Stereoselective synthesis from a process research perspective

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The process chemists' primary responsibility is to develop efficient and reproducible syntheses of pharmaceutically active compounds. This task is complicated when dealing with chiral molecules that often must be made as single isomers according to regulatory guidelines. The presence of any isomeric impurity in the final product, even in small amounts, is usually not acceptable. This requirement necessitates an exquisite understanding of the methods employed in the construction of chiral drugs. However, the chemistry available for this purpose is sometimes limited and often requires a significant amount of effort and creativity to be made both functional and consistent.

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▼ Louis Pasteur was one of the first scientists to propose the idea of chemical 'handedness', or that organic molecules can exist as mirror images of one another [1]. This theory arose from his study of racemic tartaric acid, which is composed of visibly discernible crystalline forms of enantiomeric D- and L-tartaric acid. From his initial theories have arisen the concepts of asymmetry and chirality, which we now recognize as integral parts of nature. This is evidenced by the presence of peptides, sugars and other natural products that exist as single enantiomers. Biodiscrimination of these materials often occurs at the molecular level during common biological processes mediated by receptors or enzymes, which themselves are chiral entities. This differentiation can result in vastly different effects in the body. Lehmann and coworkers have studied this phenomenon in detail over the years and have developed a system of nomenclature to describe the varying biological activity of two enantiomeric pairs [2]. Specifically, the isomer containing the desired activity is called the 'eutomer', whereas the other antipode is referred to as the 'distomer' and is either inactive or evokes a deleterious effect. Although this specific theory is beyond the scope of the current discussion there are numerous examples from the literature that support the general argument [3–6].

As a result of this often direct correlation between drug stereochemistry and biological activity, the governing bodies that regulate the approval of new medicines in the USA [7–9] and Europe [10] have issued specific rules pertaining to the development of stereoisomeric drugs. These guidelines require that the exact isomeric makeup of each new compound be quantified in an analytical fashion, and that toxicology and pharmacology data be obtained whenever possible for both racemic and enantiomerically pure compounds. These regulations are of particular concern to the pharmaceutical industry because chiral medicines now make up more than 40%, or US$133 billion worth, of annual drug sales, according to a recent report [11].

Those responsible for drug development past the discovery stage, namely process chemists, have had to formulate robust synthetic strategies that not only exhibit fine stereocontrol but can also be efficiently performed on scale. Although this task is invariably accomplished in a different fashion from one company to another, at Merck (Rahway, NJ, USA) it is believed that all types of organic transformations are available for use, as long as they work. In some cases, this requires the optimization of existing methodologies or even the invention of new ones. Often, this philosophy clashes with traditional process dictums, which can emphasize the need for usable amounts of drug over the importance of chemical development. The purpose of this review is to present examples of stereoselective synthesis that have occurred in the Department of Process Research at Merck in the past few years. Particular emphasis will be placed on individual asymmetric transformations, many

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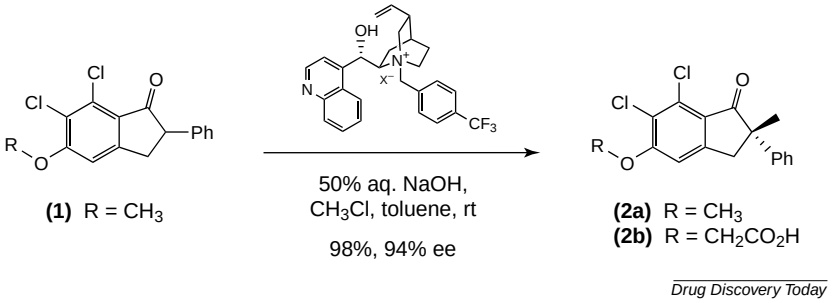


Figure 1. The synthesis of (*S*)-(+)-indacrinone [compound **(2b)**].

of which have been performed on the multi-kilogram scale. Also, where possible, the relationship between stereochemistry and biological activity will be addressed.

Synthesis of (*S*)-(+)-indacrinone

Asymmetric phase-transfer methylation

Indacrinone **(2b)** (Fig. 1) was developed at Merck in the late 1970s and early 1980s as a diuretic. According to this work, the (*R*)-(–)-enantiomer was found to have significant uricosuric activity, or the ability to cause uric acid secretion, when compared with the (*S*)-(+)-isomer **(2b)**, which was a potent diuretic [12]. Other studies have shown differences in the bioavailability [13] and ototoxicity [14] between these two antipodes. From a synthetic standpoint, although chemistry was available to obtain **(2b)** via classical resolution techniques [12], we endeavored to find an enantioselective route. After some effort, an efficient method was developed involving a *cinchona* alkaloid catalyzed asymmetric methylation of **(1)**, under phase-transfer conditions at room temperature, which gave **(2a)** in 98% yield and 94% enantiomeric excess (ee) [15]. At the time, this discovery represented a true invention, because the observed level of selectivity for this transformation was unprecedented in the literature. The intermediate methyl ether **(2a)** was then converted to (*S*)-(+)-indacrinone **(2b)** in three additional steps. In any event, both enantiomers of indacrinone could be accessed in high yield and enantiomeric purity via this process, which is reproducible on pilot plant scale (~75 kg) [16]. This chemistry has subsequently served as a foundation for the development of other asymmetric *cinchona* alkaloid catalyzed carbon–carbon-bond forming reactions [17–19].

Substance-P antagonists

Racemization–resolution, substrate-controlled reduction and hydrogenation

Mammalian tachykinin substance P is thought to have a causal role in various inflammatory conditions, such as rheumatoid arthritis [20], migraine [21], asthma [22] and inflammatory bowel disease, via interaction with the human neurokinin-1 receptor (hNK-1) [23]. More recently, it has been disclosed that substance P could be involved in the pathogenesis of depression [24]. As such, a program was undertaken in these laboratories, which resulted in the identification of several substance-P antagonists [25,26]. One of these derivatives, **(3)**, has been the subject of intensive research efforts because of its sub-nanomolar antagonism of the hNK-1 receptor (Fig. 2a). An ambitious synthetic route to this compound was developed involving two substrate-controlled reactions: (1) hydrogenation of the enol ether **(4)**, and (2) selective reduction of the lactone **(6)** followed by an *in situ* trap of the intermediate lactol with an aryl acid chloride to give **(5)**. Thus, all stereocenters found in **(3)** were to arise from enantiomerically pure **(6)**.

Though the morpholinone **(6)** was a known compound, available from (*S*)-(+)-4-fluoro-phenylglycine in two steps [27,28], the limited availability of this chiral amino acid necessitated a different approach. One route centered on the resolution of racemic (*rac*)-**(6)** [29], thereby avoiding the need for chiral starting materials (Fig. 2b). In practice, this compound was obtained in a 68% overall yield from the commercially available aldehyde **(7)** after a Strecker reaction [30], hydrolysis [31] and double alkylation of the resultant amino acid **(8)** with ethylene dibromide in the presence of diisopropyl ethylamine (iPr$_2$NEt). A partial resolution of this racemic material was accomplished using excess [(1*S*)-(*endo*,*anti*)]-(–)-3-bromocamphor-8-sulfonic acid [(–)-BCSA, 1.3 eq.] in *iso*-propyl acetate (IPAc) at room temperature, to give the salt (*S*)-**(6)**•(–)-BCSA in 27% yield and 88% ee. The enantiomeric purity of this material could be upgraded to 99% ee after a single recrystallization from dimethylformamide (DMF)–IPAc. Subsequently, it was discovered that the efficiency of this transformation could be improved through the addition of a small amount of trifluoroacetic acid during the resolution process, which gave the desired salt in 98% ee and 90% yield after 7–9 days. This unexpected increase in yield suggested a resolution–racemization process [32], whereby the undesired (*R*) enantiomer is funneled towards (*S*)-**(6)**, which in this case crystallizes from solution as a stable salt (Fig. 2b). This phenomenon relies upon the ready racemization of the substrate **(6)** in the presence of a chiral acid, and the differing solubility profile of the diastereomeric salts thus produced. Eventually, optimized conditions were discovered, wherein *rac*-**(6)** was

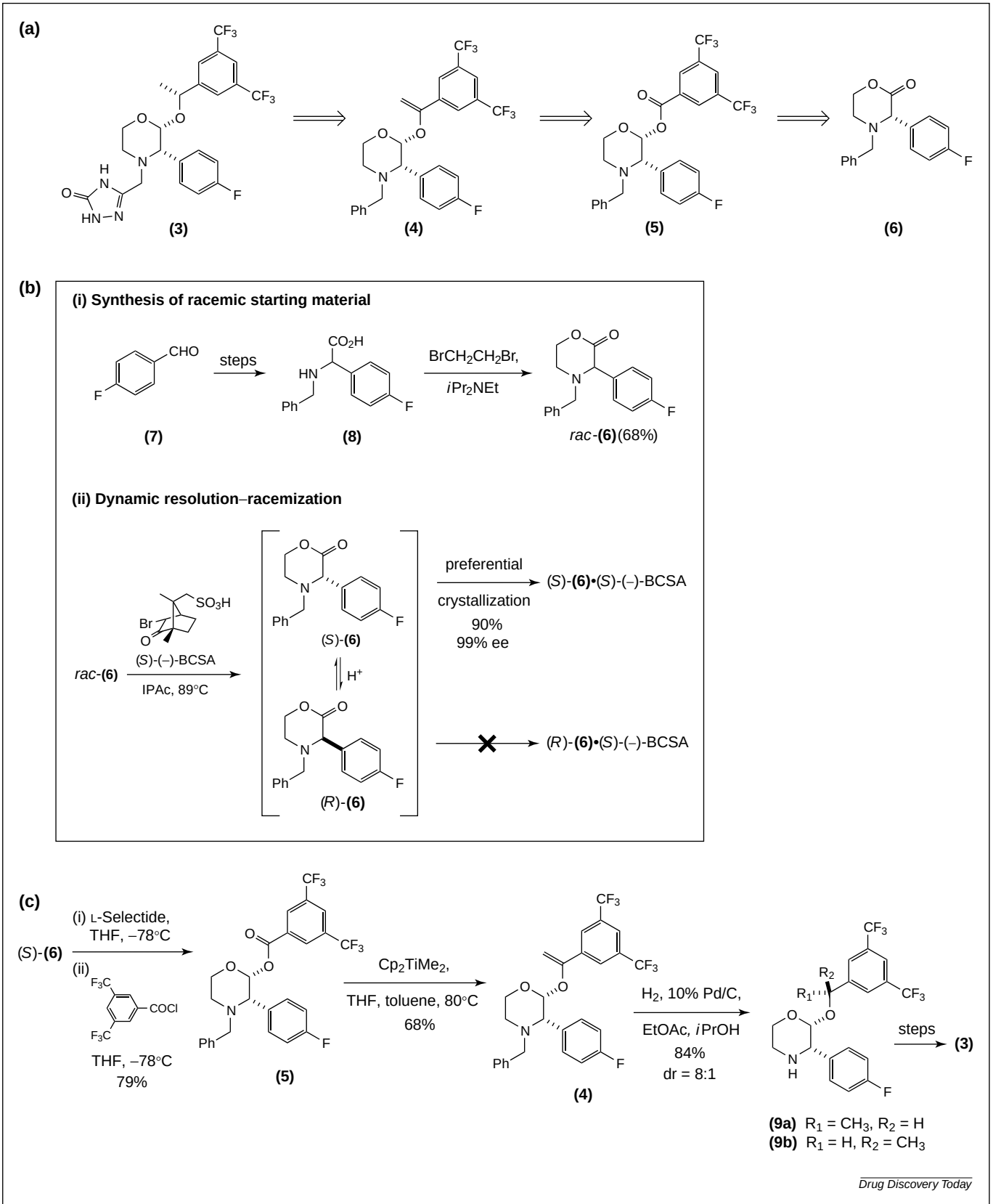


Figure 2. (a) Retrosynthesis of the substance-P antagonist, compound **(3)**. **(b)** Enantioselective resolution of the morpholine core structure, compound **(6)**. **(c)** Endgame synthesis of compound **(3)**.

seeded with a small amount of the enantiomerically enriched salt (*S*)-**(6)**•(–)-BCSA in IPAc, heated to 89°C, then treated with an excess (1.2 eq.) of (–)-BCSA to give (*S*)-**(6)**•(–)-BCSA in approximately 90% yield and 99% ee. The remaining 10% mass balance was accounted for in the mother liquor, which was found to contain a mixture (5:1) of (*R*)-**(6)** and (*S*)-**(6)**. Partitioning of the salt (*S*)-**(6)**•(–)-BCSA between toluene and aqueous ammonium hydroxide cleanly provided the free base (*S*)-**(6)** and enabled the recovery of the chiral acid (–)-BCSA resolving agent. This procedure has been performed on a multi-kilogram scale in our process plant.

With sufficient amounts of the morpholine core (*S*)-**(6)** in hand, the remaining steps towards compound **(3)** were performed (Fig. 2c). Thus, reduction of the lactone (*S*)-**(6)** with L-Selectride® (Aldrich Chemical Company, Milwaukee, WI, USA) (lithium tri-*sec*-butylborohydride) at –78°C, and *in situ* trapping of the intermediate lactol with the acid chloride of 3′,5′-bistrifluoromethyl benzoic acid gave **(5)** as a single anomer in 79% yield [25,26]. The choice of reducing reagent and reaction temperature in this step were found to be crucial for production of the desired *cis* stereochemistry. This is particularly important because related compounds having the *trans* orientation between the anomeric and α-aryl stereocenters have approximately 157-times less affinity for the hNK-1 receptor. Subsequently, the ester was methylenated [33,34] and hydrogenated [10% Pd/C, ethyl acetate (EtOAc)/*iso*-propyl alcohol (*i*PrOH)] to provide a mixture (8:1) of diastereomers favoring **(9a)** at the newly formed α-(*R*) methyl center, in 57% overall yield from **(5)**. The selectivity of this hydrogenation has since been improved to 13:1 through the use of palladium (Pd) on aluminum oxide (Al_2O_3) solid support.

Taken together, the preceding steps represent a short and efficient synthesis of the morpholine core of compound **(3)**. Known resolution–racemization methodology was used as a point of departure from which the remaining two stereocenters were elaborated. No other external sources of chirality were required beyond the initial acid (–)-BCSA, which is cheap and readily available. The desired diastereomer **(9a)** can be isolated from the crude hydrogenation mixture via simple recrystallization and has been carried on to the final product **(3)** in two additional steps. Interestingly, an analog of **(3)**, prepared from the undesired (*S*) diastereomer **(9b)**, exhibited 10-times less antagonist activity than did **(3)** in hNK-1 receptor binding assays [26].

Piperidine-containing substance-P inhibitors

Concomitant with the development and evaluation of compound **(3)**, two related hNK-1 receptor antagonists, **(10)** and **(11)**, were discovered, which contained piperidine core structures (Fig. 3a) [35–37]. Although these compounds were structurally similar to the morpholine derivatives discussed in the previous section, completely different strategies were required for their construction.

Diastereoselective ring-expansion

The *cis*-substituted piperidine **(10)** was synthesized using a known ring expansion reaction of a chiral pyrrolidinol as the key step [38]. However, this chemistry served only as a template for the task at hand. We needed to find a way to produce the desired *cis*-stereochemistry of **(10)**, along with the appropriate ether functionality. According to the literature, pyrrolidinols such as **(14)** (Fig. 3b) react with mesyl chloride to give 3-chloro-2-phenyl piperidines **(17)**, because of attack of chloride ion on the proposed aziridinium ion species **(15)** [39]. In this case, this was avoided by using acetate anion as an external nucleophile, which gave **(16)** as the exclusive product in 85% yield with 99% ee. None of the chlorinated derivative **(17)** was detected. The source of chirality in this sequence was the optically enriched epoxide **(13)** (94% ee), obtained via a Jacobsen epoxidation of **(12)** in a 75% yield [40]. In this way, either epoxide antipode was available, depending upon the enantiomeric catalyst employed in this reaction. The pyrrolidinol **(14)** was obtained in good yield (65%) after treatment of **(13)** with benzylamine in refluxing acetonitrile (CH_3CN).

The exact stereochemistry about the piperidine core of **(10)** is particularly important for potent binding to the hNK-1 receptor [35]. For example, inversion of the chiral secondary ether results in a 300-times loss in activity. Perhaps even more striking is the fact that the enantiomer of **(10)** is 350-times less active than the desired antipode. As such, both a diastereoselective and enantioselective synthesis of the final target was of the utmost importance.

Diastereoselective ring closing metathesis and reductive heck arylation

Synthesis of the spirocyclic piperidine **(11)** was accomplished via a novel diastereoselective, double-ring closing metathesis (RCM) reaction (Fig. 3c) [41] and a Heck reductive arylation [42]. The first part of this plan was based on chemistry previously developed at Merck wherein tetraenes, such as **(18)** (R = Me, *i*Pr, *i*Bu, Bn), were found to undergo selective cyclization, thus providing **(19)** in high yields (74–87%) and outstanding diastereomeric excess (de; 92%) [43]. Construction of a suitable tetraene **(22)** for this project was accomplished in three steps from the commercially available methyl ester of L-phenylglycine **(20)** without loss in optical purity. The subsequent double RCM reaction was performed using a Grubbs reuthenium catalyst to give a diastereomeric mixture (2.3:1) favoring **(23)** in 86% yield

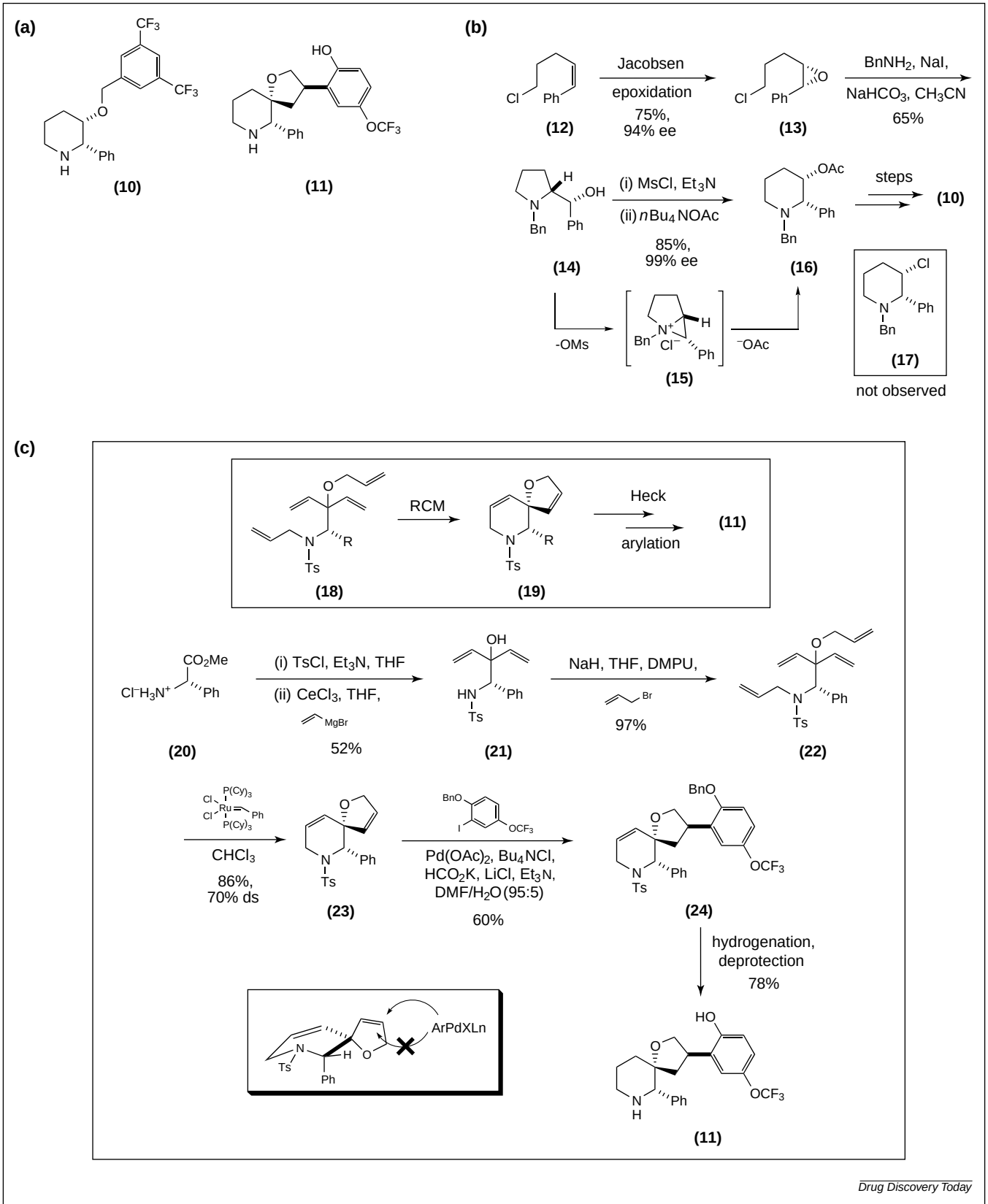
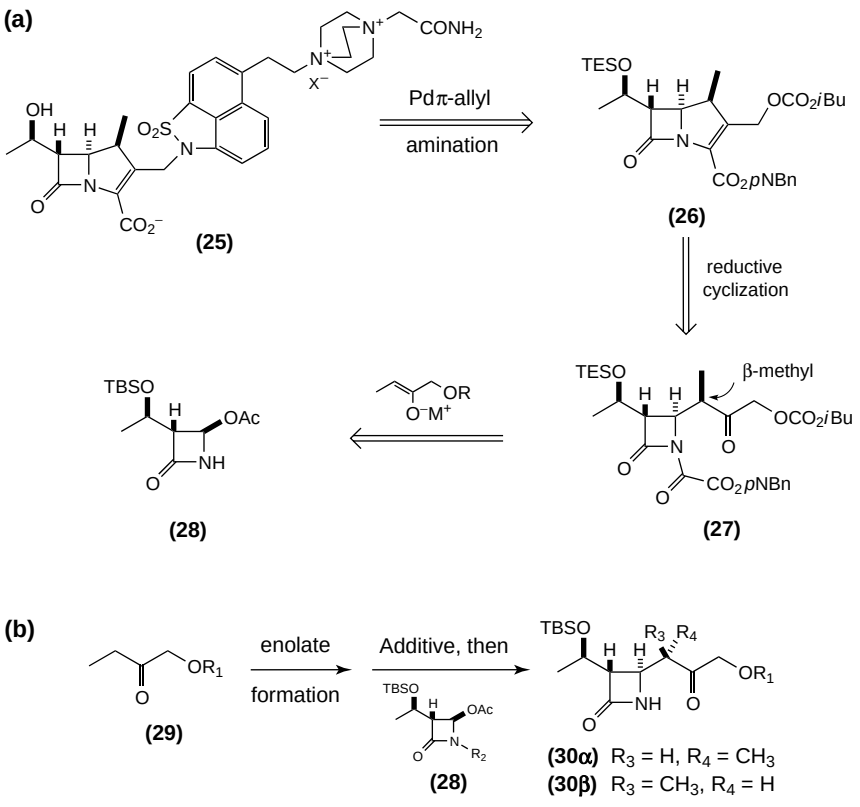


Figure 3. (a) Piperidine-containing hNK-1 antagonists. **(b)** Synthesis of compound **(10)** via ring expansion. **(c)** Synthesis of the spiro-piperidine substance P antagonist, compound **(11)**. Double diastereoselective ring-closing metathesis (RCM) and reductive Heck arylation.



R_1	Enolate formation	R_2	Additive	dr (α:β)
H	LiHMDS	H	None	1:1
"	TMSOTf, Et_3N	"	$ZnCl_2$	66:34
"	"	TBS	TMSOTf	10:1
CO_2iBu	$TiCl_4$	H	Bu_3N	5:95

Figure 4. (a) Retrosynthesis of an anti-methicillin resistant *Staphylococcus aureus* (MRSA) β-methylcarbapenem, compound **(25)**. **(b)** Optimization of the azetidinone and enolate condensation reaction.

[44]. Although the diastereoselectivity (ds) obtained in this reaction was not high, the level of differentiation between the potentially reactive olefinic moieties was impressive. In addition, this route offered the most direct entry into this highly complex system using only the amino acid **(20)** as the sole source of chirality.

The final key step in this sequence involved a regio- and diastereoselective Heck reductive arylation of the spirocyclic diene **(23)**. Ideal conditions were identified (Fig. 3c), wherein **(24)** was produced in a 60% yield as a 9:1 mixture of diastereomers. Considering that as many as eight different products could have been formed, this result was quite gratifying. The relatively high degree of diastereoselectivity could be because of the approach of the aryl palladium species from the less hindered face of the molecule, as indicated. It should also be noted that the presence of water in the reaction mixture (ca. 5%) was essential for optimum regioselectivity of the reductive arylation. The spirocyclic ether **(24)** was then hydrogenated and deprotected to afford the title compound **(11)** in 78% overall yield for the two steps. Biological data for derivatives containing this spirocyclic piperidine core will be reported in due course.

Anti-MRSA carbapenem antibiotics

Substrate-controlled enolate addition

Carbapenem-based antibiotics have been the subject of intense interest over the years because of their ability to combat the spread of infection. We have been able to develop efficient syntheses of similar compounds, such as imipenem [45] and Invanz™ (Merck, Whitehouse Station, NJ, USA) [46], which are currently being carried out at factory scale. However, a different developmental carbapenem **(25)** [47,48] (Fig. 4a) has recently been discovered to have significant anti-methicillin resistant *Staphylococcus aureas* (MRSA) activity without accompanying immunotoxicity [49]. This new target required an entirely different synthetic strategy, which involved a Pd π-allyl amination of the allylic carbonate **(26)** [50]. Though some of the chirality found in the final product could be purchased rather than made, we had to install a β-methyl stereocenter in the oxalimide **(27)** before subsequent oxidative ring closure. Thus, a key transformation in our synthesis was to be an unprecedented double-diastereoselective condensation of a carbonate equivalent with the commercially available azetidinone **(28)**.

The diastereoselective addition of enolates to azetidinones is known, and has been used in our synthesis of imipenem [45]. However, this transformation needed to be re-engineered in this case to enable the formation of two stereocenters instead of one. Initial studies involving the

condensation of **(28)** with carbonate enolate equivalents were encouraging (Fig. 4b). For example, reaction of the azetidinone with the lithium enolate of 1-hydroxy-2-butanone **(29)** provided a 1:1 diastereomeric mixture of the α,β-condensation products **(30)**, but in a rather disappointing 33% yield. However, when the trimethylsilyl (TMS)-enolate of **(29)** was preformed with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine (Et_3N), then reacted with **(28)** in the presence of $ZnCl_2$ (zinc chloride), a different ratio (66:34) of products was obtained, favoring the undesired diastereomer of **(30α)**. Interestingly, the use of a different Lewis acid catalyst (TMSOTf) and protection of the azetidinone amide nitrogen (R_2 = TBS, *tert*-butyldimethylsilyl), gave a ratio of products (10:1) further favoring **(30α)**. Although this result did not provide the desired diastereomer, it led us to examine the effect of other Lewis acid–base combinations on the course of this transformation. Consequently, outstanding selectivity was eventually achieved through the use of the carbonate of **(29)** (R_1 = CO_2*i*Bu), $TiCl_4$ (titanium tetrachloride) and tributylamine (Bu_3N) in toluene [51]. Careful quenching of the crude reaction into acid provided the desired β-diastereomer of **(30)** in 82% yield. This chemistry has been performed on a sufficient scale to produce 45 kg of **(30β)**. Although the specific reasons for the unprecedented diastereoselectivity of this transformation are not entirely understood, it has been proposed that a closed-type cyclic transition state between the putative acyl iminium ion and titanium enolate might be involved. Preliminary study of the carbonate enolate geometry has indicated that the *Z*-conformation is preferred [50]. In any event, this chemistry is an excellent example of the power of reaction optimization, wherein existing methodology [diastereoselective addition of enolates to **(28)**] was modified to fit new purposes.

Endothelin receptor antagonists

Chiral auxiliary-mediated synthesis

Chiral auxiliaries have played an important role over the years in the stereoselective synthesis of organic molecules, both in academia and industry [52]. However, because of the advent of catalytic asymmetric transformations, the application of these intermediaries has decreased somewhat. This is especially true on larger scale because chiral auxiliaries must often be used in stoichiometric quantities, and recovered wherever possible for economic reasons. Despite this fact, these stereodirecting functionalities are still used as key ingredients in process chemistry today. For example, in the early 1990s *cis*-1(*S*)-amino-2(*R*)-indanol **(31)** was developed at Merck for the synthesis of the human immunodeficiency virus (HIV)-1 protease inhibitor

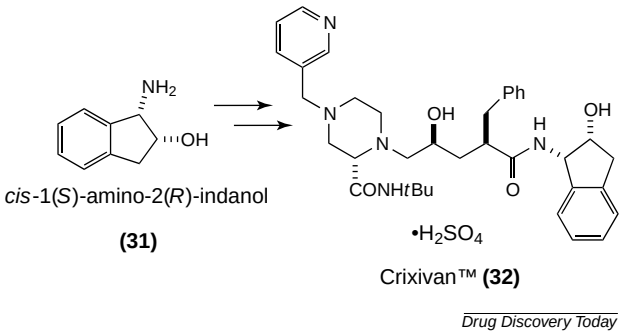


Figure 5. One use of the amino indanol auxiliary.

Crixivan™ **(32)** (Fig. 5) [53]. Not only did this auxiliary serve to impart stereochemistry onto the desired target, but it was eventually incorporated into the final product [54]. More recently this auxiliary has been employed in the synthesis of a highly complex endothelin (ET) receptor antagonist.

Endothelin is a 21 amino acid peptide that interacts with the ET_A/ET_B receptors resulting in constrictor activity of the vascular smooth muscle, which could have a causal role in congestive heart failure, hypertension and other pulmonary diseases [55]. Non-peptide antagonists have recently been found to have nanomolar binding affinity for these receptors, thus offering a viable new class of developmental candidates [56]. One such antagonist, **(33)** (Fig. 6a), was targeted by Merck and represented a significant synthetic challenge to us. The most striking feature of this molecule is the highly functionalized all *trans*-substituted cyclopentane core, which contains three of the four stereocenters found in the molecule. We envisioned a linear synthetic approach to this compound that relies upon the different enantiomers of the amino indanol auxiliary for chirality [57].

The first key reaction in this synthesis involved a diastereoselective addition of the aryl lithium **(36)** to the α,β-unsaturated ester **(35)** [58]. Similar chemistry has been performed by others [59], but only with simplified substrates and an excess of aryl organocuprate reagent. Because of the valuable nature of our aryl lithium species **(36)**, we wanted to use only a slight excess of this nucleophile while maintaining the selectivity and yield of the reaction. To add to the challenge, **(36)** is not commercially available, so the corresponding aryl halide needed to be made (Fig. 6b). This was accomplished by alkylation of the *cis*-1(*R*)-amino-2(*S*)-indanol-derived amide **(37)**, followed by *in situ* hydrolysis of the auxiliary to give the carboxylate **(38)** in 60% overall yield and 96% ee. This acid was reduced to the primary alcohol and the ee of this product was upgraded

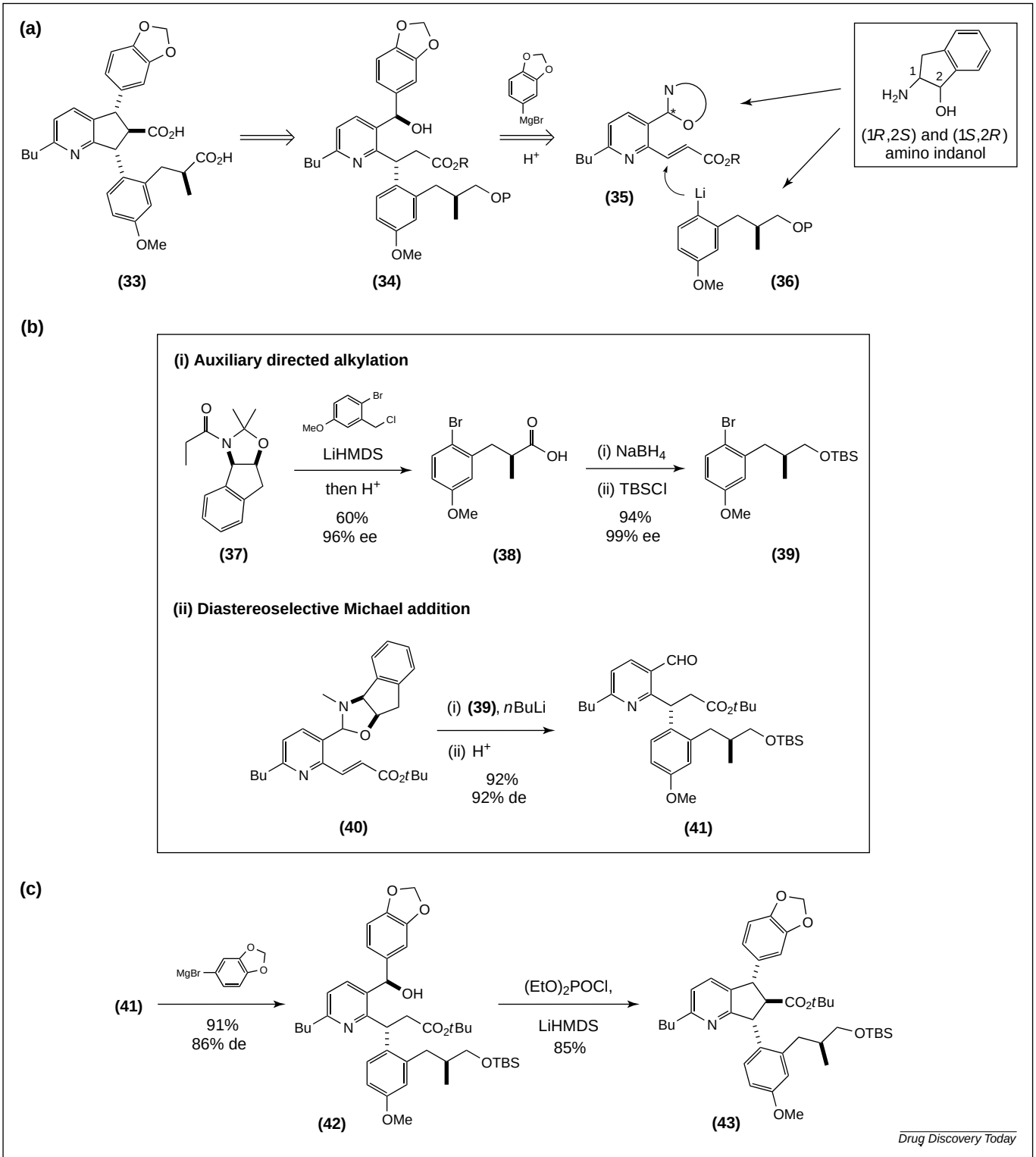


Figure 6. (a) Chiral auxiliary directed retrosynthesis of an endothelin receptor antagonist, compound **(33)**. **(b)** Use of both enantiomers of the amino indanol chiral auxiliary. **(c)** Final asymmetric transformations in the synthesis of compound **(33)**.

to 99% by a single recrystallization from hexanes. Subsequent protection of this alcohol with TBSCl gave **(39)** in 94% yield from **(38)**. The Michael acceptor **(40)** was then prepared from the corresponding aldehyde by condensation with *N*-methyl-*cis*-1(*S*)-amino-2(*R*)-indanol in quantitative yield. Lithiation of the aryl bromide **(39)** was accomplished with

n-butyl lithium (*n*BuLi) in toluene/THF (tetrahydrofuran) (4:1) at –65ºC, and this reagent was added to a solution of **(40)** at –50 ºC. Subsequent acidic workup of the reaction provided the crude aldehyde **(41)** in high yield (~90%) and diastereomeric excess (92%). Not only was this transformation highly selective, but our goal of using only a slight excess (1.1 eq.) of the aryl lithium reagent **(36)** was achieved. Thus, two of the stereocenters found in the final product were introduced through the efficient use of the amino indanol chiral auxiliary. The remaining chemistry would be influenced by the asymmetry incorporated in these initial steps.

Treatment of the crude aldehyde **(41)** with the commercially available aryl Grignard reagent gave the benzylic alcohol **(42)** in 91% yield and 86% de according to high performance liquid chromatography (HPLC) analysis (Fig. 6c). The selectivity of this substrate-controlled addition was influenced by the adjacent α-aryl benzylic center, established in the previous Michael addition (Fig. 6c). Subsequent intramolecular cyclization was accomplished by treatment of **(42)** with $(EtO)_2PCl$ (diethyl chlorophosphite) and lithium hexamethyldisilazane (LiHMDS) at 0ºC to give exclusively the all *trans* diastereomer **(43)** in 85% yield. The use of other activating groups, such as sulfonates (i.e. mesyl and tosyl), gave lower yields and poor diastereoselectivity. The final target, **(33)**, was obtained after removal of the *t*-butyl and TBS protecting groups and oxidation of the primary alcohol to the carboxylic acid. This chemistry has been performed in the pilot plant by our colleagues at Banyu Pharmaceuticals (Okazaki, Japan) and has proven sufficiently robust to have application in the synthesis of other ET receptor antagonists [60].

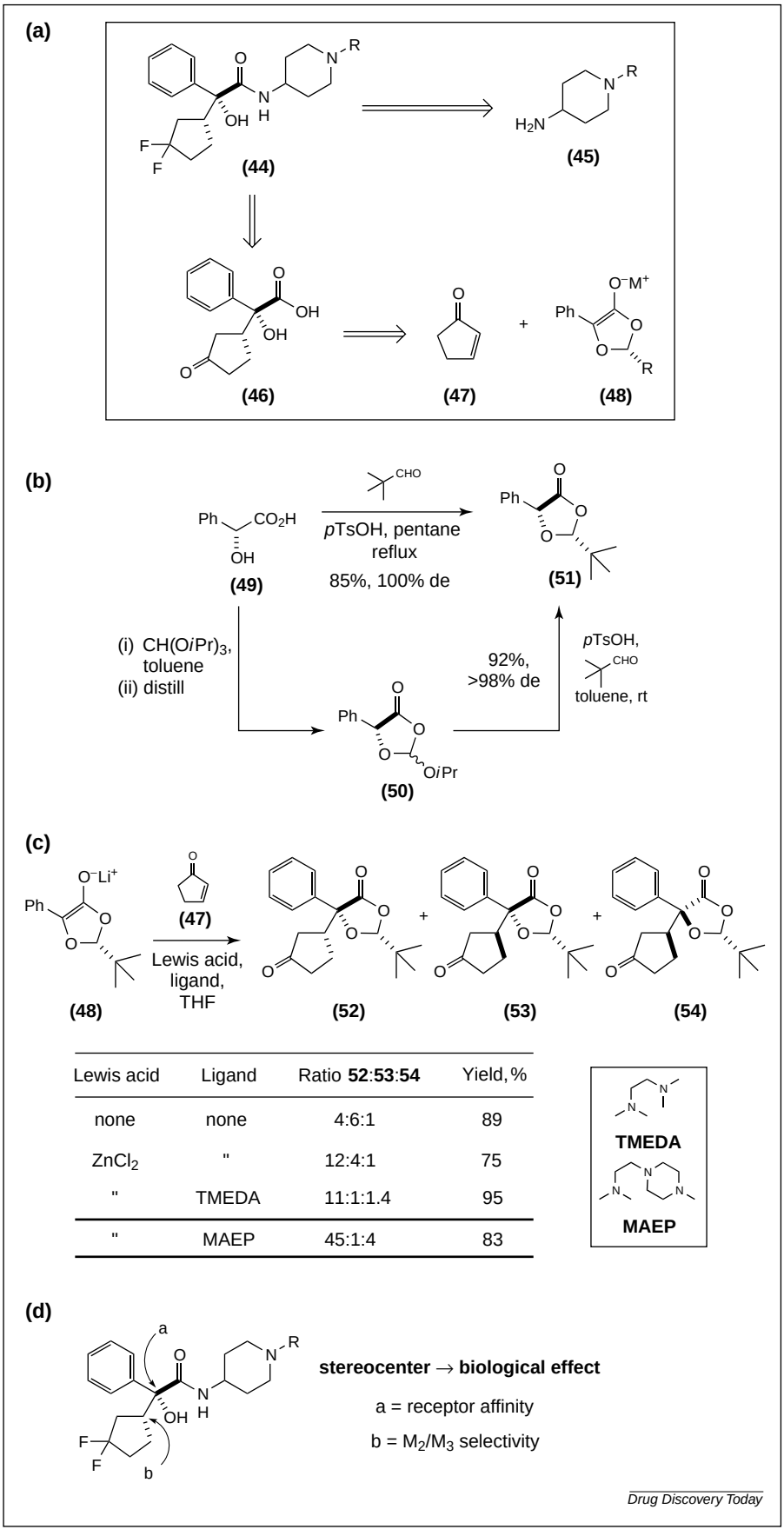
Muscarinic receptor antagonist

Diastereoselective Michael addition of a chiral enolate

The asymmetric synthesis of quaternary centers is a key challenge to organic chemists, for which relatively few methods are available [61]. We recently encountered this difficult problem in a series of muscarinic receptor antagonists similar to **(44)** (Fig. 7a) [62]. These compounds are interesting because they exhibit affinity for the muscarinic M_3 receptor over the M_2 subtype [63]. This is of pharmaceutical relevance because alternative ligands (i.e. antagonists) for the muscarinic receptor M_3 could act in therapeutic fashion towards the treatment of various cardiovascular diseases, bronchial afflictions and incontinence of the urinary system [64]. Alternatively, interaction with the M_2 receptor has been demonstrated to potentiate bronchial constriction [65]. From a synthetic standpoint, we were concerned with the tertiary α-hydroxy amide center of **(44)**, which is flanked by a chiral cyclopentane ring. Although some methods have been developed for the synthesis of chiral tertiary alcohols, these techniques generally do not address consecutive asymmetric centers [66]. Therefore, our goal was to construct the α-hydroxy acid precursor **(46)** in direct fashion via a selective Michael addition of a chiral enolate **(48)** to the commercially available enone **(47)**. This strategy required the invention of new reaction conditions because the existing methodology in this area was not known to be selective [67].

Preparation of the chiral enolate **(48)** began from (*R*)-mandelic acid **(49)**, which was heated in the presence of pivalaldehyde and catalytic *p*-toluene sulfonic acid (*p*TsOH) in pentane with azeotropic removal of water (Fig. 7b). This procedure worked rather well on a small scale to provide **(51)** as a single diastereomer in 85% yield. The use of solvents other than pentane eroded the diastereomeric purity of the product. However, because large-scale pilot plant work often precludes the use of highly volatile solvents, a slightly different procedure was required. Thus, stirring of the mandelic acid starting material with triisopropyl orthoformate [$CH(OiPr)_3$], followed by distillation-driven removal of *iso*-propyl alcohol, provided **(50)** as a mixture of anomers. Pivalaldehyde was then added to this crude product, and after stirring with a catalytic amount of *p*TsOH-H_2O in toluene at room temperature, **(51)** was obtained as a 120:1 mixture of diastereomers. Trituration of the crude product with *n*-heptane gave diastereomerically pure **(51)** in 92% overall yield. This chemistry has been performed safely on a large scale to produce >9.0 kg of material.

With the requisite auxiliary in hand, the Michael addition was examined. Optimal conditions were identified through a systematic study of various reaction conditions (Fig. 7c). Lewis acid promoters, solvent and other additives were analyzed to obtain reproducible results. For example, reaction of the lithium enolate **(48)** and the enone **(47)** in THF at –78ºC gave a mixture (4:6:1) of products favoring **53** in 89% total yield. We were gratified to find that no 1,2-addition of the enolate to the ketone had occurred and that the Michael reaction was the major pathway. *In situ* conversion of the lithium enolate to the zinc species resulted in a reversal of selectivity providing a 12:4:1 ratio of the diastereomers **(52)**, **(53)** and **(54)** in reasonable yield (75%). This key experiment led us to examine the use of metal chelating ligands, which could interact with the presumed zinc enolate, thereby changing its reactive conformation. As such, the use of tetramethylethylenediamine (TMEDA, 20 eq.) provided an 11:1:1.4 mixture of products in 95% yield favoring the desired adduct **(52)**. The amount of TMEDA could be reduced significantly to 5 eq. if the reaction was performed in a DME–toluene (1:1) solvent mixture instead of THF, which is a highly coordinating



Lewis acid	Ligand	Ratio **52**:**53**:**54**	Yield, %
none	none	4:6:1	89
$ZnCl_2$	"	12:4:1	75
"	TMEDA	11:1:1.4	95
"	MAEP	45:1:4	83

solvent. Ultimately, the ideal ligand for this reaction was identified to be 1-(2-dimethylaminoethyl)-4-methylpiperazine (MAEP), which gave a 45:1:4 mixture of **(52)**, **(53)** and **(54)**. Diastereomerically pure **(52)** could be isolated in 74% yield by recrystallization of the crude reaction mixture from ethanol:methanol:H_2O.

Thus, the Michael addition, which had initially been non-selective, was modified to favor formation of the desired diastereomer **(52)** by careful understanding and optimization of the reaction conditions. An additional advantage to this method was that MAEP was found to form a non-hygroscopic 1:1 complex with $ZnCl_2$. Also, this reagent combination was found to be effective in less than stoichiometric quantities without subsequent loss in diastereoselectivity. Consequently, these two features greatly improved the overall process in terms of both reagent cost and ease of handling. This methodology has been performed on a large scale to give >25 kg of **(52)**.

The Michael addition employed for the synthesis of the core **(46)** effectively and convergently set both centers of asymmetry in one step. This ability to construct the hydroxy acid substructure of **(44)** with a high degree of stereocontrol was key because the biological activity of these derivatives is tied to their stereochemical identity (Fig. 7d). For example, the stereochemistry of the tertiary hydroxyl center (a) is responsible for muscarinic receptor affinity in general [68]. When this center is inverted, the resultant derivative is no longer an effective antagonist.

Figure 7. (a) Retrosynthesis analysis of muscarinic receptor antagonists, compound **(44)**. **(b)** Different routes to the chiral enolate precursor, compound **(54)**. **(c)** Optimization of the diastereoselective Michael addition of the chiral enolate **(48)** to the anone **(47)**. **(d)** The correlation between stereochemistry and biological effect for this series of muscarinic receptor antagonists.

Equally as important is the cyclopentyl methine stereochemistry (b); epimerization of this center results in analogs that are ~four-times less selective for the M_3 receptor versus the M_2 subtype [63].

Conclusion

The purpose of this review has been to demonstrate that all types of organic transformations are at the disposal of the process chemist. Fine stereocontrol can be obtained through the use of classical resolution techniques, chiral auxiliary and substrate-directed synthesis, or catalytic asymmetric methodology. We hope that our view of process research has been adequately reflected by the examples presented herein: sometimes, known methodologies must be reinvented and new reactions discovered to obtain an efficient and direct synthesis of a final drug target. Admittedly, the issue of stereochemistry does complicate matters in light of the fact that final product must often be produced in enantiomerically purified form. This can be accomplished, however, even under accelerated developmental timelines in which faster is usually deemed better, without sacrificing the creativity and resourcefulness of the individual chemist. We believe that this approach to process chemistry is ideally suited for the modern pharmaceutical industry, which continues to produce developmental targets of increasing functional and stereochemical complexity.

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