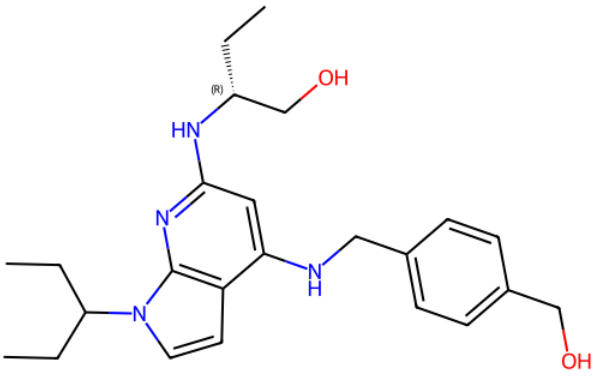
Astinova AI Platform — Retrosynthesis Report

Compound: **AST-NCE-001** — New Compound (C24H34N4O2, MW 410.56 Da) | 4,6-Diamino-7-azaindole (1H-pyrrolo[2,3-b]pyridine) — N1-(pentan-3-yl), C4-benzylamino, C6-amino-alcohol

Generated: 2026-07-22 16:56 | 28 routes returned | Best score: 0.9866 | Best route: 3 steps, 4/4 precursors in stock | Route policy: curated reaction templates

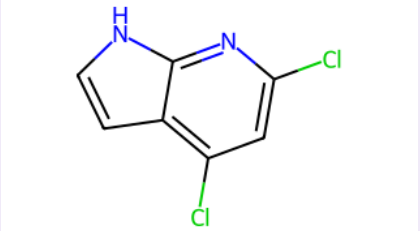
★ NEW COMPOUND — AST-NCE-001 | 1H-Pyrrolo[2,3-b]pyridine-4,6-diamine core | N1 = pentan-3-yl · C4 = 4-(hydroxymethyl)benzylamino · C6 = (2R)-1-hydroxybutan-2-ylamino ★



SMILES	CC[C@@H](NC1N=C2C(C=CN2C(CC)CC)=C(NCC2C=CC(CO)=CC=2)C=1)CO
Formula	C24H34N4O2
MW	410.56 Da
LogP	4.68
TPSA	82.3 Å²
HBD / HBA	4 / 6
RotBonds	11
Rings (aromatic)	3 (3)
Chiral centres	1
Fluorines	0 — no fluorine in this scaffold
Scaffold class	7-Azaindole (pyrrolo[2,3-b]pyridine) 4,6-diamine
Routes returned	28
Solved routes	17 / 28
Top score	0.9866
Best route steps	3
Precursors (in stock)	4 (4 in stock)

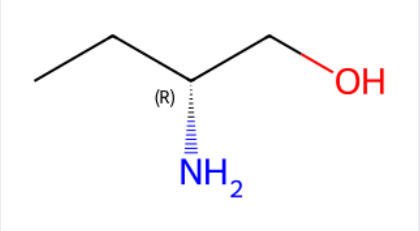
AST-NCE-001 ($C_{24}H_{34}N_4O_2$, MW 410.6 Da, 1 defined stereocentre) is a novel **4,6-diamino-1H-pyrrolo[2,3-b]pyridine** (7-azaindole) built around three points of diversity on a single bicyclic heteroaromatic core. **N1** carries a branched secondary alkyl group (**pentan-3-yl** / 1-ethylpropyl); **C6** (α to the pyridine N7, the most SNAr-activated ring position) bears a **(2R)-1-hydroxybutan-2-ylamino** group; **C4** (γ to N7, the second activated position, peri to the pyrrole ring) bears a **4-(hydroxymethyl)benzylamino** group. The retrosynthesis is dominated by two aromatic C–N bond disconnections back to a **4,6-dichloro-7-azaindole** platform, differentiated by the intrinsic SNAr reactivity gradient C6 > C4. Both exocyclic amines are anilino-type (conjugated into the electron-poor pyridine), so they are only weakly basic — a favourable feature for hERG and volume-of-distribution. Two primary –CH_2OH groups (one benzylic, one on the amino-alcohol) and the high rotatable-bond count are the main developability watch-points.

Fragment Analysis



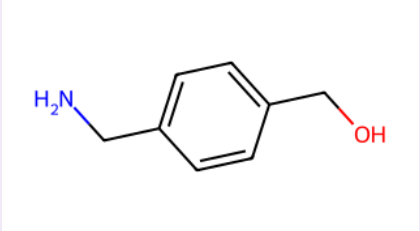
Fragment A 4,6-Dichloro-7-azaindole core + N1 group

4,6-Dichloro-1H-pyrrolo[2,3-b]pyridine (7-azaindole; PubChem CID 24729594, CAS 5912-18-5 — confirm with supplier). The two ring chlorides are the handles for the C4 and C6 amines. Install the **N1 pentan-3-yl** group **first** — either by **Mitsunobu** with **pentan-3-ol** (CAS 584-02-1; DIAD/PPh_3, THF) for a clean secondary alkylation, or by base-mediated N-alkylation with **3-bromopentane** (CAS 1809-10-5; Cs_2CO_3 or NaH, DMF). Doing N1 before the SNAr steps removes the acidic pyrrole N–H that would otherwise compete during amination.



Fragment B (2R)-2-Aminobutan-1-ol (C6 amine)

(R)-(−)-2-Amino-1-butanol (PubChem CID 2723856, **CAS 5856-63-3**) — an inexpensive chiral-pool amino alcohol that sets the sole stereocentre of the molecule with no external asymmetric step. It is coupled at **C6**, the ring position α to N7 and therefore the most SNAr-activated chloride, so C6 is functionalised **before** C4. The free primary –OH is far less nucleophilic than the amine and does not require protection for the C–N coupling.



Fragment C [4-(Hydroxymethyl)phenyl]methanamine (C4 amine)

4-(Aminomethyl)benzyl alcohol (PubChem CID 6496943, **CAS 39895-56-2**) — a commercial benzylamine building block installed at the less-activated **C4** chloride in the final C–N coupling. Because C4 is the harder SNAr position, a **Buchwald–Hartwig** Pd-catalysed amination is the more robust option here (thermal SNAr also works but needs higher temperature). The benzylic primary amine is the reactive nucleophile; the para $–CH_2OH$ is a spectator.

IP / ADME Notes

IP: the 1H-pyrrolo[2,3-b]pyridine (7-azaindole) is a well-worked, privileged kinase-hinge scaffold (e.g. the vemurafenib 7-azaindole class), so the *core* itself is not novel; freedom-to-operate here rests on the specific **4,6-diamino / N1-(pentan-3-yl)** substitution pattern. Run a dedicated FTO / substructure search on 4,6-diamino-1-(sec-alkyl)-pyrrolo[2,3-b]pyridines before nominating — no specific blocking patent is asserted in this report. **ADME**: MW 410.6, LogP 4.68 (upper end of Ro5), TPSA 82.3 Å², HBD 4 / HBA 6 — Lipinski-compliant but lipophilic. Rotatable bonds = 11 is high and, together with two primary $–CH_2OH$ groups, flags likely metabolic soft-spots (benzylic-alcohol oxidation / glucuronidation, N-dealkylation at N1 and the benzylamine). Both ring-conjugated amines are only weakly basic, so hERG and high-Vd liabilities are expected to be modest. Monitor CYP3A4 / 2C9 and aldehyde-oxidase (azaindole) early.

Key Retrosynthetic Disconnections

Bond / Disconnection	Forward Reaction	Key Reagents / Conditions
C4–N (aryl–$NHCH_2Ar$)	Buchwald–Hartwig amination (or forcing SNAr)	4-(aminomethyl)benzyl alcohol (1.2 eq) + $Pd_2(dba)_3$ (3 mol%) / BrettPhos or XPhos (6 mol%) / Cs_2CO_3 (2 eq), dioxane 100 °C, 16 h, N_2 — SNAr alternative: DIPEA (3 eq), NMP, 120–140 °C
C6–N (aryl–NHR, α to N7)	SNAr with primary amine (C6 most activated)	(R)-2-aminobutan-1-ol (1.5 eq) + DIPEA (3 eq), NMP or n-BuOH, 100–120 °C, 12–24 h (Buchwald–Hartwig is an equally valid alternative)
N1–C (pyrrole N–sec-alkyl)	Mitsunobu (preferred for sec-alcohol)	pentan-3-ol (1.2 eq) + DIAD (1.2 eq) / PPh_3 (1.2 eq), THF, 0 °C → RT, 12 h, N_2 — alternative: 3-bromopentane + Cs_2CO_3 (2 eq) or NaH (1.2 eq), DMF, 60–80 °C
Core 4,6-Cl_2	commercial building block / $POCl_3$ on 4,6-dihydroxy	4,6-dichloro-1H-pyrrolo[2,3-b]pyridine (CAS 5912-18-5); if built in-house, $POCl_3$ (3 eq) / DIPEA (4 eq), MeCN, 80 °C, 4 h on the 4,6-dioxo precursor

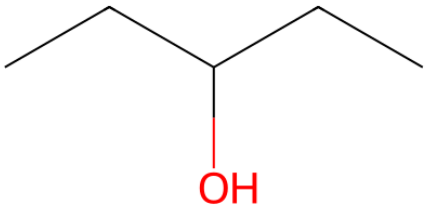
Representative Methodology References

Peer-reviewed precedent for each reaction **class**, retrieved from a scholarly literature database and independently **citation-verified** (title / author / year). These support the *transformation type* on related substrates — they are **not step-level provenance** for this exact molecule (that requires a reaction database: Reaxys / SciFinder / USPTO reactions). The N1-alkylation step is intentionally uncited — no clean substrate-class precedent surfaced, and it is textbook Mitsunobu / base-mediated azaindole N–H alkylation.

Reaction class	Verified reference (DOI)	Relevance
Buchwald–Hartwig C–N amination — C4 (aryl-Br + benzylamine)	Surasani *et al.*, *Beilstein J. Org. Chem.* **2012**, *8*, 2004–2018. doi:10.3762/bjoc.8.227	Pd-catalysed C–N bond formation on **4-bromo-7-azaindoles** with amines — near-identical bond and substrate class to the C4 step.
	Merugu *et al.*, *Molecules* **2024**, *29*, 4743. doi:10.3390/molecules29194743	Cross-coupling routes to **1H-pyrrolo[2,3-b]pyridin-4-amines** — the exact C4-amino azaindole motif.
	Mérour *et al.*, *Molecules* **2014**, *19*, 19935–19979. doi:10.3390/molecules191219935	Review of the azaindole framework in kinase-inhibitor design (scaffold context / FTO landscape).
SNAr amination — C6 (aryl-F/Cl, α to pyridine N7)	Hamper *et al.*, *Synlett* **2007**, 2257–2261. doi:10.1055/s-2007-985574	Direct uncatalysed amination of **2-chloropyridine** — the α-to-nitrogen position, directly analogous to displacing the C6 halide here.
	Lu *et al.*, *Chem. Sci.* **2022**, *13*, 12681–12695. doi:10.1039/d2sc04041g	Quantitative SNAr relative-reactivity model — a tool to rank the C6-vs-C4 halide reactivity a priori.

Route 1 / 3 · State score: 0.9866 · Reactions: 3 · Precursors: 4 · In stock: 4

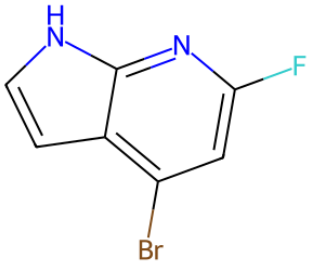
Reactants → Step 1



✔ In stock

C5H12O MW 88.2

CCC(O)CC



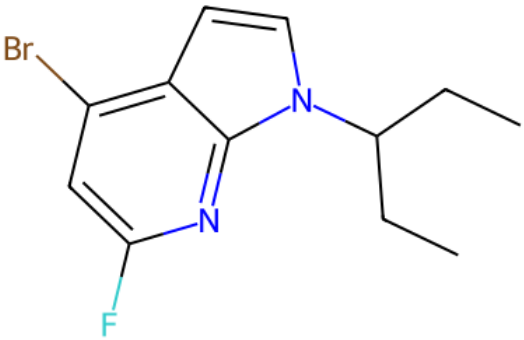
✔ In stock

C7H4BrFN2 MW 215.0

Fc1cc(Br)c2cc[nH]c2n1

Step 1: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 1 product)

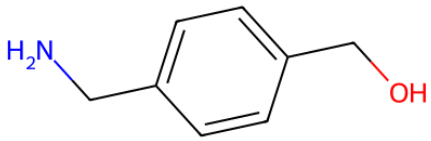
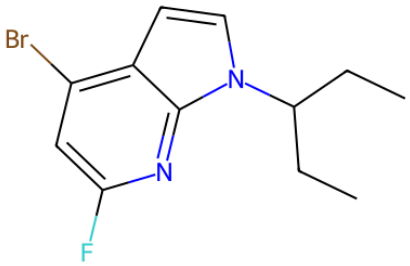
Formula: C12H14BrFN2 | MW: 285.2 Da

CCC(CC)n1ccc2c(Br)cc(F)nc21

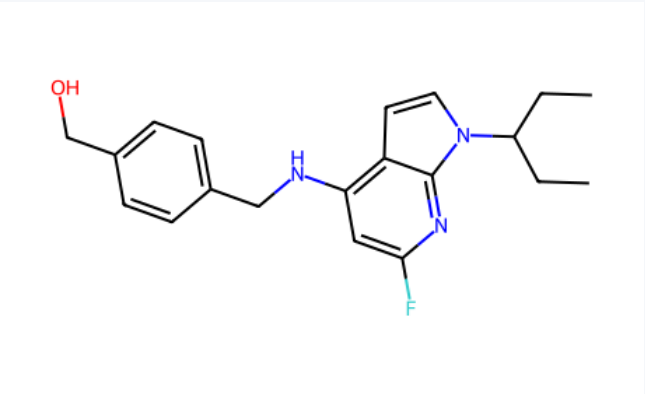
Route policy: curated reaction templates

Reaction template: [#7;a:4]:[c:5]:[n;H0;D3;+0:6](:[c:7])-[CH;D3;+0:1](-[C:2])-[C:3]>>O-[CH;D3;+0:1](-[C:2])-[C:3].[#7;a:4]:[c:5]…

Reactants → Step 2

	
✔ In stock	⚠ Needs synthesis
C8H11NO MW 137.2	C12H14BrFN2 MW 285.2
`NCc1ccc(CO)cc1`	`CCC(CC)n1ccc2c(Br)cc(F)nc21`

Step 2: Buchwald-Hartwig C–N Coupling | $Pd_2(dba)_3$ (3 mol%), XPhos or BINAP (6 mol%), Cs_2CO_3 (2 eq) | Toluene or dioxane, 100 °C, 16 h, N_2



Intermediate (Step 2 product)

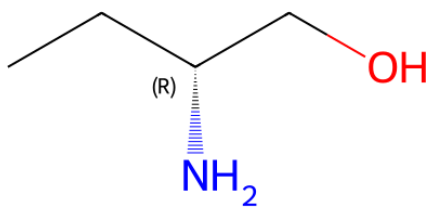
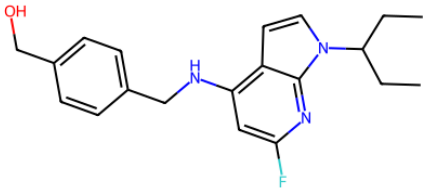
Formula: C20H24FN3O | MW: 341.4 Da

`CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(F)nc21`

Route policy: curated reaction templates

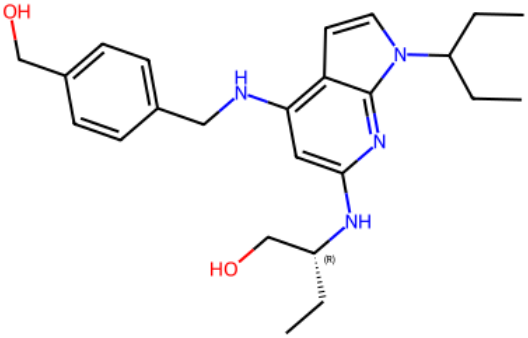
`Reaction template: [C:4]-[NH;D2;+0:5]-[c;H0;D3;+0:1](:[c:2]):[c:3]>>Br-[c;H0;D3;+0:1](:[c:2]):[c:3].[C:4]-[NH2;D1;+0:5]`

Reactants → Step 3

	
✔ In stock	⚠ Needs synthesis
C4H11NO MW 89.1	C20H24FN3O MW 341.4
CC[C@@H](N)CO	CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(F)nc21

Step 3: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



TARGET — AST-NCE-001

Formula: C24H34N4O2 | MW: 410.6 Da

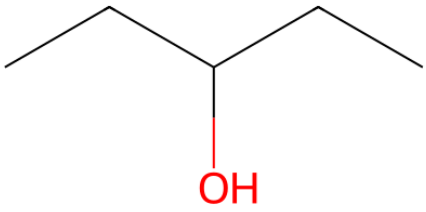
CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(N[C@H](CC)CO)nc21

Route policy: curated reaction templates

Reaction template: [#7;a:2]:[c;H0;D3;+0:1](:[c:3])-[NH;D2;+0:5]-[C:4]>>F-[c;H0;D3;+0:1](:[#7;a:2]):[c:3].[C:4]-[NH2;D1;+0:5]

Route 2 / 3 · State score: 0.9866 · Reactions: 3 · Precursors: 4 · In stock: 4

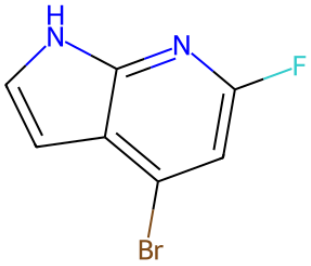
Reactants → Step 1



✔ In stock

C5H12O MW 88.2

CCC(O)CC



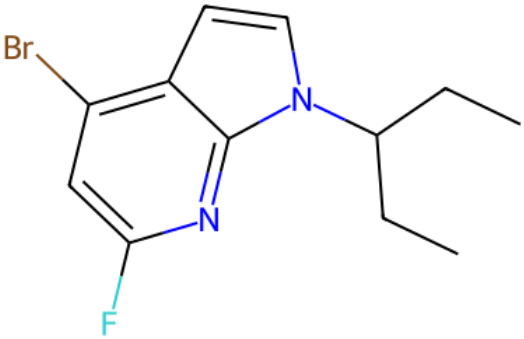
✔ In stock

C7H4BrFN2 MW 215.0

Fc1cc(Br)c2cc[nH]c2n1

Step 1: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 1 product)

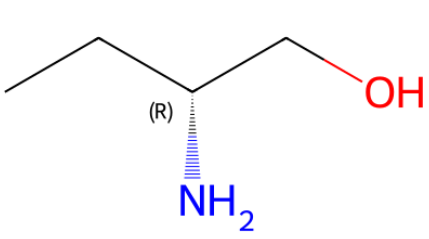
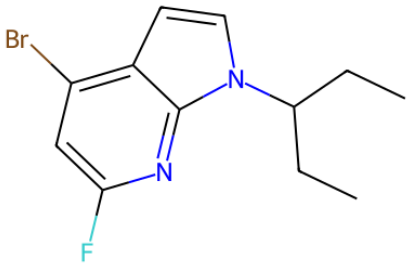
Formula: C12H14BrFN2 | MW: 285.2 Da

CCC(CC)n1ccc2c(Br)cc(F)nc21

Route policy: curated reaction templates

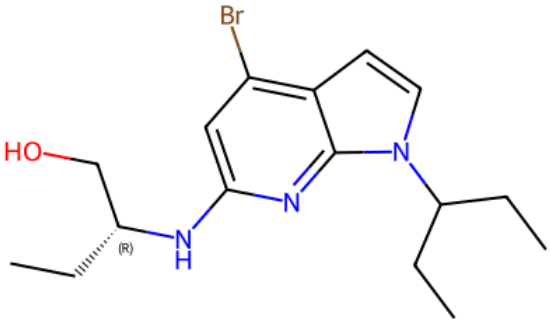
Reaction template: [#7;a:4]:[c:5]:[n;H0;D3;+0:6](:[c:7])-[CH;D3;+0:1](-[C:2])-[C:3]>>O-[CH;D3;+0:1](-[C:2])-[C:3].[#7;a:4]:[c:5]…

Reactants → Step 2

	
✔ In stock	⚠ Needs synthesis
C4H11NO MW 89.1	C12H14BrFN2 MW 285.2
`CC[C@@H](N)CO`	`CCC(CC)n1ccc2c(Br)cc(F)nc21`

Step 2: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 2 product)

Formula: C16H24BrN3O | MW: 354.3 Da

`CCC(CC)n1ccc2c(Br)cc(N[C@H](CC)CO)nc21`

Route policy: curated reaction templates

```
Reaction template: [#7;a:2]:[c;H0;D3;+0:1](:[c:3])-
[NH;D2;+0:5]-[C:4]>>F-[c;H0;D3;+0:1](:[#7;a:2]):[c:
3].[C:4]-[NH2;D1;+0:5]
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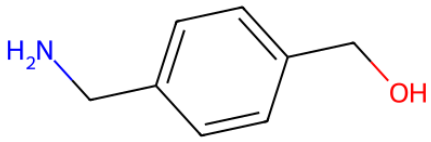
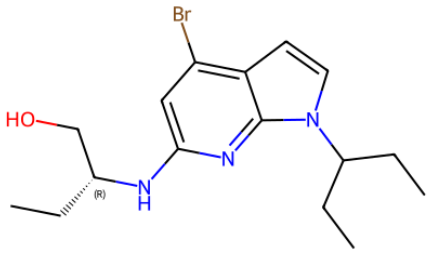
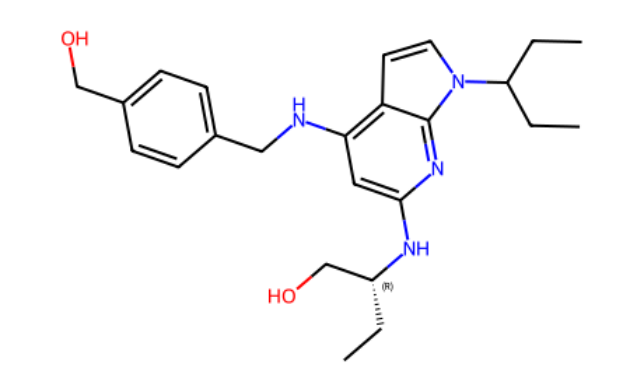
Reactants → Step 3

	
✔ In stock	⚠ Needs synthesis
C8H11NO MW 137.2	C16H24BrN3O MW 354.3
NCc1ccc(CO)cc1	CCC(CC)n1ccc2c(Br)cc(N[C@H](CC)CO)nc21

Step 3: Buchwald-Hartwig C–N Coupling	$Pd_2(dba)_3$ (3 mol%), XPhos or BINAP (6 mol%), Cs_2CO_3 (2 eq)	Toluene or dioxane, 100 °C, 16 h, N_2



TARGET — AST-NCE-001

Formula: C24H34N4O2 | MW: 410.6 Da

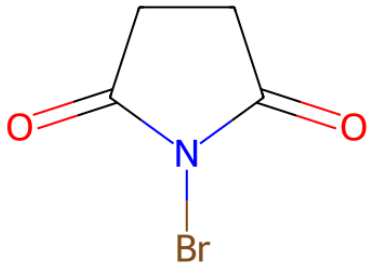
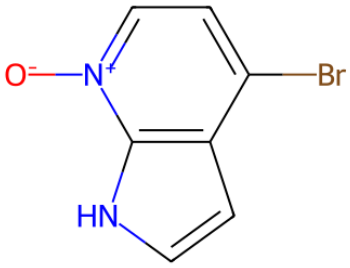
CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(N[C@H](CC)CO)nc21

Route policy: curated reaction templates

Reaction template: [C:4]-[NH;D2;+0:5]-[c;H0;D3;+0:1](:[c:2]):[c:3]>>Br-[c;H0;D3;+0:1](:[c:2]):[c:3].[C:4]-[NH2;D1;+0:5]

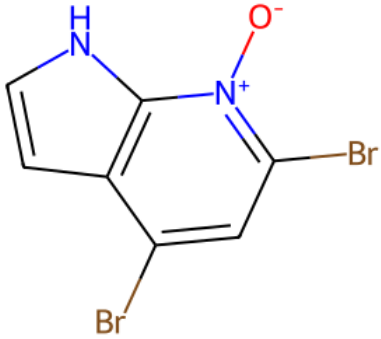
Route 3 / 3 · State score: 0.9634 · Reactions: 5 · Precursors: 5 · In stock: 5

Reactants → Step 1

	
✔ In stock	✔ In stock
C4H4BrNO2 MW 178.0	C7H5BrN2O MW 213.0
O=C1CCC(=O)N1Br	[O-][n+]1ccc(Br)c2cc[nH]c21

Step 1: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 1 product)

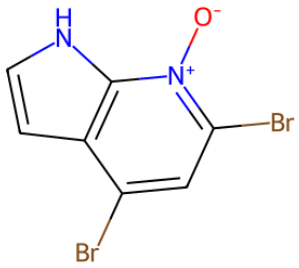
Formula: C7H4Br2N2O | MW: 291.9 Da

[O-][n+]1c(Br)cc(Br)c2cc[nH]c21

Route policy: curated reaction templates

Reaction template: [#7;a:2]:[c;H0;D3;+0:3](-[Br;H0;D1;+0:1]):[c:4]>>O=C1-C-C-C(=O)-N-1-[Br;H0;D1;+0:1].[#7;a:2]:[cH;D2;+0:3]:[c:…

Reactants → Step 2



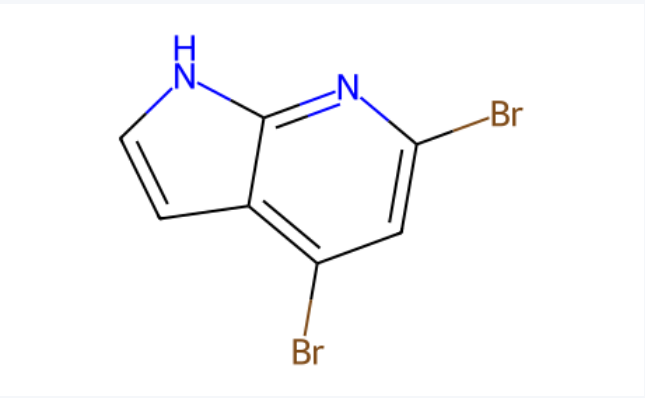
⚠ **Needs synthesis**

C7H4Br2N2O MW 291.9

```
[O-][n+]1c(Br)cc(Br)c2cc[nH]c21
```

Step 2: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 2 product)

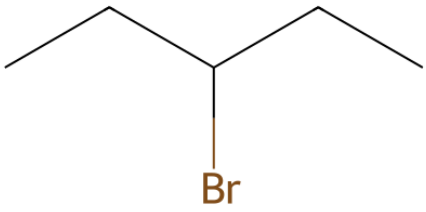
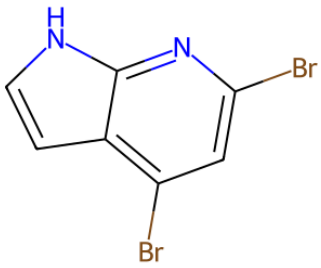
Formula: C7H4Br2N2 | MW: 275.9 Da

```
Brc1cc(Br)c2cc[nH]c2n1
```

Route policy: curated reaction templates

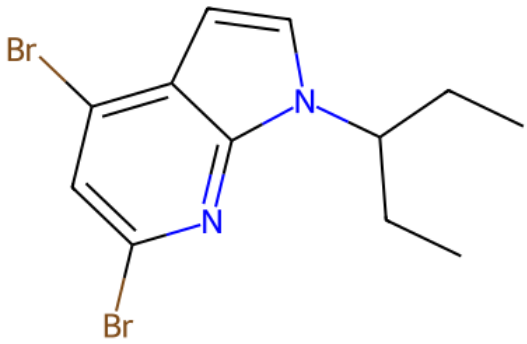
```
Reaction template: [c:2]:[n;H0;D2;+0:1]:[c:3]>>[O-]
-[n+;H0;D3:1](:[c:2]):[c:3]
```

Reactants → Step 3

	
✔ In stock	⚠ Needs synthesis
C5H11Br MW 151.0	C7H4Br2N2 MW 275.9
`CCC(Br)CC`	`Brc1cc(Br)c2cc[nH]c2n1`

Step 3: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



Intermediate (Step 3 product)

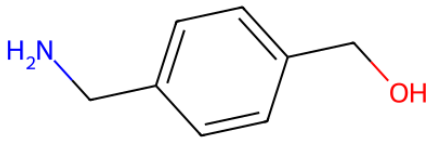
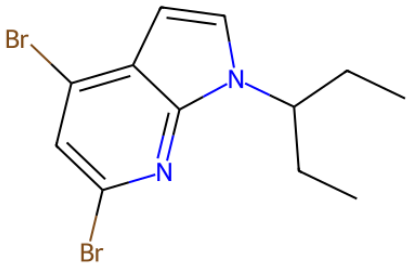
Formula: C12H14Br2N2 | MW: 346.1 Da

`CCC(CC)n1ccc2c(Br)cc(Br)nc21`

Route policy: curated reaction templates

```
Reaction template: [#7;a:4]:[c:5]:[n;H0;D3;+0:6](:[
c:7])-[CH;D3;+0:1](-[C:2])-[C:3]>>Br-[CH;D3;+0:1](-
[C:2])-[C:3].[#7;a:4]:[c:5…
```

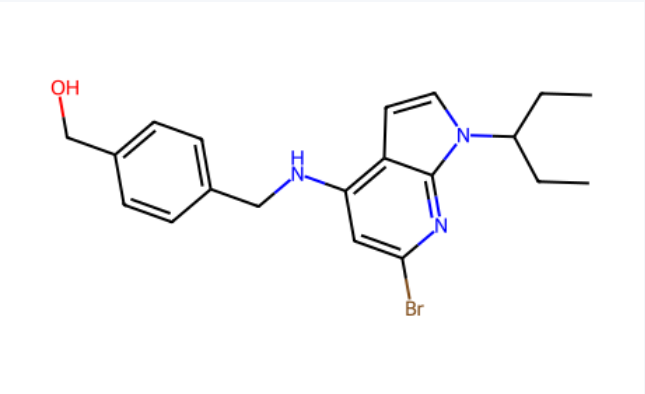
Reactants → Step 4

	
✔ In stock	⚠ Needs synthesis
C8H11NO MW 137.2	C12H14Br2N2 MW 346.1
`NCc1ccc(CO)cc1`	`CCC(CC)n1ccc2c(Br)cc(Br)nc21`

Step 4: Buchwald-Hartwig C–N Coupling

$Pd_2(dba)_3$ (3 mol%), XPhos or BINAP (6 mol%), Cs_2CO_3 (2 eq)

Toluene or dioxane, 100 °C, 16 h, N_2



Intermediate (Step 4 product)

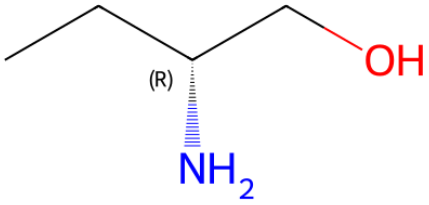
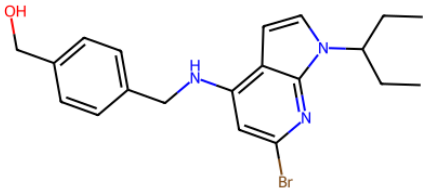
Formula: C20H24BrN3O | MW: 402.3 Da

`CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(Br)nc21`

Route policy: curated reaction templates

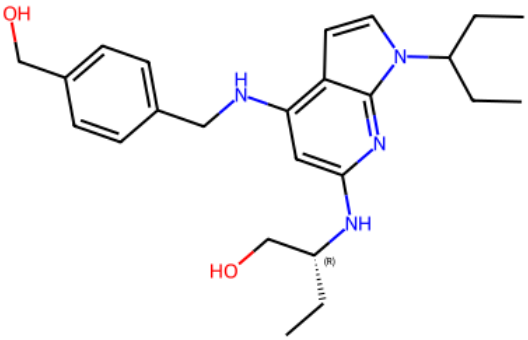
```
Reaction template: [C:4]-[NH;D2;+0:5]-[c;H0;D3;+0:1
](:[c:2]):[c:3]>>Br-[c;H0;D3;+0:1](:[c:2]):[c:3].[C
:4]-[NH2;D1;+0:5]
```

Reactants → Step 5

	
✔ In stock	⚠ Needs synthesis
C4H11NO MW 89.1	C20H24BrN3O MW 402.3
CC[C@@H](N)CO	CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(Br)nc21

Step 5: Reaction (template-defined)

Not assigned — reaction template SMARTS does not match a high-confidence rule



TARGET — AST-NCE-001

Formula: C24H34N4O2 | MW: 410.6 Da

CCC(CC)n1ccc2c(NCc3ccc(CO)cc3)cc(N[C@H](CC)CO)nc21

Route policy: curated reaction templates

Reaction template: [#7;a:2]:[c;H0;D3;+0:1](:[c:3])-[NH;D2;+0:5]-[C:4]>>Br-[c;H0;D3;+0:1](:[#7;a:2]):[c:3].[C:4]-[NH2;D1;+0:5]

Synthesis Notes & Disclaimers

• Routes generated by the Astinova AI Platform retrosynthesis engine over a curated reaction-template knowledge base (20.5M-compound building-block stock; novel-compound search budget). 28 candidate routes returned (17 fully solved). Top state score 0.9866; best route uses 3 reactions and 4/4 in-stock precursors. The platform's route trees are the machine proposal; the hand-curated fragment and disconnection analysis above is the recommended synthetic plan.

• Regiochemical logic: on a 4,6-dihalo-7-azaindole the C6 halide (α to the pyridine N7) is the more electrophilic SNAr site; C4 (γ to N7, peri to the electron-rich pyrrole) is slower and is best closed by Buchwald–Hartwig catalysis. The two top-scoring 3-step routes (state score 0.9866) exploit this by using a **differentiated 4-bromo-6-fluoro-7-azaindole** platform: the C6-fluoride is the ideal SNAr leaving group for the (R)-2-aminobutanol, while the C4-bromide is the ideal oxidative-addition handle for the Pd-catalysed benzylamine coupling — orthogonal handles that keep the two aminations cleanly separable and let them run in either order. The all-SNAr **4,6-dichloro** platform (verified commercial, CAS 5912-18-5) is the simpler fall-back. In every case, install the N1 pentan-3-yl group before either amination so the pyrrole N–H cannot compete. Neither exocyclic amine needs its primary –OH protected for the C–N couplings, though the amino-alcohol OH can be TBS-masked / TBAF-removed if a cleaner Buchwald is wanted. Confirm C6-vs-C4 selectivity by LC-MS / ^{1}H-NMR on the mono-aminated intermediate before carrying it forward.

• Reaction conditions in the green annotation boxes are populated from a curated named-reaction conditions table (SNAr, Buchwald, Mitsunobu, N-/O-alkylation, TBS / TBAF, Boc/TFA, reductive amination, etc.). Where the reaction template did not unambiguously match a named reaction, conditions are left blank rather than guessed (per the lab's 'blank > wrong' policy). The curated conditions in the disconnection table are the authoritative recommendation.

• Recommended sequence: (1) install the N1 pentan-3-yl group on 4,6-dichloro-7-azaindole (Mitsunobu with pentan-3-ol, or alkylation with 3-bromopentane) before any amination, so the acidic pyrrole N–H cannot compete; (2) SNAr the C6 chloride (α to N7, most activated) with (R)-2-aminobutan-1-ol; (3) close the less-activated C4 chloride with 4-(aminomethyl)benzyl alcohol under Buchwald–Hartwig catalysis (or forcing SNAr). Confirm C6-before-C4 selectivity on the mono-aminated intermediate by LC-MS / ^{1}H-NMR.

• Chemoselectivity: neither primary –CH_2OH (benzylic or amino-alcohol) needs protection for the C–N couplings — the amine is the far more nucleophilic partner. If a cleaner Pd amination is desired, TBS-mask the amino-alcohol OH (TBSCl / imidazole / DMF) and remove with TBAF (THF, RT) after the final coupling. The single stereocentre is carried in from chiral-pool (R)-2-amino-1-butanol, so no external asymmetric step or chiral resolution is required.

• AST-NCE-001 ADME quick-look: TPSA 82.3 Å², LogP 4.68, MW 410.56 Da, 1 chiral centre(s), RotBonds 11. Both exocyclic amines are ring-conjugated (weakly basic) → modest hERG / Vd risk. Watch benzylic-alcohol and amino-alcohol oxidation/glucuronidation and N-dealkylation at N1; screen CYP3A4 / 2C9 and aldehyde-oxidase (azaindole) early.

• Report generated: 2026-07-22 16:56 | Astinova AI Platform | Astinova curated reaction knowledge base + building-block stock.