtico.

-

1. MØtodo de con ormidad con la reivindicacin
10, caracterizado porque comprencle adem.s reducir de manera asimtrica ci .cido 3-hidroxi-<a-oxotriciclot3.3.1,1"1] decano-1-acØtico para producir Æcido (<aS)-ca-amino-3-hidroxitricic1oE3.3.1.13’7)decano-1-acØtico par aminación o transaminación.
.3J. MØtodo de conformidad con la reivindicación
10, caracterizado porque ademÆe comprende aintetizar-qulmicamente el kcido (<aS)-amino-3- i hidroxitriciclot3.3.1.17)d.ecano-1;-acØtico a partir del cido triciclot3.3.1.13’7]decano-1-acØtico. -’
14). MØtodo de conformidad con la reivindicacin
10, caracterizado porque, la (1S13S15S)2..(1) azabicc1o[3.1.0]hexano-3-carboxamida de la etapa (a) se produce por ci retiro de BOC del 1,1-dimetiletil ester del ª.cido [1S-(1<à,3<b,5<a) -3-aminocarbonil)-2--azabiciclo(3.1.0) hexano-2-carboxllico.
15;. MØtodo de conformidad con la reivindicación

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14, caracter.zado porque 1,1-thmetiletil ester del Æaido [1 -

(J Sç.] -3-aminocarbonil) -2-azabicicloE3.1.
carboxilico es producido por].a ciclopropanac16n del 1,1-dimetil ester del Æ.cido (5S)-5-aminocarbonil-4,5-dihidrO-1H-pirrol-1-carboxilico via una reaccin de

Simmons -Smith.

 --; lo

ii). MØtodo para producir el Æ.cido (<aS)-<a-amirio-3-hidroxitriciclot3.3.1. ii"] decano-1-acetico de conformidad con la reivindicacin 4, caracterizado porque compreride reducir de manera asimetrica e]. Æcido 3hidroxia(fl)  oxotriciclot3 3.1.13"]decano-1-acetico por aminaciôn 0 tra.nsaminaciOn enzimtica.

3). MØtodo para producir el acido (<aS)-<a-amino-
3-hidroxitriCiclO(3.3.3..13,7Idecano-i-ac6tico de conformidad con la reivindicación 4, caracteriza.do porque comprende:
(a) hidrolizar el Æcido triciclo(3.3.1.13"]decano-
1-ac6tico en acido c-bromotricic1o[3.3.1.13"]deCaflo-1-ac6tico;
(b) hacer reaccionar el Acido c-bromotriciclo t3.3.1.137idecano-1-ac6tiCO con H2SO4 y HNO3 para producir el Æcido cbromo-3-hidroxitricicloE3.3.1.13"1deCanO-1-aC6tiCO; (c) disolver el Æcido c-bromo-3-hidroxitriciclo 3.3.1.13"]decano-1-acticO en hidrôxido de amonio y calentar la mezcla de reacciôn;
(d) concentrar la mezcla de reacciBn para producir

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una mezcla quiral del &cido (<aS)-<a-amino- 3-1idroxitricic [3.3.1. i’j decano-1-ac6tico; y
(e) aislar el Acido (<a$)_<a-aminô-3-
hidroxitriciclo[3.3.1.13,7)decano-i-ac6tico (formula V) de la mezcla quiral.
Mtodo de conformidad con la reivindicaciOn

15, caracterizado porque el 1,1-dimetil aster del Æcido (5$)- 5-aminocarbonil-4, 5-dihidro-1H-pirrol-1-carboxIlico, 58 producido hidrolizando 5-etil6ster 1-(1,.-dimeti1eti1) del
1 ª.cido 4,5-diidro-lH-pirrol-1,5-4icarbox1ico por saponificaciOn con liidrOxido de litio y la formaciOn de una aTnida con arthidrido y cloruro de mesilo mezclados.
19. Linea celula.r, caracterizada porque es capaz
de producir &cido (.ca$)-<a-amino-3-hidroxitriciclo
15 [3.3.1.137)decano-1-ac6tico (fOrmula V) de conformidad con la
reivindicaciOn 4 por aminaciOn o transa.minaciOn reductiva
asimØtrica del Acido 3-hidroxi-.a-oxotriciclo[3.3.1. 1"]
decano-1-ac6tico (fOrmula II).
20. MØtodo pàra producir el Æcido 3-1-iidroxi-<a-
20 oxotriciclo[3.3.1.13’7jdecano-1-acØtico de conformidad con la
reivindicaciOn 3, caracterizado porque comprende tratar ci
aiquilØster del &cido dicloro- (3-hidroxi-adamantan-1-il) -
acØtico con una base de metal alcalino en presencia de un solvent* orgªnico para formar una mezcla de reacciOn que
25 contiene la sal del metal aicalino correspondiente, tratar la

mezcla de reaccin con acido para formar el produat correspondiente del Æcido 3-hidroxi-a-oxotriciclot3.3.1. decano-1-ac6tico.
21. Mºtodo de conformidad con la reivindicación
5 20, caracterizado porque la formación del producto as realiza

en un solo procedimiento de recipiente /(

22. MØtodo de conformidad con la reivindicación
20, caracterizado.porque la base de metal alcalino es
idr6xido de sodio y el Æcido es 4cido clorhidrico. (.
10 23. MØtodo para preparar 1-(l,1-dimetiletil)6ster
’ del ªcido (SB) -5-aminocarboni1-4,S-dihidro-1-pirrol-1-
carboxilico (IV) de conformidad con is, reivindicaci& 9, caracterizado porque comprende
proporcionar una sal de metal alcalino del 1 (1,1-
15 dimetiietil)Øster del Acido 4,5-dihidro-1H-pirroi-1,5-dicarboxilico, y
tratar una soluciôn de i& sal de:metal alcalino que

00, tiene Un pH abajo de 7 con cloruro de 4- (4, 6-dimetoxi-1, 3, 50

triazin-2-ii)-4-metiimorfolinio y con una base para formar el
’ 20 1- (1, l-dimetiietil)Øster del Æcido (5$) -5-aminocarbonii-4, 5-
dihidro-XH-pirrol-1-carboxllico (IV).
24. MØtodo de conformidad con is, reivindicaciin
23, caracterizado porque ia sal de metal alcalino se trata
con amonlaco como la base.
25 25. MØtodo de conformidad con la reivindicación

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ç q
23, caracterizado porque la sal de metal alcalino es formada

tratando la sal diciclohexilamina del 1(l4-

dimetiletil)Øster del &cido 4,5-dihidro-1H-pirrol-1,5-dicarboxilico con una base de metal alcalino para formar la
5 sal de metal alcalino correspondiente.
26. Mtodo de conformidad con la reivindicación
23, caracterizado porque la sal de metal a1calinoPformada proporcionando el ester etllico de l-(I,l--dimetiletil)Øster
del ficido 4,5-dihidro-lH-pirrol-1,5-dicarbox1lico(xI, tratar
el ester etilico con etanol e hidr6xido de-sodio.
1% 27. Metodo de conformldad con la reivindicación
25, caracterizado porque la sal diciclohexilamina es
preparada tratando una soluci6n de 1-(1,1-dimetiletil)6ster
del acido 4,5-dihidrolH-pirrol-1,5-dicarbox.tlico en etanol y
15 tolueno con hidróxido de sodio para formar la sal de sodio
correspondiente, y tratar la sal de sodio con t-butil metil
Øter y heptano para formar una soluciôn de la sal de sodio, reducir el pH de la soluci&i de la sal de sodio aproximadamente de 25 a aproximadamente 3 mientras que se
?20 mantiene la temperatura <5°C, separar la capa orgÆnica
resultante, y tratar la capa orgª.nica con diciclohexilamina
para formar la sal de diciclohexilamina correspondiente.
28. MØtodo pars. preparar 14-dimetiletil Øster del
cido tlS-(l<a,3<b,5cza)1 -3--(aminocarbonil)-2-azabiciclo
25 [3.1 * 0] hexano-2-carbox1lico de la:estructura

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ONH

caracterizado porque comprende
tratar una soluciôn de 5-etil6ster 1-(111-dimetiletil) del acido 4,5-dihidro-1}I-pirrol-1,5-dicarboxilico con dietil zinc y cloro yodornetano y una temperatura reducida de aproximadarnerite -20°C o menor pra formar una mezcla de syn- y anti-isómeros del ester etiiico de N-BOC-metanoprolifla, tratar la mezcla anterior de isómeros con una solución acuosa de metilamina para separar ci isómero del ester etilico de syn-BQC-415-metanoprolina,
tratar ci syri-isómero con una base fuerte para
producir syn-N-BOC-4,5-metarioprolina, y tratar syn-N-BOC-4,5-rnetanoprolin6 con N-nietilmorfolina e isobutil cloroformiato, sairnuera y arnoniaco para formar el ester etilico 1,1-dimetiletil del Æcido E1S-(1<a,3<b,5<a)-3-(aminocarboriil).-2-azabiciclo[3. 1. 0]hexano-2-carboxilico.
29. MØtodo para formar ci intermediario 1< de la estructura

7.1

SUPERINTENDENC1A DE 1NDUSTRIA V COMERCIO DIVISION DE NUEVAS CREACIONES

D.C. 07/09/2009

Alvaro Correa Qrdohez.
(Apoderado)

ASUNTO RadicaciOn TrÆmite
Evento
Actuaciôn
Oficio
Folios

Patente do Inven.ciOn MR

Via Nacional

Via PCT (fase nacional)

0118851
002
001
430

013

Pateætede Modelo de Utilidad

Cap. Cap. H

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Como resultado dot examen dØfondo, realizado con fundamento en el articulo 45 do la Decision 486 do la ComisiOæde, la Comunidad Andina, se le comunica:

1. ’Docurnentos estudiados:

1.1. Descrhción: Folios: 8 a 210

1.2. Reivindlcaciones: Folios: 211 a 226
Folios: 411 a.422 Memorial do 08/06/2005
Folios 443 a 451 Memorial de 31/01/2007
Folios: 532 a 535 Memorial do 06/06/2007

1.3. Prioridad: US60/1 88, 555 do 10/03/2000

1.4. Respuesta del splicitant: Folios: 440 a 455 Memorial do 31/01/2007
Fobs: 521 a 547 Memorial de 06106/2007
Folios 552’a 587 Memorial de 28/07/2009

2. Objeto do la lnvenciOfl

Titu lode la ’softcitud: S

’InhibidOres a base do plrrolidlna fusionacla con ciclopropilo do dipeptldilpeptldasä IV mØtodo" Reivindlcaclones: S

605

La invencion hace referencia a inhbidores de dipeptidd peptidasa IV (DP-4) a base de ç irrolidina fusionada con cic)opropdo, a un mØtodo pare tratar la diabetes, en especial e tipo H, asi como la hiperghcemia, sindrome X, comphcaciones diabeticas, tiperinsuIinernia, obesidad, aterosolerosis y enfermedades relacionadas.

dipeptidil.peptidasa IV es una: aminopeptidasa de sØrina no clÆsica, eniazadaa na membrana la cual se localiza en una vanedad de tejidos (intestino, hgado, pulmón, r,æon),asi como en Is ctrculaciôn en donde la enzima as conocida como CD -
6. S

Una vez catalogada la invenciôn Østa se clasificó en la secciOn: A 6.1 K 8115
de la Ctasiftcaciôn Internacional de Patentee

3 Dc la solicitUd de Pateflte

3.1 Reivindicaciones (articulo 300. 486)

Segun la definicion qua aporta at sohcitante en et phego reivindicatoria de los folios 532 a 535, Is formula Markush presenta dos radlcales tipo R1 y R2 sustituyendo la posición 2 de la cadena aiquilica

Los qua segcEn la clÆusulaI puoden ser:

R1 -H, aiquilo Cl-B, cicloalquilo, bicicloalquilo, tncicloalqwlo, alquticicloalquilo, hidroxiaIquo, hidroxialquilcicloalqudo, hidroxtbicicloalquslo a htdroxitrlcicloalquflo, en donde, at cicloalquilo tiene Un anillo de 3 a 10 Ætomos de C yet bicic)oalqullo y tricicloalquilo tiene maxima 10 Ætomosde C los anitlos.

’

R2: -H, aiquilo C1-8.

Sin embargo, on ningun evento se seflala qua at radical aiqudo enlazado at carbociclo to hace par at mismo atomo de carbono par at que se enlaza at Ætomo decarbono 2 de la cadena aiquilica de 2-amino-acetoilo coma en at caso de los ejemplos 1,2 3y 7 Par otra parte, en la defintctôn aportada tampoco se indica que ditha cadena aiquilica pueda contener radicates hatogenados y dobtes enlaces como claramente se evidencia en las modalidades particulares de la invencion a qua sabre el cicto puedan presentarse sustituciones halogenadas, como es at caso particular de los ejemplos 1.y 5

jemplo I Ejemplo 2

Ejempio3

EiernDIo 5

Ejemplo 7

Ejemplo 4

Ejemplo 6

Por anterior, es preciso quo el senor soticitante aclare par quØ ciertas modalidades do la invenclon contemplan esta clase do sustituciones cuando on la defirucon quo acompaæala clausuta independiente I no so incorpora esta clase do sustttuyentes
sabre la estructura.

Con respecto at contenido do las clÆusulasdo combinaclónreivindicaciones 7
a 12 es preciso seæalarquo at incorporar el mecanismo de accion o en su defecto la categorla farmacológica 0 terapØuttca de uno do los agentes quo

componeri

la combinaciôn, et solicitante recurre a la definicion del objeto por et
resultado quo pretende alcanzar, dejando do lado los elementos esenciales y caracteristicos quo definen on estricto sØntido las combinaciones.

Por otra parte, la categoria estructural do los agentesantidiabØticos: biguanidas, sulfonilureas y su actividad farmacologica como sintetizador de insuhna, agente antiobesidad o modulador do lipidos no permrte una identificaoiOn inequivoca do la especie qulmica que so pretende combinar. Adicionalmente, la memoria descriptiva do la sohcitud no presenta sustento para todas las combinaciones quo resultan do combinar un agente derivado do la estructura Markush con cualqulera do las especies antithabØticas metformina, ghburida, gllmeptnda, glipirida, glipizida, pioghtazoria y rosightazana, par to quo para esta Superintendencia es clara quo se pretende proteccion para materia quo no ha sido objeto do comprobactOn tØcnlca respecto del efecto tØcnco quo so genera cuando so administran las combinaciones farmócolOgicas pretendidas.

En consecuencia, el pliego reivindicatorio allegado mediante memorial do fecha 06/06/2007 presenta falta do precisiOn y su contenido on to quo bone quo ver con combinaciones farmacolOgicas no so encuentra debidamente sustentado en el aparte descriptivo do la sohcitud, por to quo existe incumplimiento a las disposiclones normativas del artfcUlo 30 do la Decision 486.

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Determinación del Estado de la TØcnica

iderando que la fecha de presentación de la primera solicitud de patente de la
se reivindica prioridad es: 10/03/2000, se procedió a efectuar la büsqueda de mentos relacionados en el estado de la tØcnica con fecha de publicaciOn
ior a Østa.

NO Documento Titulo Fetha de

Publicacion
W09947545

. . .

"inhibitors of caspases" 23/09/1999

D2 EP0OOf652 "Derivatives of azabiciclo(3. I.0)hexane and a 06102/1980 process_for their prej,aration"
"Derivate der 2-azabicyclo(3. 1.0]hexan-3-
carbonsäure, Verfahren zu ihrer Herstellung,

D3 DE3324263 these enthaltende Mittel urid deren 17/01/1985 Verwendung sowie 2-azabicyclo[3. I.0]hexan-
Derivative ale Zwischenprodukte und Verfahrenzu_deren_HersteiIung
"Probing the importance of special and
64 Articulo I conformational domains in captopril analogs 1998
for angiotensina converting enzyme activity"

D5

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Articulo 2 "Synthesis of (2s,3R,48)-3,4-Methanoproline 1997 and analogues by cyclopropylidene insertion"
"N-(substituted glycyl)-2-cyanopyrrolidines

6 US60I 1155 pharmaceutical compositions containing them 04/01/2000 and their use in inhibiting dipeptidil peptidase

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Anterioridades Dl en los folios 458 a 478, D2 en los folios 502 a 505, 03 en los folios 494 a 501, 04 en
los folios 558 a 563, anterioridad D5 en los folios 564 a 583 y antenoridad D6 en los folios 479 a 493

Articulo 1. Hanessian Stephen, et al. "Probing the importance of special and conformational domains in captopril analogs for angiotensina converting enzyme activity", UniversitØ De MontrØal Canada 1998 Bloorganic & Medicinal chemistry Letters 6 (1998) 2123-2128.

Articulo 2. Tverezovsky Viatheslav V., et al. "Synthesis of (2s,3R,4S)-3,4-Methanoproline and analogues by cyclopropylidene insertion" University ofWales Bangor. Tetrahedron, Vol 53, No..43, pp
14773-14792.

5. AnØlisis do patentabilidad (att(cu!o 14 D. 486)

5.1 Nivel inventivo (artfculo18.D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre los elernentos tØcnicos caracteristicos de los compuestos reivindicados y las anticipaciones mae cercanas a la invenciôn:

Se reivindican compuestos inhibidores DP4 que presentan el nücleo azabicicio[3.1.O]hexano a continuación relacionados en las Tablas 1 y 2:

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labia 1. ComparaclØn de elementos tØcnicoS

Materia Reivindicada Antecedents 01 Antecedents D2 Antecedents D3 (0E3324263)

C)âusula I

NR2)L)(N(

R5 R4

RR

3 21Y R

0 x
Y puede ser:

Co
R1 c02R Z

ClÆusulaa3y4 V puede ser: X es un grupo aiquilo qua tiene R: -H

Ejemplo

mÆs de 5 Ætomoscia C. RI: cicloalqullo bis C, cic)oa{quenllo bis Cs-s, cictoalqullo bis C5-7, bidclo heterociclo C.
RI: -H

alquilo, -OH, ha)ogeno

Eem to B R4 R5 junto con el àtorno a) qua se enlazan on la cadena pueden
former tin sistema cic)ico de la

N
H2N

siguiente clase:

R
0
CN

IO

1I7

S

S

Anâlisis de diferencias TØcnicas:

Con respecto al documento del estado del arte Dl las diferencias tØcnicas estriban en que dicho documento incluye un sustituyente CONR6Y sobre el aniHo que forman R4 y R5 (vet folio 475 del antecedente) Y sobre et atomo de nitrogeno es que se encuentra enlaza el sustituyente Y que presenta varlas connotaciones, entre ellas los triciclos y biciclos seæalados.

Con respecto al documento D2 las diferencias estriban en que el Ætomode nitrôgeno del anhllo heterocicliôo de cinco miembros se encuentra en la posiciön 4 con respecto al anillo de ciclopropano y en que X corresponde a una cadena alquiiica que no presenta sustituyentes tb oxo a amino sobre la cadena ni grupos biciclicos o triciclicos.

Con relación a! antecedente D3 las diferencias se generan en los sustituyentes que se enlazan al grupo amino que para el caso del antecedente corresponden a un grupo alqu)l a alcoxi-carboxilo, mtentras que en el caso de la materia reivindicada este grupo no presenta sustituciones de los ªtomos de hidrogeno sobre el nitrógeno.

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Tabla I Comparaciôn de elementos tØcnicos

Materia Reivindicada Antecedents 04 -
(Articuo 1)

Antecedente 05
(ArUc4o2)

Antecedente 06
(JS801 1155)

CIÆusita 2 S

R ,, 1 9/1 5
\

2Nf"9’’i"

Me
HS.N

Acido (IR, 48, 5S)-1-meti-3-
azabicicio[atojhexano4
carboxico

Ejemplo 29

ON

(IS,2(2S),3S,55)

COOH (1R:48,5S)Ntbutoxltonhi’l
mebI-4vinil3- S

Ri esaiqullo C1-8 azabiciciot3.1.01hexano

CIâuuIas 3 y 4 S Ejemplo 38

Ejenpio 2 S

NH

CN
HO

S S

S Ejemplo 53
Eempio 4

CN

HCI

EjmpIo 6

?3 41 N

AnÆlisis dediferencias TØcnicas:

Con respecto al antecedente 04 la diferencia estnba en que la cadena que sustituye el atomo de nitrôgeno del heterociclo es de 3 atomos de carbono con un sustituyente tipo metilo y un grupo sulfihidrilo en el extremo, mientras que el caso de la materia reivindicada corresponde a un grupo amino y la cadena aiqullica puede Ilegar a tener incluso hasta diez Ætomosde carbono ya que R1 corresponde a un grupo aiquilo C1.

Con respecto al antecedente D6 la diferencia estriba en que los compuestos re.lacionados en dicho antecedente no presentan grupos amino como sustituyentes de la cadena aiquilica, mientras que en el caso del compuesto sefialado en la clÆusula2 del pliego reivindicatorlo si se encuentra este sustituyente.

Con respecto al antecedente D6 las diferencias estriban en que en dicho documento no Se menciona la fusiOn entre el anillo de pirrolidina y, el anillo de ciclopropilo y en que el grupo triciclo, biciclo o monociclo no se enlaza al Ætomo decarbono adyacente

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grupo carbonilo sino que se enlaza directamente al grupo amino, sustituyendo uno sus hidrógenos.

De acuerdo con el seæorsolicitante, los compuestos reivindicados son inhibidores de iipepbdfl peptidasa IV cuyo nucleo es de pirrohdina fusionada con ciclopropilo y presentan utilidad en el tratamiento de Ia diabetes, especialmente la tipo II.

be esta manera yen virtud de la divulgaciOn presentada ante esta Superintendencia, los agentes terapØuticos forman parte de un diseæoestructural altemativo para el
manejo de condiciones asociadas a la disfunción de la homeóstasis de la glucosa.

De la misma forma el sustento descriptivo se orienta hacia la presentaciôn de las metodologas de sintesis para la obtenciOn de los compuestos sin hacer rnencion
alguna a las ventajas terapØuticas que so consiguen con este diseæoestructural.

En consecuencia, el anÆlisis denivel inventivo realizado Øor esta Supenntendencia se
, cimienta en dos ejes fundamentales: el primero, relacionädo con la estructura de los compuestos y el segundo relacionado con la actividad de los compuestos
reivindicados.

1. Estructura:

Como se aprecia en las tablas I y2 la estructura reivindicada presenta un anillo de pirrolidina fusionado a un anillo do ciclopropilo enlazado por un puente de carbonil-alquil-amina que uno de sus carbono.interrnedios presenta como sustituyente una estructura carbociclica basica do ciclobutslo, cicIopentIo 0 ciclohexilo, o en algunos casos mÆscompleja de tipo biciclo o triciclo.

En virtud de las enseæanzas del estado del arte, esta Dependencia so permite seæalarquo al combinar las enseæanzasdel documento D3 con cualquiera de los documentos Dl 002 es posible derivar los elementos caracteristicos de la estructura
. Markush definida por la clÆusulaI, toda vez que Of se indica la fusion de ciclopropilo con el anillo de pirrolidina por la posiciOn adyacente a la quo ocupa el Ætomodo

nitrOgeno.AdemÆs

el documento 03 indica que el heteroâtomo del heterociclo puede
encontrarse sustituido por una cadena do carbonil-alquil-amino, sobre la cual se inclüye una estructura ciclica en el Ætomode, carbonq. intermedlo entre el grupo carbonilo y el grupo amino.

Como se indicô el documento D3 no presenta de manera especifica las caracteristicas de los grupos carbociclicos que se enlazan al Ætomo de carbono intermedlo, sin embargo, esta falencia se subsana cuando so analizan las enseæanzasquo revela el documento Dl, en el que claramente so indica que pueden ser de tipo:

Y a su vez el documento

S S

03 subsana la falencia que so encuentra en las enseæanzas
reveladas por Dl, con respecto a la posiciOn en la quo se enlaza el anillo de ciclopropilo al anillo de pirrolidina. S

Con respecto a la estructura quo reivindica el seæorsoliôltantŁ en la clÆusula 2para la

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’D6 US6011155 I a 12 Nivel Inventivo

Respuesta a los argumentos del solicitante:

lante memorial de 06/06/2007 el seæor solicitanteargumenta lo siguiente:

"No es clam on quo so basa el seæor examinadorparaafirmar que Ia fOrmula

- qH estructura do’(V, en la reivindicaciOn 5 deJa anterioridadDi puede
convertirse en:

Cuando dichas fOrmulas corresponden a un sustituyente on Yyno pueden ser
V de ninguna forma, porque aÆn haysustituyentos adicionales alrededorf.

Al respecto es preciso seæalar Josiguiente:

o R R5

- 11A 1-1y R;fqly-?r’
En Dl se revelan estructuras de la formula: para las que R4y R8 pueden formar de manera conjunta un anillo de cinco miembros, segin la pagina 289 del antecedente correspondiente a la pÆgina 475 dela solicitud de patente.

En tal caso si uno de los R5 forma con R4 la estructura cicHca de pirroHdina fusionada con ciclopropilo, el otro R5 es H segin la definiciOn de la clÆusula 6 que es dependiente de las clausulas I a 5 en (as que se determina esta situacion En consecuencia, se tendrian estructuras que presentan las siguientes caracterIsticas:

’

R1

SegCin la c(Æusula 4 del antecedente (folio 283) R6 es -H y V cuando toma la connotaciOn definida en la clÆusula 5 es una estructura tipo lactona de 5 a 6 miembros que depende de si m es 001 Sobre esta estructura existe un radical V, el cual puede ser: de tipo monociclo, biciclo o triciclo, por 10 que en virtud de tal situaciOn se podrian obtener las siguientes connotaciones para el grupo Y:

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(de esta manera obtener estructuras con las siguientes caracteristicas:

Donde X es y R3 es H S S
R1 y R2.es -H

$1 bien es cierto, existe un grupo.heterociclico intermedtario entre Ia.estructura do pirrolidina fusionada con ciclopropilo y el aniflo carbociclico, corno Se seflata en el presente examen tØcnico si so combinan las enseæanzasdel documento Dl con (as
del documento D3 (DE3324263) una persona versada en cioncias farmacØuticas estaria capacidad do anticipar las caracteristicas tØcnicàs de!°s compuestos reMndicados, toda vez que en 03.81 so determina que el grupo ciclico complejo se presents sobre un Ætomode carbono intermedio entre el grupo.carbonhlo yet grupo
amino.

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.En consecuenofa, Y quo contiene las connotactones do V puede ser a su
vez el radical V puede seruna estructura carbocictica compleja corno las senaladas pore seæorsolicitante en su pliego reivindicatorio

Adicionalrnente, esta Superintendencia ha aco9Id6 las consideraciones del reporte de. bisqueda Internacional para el presente caso, en el quo claramente so evidencia quo I of documento Dl W09947545 - es catalogado porque afecta of nivel inventivo do Is materia reivindicada, toda vez que anticipa en gran medida los elementos caractŁrlsticosdo loscompuestos definidos en Ia. clÆusula 1.

Con respecto at documento del estado del arte U$6011155, antes D2 y en adelante documento D6, el seæorsotIcitante arguments to siguiente:

"No es clam, a partir do los escasos argumentos presentados por el seæor exarninador, apreciaren quØ punto Ia anterioridad 02 ensefia 0 sugiere Ia posibilidad do transformer ese anile do ciclohexano en un anillo heterociclico do cinco mlembros, menos eOn como puede un tØcnico con habilidad ordinana on la matena,
S

1 en su diarlo trasegar, liegarde manera obvià at compuesto dole presente solicitud".

Con respecto at argumento del seflor soHcitante es preciso seæalar tosiguiente:

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__ S.

V

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I bien es’ clerto los ejemplos que revefa este documento no presentan un anillo de rrolidina fusionado a un anillo de ciclopropilo y el anillo de ciclohexano a el anillo ciclico no se encuentra enlazado al Ætomode carbono intermedlo entre el grupo rbonilo.y el grupo amino como se establece en el pliego revindicatorio aportado, es iportante que el solicitante no desestime las analoglas estructurales seæaladas par ta Superintendencia ya quØ como se evidencia en Is Tabla 3, su configuraciOn structural es rnuy similar, tan es asi que consØrvan Is misma actividad farmacolOgica r 10 que para esta Superintendencia es claro que Se trata de series bloisOsteras Lie conservan Is misma distribución de carga, tamaæo yvolumen to que tes permits resentar Is misma reactMdad biolOgica y por tanto Is uniOn at receptor endogeno

labia 3.
Materia Relvindicada Antecedente D6.
. (US6011155)

HON N.

HO

Asi las cosas, Is presencia a ausencia de la fusion ciclopropilo-pirrolidina no parece modificar Is activldad farmacolOgica de las molØculas, por Jo que esta diferencia no confiere ningün efecto tcnico que permitiera reconocer un verdadero salto en la regla tØcnica, por to que pare esta Superintendencia continian slendo vÆlidaslas
enseæanzasdel documento US6011155

Par otra parts, esta Superintendencia.se permits informar al seæor solicitante
que exists una solicitud que adelanta el mismo trÆmite administrativoante Is DivisiOn de Nuevas Creaciones, mediante Is cual se estÆn reMndicando algunas de las especies quimicas seatadas en las clÆusulas I y 2 de (a presente solicitud. Esta situaciOn se puede corroborar medianteanÆlisisdel capitulo reivindicatorio de Is solicitud 05-56006 presents en los folios. 582 a 602, en (a que.se rectamaprotecciOn pØra el compuØsto:

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En cumplimiento del articulo 45 dØ la Decision 486 de la: ComisiOn de la Comunidad Andina, se to indica quo debe dar respuesta dentro del tØrmino do sesenta dias ontados a partir de la fecha do la notificaciOn de la presente comunicación. En caso
Ie no dar respuesta at presente requerimiento, o si a pesar de la respuesta ubsistieran los impedimentos para la concesiOn, se denegarÆ lapatente.

fIquese el presente oficlo nf rme a to dispuesto en el numeral 5.2, literal e), del
5 del titulo pri!)4lero e Ia Circular Unica NO 10 de 2001.

CARMENI9(CESPEDES DE VERGEL
de la DiVi46n de Nuevas Creaciones

I anterior requerimiento fue notificado porfijaciOn en lista, do fecha S(2Lm

CONCEPTO TECNICO No. 3153 EXAMINADOR TECNICO

C6i90 No. 202044