Spirocyclic Piperidines in Drug Discovery

Key Points

- Giving rise to more potent and selective drugs
- Superior physiochemical properties including higher aqueous solubility
- Potential to create novel intellectual property spaces

Overview

Spirocyclic scaffolds in general, spirocyclic piperidines in particular, have several advantages over sp^2-carbon rich, flat structures. Their 3-D trajectory offers more points of contact with the protein target of interest and can give rise to more potent and selective drugs. The sp^3-carbon rich molecules are also blessed with superior physiochemical properties such as higher aqueous solubility. Finally, unexplored new spirocyclic architectures can create novel intellectual property spaces. The success of Novartis' allosteric SHP2 inhibitors underscores the utility of spirocyclic scaffolds. Their applications in medicinal chemistry are destined to grow rapidly, especially since many of them are now commercially available.

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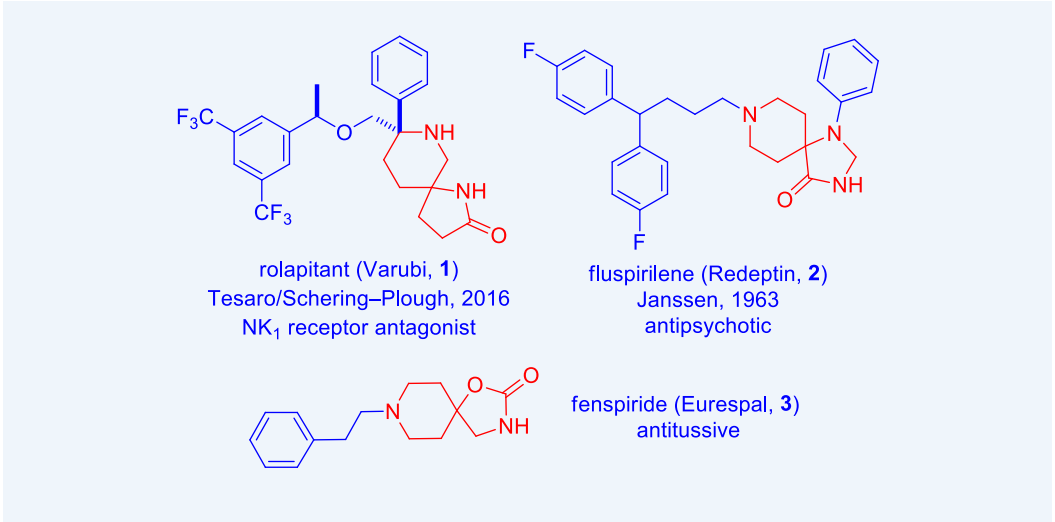
Spirocycles have made appearance in drugs as both core structures and peripheries of the molecules. They are advantageous in several aspects. First and foremost, spirocyclic scaffolds are inherently three-dimensional and can project functionalities in all three dimensions to interact more extensively with the protein target of interest and lower off-target effects. In addition, they are sp^3-carbon rich with high fraction of saturated carbon (Fsp^3, defined as equation 1) and correlated with favorable physiochemical properties such as higher aqueous solubility.[1] Last but not the least, spirocycles often offer new chemical space to create novel intellectual properties.[2] Recently, spirocyclic piperidines have found impressive utility in Novartis' allosteric SHP2 inhibitors program (*vide infra*).

$$Fsp^3 = (\text{number of } sp^3\text{-hybridized carbon})/(\text{total carbon count}) \quad (1)$$

Spirocyclic Piperidine-containing Drugs

Only one spirocyclic piperidine-containing drug is currently on the market: Tesaro/Schering–Plough's NK_1 receptor antagonist rolapitant (Varubi, **1**). It was approved by the FDA in 2016, in combination with other antiemetic agents, for the prevention of delayed chemotherapy-induced nausea and vomiting (CINV) associated with initial and repeat courses of emetogenic cancer therapy.[3]

An old antipsychotic fluspirilene (Redeptin, **2**) also possesses a spirocyclic piperidine motif.[4] Fenspiride (Eurespal, **3**), an old antitussive with a spirocyclic piperidine fragment approved in Russia and France, was withdrawn from the market due to QT elongation-associated adverse effects such as torsades de pointes.[5]



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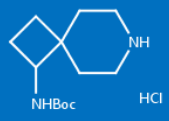

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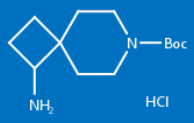

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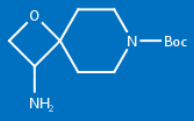

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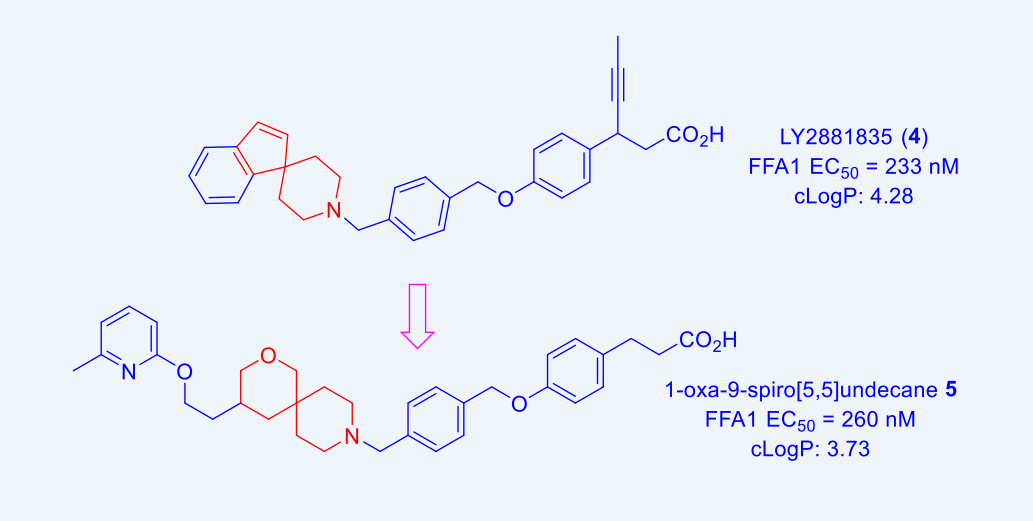
Spirocyclic Piperidines in Drug Discovery

The G-protein-coupled receptor 40 (GPR40) is also known as free fatty acid receptor 1 (FFA1). Since endogenous ligand binding to FFA1 regulates secretion of insulin in pancreatic β cells. FFA1 agonists have potential as a treatment of type 2 diabetes mellitus (T2DM). Lilly's FFA1 agonist LY2881835 (**4**), now in phase I clinical trials, has been shown to increase insulin and glucagon-like protein-1 (GLP-1) secretion in preclinical animal models.[6] It contains a spirocyclic piperidine substituent in addition to the 3-phenylpropanoic acid pharmacophore. Toxicity has been associated with high lipophilicity of earlier FFA1 agonists. Conspicuously, Takeda's greasy fasiglifam (TAK-875) failed phase III clinical trials in 2013 due to idiosyncratic liver toxicity. Krasavin et al. sought to lower the drugs' lipophilicity by adding an oxygen atom to Lilly's spirocyclic piperidine periphery. In due course, they arrived at 1-oxa-9-spiro[5.5]undecane **5**, which not only had similar efficacy to that of LY2881835 (**4**), it also demonstrated excellent aqueous solubility and Caco-2 permeability although it showed somewhat rapid metabolism in the presence of human liver microsomes (HLMs).[7]



The same spirocyclic piperidine core structure found utility in soluble epoxide hydrolase (sEH) inhibitors, which may serve as potential treatment of cardiovascular disease, inflammation, and pain. Employing two existing sEH inhibitors 2,8-diazaspiro[4.5]decane **6** and 1-oxa-4,9-diazaspiro[5.5]undecane **7**, Lukin and colleagues arrived at a polar spirocyclic scaffold 1-oxa-9-spiro[5.5]undecane-4-amine **8** in an attempt to improve the drug's bioavailability.[8]

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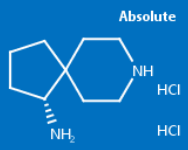

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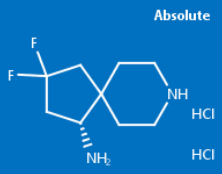

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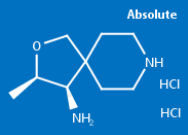

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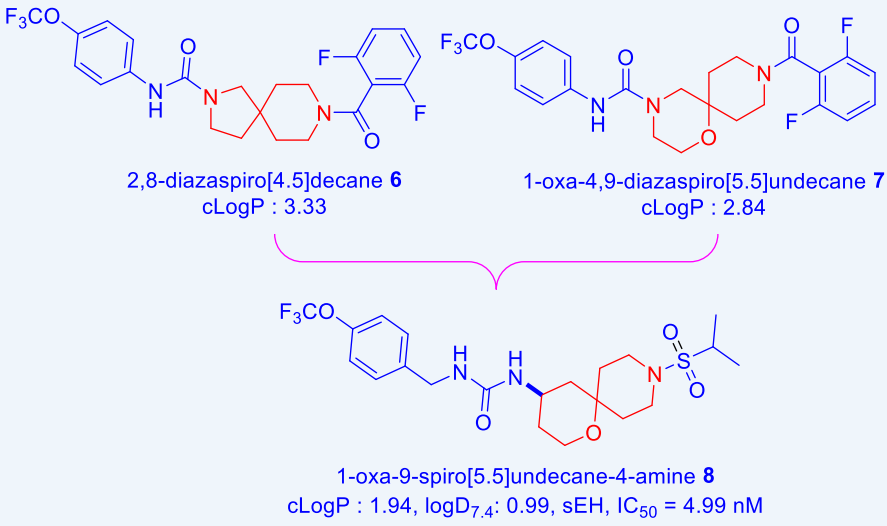
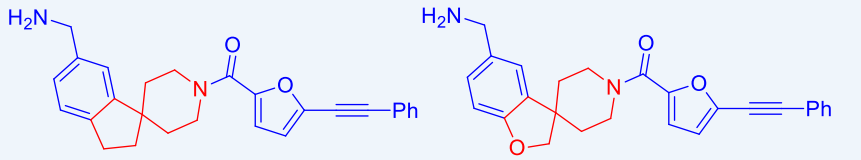
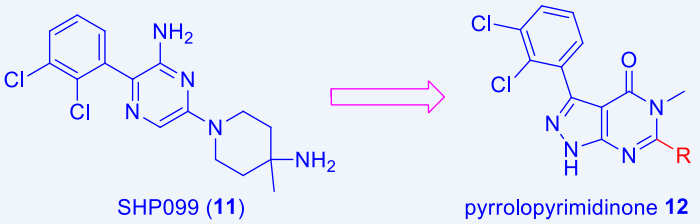


Certain spirocyclic piperidine amides served as potent, non-peptide inhibitors of human mast cell tryptase. Transforming spirocyclic piperidine-indane **9** to the more polar spirocyclic piperidine-dihydrobenzofuran **10** reduced lipophilicity by nearly one log as measured by cLogP (from 4.36 to 3.40) while still maintaining their potency for tryptase. Both **9** and **10** have excellent selectivity over trypsin (5,000× and 2,500×, respectively).[9]





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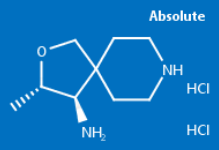

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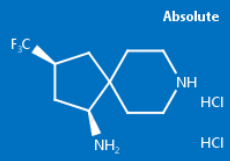

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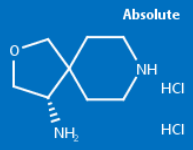

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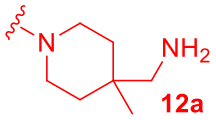
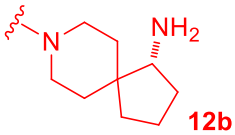
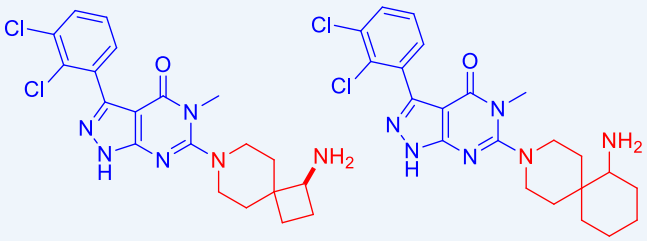
R	SHP2 IC_{50} (nM)	*p*-ERK IC_{50} (nM)	antiproliferation IC_{50} (μM)	cLogP/LipE	hERG IC_{50} (nM)
 **12a**	34	355	13.49	3.1/3.1	980
 **12b**	31	30	0.465	3.4/3.2	250
 **12c**	50	123	1.73	2.3/4.7	930
 **12d**	28	12	0.167	2.9/4.0	290

SHP2 (Src homology region 2-containing protein tyrosine phosphatase), an oncogenic, non-receptor protein tyrosine phosphatase and scaffold protein, operates downstream of multiple receptor tyrosine kinases as a positive transducer in numerous oncogenic signaling cascades (e.g., RAS-ERK, PI3K-AKT, JAK-STAT). Due to its significant potential in cancer treatment, SHP2 inhibitors have been pursued with rigor during the last two decades. Regrettably, earlier SHP2 inhibitors displayed low selectivity, cell permeability, and oral bioavailability, largely due to the highly solvated nature of the catalytic pocket and the polar substituents needed for enhanced binding potency. Novartis made a breakthrough with a new pyrazinyl class of SHP2 allosteric inhibitors as exemplified by SHP099 (**11**), which functions as a "molecular glue", stabilizing an inactive conformation of concurrent binding to the interface of the *N*-terminal SH2, *C*-terminal SH2, and protein tyrosine phosphatase domains. More importantly, SHP099 (**11**) is potent (SHP2 IC_{50} = 70 nM, *p*-ERK IC_{50} = 250 nM), selective, orally bioavailable, and efficacious in KYSE-520 tumor-bearing nude mouse model.[10a]

Improving upon SHP099 (**11**) via scaffold morphing resulted in many diverse series. Among them, pyrrolopyrimidinone **12** was explored with regard to the SAR of the piperidine-amine moiety. Extending **11**'s basic piperidine-amine by one methylene to displace the proposed water gave **12a** with slight improvement in biochemical assay and hERG selectivity. Yet, little improvement was observed for its *p*-ERK or KYSE proliferation cellular assays. Cyclization to spiro[4.5]-amine led to **12b** with no boost of biochemical potency but provided > 10-fold improvement in the *p*-ERK or KYSE proliferation cellular assays. Tetrahydrofuran-fused piperidine was designed to attenuate the basicity of the amine, the resulting **12c** lost some potency for all three assays but its lipophilicity efficiency (LipE) was improved since it had a one log reduction in lipophilicity. The expected lipophilicity and basicity offered by **12c** produced only a minor benefit to hERG inhibition. Finally, in an attempt to restore cellular potency by rebalancing lipophilicity, the spirocyclic ether was methylated and the resulting **12d** was bestowed with improved cellular potency in both *p*-ERK and KYSE proliferation cellular assays.[10b]

Although not thoroughly profiled, spirocyclic amines **12e** and **12f** were investigated for their biochemical activities by the Novartis team. Analogs **12e** with a spirocyclic pipridine-cyclobutylamine and **12f** with a spirocyclic pipridine-cyclohexylamine were both somewhat less potent than **12d**.[11]



pyrrolopyrimidinone **12e**
SHP2 IC_{50} = 44 nM

pyrrolopyrimidinone **12f**
SHP2 IC_{50} = 72 nM

Synthesis of Some Spirocyclic Piperidines

Since spirocyclic piperidines can be readily installed on to the core structure via S_NAr reactions to make **12b**–**12f**, only synthesis of the di-amines is summarized here.

Preparation of spirocyclic piperidine-cyclobutylamine **16** began with condensation between cyclobutanone **13** and the (*R*)-2-*t*-butyl-2-sulfinamide (**14**) with the aid of titanium isopropoxide. The resulting imine was reduced by lithium borohydride to afford (*S*)-spirocyclic amine **15** and its Boc protective group was readily removed using TFA in methylene chloride to produce **16**. The chiral auxiliary on **16** was then removed under alcoholic acidic conditions to expose the free spirocyclic bis-amine **17**.[11]

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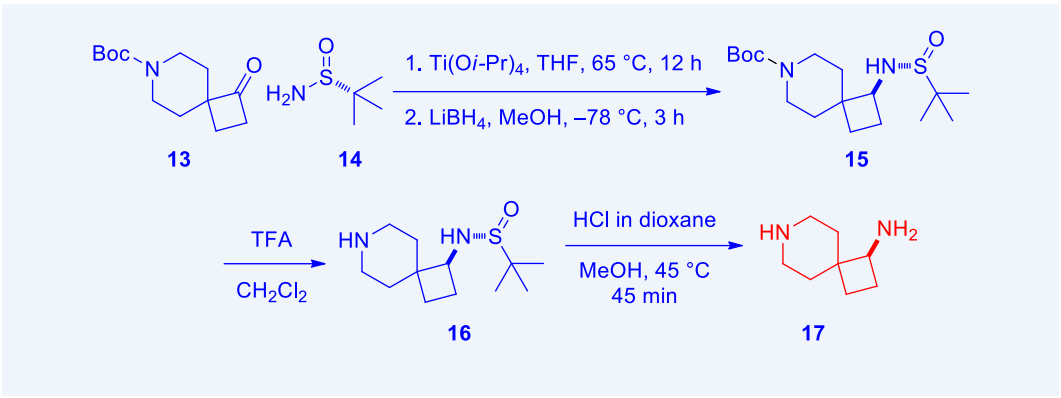
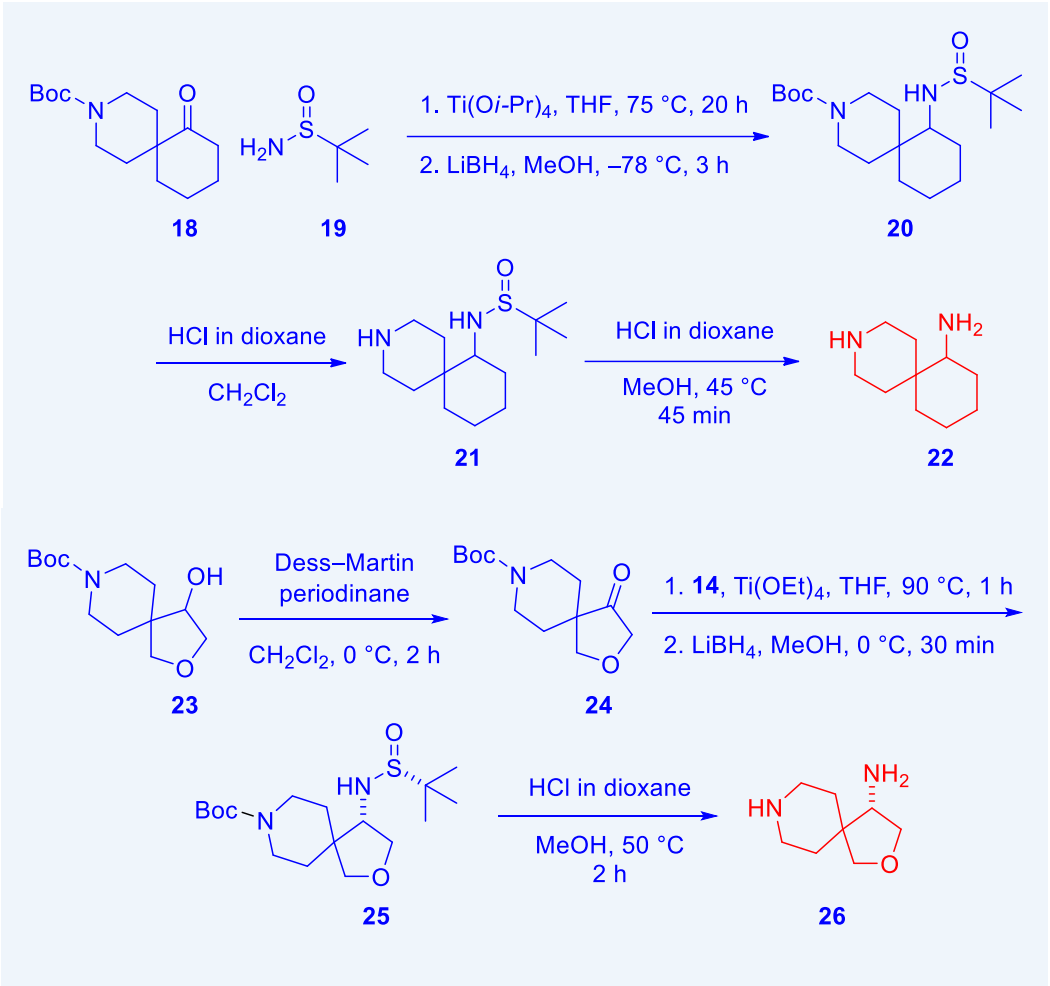


The spirocyclic piperidine fragment of **12f** is 3-azaspiro[5.5]undecan-7-amine (**22**). Since it is racemic, the auxiliary does not have to be chiral. Thus, condensation of cyclohexanone **18** with 2-*t*-butyl-2-sulfinamide (**19**) was followed by reduction to provide **20**. Removal of the Boc group on **20** gave **21**, which was treated with HCl in methanol to deliver **22**.[11]



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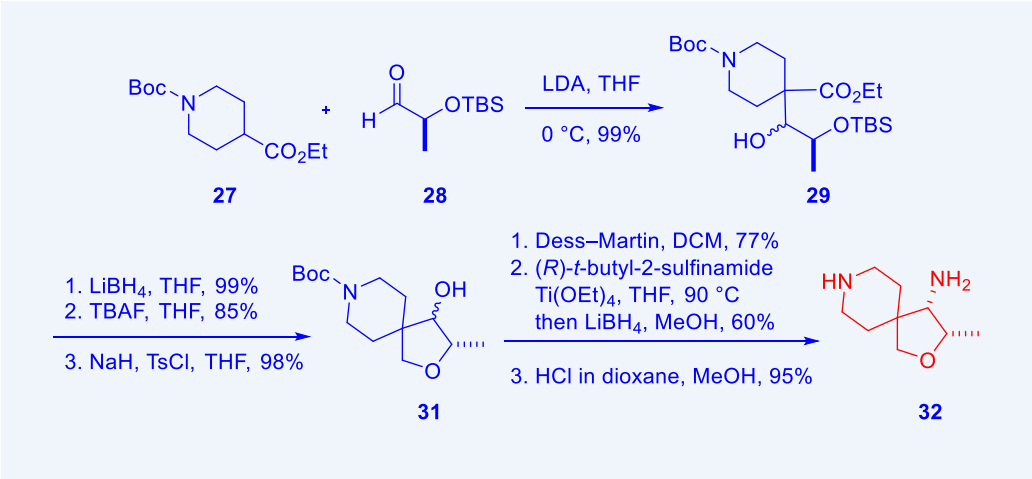
Preparation of the spirocyclic amine **26** on **12c** commenced with the Dess–Martin oxidation of alcohol **23** to afford ketone **24**. Installation of Ellman's chiral auxiliary (*R*)-2-*t*-butyl-2-sulfinamide (**14**) was followed by reduction of the resulting imine with $LiBH_4$ in methanol to give intermediate **25**. Acidic removal of the sulfonamide chiral auxiliary then led to spirocyclic bis-amine **26**.[11]

Synthesis of spirocyclic bis-amine **32** is relatively lengthy since there are two chiral centers. LDA lithiation of piperidine ester **27** was followed by quenching the resulting enolate with chiral aldehyde **28** to assemble adduct **29**. Although the hydroxyl group was generated without selectivity, it was inconsequential since it would be oxidized later on. Thus, compound **29** was reduced to give a diol. After removal of the silyl protective group, the new alcohol was converted to the corresponding tosylate and a concurrent S_N1 displacement reaction led to alcohol **31**. The Dess–Martin oxidation of **31** was followed by installation of the Ellman's chiral auxiliary (**14**), reduction, and removal of the sulfonamide to deliver **32**.[11]



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