Supplementary Material

Diels-Alder Adducts of Morphinan-6,8-dienes and their Transformations

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1. ABBREVIATIONS

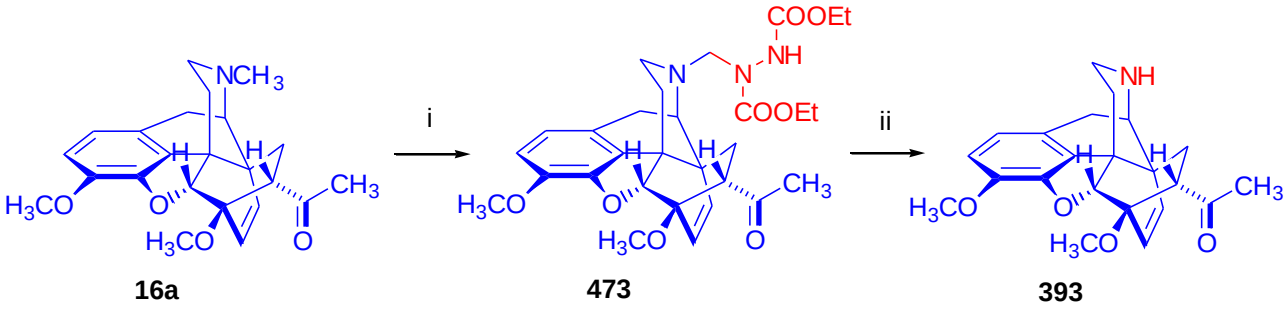
Compound, Term, Acronym	Comp.	Name, Synonyms
6,14-amidoHap	**251**	6,14-amido heroin hapten
14-amidoMorHap	**255**	14-amido morphine hapten
14-amidoHerHap	**256**	14-amido heroin hapten
Banyu compound-24 (C-24)	**-**	(2*R*)-1-(phenylmethyl)-*N*-(3-spiro[1*H*-2-benzofuran-3,4'-piperidine]-1'-ylpropyl) pyrrolidine-2-carboxamide; CAS RN: [475150-69-7]
BBB	**-**	blood brain barrier
benzyne	**-**	aryne; higly reactive species derived from an aromatic ring by removing two substituents
BHT	**-**	2,6-di-*tert*-butyl-4-methylphenol, 2,6-di-*tert*-butyl-*p*-cresol, CAS RN: [128-37-0]
Boc	**-**	*tert*-butoxycarbonyl group
BPN	**96**	buprenorphine, CAS RN: [52485-79-7]
[^{11}C]BPN	**460b**	[^{11}C]buprenorphine, [6-*O*-methyl-^{11}C]buprenorphine
BrCN	**-**	cyanogen bromide, CAS RN: [506-68-3]
BU08028	**101**	(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*S*)-17-cyclopropylmethyl-α-(1,1-dimethylpropyl)-4,5α-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol, CAS RN: [1333904-22-5]
BU127	**396g**	N^{17}-cyclopropyl-20*S*-phenyl-dihydronororvinol; (5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*S*)-17-(cyclopropylmethyl)-4,5α-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-α-phenyl-6,14-ethenomorphinan-7-methanol; CAS RN: [1417783-62-0]
BU128	-	(5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*R*)-17-(cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-7-methyl-α-phenyl-6,14-ethenomorphinan-7-methanol CAS RN: [1417783-82-4]
BU10112	**-**	(1'*R*,5α,6R,7R,14α)-1'-(3-methylphenyl-1'-(4,5α-epoxy-7,8-dihydro-3-hydroxy-6-methoxy-7β-methyl-17-cyclopropylmethyl-6,14-ethenomorphinan-7-yl)-methan-1'-ol, CAS RN: [1417783-97-1]
BU10119	**102**	(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*R*)-17-(cyclopropylmethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-7-methyl-α-phenyl-6,14-ethenomorphinan-7-methanol CAS RN: [1417783-94-8]
BU10120	**103**	(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*R*)-17-(cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-7-methyl-α-(4-fluorophenyl)-6,14-ethenomorphinan-7-methanol CAS RN: [1417783-90-4]
Caf		carfentanil, 1-(2-phenylethyl)-4-[(1-oxopropyl)phenylamino]-4-piperidine carboxylic acid methyl ester, R-31,833, 4-carboxymethyl-fentanyl, CAS RN: [59708-52-09]
[^{11}C]Caf		[^{11}C]carfentanil, CAS: [122402-12-4]
Cbz	**-**	benzyloxycarbonyl group, Z
CNS	**-**	central nervous system
COSY	**-**	correlated spectroscopy, two-dimensional shift correlations via spin-spin coupling
CPCO	**-**	cyclopropylcarbonyl group
CPM	**-**	cyclopropylmethyl group
Cypre	**-**	cyprenorphine, RX285M, 17-cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-α,α-dimethyl-6,14-ethenomorphinan-7-methanol, CAS RN: [44065-22-8]
DA reaction	**-**	Diels-Alder reaction
DAMGO	**-**	Tyr-*D*-Ala-Gly-(*N*Me)Phe-Gly-ol
DBU	**-**	1,8-diazabicyclo[5.4.0]undec-7-ene, CAS RN: [6674-22-2]
DBN	**-**	1,5-diazabicyclo[4.3.0]non-5-ene, CAS RN: [3001-72-7]
DEAD	**-**	diethyl azodicarboxylate, CAS RN: [1972-28-7]
DHE		dihydroetorphine, CAS RN: [14357-76-7]
DIBAL	**-**	diisobutylaluminum hydride CAS RN: [1191-15-7]
dihydrothevinone	**104**	4,5α-epoxy-18,19-dihydro-17-methyl-3,6-dimethoxy-7α-acetyl-6,14-ethenomorphinan, CAS RN: [16196-82-0]

Compound, Term, Acronym	Comp.	Name, Synonyms
DIPEA	**-**	ethyldiisopropylamine, *N*,*N*-diisopropylamine, Hünig's base
9,10-DMA	**201**	9,10-dimethylantracene, CAS RN: [781-43-1]
DMAD	**-**	dimethyl acetylenedicarboxylate, CAS RN: [762-42-5]
DMAP	**-**	*N*,*N*-dimethylpyridin-4-amine, 4-dimethylaminopyridine, CAS RN: [1122-58-3]
DMF	**-**	*N*,*N*-dimethylformamide
DMP	**-**	Des-Martin periodane
DMSO	**-**	dimethyl sulfoxide, $(CH_3)_2SO$, CAS RN: [67-68-5]
δ-OR	**-**	δ-opioid receptor
DPDPE	**-**	[*D*-Pen^2,*D*-Pen^5]enkephalin, CAS RN: [88373-73-3]
DPN	**95**	diprenorphine, Revivon, M5050, CAS RN: [14357-78-9]
[^{11}C]DPN	**460a**	[^{11}C]diprenorphine, [6-*O*-methyl-^{11}C]diprenorphine
ED_{50}	-	effective dose
EDG substituent	**-**	electron donating substituent
EDTA	-	ethylenediaminetetracetic acid, CAS RN: [60-00-4]
ε-OR	**-**	ε-opioid receptor
EP	**-**	ethyl propiolate, ethyl acetylenecarboxylate, CAS RN: [623-47-2]
EWG substituent	**-**	electron withdrawing substituent
FAO	**300**	fumaramidooripavine
[^{18}F]FcyF	**-**	[^{18}F]cyclofoxy, 6-deoxy-6*β*-[^{18}F]fluoro-naltrexone, CAS RN: [103223-58-1]
FE-BPN		6-*O*-(2-fluoroethyl)-6-*O*-desmethyl-buprenorphine
FE-DPN		6-*O*-(2-fluoroethyl)-6-*O*-desmethyl-diprenor phine, CAS RN: [1391522-66-9]
FE-PEO		6-*O*-(2-fluoroethyl)-6-*O*-desmethyl-phenethyl-orvinol
[^{18}F]FE-BPN	**471**	6-*O*-(2-[^{18}F]fluoroethyl)-6-*O*-desmethyl-buprenorphine
[^{18}F]FE-DPN	**468**	6-*O*-(2-[^{18}F]fluoroethyl)-6-*O*-desmethyl-diprenorphine
[^{18}F]FP-*nor*BPN	**467**	N^{17}-(3-[^{18}F]fluoropropyl)-*nor*-buprenorphine
[^{18}F]FP-*nor*DPN	**466b**	N^{17}-(3-[^{18}F]fluoropropyl)-*nor*-diprenorphine
[^{18}F]FE-PEO	**470**	6-*O*-(2-[^{18}F]fluoroethyl)-6-*O*-desmethyl-phenethyl-orvinol
[^{18}F]FEOTos	**-**	2-[^{18}F]fluoroethyl tosylate
β -FNA	**-**	β -funaltrexamine
GPI	**-**	Guinea-pig ileum
GR103545	**-**	[(3,4-dichlorophenyl)acetyl]-(3*R*)-(1-pyrrolidinylmethyl)-1-piperazine carboxylic acid methyl ester
[^{11}C]GR103545	**-**	[(3,4-dichlorophenyl)acetyl]-(3*R*)-(1-pyrrolidinyl methyl)-1-piperazine carboxylic acid methyl-^{11}C ester
HATU	**-**	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate, CAS RN: [148893-10-1]
HDA reaction		hetero Diels-Alder reaction
HMPA		hexamethylphosphoramide, CAS RN: [680-31-9]
HOMO		highest occupied molecular orbital
IA-DPN		iodoallyl-diprenorphine
9-I-9BBN	**-**	9-iodo-9-borabicyclo[3.3.1]nonane, CAS RN: [70145-42-5]
IDA	**-**	iminodiacetic acid, CAS RN: [142-73-4]
***iso*-BPN**	**-**	3-*O*-methyl-6-*O*-desmethyl-buprenorphine
JDTic	**-**	1,2,3,4-tetrahydro-7-hydroxy-*N*-[(1*S*)-1-[[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-(3*R*)-isoquinolinecarboxamide, CAS RN: [361444-66-8]
κ-OR	**-**	κ-opioid receptor
K_i	**-**	inhibition constant
KHMDS	**-**	potassium bis(trimethylsilyl)amide, CAS RN: [40949-94-8]
LDA	**-**	lithium diisopropylamide, $LiN[CH(CH_3)_2]$, CAS RN: [4111-54-0]
LH	**-**	Luteinizing hormone
L-Selectride	**-**	Lithium-tri-*sec*-butylborohydride
LTA	**-**	lead tetraacetate, CAS RN: [546-67-8]
LUMO	**-**	lowest unoccupied molecular orbital

Compound, Term, Acronym	Comp.	Name, Synonyms
M99	**97**	etorphine, Immobilon, CAS RN: [14521-96-1]
M320	**-**	isopentyl orvinol
***m*CPBA**	**-**	3-chloroperbenzoic acid, CAS RN: [937-14-4]
16α-Me-Cypre	**-**	16α-methylcyprenorphine, 17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-α,α,16α-trimethyl-6,14-etheno morphinan-7-methanol, CAS RN: [40994-80-7]
[^{11}C]MeNTI	**-**	*N*1′-[^{11}C]methyl-naltrindole
μ-OR	**-**	μ-opioid receptor
MORV	**-**	20-methylorvinol
MP	**-**	methyl propiolate, methyl acetylenecarboxylate, CAS RN: [922-67-8]
MTBD	**-**	1-Methyl-2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-a]pyrimidine CAS RN: [84030-20-6]
MVD	**-**	mouse vas deferens
Naloxone	**-**	N^{17}-allyl-14-hydroxy-dihydromorphinone, N^{17}-Allyl-noroxymorphone, CAS RN: [465-65-6]
Naltrexone	**-**	N^{17}-cyclopropylmethyl-14-hydroxy-dihydromorphinone, N^{17}-cyclopropylmethyl-noroxymorphone, NTX, CAS RN: [16590-41-3]
NBS	**-**	*N*-bromosuccinimide
NCS	**-**	*N*-chlorosuccinimide
NCA	**-**	no-carrier-added
nepenthone	**16b**	7α-benzoyl-4,5α-epoxy-17-methyl-3,6-dimethoxy-6,14-ethenomorphinan CAS RN: [464-66-4]
nociceptine	**-**	Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln
NOP	**-**	nociceptin/orphanin receptor
***nor*BNI**	**-**	norbinaltorphimine, CAS:[105618-26-6]
NTI	**-**	naltrexone-indole, naltrindole, CAS RN: [111555-53-4]
ORs	**-**	opioid receptors
PEO		20*R*-phenethyl-orvinol, CAS RN: [14521-98-3]
[^{11}C]PEO		[6-*O*-methyl-^{11}C]phenethyl-orvinol
PET	**-**	positron emission tomography
PTAD	**-**	4-phenyl-4*H*-1,2,4-triazoline-3,5-dione
RIA	**-**	radioimmunoassay
RVD	**-**	rat vas deferens
SLL-004C	**422c**	*p*-amino-nepenthone, CAS RN: [2084834-43-3]
SLL-020ACP	**390a**	N^{17}-cyclopropylmethyl-nornepenthone, CAS RN: [188340-60-5]
SLL-039	**434**	*N*-cyclopropylmethyl-7α-[4′-(*N*′-benzoyl)amino-phenyl]-6,14-endoethano-tetrahydronorthebaine
SLL-1206	**437j**	*N*-cyclopropylmethyl-7α-[3′-(p-methoxybenzyl)amino-phenyl]-6,14-endoethano-tetrahydronorthebaine
SLL-603	**430**	N^{17}-cyclopropymethyl-7α-methyl-dihydronornepenthone CAS RN: [2246405-55-8]]
SPECT	**-**	single-photon emission computed tomography
TAN-821	**333**	17-(cyclopropylmethyl)-4,5-α-epoxy-3,6-dihydroxy-*N*-methyl-*N*-(2--phenylethyl)-6,14-ethenomorphinan-7-α-carboxamide, CAS RN: [214064-71-8]
TAN-1014	**335**	(4b*S*,8*R*,8a*R*,9a*S*,13a*R*,13b*R*)-7-(cyclopropylmethyl)-5,6,7,8,9,9a,11,12-octahydro-1-hydroxy-11-(2-phenylethyl)-10*H*,13b*H*,8a,13a-etheno-4,8-methanobenzofuro [3,2-h]pyrido[3,4-g][1,3]benzoxazine-10-one, CAS RN: [757232-46-5]
TBDMS	**-**	*tert*-butyldimethylsilyl group
TBTU	**-**	O-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate CAS RN: [125700-67-6]
TDBPN	**461b**	3-*O*-trityl-6-*O*-desmethyl-buprenorphine, CAS RN: [157891-93-5]
TDDPN	**461a**	3-*O*-trityl-6-*O*-desmethyl-diprenorphine, CAS RN: [157891-92-4], «*Luthra-precursor*», TDDPN was the first product of the company *ABX advanced biochemical compounds* Biomedizinische Forschungsreagenzien GmbH, Radeberg in 1997

Compound, Term, Acronym	Comp.	Name, Synonyms
TE-TDPEO	**469**	6-*O*-(2-tosyloxyethyl)-6-*O*-desmethyl-3-*O*-trityl-phenethyl-orvinol, CAS RN: [1614258-10-4]
TDPEO	**463**	3-*O*-trityl-6-*O*-desmethyl-phenethyl-orvionol, CAS RN: [1187551-69-4]
thevinone	**16a**	4,5*α*-epoxy-17-methyl-3,6-dimethoxy-7*α*-acetyl-6,14-ethenomorphinan, CAS RN: [15358-22-2]
thienorphine	**100**	(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*R*)-17-cyclopropylmethyl-4,5*α*-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-*α*-methyl-*α*-[2-(2-thienyl)ethyl]-6,14-ethenomorphinan-7-methanol, CAS RN: [852100-94-8]
TMS	**-**	trimethylsily group
TMEDA	**-**	tetramethylethylenediamine, CAS RN: [110-18-9]
Tos	**-**	tosyl group
Tr	**-**	trityl group; triphenylmethyl group
Troc	**-**	2,2,2-trichloroethoxycarbonyl group
TT	**-**	tetanus oxide
U69,593	**-**	(+)-*N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-pyrrolidin-1-yl-1-oxaspiro[4.5]decan-8-yl]acetamide, CAS RN: [96744-75-1]

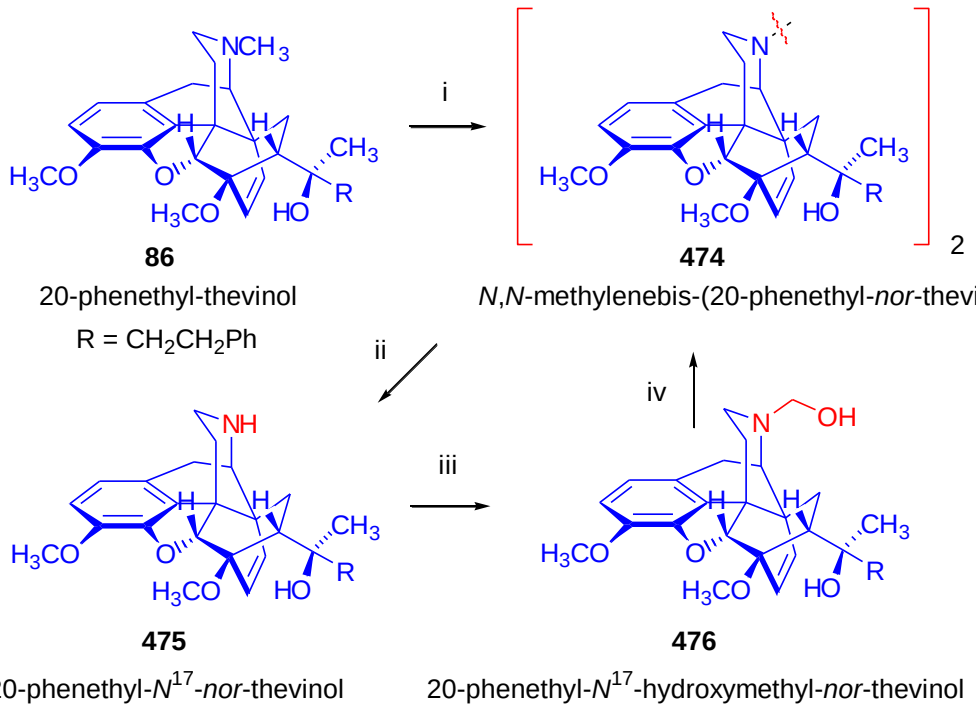
2. SUPPLEMENTARY FIGURES (to section 2.3.6.)



16a **473** **393**

2.1. Figure S1 Synthesis of ^{17}N-northevinone

Reagents and conditions: (i): diethyl azodicarboxylate, benzene, reflux, 7 h; (ii): pyridinium chloride, EtOH, room temperature, 8 h



86
20-phenethyl-thevinol
R = CH_2CH_2Ph

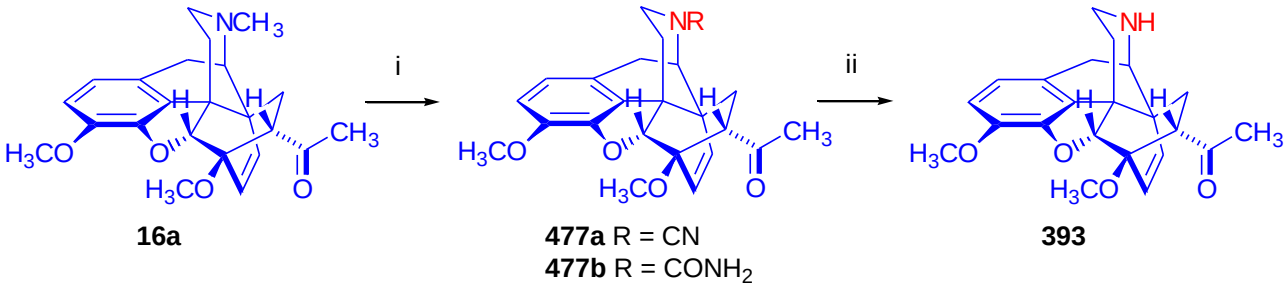
474
N,*N*-methylenebis-(20-phenethyl-*nor*-thevinol)

475
20-phenethyl-N^{17}-*nor*-thevinol

476
20-phenethyl-N^{17}-hydroxymethyl-*nor*-thevinol

2.2. Figure S2 Reaction of 20-phenethyl-thevinol with diethyl azodicarboxylate

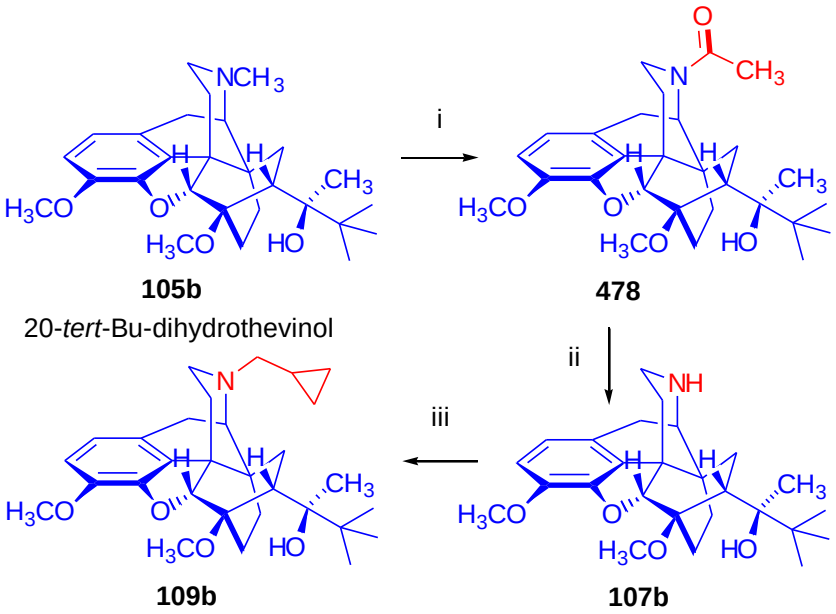
Reagents and conditions: (i): diethyl azodicarboxylate, acetone, reflux 1h; (ii): 6% acetic acid, Δ; (iii): 30% aqueous formaldehyde, EtOH, 45 °C, 30 min; (iv): **A**. EtOH, Δ, or **B**. **476**, EtOH, Δ



16a **477a** R = CN **393**
477b R = $CONH_2$

2.3. Figure S3 N^{17}-demethylation of thevinone using the *von* Braun method

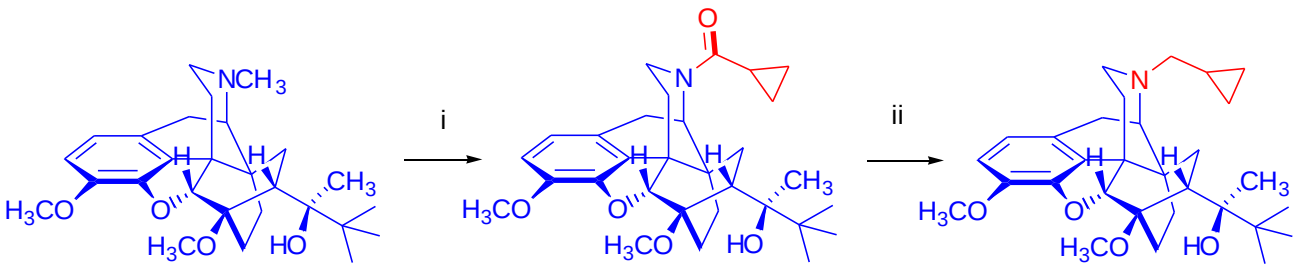
Reagents and conditions: (i): BrCN, $CHCl_3$, reflux, 12 h; (ii): 2 M HCl, reflux, 2 h



105b **478**
20-*tert*-Bu-dihydrothevinol
109b **107b**

2.4. Figure S4 The Hudlický route for preparation of buprenorphine methylether

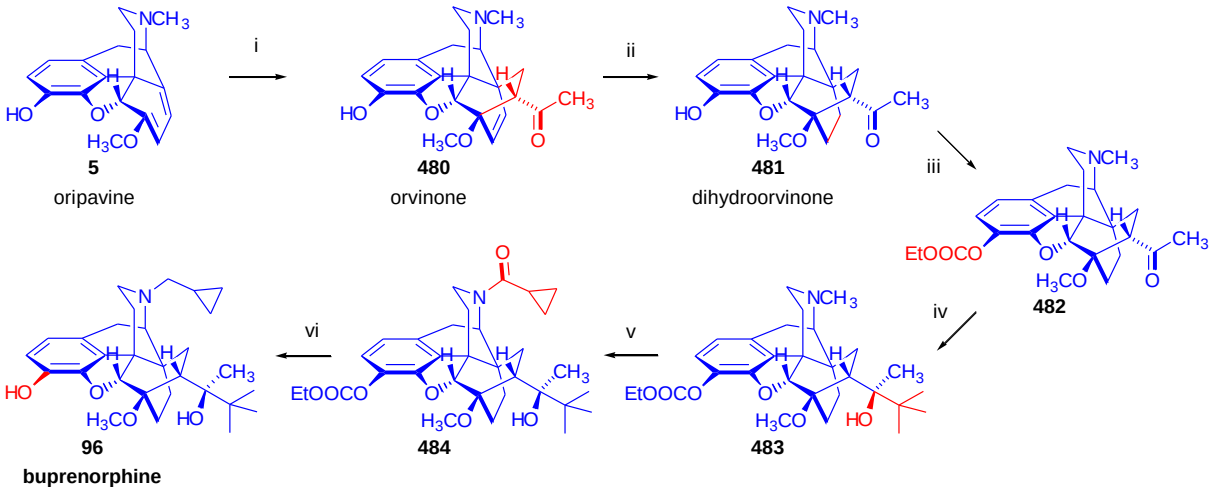
Reagents and conditions: (i): $Pd(OAc)_2$, $Cu(OAc)_2$, AcO, dioxane, 80 °C, air or O, 23 h, 95 %; (ii): Schwartz reagent: chlorodicycliopentadienylhydrozyrconium (Cp_2ZrHCl, 3 equiv.), THF, room temperature, 40 min, 90 %; (iii): cyclopropylmethyl bromide, $NaHCO_3$, *N*-methylpyrrolidine, 85 °C, 18 h, 88 %



105b **479** **109b**
20-*tert*-Bu-dihydrothevinol

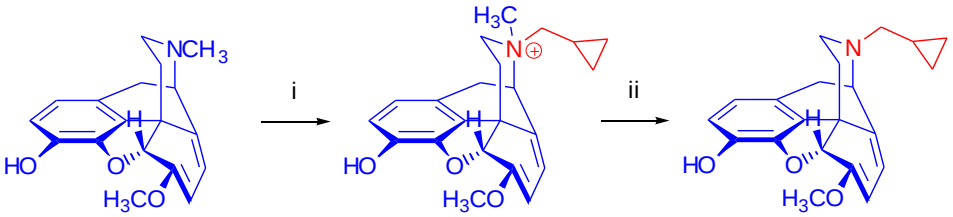
2.5. Figure S5 Synthesis of BPN methylether from 20-*tert*-butyl-dihydrothevinol using the *N*-demethylation/*N*-acylation reaction sequence

Reagents and conditions: (i): cyclopropanecarboxylic anhydride, $Pd(OAc)_2$, air or O_2, 100 °C, dioxane, 40-48 h, 90-95 %; (ii): LiAlH4, THF, 70 °C, 72 %, or Karstedt's catalyst, polymethylhydrosiloxane (PMHS), 87 %



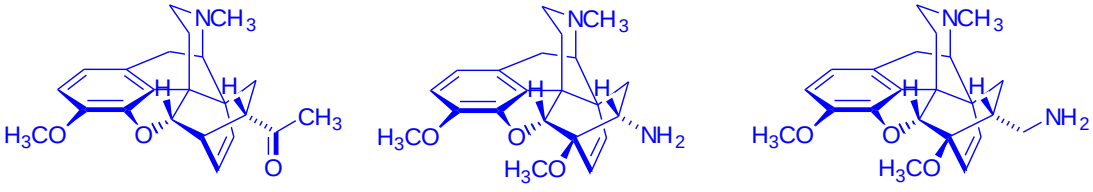
2.6. Figure S6 Synthesis of buprenorphine from oripavine

Reagents and conditions: (i): methyl vinyl ketone, toluene, 80 °C, 75%; (ii): H_2, 10% Pd-C, tartaric acid, water, atmospheric pressure, 16 h, 80 °C, 84%; (iii): EtCOOCl, Et_3N, toluene, 40 °C, 82%; (iv): tert-BuMgCl, cyclohexane, THF, toluene, room temperature, 71%; (v): cyclopropanecarboxylic anhydride, $Pd(OAc)_2$, $Cu(OAc)_2$, dioxane, O_2, 80 °C, 12 h, 80%; (vi): *bis*(2methoxyethoxy)aluminium hydride, THF, toluene, 80 °C, 30 min, 81%.



2.7. Figure S7 Synthesis of N^{17}-cyclopropylmethyl-nororipavine from oripavine

Reagents and conditions: (i): cyclopropylmethyl bromide, DMF, 80 °C, 94%; tert-dodecanethiol, EtONa, DMSO, 80 °C, 53%



2.8. Figure S8 Chemical structures of non-acid-sensitive 6,14-ethenomorphinans 3-*O*-demethylated with boron tribromide